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Heterocyclic Scaffolds II: Reactions and Applications of Indoles

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will also be included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.
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Aims and Scope

The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences etc. Metabolism is also included which provides information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic ring are also dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.

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The individual volumes of *Topics in Heterocyclic Chemistry* are thematic. Review articles are generally invited by the volume editors.

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Dedicated to the memory of my devoted parents, Waldron and Jane,
who with their love, inspiration, and guidance sparked my interest
at a young age in both science and chemistry

Preface

This volume consists of 11 chapters covering the chemistry and applications of indole and indole derivatives. Often considered to be the pre-eminent heterocycle and the molecular scaffold of greatest medicinal importance, indole continues to captivate chemists and biologists alike.

In Chap. 1, Wu concisely summarizes of "New Indole-Containing Medicinal Compounds", including both existing indole and oxindole drugs, such as sumatriptan, ondansetron, and fluvastatin, and those in current clinical trials, such as cediranib, bravanib, and vilazodone.

In Chap. 2, "Indoles: Industrial, Agricultural and Over-the-Counter Uses", Barden continues the theme of indole applications from the first chapter by illustrating the role of indoles as agricultural compounds, dyes, pigments, dietary supplements, nutraceuticals, perfumes, and flavoring agents.

In Chap. 3, Sundberg, an indole pioneer and the author of the 1970 classic monograph "The Chemistry of Indoles", covers thoroughly "Electrophilic Substitution Reactions of Indoles", which is probably the most ubiquitous reaction of indole and one that continues to be extraordinarily useful in synthesis.

In Chap. 4, Kishbaugh reviews the less well known but emerging "Reactions of Indole with Nucleophiles", with a rich collection of both nucleophilic additions to electron-deficient indoles and nucleophilic substitution reactions of indole.

In Chap. 5, "Metalation of Indole", Pelkey comprehensively reviews the enormous literature of direct and directed metalation and halogen-metal exchange, reaction protocols that have assumed incredible utility in indole chemistry.

In Chap. 6, a companion to the preceding chapter, Li and Gribble document "Metal-Catalyzed Cross-Coupling Reactions for Indoles", which covers palladium, copper, rhodium, iron, and nickel cross-couplings of indole – a suite of reactions that has assumed great importance in indole synthesis and chemistry.

In Chap. 7, Badenock reviews the relatively new area of "Radical Reactions of Indole", with extensive coverage of both intermolecular reactions and intramolecular cyclizations, including application to the facile construction of medium-size rings.

In two complementary reviews, Chaps. 8 and 9, Berthel, Firooznia, and Kester discuss in great depth the enormously flexible cycloaddition reactions of indoles. Chapter 8 is an array of "[2+2], [3+2], and [2+2+2] Cycloaddition Reactions of Indole Derivatives", while Chap. 9 covers "[4+2] Cycloaddition Reactions of

Indole Derivatives", wherein the versatile indole double bond can serve as either dienophile or part of a diene.

In Chap. 10, Russel presents "Oxindoles and Spirocyclic Variations: Strategies for C3 Functionalization" of indoles and the role this emerging strategy plays both in the asymmetric introduction of C3 quaternary centers and in the synthesis of oxindoles and myriad-related natural products, including oxaspirocycles and azaspirocycles.

In Chap. 11, Fu continues the theme of indole-containing natural products with an exhaustive treatment of the "Advances in the Total Syntheses of Complex Indole Natural Products", with a focus on indole alkaloids of recent interest such as diazonamide, chartelline, penitrem, yatakemycin, welwitindolinone, and several others.

I am indebted to my authors for their truly outstanding contributions to what I believe is a long overdue and important addition to the literature of indoles. I particularly thank my former students (Barden, Kishbaugh, Pelkey, Badenock, Berthel, and Fu) for their willingness to participate in this endeavor, and my heterocyclic colleagues and friends (Wu, Sundberg, Li, and Russel) for their equally hard work. I especially thank my series editor Bert Maes for the opportunity to be the editor of this volume.

Hanover, New Hampshire Gordon W. Gribble
2010

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New Indole-Containing Medicinal Compounds

Yong-Jin Wu

Abstract This chapter summarizes the relatively new indole-, indoline-, and oxindole-containing drugs on the market. The indole-, indoline-, and oxindole-based clinical candidates are also presented.

Keywords AG-14699 · Alosetron · Bazedoxifene · BMS-250749 · Brivanib · Cediranib · Dacinostat · Dalavirdine · Daptomycin · Enzastaurin · Eptifibatide · Flindokalner · Fluvastatin · Indole · Indoline · Intedanib · Lestaurin · Midostaurin · MKC-1 · Motesanib · Obatoclax · Ondansetron · Oxindole · Panobinostat · Pipendoxifene · Pruvanserin · Ropinirole · Ropinirole · Ruboxistaurin · Satavaptan · Semaxanib · Sertindole · Silodosin · Sotrastaurin · Sunitinib · Sunitinib · Tadalafil · Tegaserod · Tiplaxtinin · Triptan · TSU-68 · UCN-01 · Vilazodone · Zafirlukast · Ziprasidone · Ziprasidone

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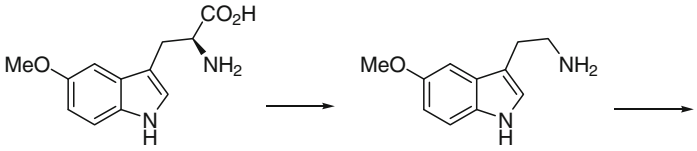
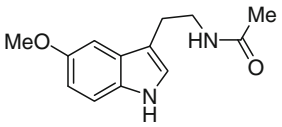
1 Introduction

The indole nucleus is embedded in many biological systems including the essential amino acid tryptophan, the neurotransmitter serotonin, and the mammalian hormone melatonin. Tryptophan is a structural constituent of many proteins as well as the biosynthetic precursor of serotonin, which in turn serves as the precursor of melatonin. Serotonin plays a critical role in neuronal cell formation and maintenance, sleep, cognition, appetite, and mood, while melatonin is a natural bioregulator that induces and maintains sleep [1, 2].

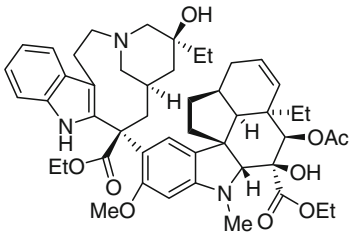


Tryptophan Serotonin

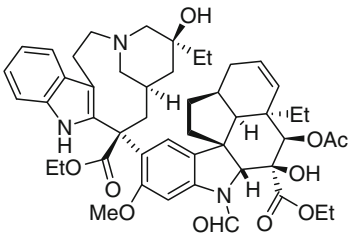


Metatonin

The indole ring system is also ubiquitous in biologically active alkaloids such as the first plant-derived agents to advance into clinical use, the so-called vinca alkaloids vinblastine and vincristine [3].[1] These alkaloids were first isolated in the late 1950s from the Madagascar periwinkle plant used by various cultures for the treatment of diabetes. The plant was initially evaluated as a source of potential oral hypoglycemic agents, but the serendipitous observation that the extracts of this plant reduced circulating white blood cell counts and bone marrow depression in rats led to the discovery of the active compounds, vinblastine and vincristine, as antitumor agents. These agents were brought to the market by Eli Lilly in the early 1960s for the treatment of certain kinds of cancer. Both compounds act by inhibiting microtubule formation through binding to tubulin which is the basic building block of microtubules, and preventing their aggregation. Reserpine represents another important indole alkaloid, which was isolated from the extract of the snakeroot plant (*Rauwolfia serpentine*). This plant extract served as an ancient natural remedy for melancholia (depressed mood) [1]. Reserpine has been also used for the treatment of high blood pressure.

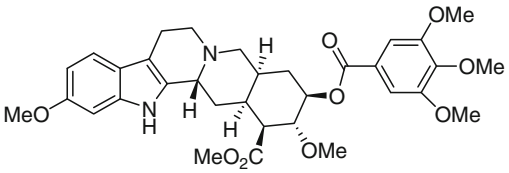


Vinblastine (Velban™)
Eli Lilly



Vincristine (Oncovin™)
Eli Lilly

[1]Wikipedia, the free encyclopedia via http://en.wikipedia.org/wiki/generic name.



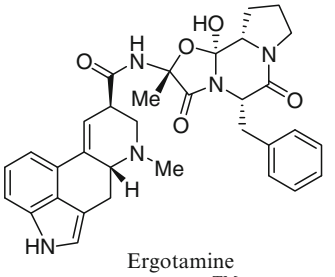
Reserpine

The wide distribution of the indole nucleus in biological systems and biologically active natural products has prompted medicinal chemists to apply indole chemistry to drug synthesis, and these efforts have culminated in the discovery of several successful drugs such as sumatriptan and vardenafil for the treatment of migraine and male erectile dysfunction (ED), respectively. This chapter provides a brief review of representative indole-, indoline, and oxindole-containing drugs on the market as well as investigational drugs under clinical evaluations.

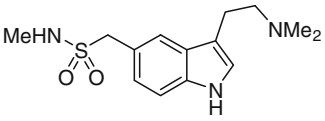
2 Indole-Containing Drugs

2.1 Triptans

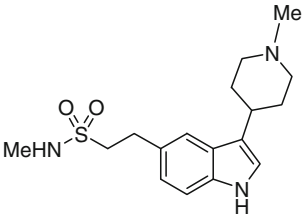
The discovery of triptans started with the ergot alkaloids such as ergotamine, a powerful vasoconstrictor [4]. This alkaloid is used for the treatment of acute migraine attacks (sometimes in combination with caffeine). The antimigraine effect of ergotamine results from both constriction of the intracranial extracerebral blood vessels through the 5-HT_{1B} receptor and inhibition of the trigeminal neurotransmission by 5-HT_{1D} receptors. It is its action on the D_2 dopamine and 5-HT_{1A} receptors that can cause some side effects. Thus, significant efforts have gone into the development of selective 5-$HT_{1B/1D}$ agonists for the treatment of migraine, and these efforts led to the identification of sumatriptan as the first specific antimigraine medication. Since its approval by the US FDA in 1991, sumatriptan has become one of the most prescribed drugs for migraine treatment (it was ranked the top 35 drug for 2008 by US sales ($973 million)) (http://www.drugs.com). Despite its huge success, it still suffers from several limitations including poor bioavailability, short half-life, and a high headache recurrence rate. Thus, several second-generation triptans have been developed, including zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan. These triptans generally have improved oral bioavailability and plasma half-life. There are subtle differences with each of the triptans in terms of efficacy, speed of onset of action, duration of action, headache recurrence rate, side effects, and convenience of administration.



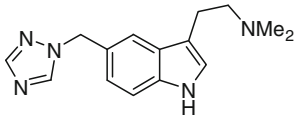
Ergotamine
(Ergostat™)



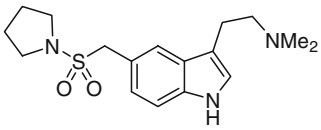
Sumatriptan (Imitrex™)
GlaxoSmithKline



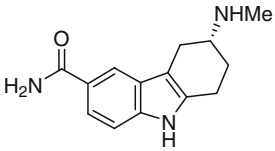
Naratriptan (Amerge™)
GlaxoSmithKline



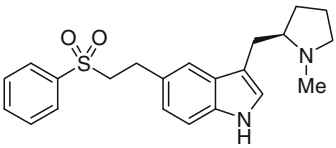
Rizatriptan (Maxalt™)
Merck



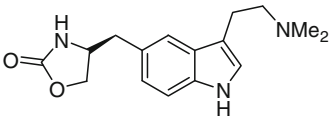
Almotriptan (Axert™)
Almirall/Janssen



Frovatriptan (Frova™)
GlaxoSmithKline



Eletriptan (Relpax™)
Pfizer



Zolmitriptan (Zomig™)
GlaxoSmithKline/AstraZeneca

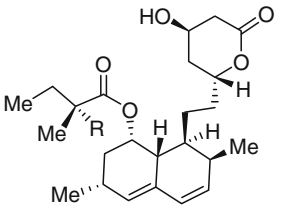
2.2 Fluvastatin

Statins are a class of drugs that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver. These drugs work by inhibiting hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining

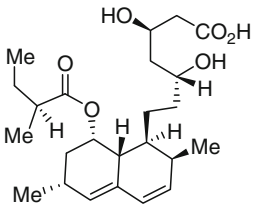
enzyme located in hepatic tissue that produces mevalonate, a small molecule used in the synthesis of cholesterol.

Statins can be classified as natural statins and synthetic statins. Lavastatin, simvastatin, and pravastatin are the first three natural statins to reach the market. Lavastatin and pravastatin are natural products isolated from fermentation broths, while simvastatin is a semisynthetic statin derived from lavastatin. Fluvastin was the first truly synthetic statin brought to the market by Sandoz pharmaceutical company (now part of Novartis), and it was obtained by replacing the hexahydronaphthalene core structure of the natural statins with the indole nucleus [5]. It was the discovery of fluvastin that opened up the opportunity of more potent synthetic statins including atorvastatin, the most prescribed drug in the world.

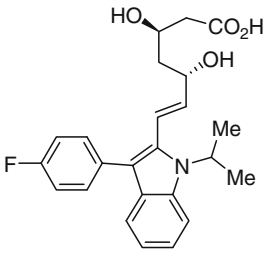
Even though fluvastatin is relatively unknown as compared with other statins on the market, it still earned $645 million for Novartis in 2008, and the annual sales of fluvastatin reached its peak at $734 million in 2003.



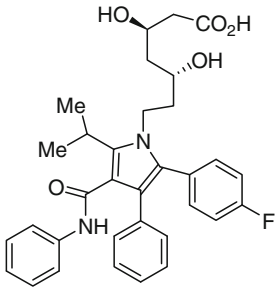
Lovastatin (Mevacor™) (R = H)
Simvastatin (Zocor™) (R = Me)
Merck



Pravastatin (Pravachol™)
Bristol-Myers Squibb



Fluvastatin (Lescol™)
Novartis



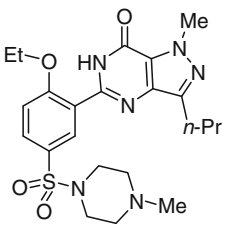
Atorvastatin (Lipitor™)
Pfizer

2.3 *Tadalafil*

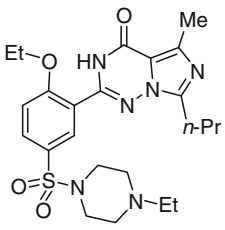
Since the discovery of sildenafil for the treatment of ED in 1993, two additional products, vardenafil and tadalafil, have been introduced to the market [6, 7]. All these three drugs work by inhibiting type 5 phosphodiesterase (PDE5). This inhibition increases the amount of cyclic guanosine monophosphosphate (cGMP), which

relaxes smooth muscle and increases blood flow to the corpus cavernosum, thus enhancing erectile function.

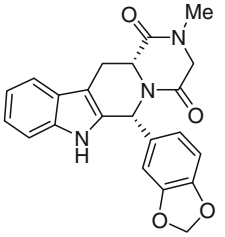
Structurally, tadalafil is different from both vardenafil and sildenafil, while vardenafil and sildenafil are closely related. Presumably due to its unique structure, tadalafil exhibits much longer half-life (17.5 h) than both sildenafil (4–5 h) and vardenafil (4–5 h), resulting in longer duration of action. This pharmacological distinction has earned tadalafil the sobriquet, "The Weekend Pill". Tadalafil is also approved in several world regions for treating pulmonary arterial hypertension (see footnote 1). Tadalafil was ranked the top 66 drug for 2008 by US sales ($555 million) (cf. sildenafil: top 38, $920 million) (http://www.drugs.com).



Sildenafil (Viagra™)
Pfizer



Vardenafil (Levitra™)
Bayer



Tadalafil (Cialis™)
ICOS/Lilly

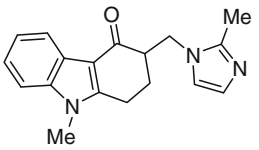
2.4 Ondansetron and Alosetron

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) activates at least seven distinct (5-HT_1 to 5-HT_7) receptors in the central and peripheral nervous systems to produce important modulatory effects. With the exception of the 5-HT_3 receptor, all 5-HT receptors are members of the G protein-coupled receptor family that function through adenylyl cyclase or phospholipase C second messengers. The 5-HT_3 receptor, however, is a member of the superfamily of ligand-gated ion channels and serves to moderate neuronal depolarization by increasing the flux of Na^+, K^+, and Ca^{2+} [8].

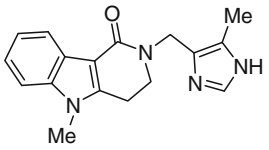
5-HT_3 receptor antagonists were initially hailed as potential treatments for anxiety, Alzheimer's disease, schizophrenia, pain, and drug dependence. Despite some early encouraging results, no 5-HT_3 antagonists have been approved for the treatment of schizophrenia and Alzheimer's disease. Fortunately, 5-HT_3 receptor antagonists such as ondansetron have proven to be the most effective antiemetic products to date. These compounds reduce the activity of the vagus nerve, which activates the vomiting center in the medulla oblongata, and also block serotonin receptors in the chemoreceptor trigger zone. However, they do not work on vomiting caused by motion sickness.

Among all 5-HT_3 receptor antagonists marketed as antiemetics, ondansetron is the most widely prescribed (its US sales reached $1.44 billion in 2005). Other indole-based antiemetic 5-HT_3 receptor antagonists include romosetron, dolasetron, and tropisetron.

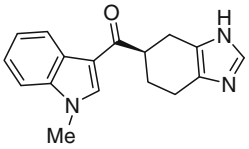
Alosetron, another 5-HT_3 antagonist, has been used for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) in women only. Unlike ondansetron, it is not approved as an antiemetic. As 5-HT_3 receptor stimulation enhances gastrointestinal motility, 5-HT_3 antagonism with alosetron reduces the movement of fecal matter through the large intestine, thus relieving IBS.



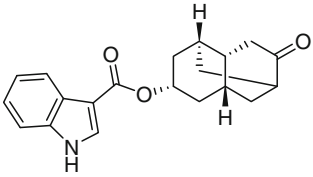
Ondansetron (Zofran™)
GlaxoSmithKline



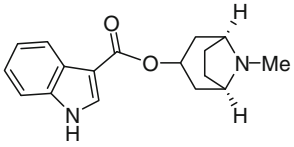
Alosetron (Lotronex™)
GlaxoSmithKline/Prometheus Lab



Romosetron (Nasea™)
Astellas Pharma



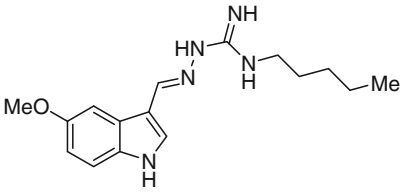
Dolasetron (Anzemet™)
Sanofi-Aventis



Tropisetron (Navoban™)
Asta Medica

2.5 *Tegaserod*

Tegaserod [9], a 5-HT_4 agonist, was launched in the market in 2004 for the management of IBS and constipation. Three years later, the US Food and Drug Administration (FDA) requested that Novartis withdraw tegaserod from shelves due to concerns over increased risks of heart attack or stroke. However, tegaserod is still available in many countries across the world (see footnote 1).

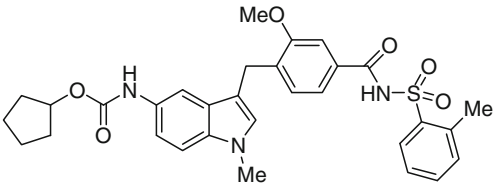


Tegaserod (Zelmac™)
Novartis

2.6 Zafirlukast

Zafirlukast is an oral leukotriene receptor antagonist (LTRA) for the treatment of asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator. Zafirlukast blocks the action of the cysteinyl leukotrienes on the CysLT1 receptors, thus reducing constriction of the airways, build-up of mucus in the lungs and inflammation of the breathing passages.

Zafirlukast was introduced 2 years earlier than another LTRA, montelukast (Singulair), but is less widely used, in part, because it is usually administered twice daily while montelukast is taken once daily (see footnote 1).



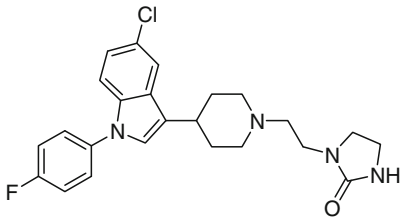
Zafirlukast (Accolate™)
AstraZeneca

2.7 Sertindole

Sertindole is one of the newer antipsychotic medications for the treatment of schizophrenia. It mainly affects dopamine D_2, serotonin 5-HT_2, and α_1-adrenergic receptors. In contrast to other antipsychotics, sertindole is not associated with sedative effects; sedation may add to the cognitive problems inherent in schizophrenia.

Sertindole was voluntarily withdrawn from the market in 1998 due to concerns over the risk of cardiac arrhythmia and sudden death. However, it has been shown that sertindole is comparable with risperidone or olanzapine, and that the risk/benefit

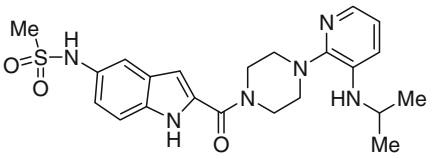
profile of sertindole did not support a permanent withdrawal from the market. Thus, the regulatory agencies in many countries have now implemented the approval of sertindole, and it is available in more than 20 countries across the world (see footnote 1).



Sertinole (Compazine™)
Lundbeck

2.8 Delavirdine

Delavirdine, a nonnucleoside reverse transcriptase inhibitor, is used as part of antiretroviral therapy. Because of its moderate efficacy and inconvenient dosing (three times a day) as well as interaction with other protease inhibitors, delavirdine is currently rarely used (see footnote 1).

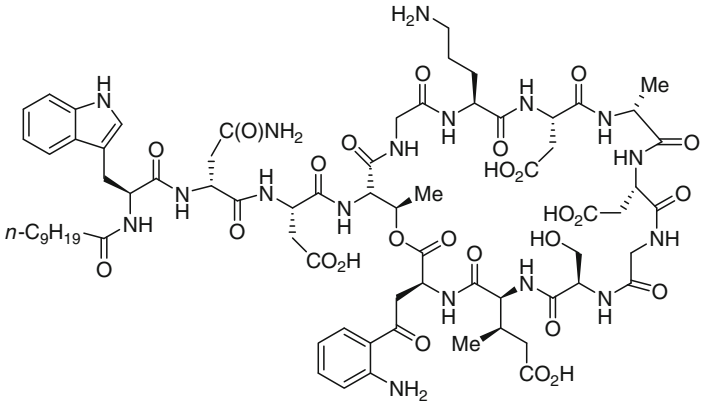


Delavirdine (Rescriptor™)
Pfizer

2.9 Daptomycin

Daptomycin was originally isolated from the soil saprotroph *Streptomyces roseosporus* by scientists at Eli Lilly and Company in the 1980s. It is a novel lipopeptide antibiotic used in the treatment of certain infections caused by Gram-positive organisms. The proposed mechanism of action involves insertion of the lipophilic daptomycin tail into the bacterial cell membrane, causing rapid membrane depolarization and a potassium ion efflux. This leads to the arrest of DNA, RNA, and protein synthesis, resulting in bacterial cell death (see footnote 1).

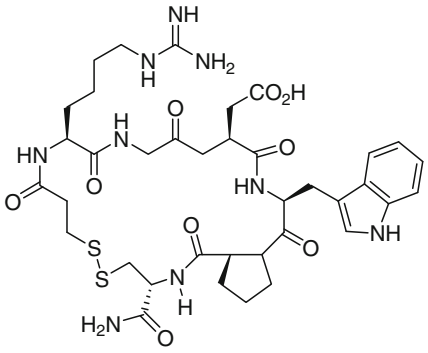
Daptomycin represents the first lipopeptide agent to be released onto the market, and its worldwide sales are expected to be $520 million for 2009.



Daptomycin (Cubicin™)
Lilly/Cubist

2.10 *Eptifibatide*

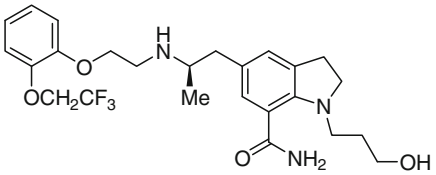
Eptifibatide [10] is a synthetic cyclic heptapeptide glycoprotein IIb/IIIa antagonist and platelet aggregation inhibitor. It reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to glycoprotein IIb/IIIa. Eptifibatide keeps the platelets in the blood from coagulating (clotting) to prevent undesired blood clots that can occur with certain heart or blood vessel conditions. Eptifibatide is indicated for the treatment of patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI), including those undergoing intracoronary stenting.



Eptifibatide (Integrilin™)
COR Therapeutics/Schering-Plough

3 Indoline-Containing Drug: Silodosin

Silodosin [11], an alpha 1A adrenoceptor antagonist selective for prostatic receptors, has been shown to relax smooth muscles in the prostate and bladder neck. This compound has been launched recently for the treatment of urinary dysfunction associated with benign prostatic hyperplasia (BPH).

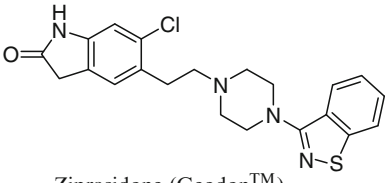


Silodosin (Rapaflo^{TM})
Watson

4 Oxindole-Containing Drugs

4.1 Ziprasidone

Ziprasidone is an atypical antipsychotic in clinical use for both schizophrenia and bipolar disorder (see footnote 1). It has a high affinity for dopamine, serotonin, and alpha-adrenergic receptors and a moderate affinity for histamine receptors. The exact mechanism of action of ziprasidone is unknown. However it has been presumed that its antipsychotic activity is mediated primarily by antagonism at dopamine receptors, specifically D_2. Serotonin antagonism may also play a role in the effectiveness of ziprasidone. Antagonism at histaminic and alpha adrenergic receptors are likely responsible for some of the side effects of ziprasidone, such as sedation and orthostasis. The worldwide sales of ziprasidone are expected to be $1 billion in 2009.

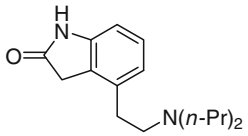


Ziprasidone (Geodon^{TM})
Pfizer

4.2 Ropinirole

Ropinirole is used for the treatment of Parkinson's disease and restless legs syndrome (RLS) (see footnote 1). It acts as a dopamine D_2, D_3, and D_4 receptor

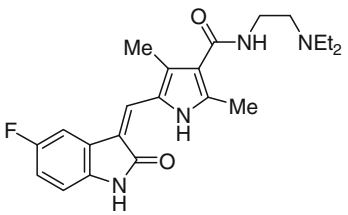
agonist with the highest affinity for D_3. Ropinirole exhibits weak activity at the 5-HT_2 and α_2-adrenergic receptors and shows little affinity for the 5-HT_1, benzodiazepine, GABA, muscarinic, α_1- and β-adrenergic receptors. Ropinirole was ranked the top 95 drug for 2007 by US sales ($408 million (http://www.drugs.com)).



Ropinirole (Requip™)
GlaxoSmithKline

4.3 *Sunitinib*

Sunitinib [12] is an orally bioavailable, multitargeted receptor tyrosine kinase inhibitor that was approved by the US FDA for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumor in 2006 (see footnote 1). Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases, including all receptors for platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). The simultaneous inhibition of these targets therefore leads to both reduced tumor vascularization and cancer cell death, and ultimately tumor shrinkage. As sunitinib targets many different receptors, it suffers from many side effects such as the classic hand–foot syndrome, stomatitis, and other dermatologic toxicities. The worldwide sales of sunitinib are expected to reach $1 billion in 2009.



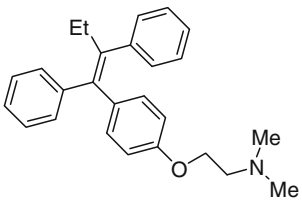
Sunitinib (Sutent™)
Sugen/Pfizer

5 Indole-Containing Clinical Candidates

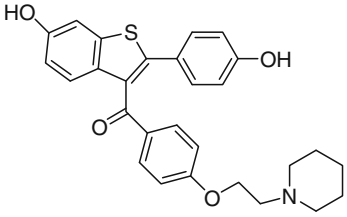
As numerous indole-based compounds are currently undergoing clinical studies, only representative investigational drugs are presented. Some of the information shown below including the status of the drug candidates was obtained from Thomson Pharma website (https://www.thomson-pharma.com).

5.1 *Bazedoxifene and Pipendoxifene: SERMs (Breast Cancer and Osteoporosis)*

Selective estrogen receptor modulators, or SERMs, selectively stimulate or inhibit the estrogen receptors of different target tissues. For example, a SERM might inhibit the estrogen receptor found in breast cells but activate the estrogen receptor present in uterine endometrial cells. Thus, SERMs can be used for the treatment of both breast cancer and osteoporosis. For example, tamoxifen, one of the oldest and most effective SERMs, is the standard endocrine (antiestrogen) therapy for hormone-positive early breast cancer, while raloxifene, a synthetic estrogen, is used in the prevention of osteoporosis in postmenopausal women.

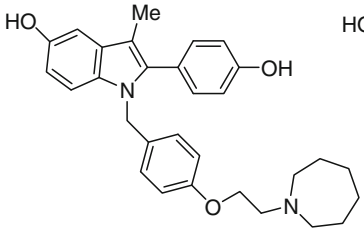


Tamoxifen (Nolvadex™)
AstraZeneca

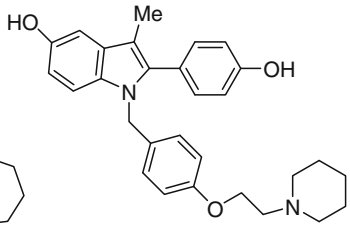


Raloxifene (Evista™)
Eli Lilly

Among several new SERMs in clinical evaluations are the two 2-phenylindole analogs, bazedoxifene [13] and pipendoxifene [14]. The only structural difference between these two indole molecules is the side chain amine moiety: pipendixifene bears piperidine while bazedoxifene contains azepane. Bazedoxifene is being developed for the prevention and treatment of postmenopausal osteoporosis. It is approved in the European Union, and is currently in the late phases of review by the US Food and Drug Administration. When approved, bazedoxifene will be marketed by Pfizer under the tradename Viviant in the US and Conbriza in the EU. Pipendoxifene was used in phase II studies as a treatment for metastatic breast cancer. However, pipendoxifene was classified as the backup to bazedoxifene. Presumably, it would not be developed further unless bazedoxifene failed.



Bazedoxifene (Viviant™)
Wyeth (now Pfizer)
under regulatory review



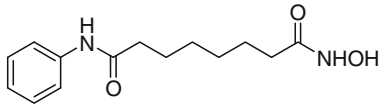
Pipendoxifene
Phase II
Wyeth (now Pfizer)

5.2 *Dacinostat and Panobinostat: HDAC Inhibitors (Cancer)*

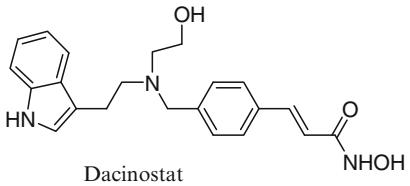
Histone deacetylases (HDAC) are a class of enzymes that catalyze the removal of acetyl groups from the *N*-acetylated lysine residues of histone. Histones are the major protein components of chromatin, act as spools around which DNA winds, and play an important role in gene regulation. As certain tumors overexpress HDAC, inhibition of HDAC results in accumulation of acetylated histones, thereby causing cell cycle arrest and apoptosis.

Vorinostat [15], also known as suberoylanilide hydroxyamic acid (SAHA), is the first anticancer agent that acts by inhibiting HDAC, and its discovery started with an interesting finding by Charlotte Friend in 1971 that dimethyl sulfoxide (DMSO), a common organic solvent, can cause growth arrest and terminal differentiation of transformed cells. However, DMSO is not potent enough, so in 1974 Breslow and coworkers at Columbia University undertook a medicinal chemistry program to identify compounds with improved potency and acceptable safety profile. These efforts led to the development of vorinostat as a second-line therapy for cutaneous T-cell lymphoma, a rare subtype of non-Hodgkin's lymphoma.

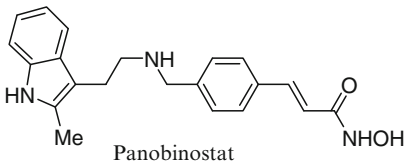
The second-generation of HDAC inhibitors have shown improved potency over vorinostat, and these include the indole-based dacinostat and panobinostat (http://www.novartisoncology.com/research-innovation/pipeline.Jsp) [16] originated from Novartis. Both agents inhibit HDAC and the proliferation of cancer cell lines at low nanomolar concentrations and have demonstrated efficacy in a number of solid tumor xenografic models. Dacinostat was advanced to phase I clinical trials in 2002 but discontinued in 2005. Panobinostat is currently in phase II/III studies for the treatment of hematological cancers.



Vorinostat (Zolinza^{TM})
Aton/Merck



Dacinostat
Discontinued after phase I
Novartis

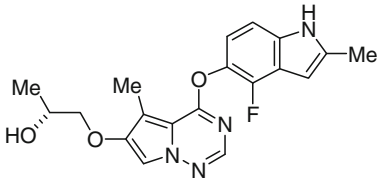


Panobinostat
Phase II
Novartis

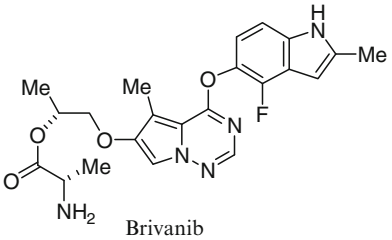
5.3 Brivanib: Angiokinase Inhibitor (Cancer)

Angiogenesis is an important natural process occurring in the body, both in health and in disease. In a healthy body, angiogenesis is involved in wound healing to restore blood flow to damaged tissues. However, when angiogenesis occurs in diseases like solid tumor, the new blood vessels supply diseased tissues with oxygen and nutrients, thus promoting tumor growth and spread (metastases). The receptor classes involved in angiogenesis include vacular endotheliam growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), and fibroblast growth factor receptors (FGFR). Angiogenesis inhibitors interfere with steps in the angiogenesis signaling cascade, thereby preventing growth and spread of the tumor.

BMS-540215 is a member of angiokinase inhibitors. It exhibits potent dual inhibition against VEGFR-2 and FGFR-1, excellent kinase selectivity, and robust in vivo efficacy in several human lung carcinoma xenografts implanted in athymic mice. However, it possesses poor solubility, thus resulting in dissolution rate-limited absorption, particularly at high doses. This potential developmental issue has been solved by the introduction of the L-alanine prodrug brivanib [17, 18] (http://www.bms.com/research/pipeline/Pages/default.aspx). This prodrug exhibits high aqueous solubility, high solid state stability, and acceptable solution stability. It is rapidly converted to its parent drug, BMS-540215, in human intestinal microsomes. Brivanib is currently undergoing phase III clinical studies for various cancer treatments.



BMS-540215

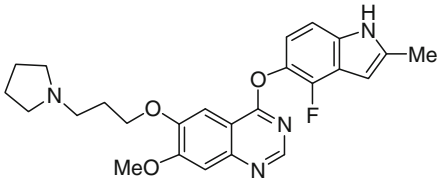


Brivanib
Bristol-Myers Squibb
Phase III

5.4 Cediranib: Angiokinase Inhibitor (Cancer)

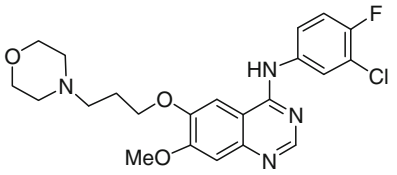
Cediranib [19] (http://www.astrazeneca.com/media/?itemId=6746833) is an orally bioavailable tyrosine kinase inhibitor of all three VEGF receptors (VEGFR1-3),

PDGF receptor β (PDGFRB), and c-kit, a cytokine receptor expressed on the surface of hematopoietic stem cells as well as other cell types. As compared with the two drugs on the market, sorafenib (Nexavar) by Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals, Inc. and sunitinib (Sutent) by Pfizer, Inc., cediranib inhibits VEGFR targets with improved potency. It is currently in Phase II/III development for advanced non-small cell lung cancer and advanced colorectal cancer.

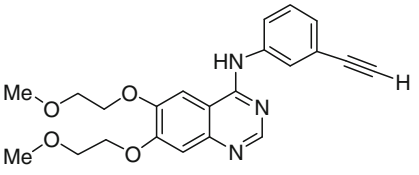


Cediranib (Recentin™)
Astra-Zeneca
Phase III

Structurally, cediranib shares the same quinazoline core as the two marketed cancer drugs: gefitinib and erlotinib, which act by selectively inhibiting tyrosine kinase epidermal growth factor receptor (EGFR). Apparently, replacement of the phenyl anilinyl in gefitinib and erlotinib to 1*H*-indol-5-yloxy switches the activity from EGFR to VEGFR. Also of note is that both cediranib and brivanib (*vide supra*) possess the same 4-fluoro-2-methyl-1*H*-indole side chain, which presumably contributes the activity towards VEGFR.



Gefitinib (Iressa™)
Astra-Zeneca

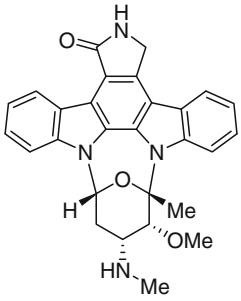


Erlotinib (Tarceva™)
OSI/ Genetech / Roche

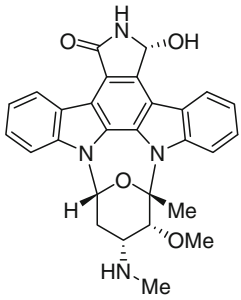
5.5 *UCN-01 and Midostaurin: PKC inhibitors (Cancer)*

The protein kinase C (PKC) family of serine/theronine kinases consists of at least 11 isoforms that are involved in cell proliferation, cell differentiation, gene transcription, tumorigenesis, and angiogenesis. PKC overexpression has been linked to several types of cancer such as breast, colon, renal cell, hepatocellular, non-small cell lung and prostate cancer. Therefore, PKC inhibitors may have potential for the treatment of various cancers.

The first-generation of PKC inhibitors include staurosporine, a natural product originally isolated in 1977 from bacterium *Streptomyces staurosporeus*. Staurosporine was the first of over 50 alkaloids to be isolated with this type of bis-indole core structure. However, staurosporine inhibits PKC isoforms non-selectively, and this lack of specificity precludes its clinical use due to toxicity concerns. Nevertheless, staurosporine has become a valuable research tool to induce apoptosis. In addition, staurosporine serves as a versatile starting material for the synthesis of novel semisynthetic analogs.



Staurosporine

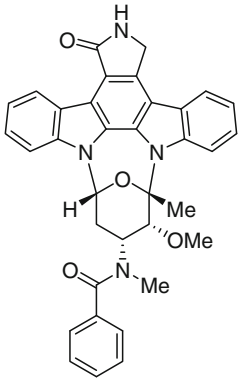


UCN-01
(7-Hydroxystaurosporine)
Kyowa/NIH
Phase II

UCN-01 [20] (http://www.novartisoncology.com/research-innovation/pipeline.jsp) also known as 7-hydroxystaurosporine, is a non-specific inhibitor of kinases with good activity against PKC, the cyclin-dependent kinases (CDKs) and checkpoint kinase I (Chk1), and it is in phase II studies for the potential treatment of cancer - in particular chronic lymphocytic leukemia.

Midostaurin, a semisynthetic derivative of staurosporine, is an orally bioavailable multitargeted kinase inhibitor. It potently inhibits the FLT-3 receptor tyrosine kinase, which is mutated in approximately one third of acute myelogenous leukemia (AML) patients, and is implicated in poor prognosis. It also inhibits multiple other targets thought to be important for the pathogenesis of AML. These targets include VEGFR-2, PDGFR, c-KIT, and the Pgp-mediated multidrug resistance gene MDR. In addition, midostaurin inhibits multiple isoforms of the serine/threonine PKC. When evaluated in preclinical models, midostaurin demonstrated

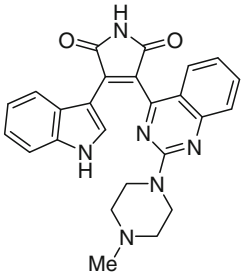
broad antiproliferative activity against various cancer cell lines, including those resistant to some existing chemotherapeutic agents. This agent is in phase III trials in AML, and a separate clinical study in aggressive systematic mastocytosis is also underway. In addition to cancer treatments, midostaurin also showed some beneficial effects in diabetic macular edema, but serious toxicity excludes its clinical applications in diabetic patients.



Midostaurin
Novartis
Phase II/III

5.6 Sotrastaurin: PKC inhibitor (transplant rejection)

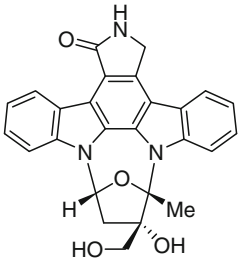
Sotrastaurin [21] a PKC inhibitor, is being developed for the potential oral prevention of organ transplant rejection, and also for the potential treatment of psoriasis, uveitis, and ulcerative colitis. This compound acts by selectively inhibiting the classic and novel forms of PKC, thereby blocking early T-cell activation and subsequent IL-2 production. In preclinical studies, sotrastaurin demonstrated efficacy in reducing the rejection of allogeneic solid organ and islet transplants and interacted synergistically with cyclosporine, an immunosuppressive agent. Sotrastaurin has the potential to become an alternative or adjunct to calcineurin inhibitors.



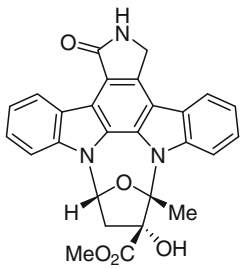
Sotrastaurin
Phase II
Novartis

5.7 *Lestaurtinib: TRK Inhibitor (Cancer)*

Lestaurtinib [22] is an orally active multiple tyrosine kinase inhibitor with specificity for the tropomyosin receptor kinases TrkA, TrkB and TrKC, and Fms-like tyrosine kinase 3 (FLT3). As a monotherpy, it promotes transient hematological responses in patients with relapsed or refractory acute myeloid leukemia (AML). This agent is in phase III trials for the treatment of various cancers either as a monotherapy or in combination with other chemotherapeutic agents. Lestaurtinib is prepared by selective reduction of the naturally occurring ester analog K-252a utilizing either lithium aluminum hydride or lithium borohydride.



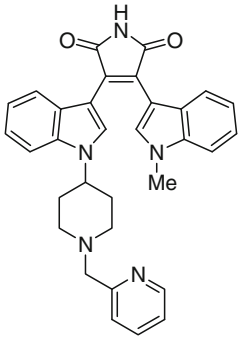
Lestaurtinib
Cephalon
Phase III



K-252a

5.8 *Enzastaurin: PKCβ Inhibitor (Cancer)*

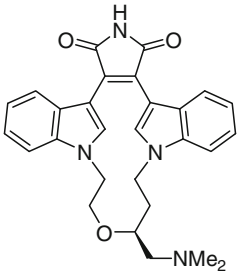
The protein kinase C β isoform (PKCβ) is implicated in several cancer types and is presumably involved in VEGF-induced tumor development and angiogenesis. Enzastaurin [23] (http://www.lilly.com/pdf/Pipeline_Slide.pdf) is an acyclic bisindolylmaleimide that potently and selectively inhibits the PKCβ isoform. It demonstrated anticancer activity in various preclinical cancer models and in clinical studies involving advanced cancer patients. Enzastaurin is currently being evaluated in a Phase III clinical trial for maintenance therapy for diffuse large B-cell lymphoma and also in several Phase II studies for hematologic malignancies and glioblastoma.



Enzastaurin
Eli Lilly
Phase III

5.9 Ruboxistaurin: PKCβ Inhibitor (Diabetic Retinopathy)

In addition to cancer treatments as described previously, inhibition of PKCβ may also ameliorate vascular dysfunctions due to diabetes. To this end, a series of macrocyclic bisindolylmaleimide compounds has been synthesized as exemplified by Ruboxistaurin [24] (http://www.lilly.com/pdf/Pipeline_Slide.pdf). This agent is under regulatory review for the potential oral treatment of diabetic retinopathy (DR) and diabetic macular edema.

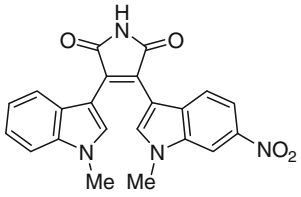


Ruboxistaurin (Arxxant™)
Eli Lilly
under regulatory review

5.10 MKC-1: Tubulin Interactive Agent (Cancer)

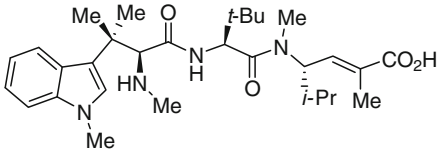
The microtubule cytoskeleton plays an important role in maintaining and regulating cell division. Microtubules are polymers that consist of α- and β-tubulin heterodimers. In the process of mitosis, microtubules undergo dynamic cycles of lengthening (polymerization) and shortening (depolymerization), and these cycles are critical for chromosome attachment to the mitotic spindle and for appropriate chromosome segregation. Thus, perturbation of microtubule dynamics by either mechanism provides effective anticancer approaches.

MKC-1 [25] a bisindolylmaleimide compound, was identified as an oral cell cycle inhibitor that induces apoptosis in cancer cells by targeting tubulin and importin beta. It was evaluated in clinical trials for the potential treatment of breast cancer, non-small-cell lung cancer, leukemia, and ovarian cancer, but it was suspended after phase II studies.



MKC-1 (Ro-31-7453)
EntreMed, Inc./Roche
suspended

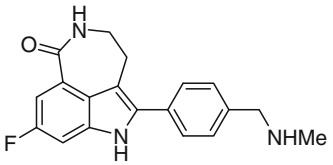
Another important indole-based tubulin binding agent is hemiasterlin [3] a potent cytotoxic tripeptide originally isolated from marine sponges. It exerts its antiproliferative effects by binding to tubulin, thus preventing tubulin polymerization and inducing mitotic arrest. Unfortunately, hemiasterlin is too toxic for clinical applications. Nevertheless, it has served as a valuable lead compound for novel anticancer agents, and several hemiasterlin analogs have been advanced into clinical trials.



Hemiasterlin

5.11 AG-14699: PARP Inhibitor (Cancer)

Poly(ADP-ribose) polymerase (PARP) plays an important role in a number of cellular processes, including DNA repair. Elevated PARP has been observed in some cancer patients, and combination of PARP inhibitors with cytotoxic agents has demonstrated synergistic effects in preclinical models. Thus, PARP inhibitors in combination with conventional DNA-damaging cancer treatments may offer a new approach to various cancers. AG-14699 [26] is the lead in a series of inhibitors of PARP and is being evaluated in phase II studies for the potential treatment of cancer including melanoma, breast cancer, and ovarian cancer.

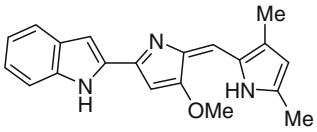


AG-14699
Phase II
Pfizer/Cancer Research, UK

5.12 Obatoclax: Bcl-2 Inhibitor (Cancer)

B-cell lymphoma-2 (Bcl-2) family proteins serve as the key regulators of apoptosis, which is associated with a variety of diseases, including cancer. Overexpression of several antiapoptotic Bcl-2 family proteins has been observed in various hematological malignancies such as non-Hodgkin's lymphoma. Thus, Bcl-2 inhibitors may be effective in the treatment of cancer. To this end, several small molecule inhibitors

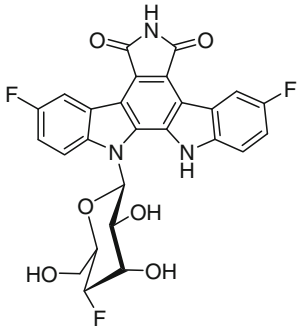
that directly target Bcl-2 proteins have entered into clinical trials, including obatoclax [27]. This agent is in phase II clinical development for the treatment of Hodgkin's lymphoma, myelodysplastic/myeloproliferative disorders, and follicular lymphoma, either as a monotherapy or as a combination therapy with rituximab.



Obatoclax
Phase II
Gemin X Biotechnologies

5.13 BMS-250749: Topo I Inhibitor (Cancer)

A series of fluoro-glycosylated fluoroindolocarbazoles was synthesized as selective topoisomerase I (topo I) inhibitors, and the lead clinical candidate from this series, BMS-250749 [28], exhibits broad spectrum antitumor activity superior to Camptosar against some preclinical xenograft models. BMS-250749 entered into phase I clinical trials, but no further developments were reported.

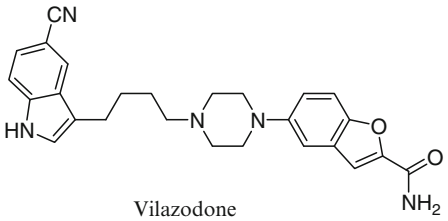


BMS-250749
Phase I
Bristol-Myers Squibb

5.14 Vilazodone: SSRI and 5-HT1A Partial Agonist (Depression)

Since their introduction in the 1980s, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, and citalopram have enjoyed tremendous clinical and commercial success due to their improved safety profile when compared with first-generation tricyclic antidepressants like imipramine. Nevertheless, they still display several side effects including gastrointestinal distress, anxiety, insomnia, weight gain, and sexual dysfunction. Like other current antidepressants,

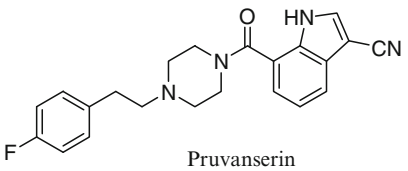
SSRIs also suffer from slow onset of action, and as a result, a significant number of depressed patients do not show signs of mood improvement until 3–4 weeks after the initial treatment. Thus, significant efforts have been made to identify compounds with rapid onset of clinical effects, broad efficacy, and reduced side effects, and one strategy to achieve quick onset of antidepressant effects is the selective agonism of postsynaptic 5-HT1A receptors. This approach led to the discovery of vilazodone [29] (http://www.pgxhealth.com/development/pipeline.cfm), an orally bioavailable, long-acting 5-HT1A partial agonist and SSRI. This agent is being evaluated in phase III clinical studies for the potential treatment of depression, and an NDA filing was scheduled for the first quarter of 2010.



Vilazodone
Clinical Data, Inc.
Phase III

5.15 Pruvanserin: 5-HT2A Antagonist (insomnia)

Serotonin $5HT_2$-receptors have been implicated in the etiology and pharmacological treatment of a number of neuropsychiatric conditions, but until recently there were few potent and specific agents available for use in human clinical studies. In this context, pruvanserin, also known as EMD-281014, was identified as a highly specific $5HT_2$-receptor antagonist, and this agent is in phase II studies for the treatment of insomnia. However, this agent has presumably been discontinued as no development has been reported for some time.

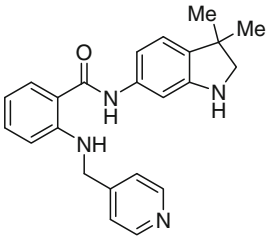


Pruvanserin
(EMD-281014)
Merck KGaA/Lilly
Phase II

5.16 Tiplaxtinin:PAI-1 Inhibitor (Arterial Thrombosis)

Tiplaxtinin [30] is a potent and selective inhibitor of plasminogen activator inhibitor-1 (PAI-1), and it demonstrated oral efficacy in multiple models of acute arterial

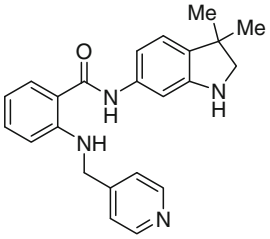
thrombosis. Tiplaxtinin was investigated in phase I clinical trials but is not in active development at this time.



Motesanib (AMG-706)
Phase III
Amgen

6 Indoline-Containing Clinical Candidate: Motesanib

Motesanib [31] (http://www.amgen.com/science/pipe.jsp) is an orally administered small molecule antagonist of VEGFR1-3, PDGFR, and stem cell factor receptor ("c-kit"). It is being investigated in phase III clinical trials as a first-line non-small cancer treatment.



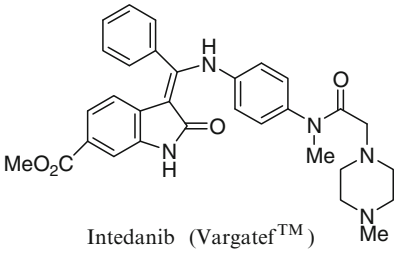
Motesanib (AMG-706)
Phase III
Amgen

7 Oxindole-Containing Clinical candidates

7.1 Intedanib: Angiokinase Inhibitor (cancer)

Intedanib [32] (http://www.boehringer-ingelheim.com/research_development/drug_discovery/pipeline.html) is a triple angiokinase inhibitor that targets three growth factor receptors simultaneously: VEGFR, PDGFR, and FGFR. In all preclinical models, intedanib has shown significant tumor growth inhibition either as a monotherapy or in combination with different standard chemotherapies. It is being

developed for the potential treatment of cancer, particularly non-small-cell lung cancer, ovarian, prostate, and colorectal cancer.



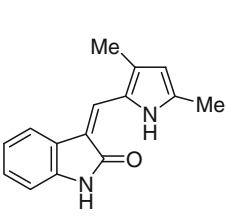
Intedanib (Vargatef^{TM})
Boehringer Ingelheim
Phase III

7.2 *Semaxanib and TSU-68: Angiokinase Inhibitors (Cancer)*

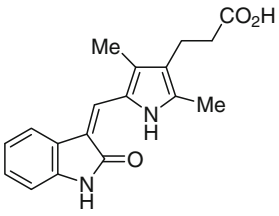
Semaxanib (SU-5416) was discovered in Sugen (owned by Pharmacia at the time, now Pfizer) as the lead compound in a series of small-molecule inhibitors of the multiple tyrosine kinase receptor for the potential treatment of cancer. In February 2002, Pharmacia made the decision to discontinue the drug based on interim results from phase III trials involving colorectal cancer patients.

TSU-68 [33] also known as SU-6668, an angiogenesis inhibitor that blocks VEGFR-2, PDGFR, and FGFR, is being developed for the potential treatment of cancer by Taiho under license from Sugen (now Pfizer). A study evaluating clinical responses and plasma angiogenic markers in patients with advanced heptocellular carcininoma suggested that TSU-68 is effective and safe in the patient population. Phase II trials are being carried out in breast cancer patients.

Structurally, both semaxanib and TSU-68 are close analogs of sunitinib (*vide supra*), and they all share the (Z)-3-((1*H*-pyrrol-2-yl)methylene)indolin-2-one core.



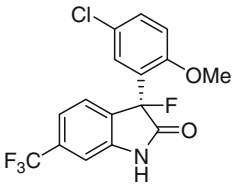
Semaxanib (SU-5416)
Sugen



TSU-68 (SU-6668)
Phase II
Sugen/Taiho

7.3 *Flindokalner: Potassium Channel Opener (Stroke)*

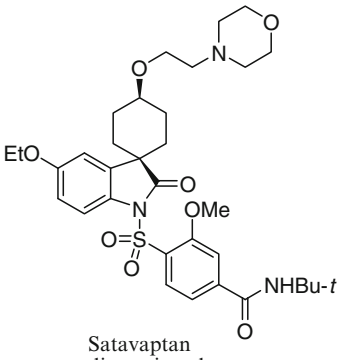
Flindokalner (MaxiPost) [34, 35] is a fluoro-oxindole potassium channel opener that was under development as a potential neuroprotectant for the treatment of acute ischemic stroke. However, no further developments were reported after phase III studies.



Flindokalner
(MaxiPost™)
Bristol-Myers Squibb

7.4 *Satavaptan: Vasopressin V2 Antagonist (Hyponatremia)*

Satavaptan [36], a vasopressin V2 receptor antagonist was developed as a potential treatment for hyponatremia in syndrome of inappropriate secretion of antidiuretic hormone (SIADH, Schwartz–Bartter syndrome) and cirrhotic ascites. However, by February 2009, development was terminated for both indications.



Satavaptan
discontinued
Sanofi-Aventis

8 Conclusion

Ever since the indole alkaloid vinblastine was approved by the FDA in 1961 for the treatment of certain types of cancer, a number of indole-, indoline-, and oxindole-containing compounds have been brought to the market. Among them, sumatriptan,

ondansetron, tadalafil, ziprasidone, and sunitinib have enjoyed great clinical and commercial success, thus making the indole-, indoline-, and oxindole-based class of drugs an integral part of the arsenal against various diseases. Recent medicinal chemistry efforts have generated several investigational drugs bearing indole, indoline, and oxindole nucleus, and these compounds have shown great promise in curing certain types of cancer, DR, and CNS disorders. As the indole scaffold has become one of the most important structural subunits for drug discovery, more indole-containing drugs will be unearthed in the future.

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Indoles: Industrial, Agricultural and Over-the-Counter Uses

Timothy C. Barden

Abstract Indole-containing compounds are best known for their medicinal properties in the pharmaceutical industry. Although to a lesser degree, the indole motif none-the-less appears in many significant products across the entire chemical industry. This chapter describes the role that indole plays in a more commodity setting and provides examples illustrating these uses.

Keywords Agriculture · Animal health · Cyanine dye · Dietary supplements · Diindolylmethane · Essential oils · Flavoring · Indigoid dye · Indole-3-carbinol · Melatonin · Nutraceutical · Perfume · Pigments · Textile dyes · Tryptophan

Contents

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1 Introduction

Although the structure of indole was not correctly assigned until 1869 by Adolf von Baeyer, its derivatives have had a prominent role in commerce for centuries [1]. In modern times, analogs based on indole are significant players in a diverse array of markets such as dyes, plastics, agriculture, vitamin supplements, over-the-counter drugs, flavor enhancers, and perfumery. This chapter does not discuss medicinal compounds based on indole, which are covered in a separate chapter in this book.

Powerful internet search engines today place a considerable amount of information at one's fingertips regarding the historical development of indole derivatives in commerce. Beyond providing leading references or search terms, I have kept this type of material at a minimum and have tried to include only enough background information to put that topic in proper perspective. My goal in this chapter is to give the reader an idea of the breadth of commodity markets still impacted by indoles and to discuss some of the most prominent examples in each industry.

2 Dyes and Pigments

The global market production of organic colorants in 2010 is forecast to be 2.1 million metric tons valued at 14.4 billion dollars and projected to grow at an annual rate of three to four percent (see http://www.the-infoshop.com/report/fd87050-dyes-organic.html). The market for inorganic colorants is roughly 5 times larger [2].

Dyes and pigments differ mainly in the method of attachment to the material that is to be colored. A material to be dyed is immersed in a solvent in which the dye is soluble whereupon the dye adheres to the material through chemical or ionic bonding. The dye is then left behind when the material is removed from the solution, rinsed and dried. Typical materials suitable for dying include textiles and paper products where water is the solvent of choice. Traditional photography takes full advantage of sensitizing organic dyes. A great variety of dyes can be applied by controlling the pH of the solution. Pigments are insoluble in the solvent used and are applied either as fine powders or as suspensions or dispersions [2–4]. Many paints are pigment-based. Pigments also are used to color most plastics. Although dyes represent the lion's share of the overall organic colorant market, pigments also are well represented in most segments. Numerous dyes are applied as pigments under different conditions and the reverse is also true.

Indole-based colorants are part of the large, diverse class of organic dyes and pigments. While not the major component of the organic colorant market, indoles never the less play an important role. A complete listing of all colorants sold today that are based on indole would be unnecessarily repetitive. Comprehensive lists can be found in several recent books and registers [2–4]. This segment will give the reader an idea of the breadth of dye and pigment markets still impacted by indole and discuss some of the most prominent examples in each field.

2.1 Textile Dyes

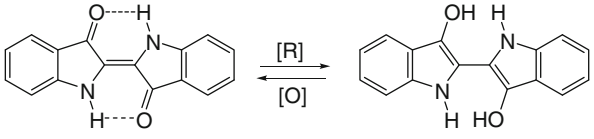
Nearly all textile-dying processes are water-based and may be done under acidic or basic conditions. Control of the pH during the process is an important factor in determining attributes such as the intensity of the hue and the strength of the dye-fabric bond (resistance to fading). Many of the indolic dyes and pigments are colored blue to green but nearly all regions of the visible region are represented by analogs having an indole core as part of the structure.

2.1.1 Indigoid Dyes

Indigo is probably the oldest and most famous colorant based on indole. It was already being used in civilizations throughout Asia when the ancient Greeks and Romans began importing it from India as a luxury item (see "Indigo dye" http://en.wikipedia.org/wiki/Indigo_dye). Indigo was a substantial commodity import into Europe from the Middle Ages until well into the nineteenth century. Historically, indigo was obtained from natural sources, but today virtually all indigo is synthetic. Indigo itself is nearly insoluble in water and can be used directly as a pigment when desired. However, its primary use in the textile industry is as a dye because the reduced form, white indigo, is much more soluble in water and can be applied in the same fashion as other dyes. Simple exposure of white indigo to air can reoxidize the molecule back to the highly colored form (Scheme 1).

Production of indigo had dropped to a mere trickle in the mid-twentieth century until blue jeans caught the public eye. The increased demand from this one product line led to over twenty thousand tons of indigo being produced in 2003, primarily as the dye for blue jeans. Indigo also is blended with other dyes under various processing conditions to give hues ranging from blue–green to violet (see http://www1.dystar.com/products/dyeranges_cellulosics.cfm?CFID=508055&CFTOKEN=95928906). An isomer of blue indigo, indirubin, seen in small amounts in the naturally derived material, is red but it is not used commercially (Scheme 2).

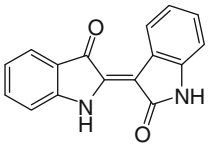
Other dyes based on the indigo motif are known, many with different hues. Tyrian Purple, 6,6′-dibromoindigo, is a natural product isolated from crushed sea shells that was quite valuable in ancient times but is not sold commercially today. However, the (5,7,5′,7′)-tetrabromo derivative (blue, "Vat Blue 4B") and the (5,5′)-bis-sulfonic acid analog (blue–green, "Blue Saxon") both are used as dyes in the



Indigo White indigo

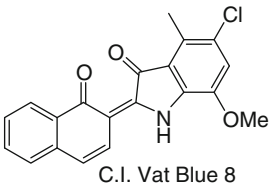
Scheme 1 Indigo-white indigo interconversion

Scheme 2 Indirubin



Indirubin

Scheme 3 C.I. Vat blue 8



C.I. Vat Blue 8
Blue to heavy shades
for cellulose, silk and wool

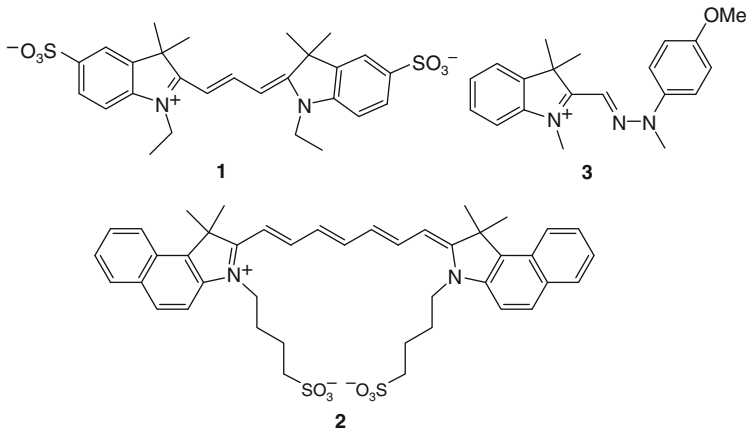
textile industry. Mixed variants such as the indigo-anthrone, C.I. Vat Blue 8, also are sold (Scheme 3).

2.1.2 Cyanine Dyes

Cyanine dyes are characterized by a central ethylene or conjugated polyolefin region capped at either end by a heterocyclic group. The length of the polyolefin varies, as do the end-caps that may or may not be the same. The indole moiety is but one of many heterocycles typically found in this large group of dyes. The uses of indolic cyanine dyes are as varied as the structures. Many such as **1** have found broad application as fluorescent probes in nucleic acid imaging [5]. Indocyanine green **2** is used in medical diagnostics to determine cardiac output and other functions. One or more olefin carbons may be replaced by nitrogen, as seen in C.I. Basic Yellow 28 **3**, a common textile dye. A dye such as Basic Yellow 28 could be seen as a cyanine dye or as a carbon variant of the large azo class of organic dyes (Scheme 4) [1].

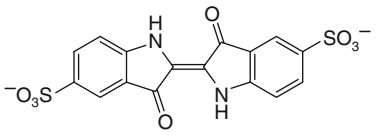
2.2 Dyes for Human Use

The list of dyes allowed by the FDA for human use is not large (see http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm). Only FD & C Blue No. 2 (indigo carmine) is on the approved list, although it is broadly approved for general use as a dye for food, cosmetics, and drugs and in medical devices, to color sutures (Scheme 5).



Scheme 4 Cyanine dye examples

Scheme 5 Indigo carmine approved for human consumption



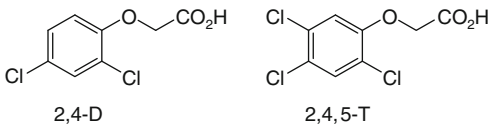
3 Agriculture

Natural products containing the indole subunit are found throughout the animal, fungal, microbial and plant kingdoms. The purposes to which the producing organisms put these varied structures often are a mystery. However, many of these components have provided an invaluable basis for research programs targeting diseases or other commercial enterprises. When successful, the vast majority of the marketed products bear little resemblance to the initial lead. The agricultural market is a prime example of this.

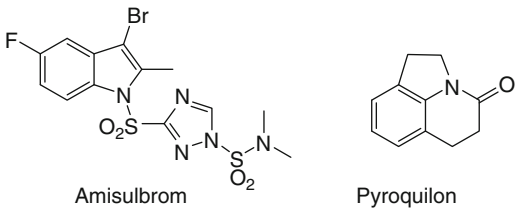
Auxins are one of the five major classes of plant-produced hormones that affect plant growth including bud formation and root initiation (see http://en.wikipedia.org/wiki/Plant_hormone#Auxins). Indole-3-acetic acid is the most common auxin found in plants. Although the small amounts produced internally have the desired effects, auxins are toxic to plants in larger amounts. The nefarious weed-control products 2,4-D and 2,4,5-T target the auxin receptor but bear little resemblance to the natural ligand. Other man-made auxins such as 1-naphthaleneacetic acid and indole-3-butyric acid are used, not to kill weeds, but to stimulate root production in cuttings taken from the parent plant (Scheme 6).

A considerable number of fungicides are based on a heterocyclic core but the indole ring only appears in a few commercial products such as amisulbrom and

Scheme 6 Herbicides that target the auxin receptor



Scheme 7 Indole fungicides



pyroquilon (http://www.alanwood,net/pesticides/class_fungicides). A somewhat larger number of fungicides containing additional heteroatoms are based more loosely on the indole core (Scheme 7).

4 Animal Health

Many of the same indoles in human medicine could have parallel application in animal health and, indeed, some are used in both arenas. Both livestock and domestic pets may benefit, if only indirectly, from the huge research efforts of the pharmaceutical industry to develop pharmaceutical products. This is fortunate for there are far fewer companies today devoted strictly to veterinary medicine and animal health. However, the registration of a drug for human use does not automatically mean that it can be used in the animal market. The approval process for a new animal health drug is similar to the one for human medicine and the two are distinct.

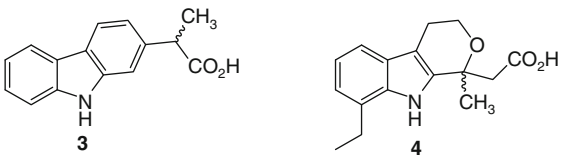
A number of pharmaceutical agents for humans are restricted in livestock or precluded altogether in order to reduce the risk of these drugs entering our food chain from this source. The risk/benefit of using many drugs in livestock remains a hotly debated topic today between some consumer advocacy groups and the government regulatory agencies. Although this is not an issue for domestic pets and the like, development of drugs for this segment of the veterinary market still often trails the human market.

Over five hundred drugs are registered for animal use, not including different formulations and combination products (see Ingredients, section 2: active ingredients of http://www.accessdata.fda.gov/scripts/animaldrugsatfda/). The list includes some unusual compounds, such as nitrofurans, arsenic derivatives and toluene (used as a dewormer). Only a handful of drugs on this list contain the indole core. Some are easily recognizable drugs from human medicine while others are only used in animals. Several of these latter are well known indole alkaloids.

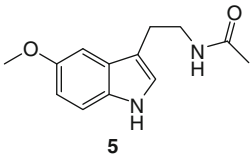
The two veterinary drugs Carprofen **3** and Etodolac **4** are better known as Rimadyl® and Lodine®, the nonsteroidal anti-inflammatory drugs approved for human use. They are especially useful for treating dogs with osteoarthritis, hip dysplasia, and other joint diseases (Scheme 8). Although generic, one estimate placed 2008 sales of Carprofen near $80 million and predicted an annual increase of ~13% (http://files.shareholder.com/downloads/GORX/895020712x0x239734/8df627c4-ffd6-420a-a84b-cb79d461562d/GORX_090208.pdf).

Melatonin **5** is another drug that has application in both animal health and human medicine. In dogs, it is commonly prescribed to calm dogs that are sensitive to loud noises or with separation anxiety (Scheme 9).

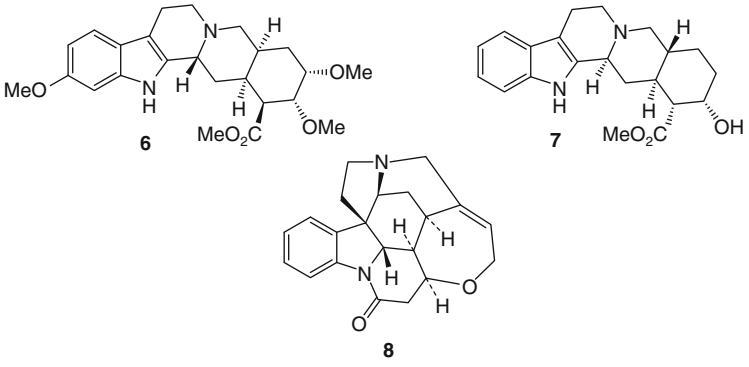
The final three indole-containing drugs approved for animals in the U.S. are indole alkaloids. Metoserpate **6** is a water-soluble reserpine alkaloid given to reduce stress and prevent hysteria in poultry. Yohimbine **7** is a central alpha-2 adrenergic antagonist. It is used in dogs to reverse the anesthesia produced by the commonly used anesthetic Xylazine. Strychnine **8** is a rodenticide (Scheme 10). There is no current approved human medical use for metoserpate although yohimbine is prescribed for erectile dysfunction. Strychnine, once used in small doses as a laxative



Scheme 8 NSAIDs used in veterinary medicine



Scheme 9 Melatonin



Scheme 10 Indole alkaloids used in animal husbandry

and as a stimulant to enhance sports performance, is not approved today for any human use (General veterinary use information for 3, 4, 5, 7 and 8 can be found at http://www.drugs.com/vet/).

5 Over-the-Counter Drugs

The pharmaceutical industry has found numerous leads for its research programs from natural products and from the careful study of key receptors involved in the therapeutic area of interest. Many of these starting points are derived from compounds with an indole core. An eventual commercial product may contain the indole nucleus but is more than likely to bear little superficial resemblance to the initial lead. Separate chapters in this book describe the recent indolic natural product discoveries and new developmental and marketed drugs. This chapter segment covers indole-containing substances that are sold over-the-counter without a prescription. This is a large and rapidly growing market, including vitamins and minerals as well as the two subcategories described below. Overall supplement 2008 sales in the U.S. alone were greater than $25 billion (http://nutritionbusinessjournal.com/pressreleases/NBJ-reviews-US-Supplement-Market/).

5.1 Dietary Supplements

Dietary supplements are compounds that are found naturally in the human body or are part of a normal diet and are sold over-the-counter, similar to vitamins. There may be no recommended minimum daily requirement established for a dietary supplement. However, the Food and Drug Administration follows reports of adverse events so that maximum recommended doses are known and published when appropriate. OTC supplements are bulk products and as such, these compounds are similar to commodity chemicals even though they are sold for human use.

5.1.1 Melatonin

The natural product melatonin **5** is found in animals and also in insects, microbes and some plants. Melatonin is mainly produced by the pineal gland in animals but it is synthesized throughout the body and readily passes through the blood–brain barrier. A diversity of biological responses is produced by the interaction of melatonin with its widespread receptors in body and central nervous system [6]. In addition to the well-documented role in regulating mammalian circadian rhythms, melatonin receptors are involved in modulating the immune system and bone growth among other processes [7]. The additional powerful antioxidant properties of melatonin are a potential bonus to those taking it for other reasons [6].

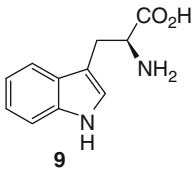
Melatonin still is available over-the-counter in the U.S. (since 1993), Canada and the United Kingdom but it is banned in many countries or is available only by prescription. U.S. sales in 2006 reached an impressive $81 million and were rising. Numerous therapeutic benefits have been ascribed to taking melatonin supplements but it is used primarily to treat sleep disorders such as insomnia and to reduce jet lag (http://www.webmd.com/sleep-disorders/circadian_rhythm_disorders).

5.1.2 Tryptophan

L-Tryptophan **9** is produced industrially by fermentation. It is an important feed additive, its primary use, and is part of a growing amino acid feed additive market that exceeded worldwide sales of $3.4 billion in 2007. Its history as a dietary supplement is more sullied, although the toxicity concerns that were raised in 1989 and led to a ban in its use as a dietary supplement for several years may not have been justified (Scheme 11) (http://thegormleyfiles.blogspot.com/2007_01_14_archive.html).

L-Tryptophan is one of the essential amino acids in animals. In addition, it is the biosynthetic precursor to other important molecules such as serotonin (thus, melatonin) and niacin. Until 1989, L-Tryptophan was sold singly over-the-counter and as a constituent in dietary supplement combinations. One of several effects that ingesting L-tryptophan has on the body is an increase in serotonin levels. Partly because of this, L-tryptophan supplements commonly were used to treat premenstrual syndrome, as a sleep aid and as a natural antidepressant [8] (http://www.webmd.com/vitamins-supplements/ingredientmono-326-L-TRYPTOPHAN.aspx?activeIngredientId=326&activeIngredientName=L-TRYPTOPHAN&source=3).

In 1989, a large outbreak of eosinophilia-myalgia syndrome in the United States was associated with the use of L-tryptophan supplements. Supplement sales were immediately restricted in the US leading to an eventual world-wide ban in 1991 even though L-tryptophan continued to be sold as a feed additive in the US and was added to baby formula. The outbreak was eventually traced to product from a single Japanese manufacturer. Despite considerable effort, no contaminant was found nor did other hypotheses to explain the outbreak bear fruit. Other theories whereby L-Tryptophan itself or its metabolites could be the cause also are unproven. There remains no conclusive link between L-tryptophan and EMS. The FDA lifted, with some caveats, the ban on sales of dietary L-tryptophan in 2001 although importation still is restricted. It is again available in the US over-the-counter



9

Scheme 11 L-Tryptophan

and by prescription. The uses to which it was put prior to 1989 are being rediscovered today, although still with some caution.

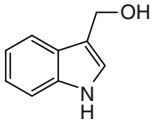
5.2 *Nutraceuticals*

Both dietary supplements and nutraceuticals are available without prescription as concentrated extracts or in pure form. Aside from that, the only statement that can be said with certainty with regard to the distinction between dietary supplements and nutraceuticals is that there is considerable disagreement. Either one can be considered a subset of the other depending on the forum. This point is quite aside from the also highly debated question of whether nutraceuticals are beneficial at all. Only for the purposes of this chapter, I define a nutraceutical as a natural product, plant or animal derived, which may be ingested in the belief of therapeutic benefit, but for which no cause-and-effect relationship has been established by rigorous clinical evaluation. Although the FDA monitors nutraceuticals to ensure that they are not overtly harmful, nutraceuticals remain a lightly regulated area of human medicine since the efficacy clinical trials that are mandated for prescription drugs generally are lacking in this area. However, the FDA is moving to more tightly regulate these products. The following examples are the noteworthy indole-derived nutraceutical products.

5.2.1 Indole-3-Carbinol

Indole-3-carbinol (I3C) **10** is a hydrolysis product of glucobrassicin **11**, both of which are found in high concentrations in cruciferous vegetables such as cauliflower (0.4 mg/g as the glucosinolate), broccoli and mustard greens (2.8 mg/g) [9]. The normal average dietary intake of **I3C** from these sources ranges from 20 to 120 mg/day (Scheme 12).

Studies have shown a correlation between diets high in cruciferous vegetables and the reduced incidence of several types of cancer [10, 11]. **I3C** has been proposed as one of the causative agents for these observations. The known estrogenic activity of **I3C** lends some support to this idea [12, 13]. However, there is some contradictory evidence from animal studies. Although **I3C** inhibited cancer



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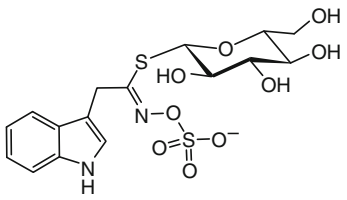


11

Scheme 12 **I3C** and glucobrassicin

development in animals when given before or simultaneous with a carcinogen administration, cancer promotion was observed in other studies where **I3C** was administered after the carcinogen exposure [14–16]. Despite these conflicting indications, there is some clinical evidence that **I3C** may have utility as a cancer therapeutic agent. The results from a single, small clinical trial in women with biopsy-proven cervical intraepithelial neoplasia were encouraging. Roughly half of the women in the trial had complete regression of cancer after 12 weeks of daily 200 or 400 mg doses of **I3C** [17]. There are several other trials currently underway to examine the utility of **I3C** for general cancer prevention, as a follow-up therapy to prostate cancer patients who have undergone prostatectomy, for treatment of Lupus and to explore the antiviral activity of **I3C** (http://clinicaltrials.gov/ct2/results?term=I3C).

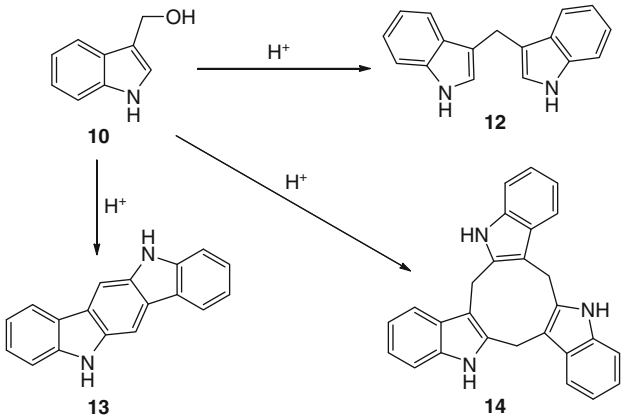
I3C supplements are sold OTC in pure form. There is no recommended daily requirement for **I3C** but there are some cautions for those taking supplements. There have been reports of skin rashes, tremors, nausea, and loss of balance during some of the clinical trials with **I3C** [18]. In addition, **I3C** has been shown to increase the activity of the liver enzymes CYP 1A1, CYP 1A2 and CYP 3A4 in rats, which raises the possibility of undesirable drug–drug interactions in humans [19].

5.2.2 Diindolylmethane

Animal studies have indicated that **I3C** primarily is a pro-drug [20, 21]. In the acid environment of the stomach, **I3C** is converted into several self-condensation products and one or more of these appear to be responsible for the intriguing biological activities ascribed to **I3C** [20]. The most prominent product is diindolylmethane (DIM) **12** (up to 20% of the product mixture). The indolocarbazole **13** (up to 6%) and trimer **14** also are generated. There are mixed in vitro results as to whether **13** overall is a cancer promoter or has cancer preventative effects [22–24]. Some in vitro studies indicate that the cyclic trimer **14** is a strong estrogen receptor agonist, suggesting that further research is warranted on the potential anticancer effects of **14** (Scheme 13) [25].

The potential of **DIM** as an anticancer agent that is predicted by in vitro assays has been reinforced by in vivo experiments. In animal models, **DIM** has shown efficacy in a similar range of carcinomas as **I3C** including prostate, breast, pancreatic, and colon cancers [26–29]. **DIM** induces apoptosis of cancer cells directly by several mechanisms and enhances the effectiveness of some cancer drugs. It also has antiproliferative effects in some cancer cell lines and exhibits protective activity against invasion of normal cells.

There are several clinical trials underway to investigate **DIM** as a cancer treatment therapy (see http://clinicaltrials.gov/ct2/results?term=diindolylmethane). In one completed study, a small group of women with a history of early-stage breast cancer were treated with **DIM** at 108 mg/day for 30 days. Urinalysis showed significant improvement in the levels of several key metabolite markers, but it is not yet known whether this encouraging result translates into a reduced risk of



Scheme 13 Acid condensation products from **I3C**

breast cancer [30]. There also are reports of clinical trials investigating the antiviral and antibacterial effects of **DIM**.

Purified **DIM** supplements are available OTC although the preventative benefits of **DIM** supplements are unproven and largely unexplored. As yet, there have been no reports of **DIM**-related side effects from the clinical trials involving **DIM**. This contrasts with the documented side effects produced by **I3C** in some people and at some of the higher doses. In view of the wide range of activity of **DIM** on critical biological pathways and the, as yet, unproven cancer preventative benefit to healthy people, due caution would seem to be indicated before embarking on a regimen of **DIM** supplements.

6 Essential Oils

Essential oils are concentrated extracts or steam distillates of aromatic plants. Oils such as wintergreen or jasmine have been added to enhance the flavor and smell of food for centuries and are key components of perfumes. Chemical analysis of these oils reveals that the overall smell is due to complex mixtures of small molecules, many of which contribute to the smell of the oil. Indole and indolic compounds are common components of these mixtures. Natural jasmine oil typically contains about 2.5% indole. Over time, the increasing cost of raw materials and processing has led to efforts to produce simpler mixtures that would have the same sensory effect. Reasonable approximations of many of these oils can be made today with completely synthetic components. Despite these advances, the import/export market for natural essential oils in 2008 still was a respectable $2.5 billion (See PDF download from http://www.crnm.org/index.php?option=com_docman&task).

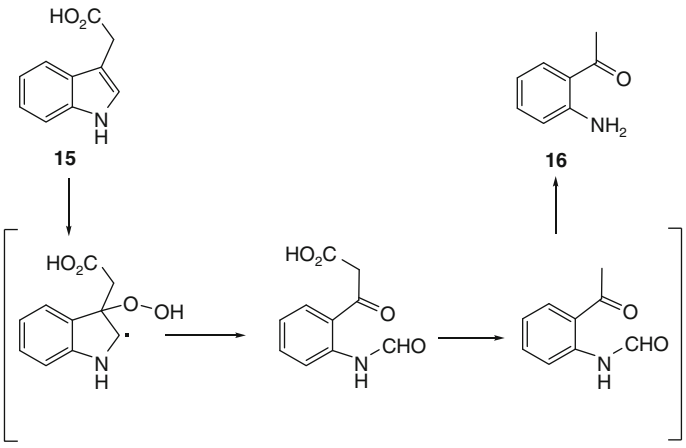
Indole and many of its derivatives have a relatively high vapor pressure well within the capability of the human nose to detect. Thus, an indole can affect the

flavor of food or contribute to the aroma of a perfume. Whether the smell is sensed as pleasant or odiferous, of course, varies from person to person but it also is highly concentration and substituent dependent. For example, the main component responsible for the odor of feces is skatole, 3-methylindole. At high concentrations, indole has a similar smell, but indole generally is perceived as having a sweet aroma at low concentration. Many indole derivatives are perceived as having floral scents.

6.1 Flavor Enhancers

Indoles are found naturally in many foods, some contributing to both the smell and taste while other indoles such as tryptophan provide nutritional value. Indole and skatole, in particular, are important components that affect the flavor and smell of foods such as green tea, coffee, cooked vegetables, whole grains, uncured meat, shellfish, and fresh fruit [31]. This can be useful to the analytical chemist. The amount of indole along with several other volatile flavoring compounds in the different types of tea is characteristic of that variety. In order to aid customs agents and tea vendors, a gas chromatographic method has been proposed to distinguish between the tea varieties [32].

The presence of indole or an indole derivative in a food is not always desirable. Some white wines develop an off-flavor described as "...floor polish like..." within a few months of storage [33]. The chemical responsible for this unpleasant flavor was identified as 2-aminoacetophenone **16** in 1993 [34]. Reported in a series of papers over the next 10 years, researchers traced the ultimate source of this agent to indole-3-acetic acid **15** that was present in the grapes before harvesting! Indole-3-acetic acid itself is derived from another indole: L-tryptophan. The proposed mechanism for this transformation is shown in Scheme 14 [35].



Scheme 14 Mechanism for conversion of indole-3-acetic acid to 2-aminoacetophenone

The authors present evidence that the process begins after sulfite is added to halt the fermentation. Superoxide radicals are formed with concomitant oxidation of sulfite to sulfate. Pyrrole cleavage followed by decarboxylation gives the formamide that spontaneously hydrolyzes to the observed end product **16**. With this understanding, vintners have made a considerable effort to prevent this process from tainting their product. Significant portions of symposia have been devoted to just this topic (http://www.oenology.de/texte/symp_02_engl/symp02_4_engl.html). Although **16** can be a serious problem in white wines, the pathway for its generation is blocked by the greater amount of phenolic radical scavengers present in red wines.

6.2 Perfumes

While the public disclosure of food additives is government-mandated, the exact ingredients and ingredient ratios in perfumes are closely held secrets even today. However, two lines of evidence indicate that indole and its derivatives still are crucial components in many perfume formulae and that additional novel indole additives are being sought. Experts reviewing new perfumes often refer to the "...jasmine indoles..." and "...floral indoles..." in their discourses (http://www.mimifroufrou.com/scentedsalamande). A recent application describing the floral scents of *N*-carboxy esters of indole is but one example of the numerous recent patent applications which attests to the continuing interest in finding indole derivatives having new and novel aromas (see UA20090036690A1).

7 Summary

Centuries before the structure of indole was known, many of its derivatives were important commercial products. Ancient textile dyes and perfumes are but two of the markets described above in which indole has had a rich history. Indoles continue to impact both of these markets today. The use of indoles has expanded into facets of agriculture, animal health and the relatively new areas of dietary supplements and nutraceuticals. These are all commodity markets, distinct from the explosion of medicinal uses that have been discovered for indole-containing substances.

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Electrophilic Substitution Reactions of Indoles

Richard J. Sundberg

Abstract The topic of this chapter is electrophilic substitution of indole and its derivatives. The indole ring is highly reactive at its 3-position toward protonation, halogenation, alkylation and acylation. Electrophilic substitution can be combined with inter- or intramolecular addition at C-2. Intramolecular alkylation by iminium ions (Pictet-Spengler reaction) is particularly useful. Enantioselectivity can be achieved in many conjugate addition reactions. These reactions have been applied to synthesis of both natural products and drugs.

Keywords Acylation · Alkylation · Aminoalkylation · Conjugate addition · Electrophilic substitution · Halogenations · Indole

Contents

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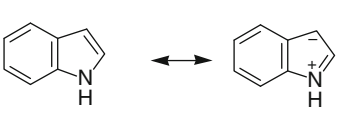
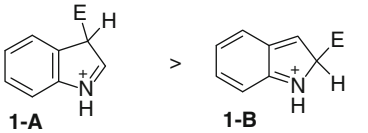
1 Introduction

The topic of this chapter is electrophilic substitution of indole and its derivatives. We will review the developments of approximately the last 15 years, set in the context of the earlier research in this area. Indole is a π-excessive aromatic heterocycle and is highly reactive towards classical electrophilic substitution reactions such as protonation, halogenation, alkylation and acylation. The 3-position is the most reactive site on the unsubstituted ring, by virtue of is increased electron density and the greater stability of intermediate **1-A** as compared to **1-B**.



dominant resonance structures



1-A **1-B**

preferred substitution intermediate

Most of the synthetic methods that depend on electrophilic substitution are well established. However, there has been considerable emphasis on more economic and environmentally benign procedures and also on achieving enantioselectivity. Another area of recent activity has been exploration of solid phase methods applicable to combinatorial approaches in synthesis.

1.1 Experimental Measures of Reactivity

We might ask just how reactive indole is in comparison with other aromatic rings. Mayr and his coworkers have carried out extensive studies on relative nucleophilicity, *N*, by examining reactivity towards a series of benzhydryl carbocations [1]. In this comparison, indole was found to have the relative reactivity 5.55. The 1-methyl (5.75) and 1,2-dimethyl derivatives are more reactive, while 2-methylindole is somewhat less reactive (4.42) because of its steric effects [2]. Pyrrole is less reactive with an *N* value of 4.63. Indole is substantially less reactive than representative enamines, such as 1-pyrrrolidinocyclohexene, for which *N* is 14.91 [3]. Being a logarithmic scale, this indicates that indole is some 15 times more reactive than pyrrole, but 10^{-10} less reactive than the cited enamine. For simpler aromatics, 1,3-dimethoxybenzene is assigned an *N* value of 2.48 and toluene, −4.47 Thus, indole is about 10^{10} more reactive than toluene.

Other electrophiles have been used to compare reactivity of aromatic compounds. One such compound is 4,6-dinitrofuroxan. It reacts to give 3-substituted indoles and has been used to measure rates for a series of 5-substituted indoles. The results are correlated both by the Hammet equation ($\rho = -3.85$) and with indole basicity. A 2-methyl group is rate-retarding by a factor of about 30 [4, 5]. 7-Chloro-4,6-benzofuroxan is another neutral "super-electrophile". Several 5-substituted indoles were compared and their reactivity correlates with basicity, indicating a normal electronic substituent effect. A 1-methyl substituent causes somewhat enhanced reactivity while a 2-methyl substituent exerts a retarding steric effect toward this electrophile of about 20 [6]. These results suggest a general order of reactivity of 1-methylindole > indole > 2-methylindole. However, the reference electrophiles are bulky and the 2-methyl group would be expected to show enhanced reactivity to smaller electrophiles. Indeed, acid-catalyzed exchange at C-3 is about 80 times faster for 2-methylindole than for indole [4, 5].

The rate of reaction of indole and 3-methylindole have been measured with a series of substituted benzenediazonium ions and give Hammett correlations with ρ of +3.4 and +3.8, respectively. The 3-methyl derivatives are about an order of magnitude slower. The second order kinetics, are consistent with a classical electrophilic substitution mechanism [7].

1.2 Theoretical Measures of Reactivity

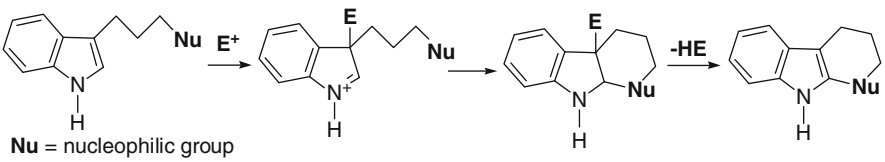
There has also been considerable interest in the theoretical analysis of the relative reactivity of the position on the indole ring. One of the quantities that can be calculated is the condensed Fukui function [f^-], which, in the context of density function theory, provides a measure of response to an approaching electrophile [8]. For indole, the 1-, 2-, and 3-positions are calculated as 0.08, 0.05, and 0.18, consistent with the observed preference for substitution at C-3 [9].

1.3 Application of Electrophilic Substitution in Synthesis

The fundamental characteristics of the indole ring, its high reactivity and good 3 > 2 regioselectivity, have been widely exploited for synthesis. In recent years, many improved reaction conditions have been developed. Among those to be discussed in the following sections are Pd- and Pt-mediated alkylations, reactions with carbonyl compounds, alkylation by conjugate addition, and amino- and amidoalkylation (the Mannich reaction). Several of these reactions have proven to be amenable to enantioselectivity by use of chiral catalysts and modifiers. Indeed, because of its high reactivity, indole is a particularly good reactant in many systems.

Another important aspect of indole chemistry is the ability to achieve regioselectivity for the N-1 position. The formation of the anion usually results in this position being the most nucleophilic site. For example, deprotonation and subsequent reaction with an alkyl halide or sulfonate is a standard method for introduction of a nitrogen substituent. However, this reactivity can also be exploited in catalytic systems. We will encounter several cases where N-1 or C-3 selectivity can be achieved by the choice and strength of a base.

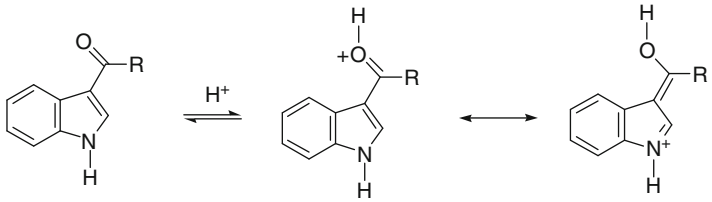
These various synthetic methods have been applied to many syntheses of potential drugs, alkaloids and other natural products. Ring-forming reactions are particularly valuable and the high reactivity of the indole 3-position can be used to induce nucleophilic addition at C-2. Depending on the electrophile, it may subsequently be eliminated, reestablishing aromaticity.



2 Protonation and Acid-Catalyzed Oligomerization

2.1 Equilibrium Protonation

The simplest electrophile is the proton and the rate of H^+-catalyzed exchange is one measure of reactivity of aromatic rings. Protonation of indole occurs at C-3 and can be observed as an equilibrium protonation or as acid-catalyzed dimerization, trimerization or oligomerization. There is some variation in the pK_a values reported for indole but have converged around −3.5, the value originally reported by Hinman and Lang [10, 11]. A 1-methyl substituent increases basicity slightly, while a 2-methyl group shifts the pK_a to 0.28. In contrast, a 3-methyl group decreases the basicity and the p*K*a is −4.6, as indicated in Table 1. The enhancement of basicity by a 2-alkyl group derives from the stabilization of the conjugate acid, while the decreased basicity of the 3-alkyl derivatives is attributed to loss of stabilization when C-3 is protonated and removed from conjugation. Data is also available for many 5-substituted indoles[6]. 3-Acyl substituents lead to a modest *increase* in basicity as the result of O-protonation and formation of a resonance-stabilized cation.



N-Benzoylindole and its 3-methyl and 5-methoxy derivatives are protonated at the carbonyl oxygen, with a pK_a of ∼−4 [12].

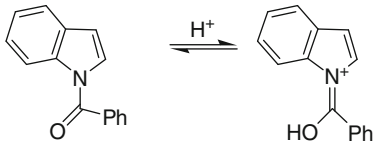


Table 1 pK_a values for substituted indoles

		Ref
Indole	−3.5	10
1-Methylindole	−2.3	10
2-Methylindole	0.28	10
3-Methylindole	−4.6	10
2,3-Dimethylindole	−1.5	10
3-Formylindole	−1.7	11
3-Acetylindole	−1.4	11

Cohen and Cohen showed that the Hinman–Lang data for both unsubstituted and *N*-methylindoles fit a multi-parameter linear free energy relationship using composite substituent constants developed to describe protonation of alkenes. The form of the correlation with a stronger contribution from the C-2 group is consistent with C-3 protonation

$$\text{Unsubstituted: } \text{p}K\text{a} = -10.05\Sigma\sigma - 3.94,$$

$$\text{N-Methyl: } \text{p}K\text{a} = -8.64\Sigma\sigma - 2.80,$$

where

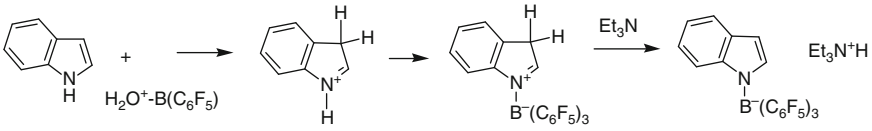
$$\Sigma\sigma = \sigma^{+}{}_{p}(\text{C-2}) + 0.60\ \sigma^{+}{}_{m}(\text{C-3}) + 0.08\text{D}_{\text{s}} - 0.084.$$

The pK_a values of several 4-substituted indoles correlate with a Hammett equation:

$$\text{p}K_{\text{a}} = -0.69\sigma^{\text{o}}{}_{m} - 2.48$$

The relatively low value for ρ and the correlation with $\sigma^{\text{o}}{}_{m}$ indicate that there is only weak resonance interaction with the 4-substituents [13]. Proto-detritiation rates have been measured for indole and a number of substituted derivatives. There is a good correlation with pK_a data and no indication of a retarding steric effect by 2-methyl or 2-(*t*-butyl) substituents [4, 5].

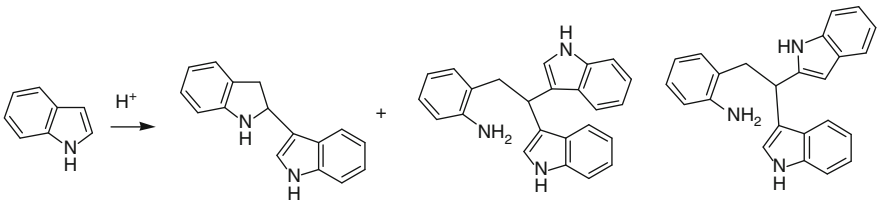
Zwitterionic conjugate acids of indole have been isolated and characterized by reaction with the powerful Lewis acid $(C_6F_5)_3B$. Similar adducts were formed with 2- and 3-methylindole. These 3-protonated indoles are, as expected, strongly acidic [14]. It is suggested that adducts form after a 3-protonation, rather than by direct reaction at nitrogen.



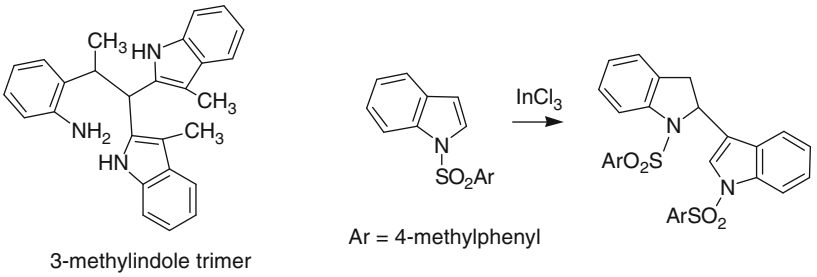
2.2 *Acid-Catalyzed Oligomerization*

Indole forms a dimer and a trimer under various acidic conditions. The dimer is formed by electrophilic attack on indole by the 3-protonated species. The structure of the trimer, first proposed by G. F. Smith [15], was proven by synthesis [16]. Trimer results from acid-catalyzed opening of the indoline ring in the dimer, followed by electrophilic attack on a second indole. The dimerization-trimerization process is evidently reversible in 0.5 M H_2SO_4. A composition of approximately 1:0.4:0.3 is reached from the indole, the dimer or the trimer [17]. An isomeric trimer **5-C** can be

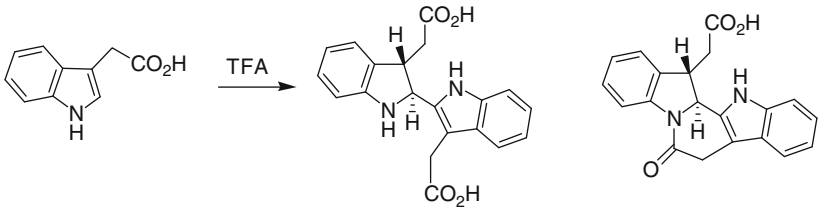
isolated using *p*-TSA in benzene. This compound is believed to be formed by acid-catalyzed (Plancher) rearrangement of the major trimer. This isomerization also can be observed in the presence of Lewis acids, including BF_3 and $ZnCl_2$ [18].



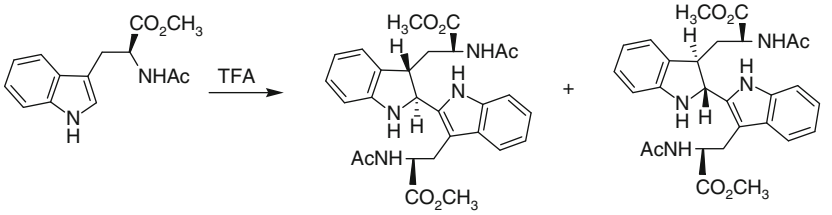
3-Methylindole undergoes trimerization with ring-opening when treated with BF_3-OEt_2 in CH_2Cl_2. In this case, the indole ring is substituted at the 2-position [19]. Several substituted indoles, including 1-sulfonylindoles, are dimerized and/or trimerized by exposure to 20 mol % $InCl_3$ in CH_2Cl_2 [20].



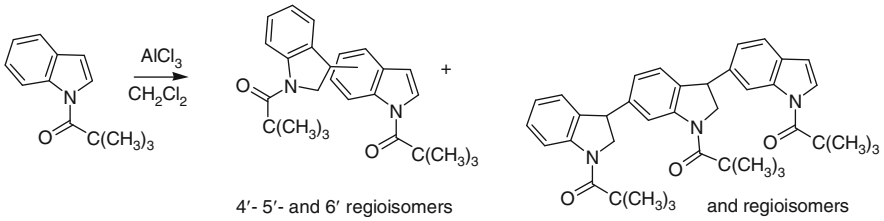
Other 3-substituted indoles such as indole-3-acetic acid give 2,2′-dimers [21]. The dimer has *trans* stereochemistry at the indoline ring, as was determined by X-ray crystallography on a derived lactam [22].



Other compounds that give high yields of 2,2′-dimers are the methyl esters of indole-3-acetate, indole-3-butanoate, and the N^b-acetyl derivative of tryptamine [23]. For the corresponding tryptophan derivative, the dimerization is stereoselective giving two dimers, each having *trans* orientation in the indoline ring [24].

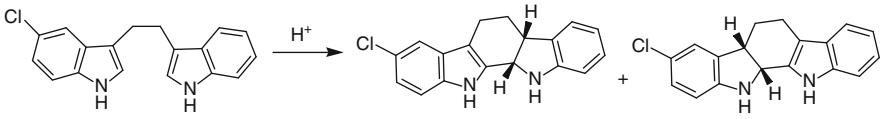


A mixture of dimers and trimers is formed when *N*-pivaloylindole is exposed to $AlCl_3$ in CH_2Cl_2. These products are the result of substitution in the carbocyclic ring [25]. The electrophile might be the $AlCl_3$ complex, or conceivably the protonated species if any water is present.



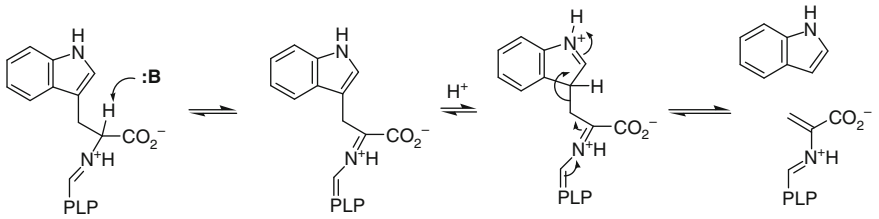
2.3 Acid-Catalyzed Cyclization

The C-3 protonation of the indole ring can be used to induce a cyclization if a nucleophilic group is positioned to capture the resulting cation. A case that has been examined in terms of regioselectivity is the cyclization of 1,2-*bis*-(3-indolyl)ethane. The product composition can be controlled by adjusting the reaction conditions. Kinetic control is realized using two equiv. of camphorsulfonic acid, and favors isomer **10-B** (6:1), while in neat TFA thermodynamic control results in the formation of **10-A** (12:1) [23]. The kinetic conditions favor protonation of the more basic of the two indole rings, while the strongly acidic neat TFA drives the reaction to the more basic product.



2.4 Enzymatic Protonation

Indole protonation is a functional step in the cleavage of tryptophan by tryptophan indole-lyase, based on kinetic isotope effect measurements [26].

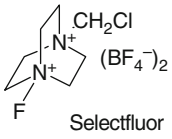


3 Halogenation and Related Reactions

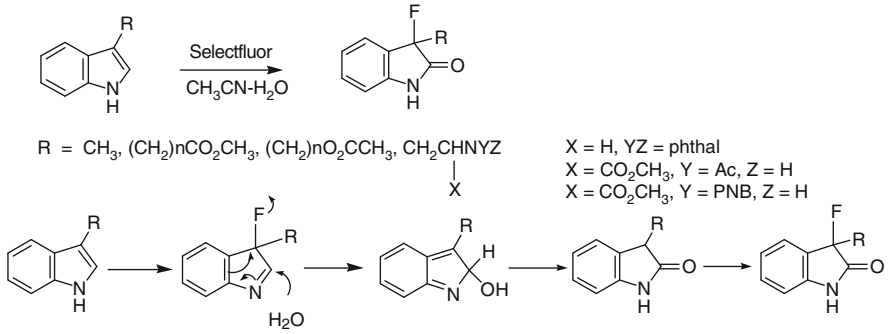
Halogenated indoles are of interest for several reasons. The extensive development of transition metal-catalyzed coupling reactions have made them valuable synthetic intermediates [27]. Halogenated compounds are often included in series seeking specific biological activity [28, 29]. There are also a significant number of naturally-occurring halogenated indoles, especially from marine sources [30, 31]. Many halogenated indoles, particularly those substituted in the carbocyclic ring, are prepared from halogenated starting materials by standard indole ring constructions [32]. In this section, we will focus on the introduction of halogens on to indole rings by electrophilic substitution. The simple 2- and 3-haloindoles are unstable to acidic aqueous solutions but more stable in base. The fundamental characterization of indole halogenations was carried out with reagents such as NaOCl [33], *N*-chlorosuccinimide [34], sulfuryl chloride [35], *N*-bromosuccinimide (NBS) [36], and pyridinium bromide perbromide [37], as well as Br_2 [38] and I_2 [39]. Recent work has examined a number of other reagents.

3.1 Fluorination

Fluorination is the most recently explored of the direct halogenation methods and has become practical with the development of commercially available fluorinating agents such as Selectfluor.

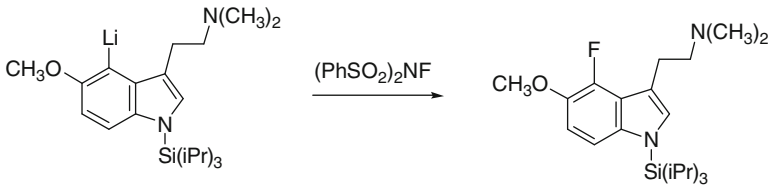


Selectfluor gives mainly 3-fluorooxindoles from 3-substituted indoles in acetonitrile. The reaction is proposed to proceed through a 2-hydroxy intermediate [40].



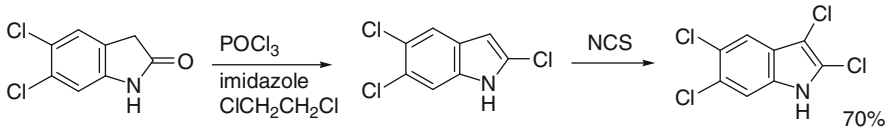
When the reaction of 3-methylindole is done in a 1:1 mixture of methanol and the ionic solvent [bmim$^+$ BF_4^-] an essentially quantitative yield of the 3-fluorooxindole is obtained [41]. Combining Selectfluor with dihydroquinidine acetate leads to fluorination of oxindoles in up to 80% ee. The reaction is believed to proceed by "transfer fluorination" in which the *N*-fluoro alkaloid is the immediate fluorinating agent [42].

Indirect fluorination has been carried out using metallo-indoles. Hodgson et al used *ipso* substitution of 2- and 3-(trimethylstannyl)-1-(*p*-toluenesulfonyl)indoles. Of several fluorinating agents tried, cesium fluorosulfate was the best [43]. 5-Methoxyindoles lithiated in the 4-position were fluorinated by *N*-fluorobenzenesulfonimide to prepare 4-fluoro analogs of serotonin and melatonin [44].



3.2 Chlorination

Sulfuryl chloride has been used successfully in the preparation of 3-chloroindole [35]. 2,3,5,6-Tetrachloroindole has been used in the preparation of polyhalogenated indole nucleosides. It was prepared from 5,6-dichlorooxindole by conversion to 2,5,6-trichloroindole, then 3-chlorination by *N*-chlorosuccinimide [45].

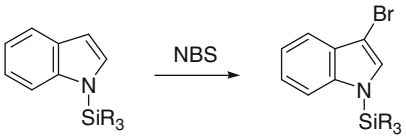


Electrophilic chlorination with reagents such as *t*-butyl hypochlorite and *N*-chlorosuccinimide can be used to induce nucleophilic addition at the 2-position (see Sect. 3.5).

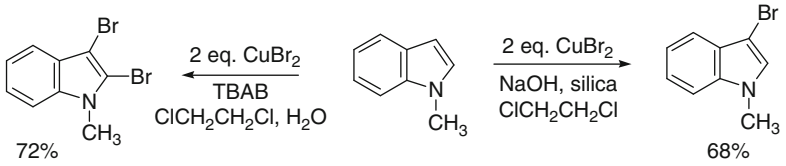
3.3 Bromination

Indole reacts readily with electrophilic brominating agents such as *N*-bromosuccinimide [36] and pyridinium bromide perbromide [37]. In hydroxylic solvents oxindoles are formed by hydrolytic capture of the 3-bromoindolenine intermediate [46]. Recently, indole was among a number of reactive aromatics brominated using NBS under UV irradiation. A good yield of 3-bromoindole was reported, but the mechanism under these conditions is not clear [47].

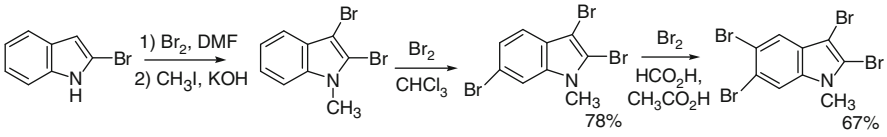
The 1-(*t*-butyldimethylsilyl) [48] and 1-(tri-isopropylsilyl) [49] groups permit clean 3-bromination of indoles and the products have been used as precursors of the corresponding 3-lithioindoles.



Wang and coworkers have explored and extended the utility of halogenations of indoles by $Cu(II)Cl_2$ and $Cu(II)Br_2$ [50]. The best results were obtained in dichloromethane or acetonitrile in the presence of NaOH and silica gel. Similar conditions were successfully applied to C-ring substituted 1-methylindoles. When the reaction mixture included water and *tetra*-butylammonium bromide, the 2,3-dibromo products were formed. 1,3-Dimethylindole gave a good yield of the 2-bromo product under the latter conditions. 1-Unsubstituted indoles often present problems, but by using NaOH/silica and $CuCl_2$, 2-chlorination of 3-methylindole was achieved in 86% yield.



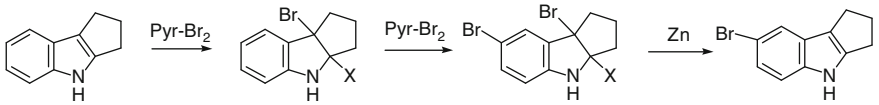
2-Bromoindole can be prepared by indirect bromination through *N*-(lithiocarboxy)-2-lithioindole [51]. Subsequent 3-bromination followed by *N*-methylation gives 2,3-dibromo-1-methylindole in 92% yield. C-Ring bromination can then be carried out with one or two equivalents of bromine, giving the 2,3,6-tribromo and 2,3,5,6-tetrabromo derivatives [52].



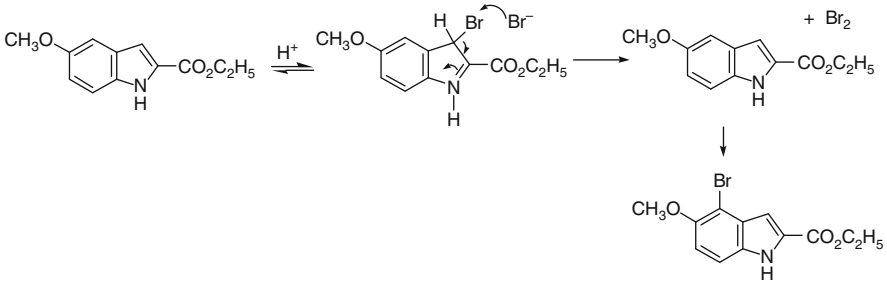
Gribble and coworkers also developed a protocol for 2,3-dibromo and the 2,3- and 3,2-bromoiodoindoles starting with 1-(phenylsulfonyl)lindole. The compound

was first brominated in the 3-position. Lithiation at C-2 was then used to introduce a Br (BrCN) or I (I_2). Similarly, 3-iodo-1-(phenylsulfonyl)indole can be lithiated and then brominated or iodinated [53, 54].

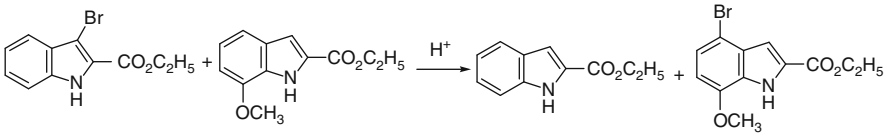
Cyclopenta[b]indole gave 5-bromo (61%), 7-bromo (9%) and the 5,7-dibromo products on treatment with excess pyridine-Br_2 complex followed by Zn [55]. This reaction is thought to proceed through a 2,3-adduct. C-5-substituted analogs behave similarly, with both donor and acceptor substituents giving the C-7 product. These results are consistent with a controlling directive effect by the indoline-type nitrogen in the adduct. Unfortunately, these reactions are not applicable to tetrahydrocarbazoles.



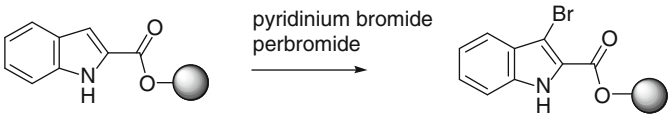
Murakami and coworkers examined the bromination of all four C-methoxy derivatives of ethyl indole-2-carboxylate using Br_2 in acetic acid, pyridinium bromide perbromide, and NBS as brominating agents. The latter two reagents generally give the 3-substituted indole, while Br_2 gave C-ring products, as directed by the methoxy group [56]. Kruse and Meyer had previously noted the preferred C-4 bromination of the 5-methoxy isomer and shown that it resulted from acid-catalyzed intermolecular bromine transfer from the initial 3-bromo product [57]. The stability of the 3-products with the other brominating agents is due to the absence of an acid catalyst under those conditions.



Murakami et al. were able to confirm this process by demonstrating bromine transfer from ethyl 3-bromoindole-2-carboxylate to form 4-bromo-7-methoxyindole-2-carboxylate.



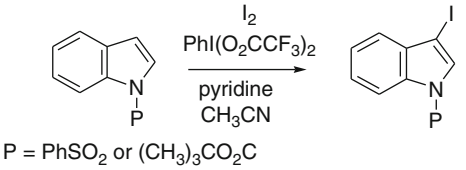
Solid phase bromination of indole-2-carboxylic acids linked to Merrifield resin by pyridinium bromide perbromide gives 3-bromo derivatives that were subsequently coupled via Suzuki reactions [58].



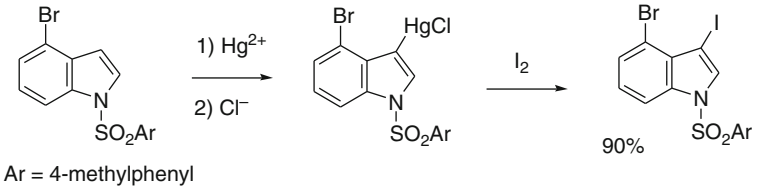
3.4 Iodination

Iodination of 2-(trimethylsilyl)indole by *bis*-pyridine iodonium tetrafluoroborate gives the 3-iodo derivative. With two equivalents of this reagent the 2,3-diodo product is formed by *ipso* substitution. 5-Chloro- and 5,7-dimethylindole were iodinated at C-3 in excellent yield by this reagent [59].

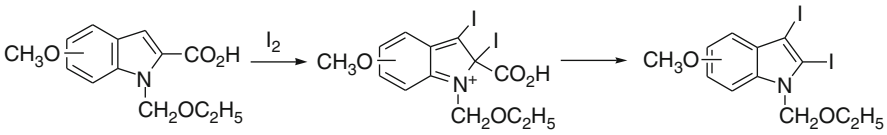
N-Protected indoles can be iodinated by I_2 and phenyliodoinum *bis*-trifluoroacetate [60].



An alternative route to 3-iodo-1-(phenylsulfonyl)indoles is by electrophilic mercuration, followed by iodinolysis using a method developed by Harrington and Hegedus [61].

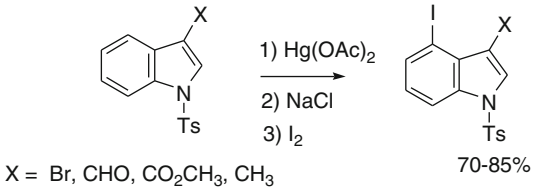


1-(Ethoxymethyl) indole-2-carboxylic acids give 2,3-diiodo products on reaction with I_2. C-Ring methoxy-substituted compounds gave the highest yields [62]. These reactions are believed to proceed by successive iodination at C-3, then C-2. The beneficial effect of the methoxy substituents is attributed to enhanced reactivity toward the second iodination.



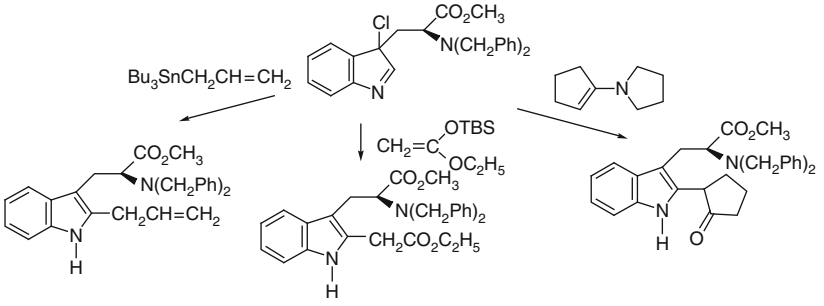
5-Nitroindole was iodinated at C-3 in good yield using sodium chlorite and sodium iodide [63]. Indole, and its 1-phenylsulfonyl and 2-methyl derivatives were iodinated in good yield by NaI-$FeCl_3$ [64].

N^b-Acyl tryptophan methyl esters are readily iodinated at C-2 by the mercuration-iodinolysis method [65, 66]. The mercuration-iodinolysis route was also applied to several 4-substituted indoles when the 3-position was blocked by a substituent [67].



3.5 *Synthetic Applications of 3-Haloindolenine Intermediates*

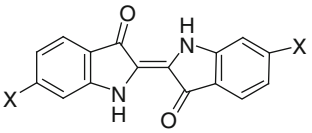
Several synthetic methods employ the 3-halo indolenine intermediates generated by halogenations as intermediates. Danishefsky and coworkers found that the chloroindolenine from the methyl ester of N^b,N^b-dibenzyltryptophan can be converted to 2-substituted products using a variety of nucleophiles, including allylic boranes and stannanes, enamines and ester silyl enol ethers [68].



This method has proven especially useful for the synthesis of a variety of natural products containing the prenyl (3-methyl-2-butenyl) or *tert*-prenyl (1,1-dimethyl-2-propenyl) groups, as will be discussed in Sect. 4.2.3)

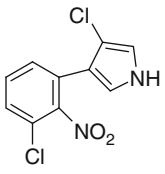
3.6 Enzymatic Halogenation

One of the first indole derivatives to find a utilitarian application was the 6,6′-dibromo derivative of indigo, which was extracted from a Mediterranean mollusk to provide the dye Tyrian purple, long known to be a symbol of royalty. The parent compound, indigo, was also one of the first dyes to be manufactured by synthesis.

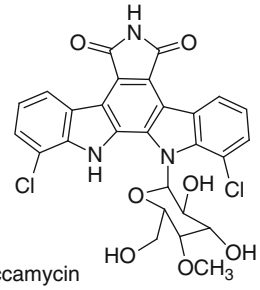


X = H indigo (indigotin)
X = Br tyrian purple

In recent years, the enzymes responsible for the introduction of halogen in biological systems have been identified. One group of vanadium bromoperoxidases is found in marine algae [69–71]. 7-Chlorination of tryptophan is involved in the biosynthesis of materials such as pyrrolnitrin and rebeccamycin. The enzyme is a flavin-dependent monooxygenase that generates hypochlorite ion. The structure of the enzyme is such that the $^{-}$OCl ion is conducted to the indole binding site over a distance of about 10 Å [72, 73].



pyrrolnitrin



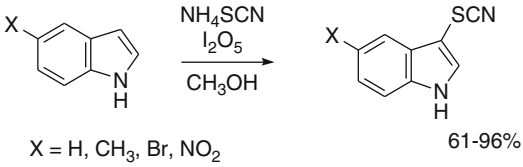
rebeccamycin

3.7 Sulfenylation, Thiocyanation and Cyanation

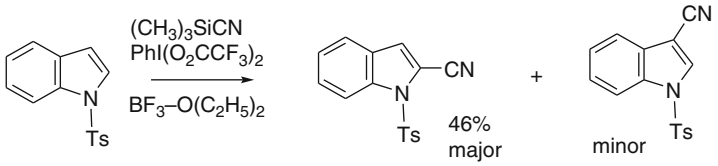
2-Methylindole undergoes clean 3-sulfenylation with *N*-methylthiomorpholine in TFA. Indole itself gives mainly 3-methylthioindole (57%) with 1.5 equiv. of the reagent, but the 1,3- (61%) and 2,3- (22%) *bis*-sulfenyl derivatives are the main products with 2.5 equiv. [74].

Indole, 1- and 2-methyl and C-substituted derivatives give good yields of 3-thiocyano indoles when treated with NH_4SCN and I_2 in methanol [75]. Ammonium thiocyanate and diiodine pentoxide also give 3-thiocyanation of indole and

several 5-substituted analogs [76]. The same reaction can be done using *o*-iodoxybenzoic acid as the oxidant [77].



Oxidative cyanation of the indole ring at C-2 and C-3 has been observed for *N*-tosyl indoles on reaction with trimethylsilyl cyanide and phenyliodonium *bis*-trifluoroacetate in the presence of BF_3 [78]. The reaction is distinctive in giving a preference for 2-substitution and is thought to proceed through radical cation intermediates.

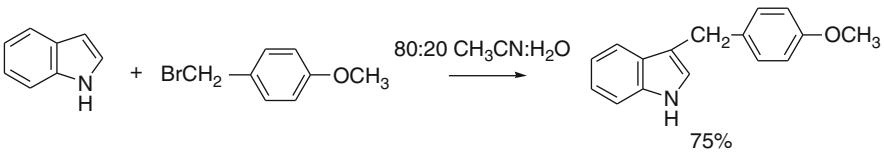


4 Friedel–Crafts Alkylation

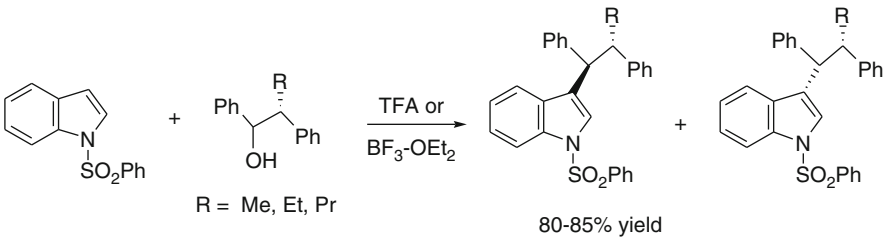
Examples of direct alkylation of indoles under classical Friedel–Crafts conditions with strong Lewis acids are sparse. This fact probably reflects the tendency of indole to undergo oligomerization with such reagents (Sect. 2.2). The successful conditions for direct indole alkylation usually involve reagents that can generate carbocations under mild conditions, such as benzylic and allylic systems. Palladium-mediated allylations provide another approach.

4.1 Benzylation

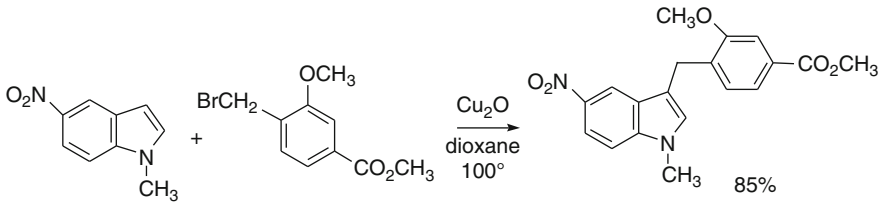
An example of direct benzylation under solvolytic conditions has been reported by Mayr and coworkers (vide infra for a similar allylation) [79].



1-(Phenylsulfonyl)indole reacts with chiral benzylic alcohols under the influence of either a protic (TFA) or Lewis (BF_3-OEt_2) acid. The reactions proceed through the corresponding cation and are moderately selective for the *anti* products. The selectivity increases with the size of the R group [80].



A direct benzylation step is used in the scaled-up synthesis of the asthma drug zasirulast. The reaction involves 1-methyl-5-nitroindole and was done in the presence of Cu_2O (three equiv.). The product is obtained in 85% yield, along with two by-products, one of which is the 2,3-disubstituted product [81].

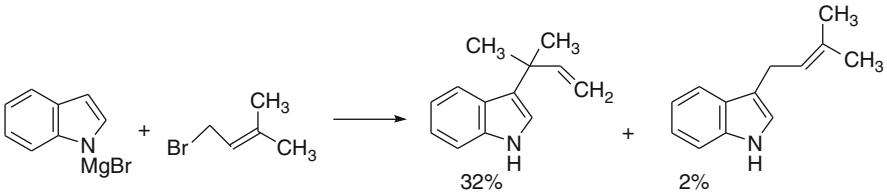


An alternative method for benzylation using aromatic aldehydes is discussed in Sect. 5.1.

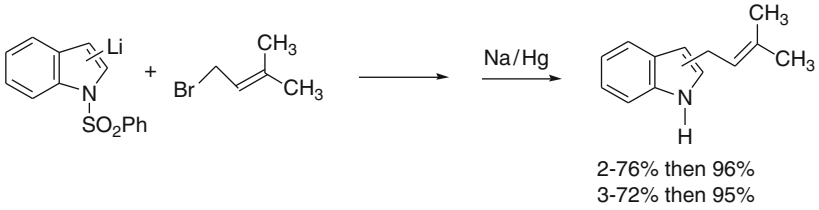
4.2 Allylation and Prenylation

4.2.1 Allylation by Halides and Alcohols

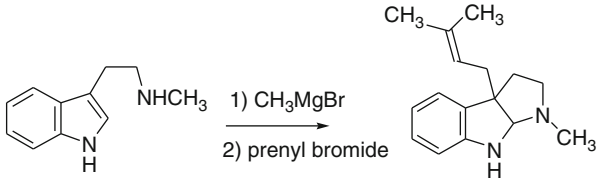
The existence of a large number of natural products, some with significant biological activity, that contain prenyl (3-methyl-2-butenyl) or *tert*-prenyl (1,1-dimethyl-2-propenyl) groups has inspired efforts to develop methods for the introduction of these groups. Model and mechanistic studies have often included other allylic systems. Wenkert explored the allylation of magnesio-indole in the course of searching for effective syntheses of 2- and 3-prenyl indoles [82]. The most direct approach, reaction with the allylic bromide, was only marginally successful and the major product had an inverted allylic group.



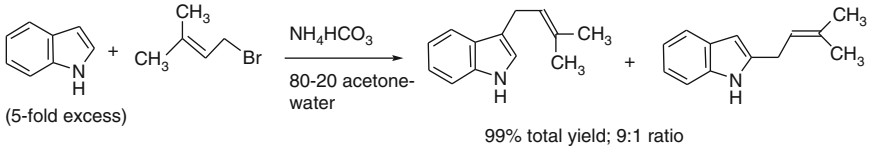
Indirect alkylation via lithio-1-(phenylsulfonyl)indoles was more successful for making both the 2- and 3-substituted products. In the case of the 3-isomer, the lithio indole was first converted to the cuprate. The *N*-phenylsulfonyl group was removed by reduction.



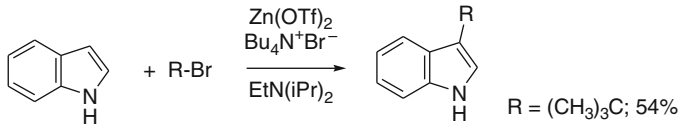
Both the direct magnesium allylation and the allylation via a 3-lithio indole were employed in the synthesis of 1,3-diallylindole [83]. Somewhat in contrast to Wenkert's results, both geranyl and farnesyl bromide are reported to give about 30% yield of the not rearranged 3-allylation products with indole magnesium iodide [84]. Prenylation of the magnesium salt of N^b-methyltryptamine proceeds with intramolecular capture of the amino group [85, 86].



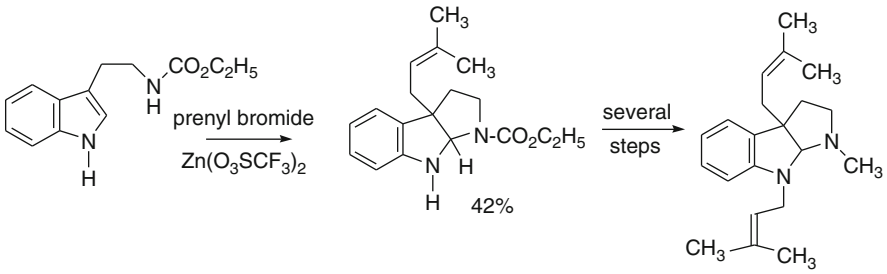
Using Mayr's nucleophilic scale (see Sect. 1.1) as a guide, Westermaier and Mayr concluded that indole should compete with solvent for allylic cations in aqueous acetonitrile or acetone. This was shown to be the case experimentally [87]. Several allylic chlorides and bromides react with indole or 1-methylindole to provide allylation products. Unsymmetrical cations react at the less substituted position. Interestingly, significant amounts of 2-substituted indoles are generated under these conditions (usually about 10:1 for C-3:C-2).



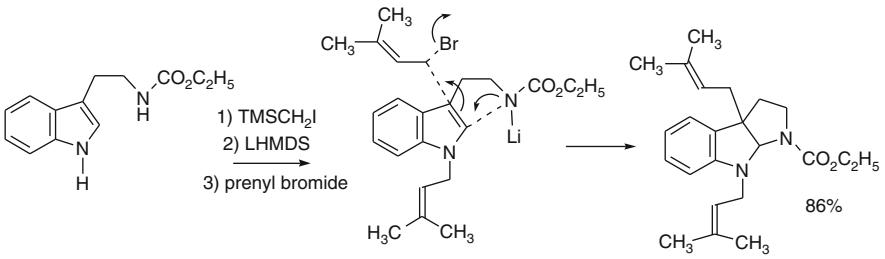
Ganesan and coworkers found that $Zn(O_3SCF_3)_2$ and Hunig's base was the optimum combination for allylation of indole with a range of allylic bromides, including prenyl, geranyl and farnesyl bromide [88]. Benzyl and *tert*-butyl groups can also be introduced with this reagent combination.



C-Ring substituted indoles, including 4-nitroindole, are also allylated under these conditions. The reaction is believed to proceed by an S_N1 mechanism, with the $Zn(O_3SCF_3)_2$ acting as a Lewis acid catalyst. There may also be some N–H deprotonation by the amine. 1-Methylindole reacts under these conditions, but with reduced yield. The $Zn(O_3SCF_3)_2$-mediated reaction was used in tandem with intramolecular nucleophilic capture to synthesize the flustramine structure [89].

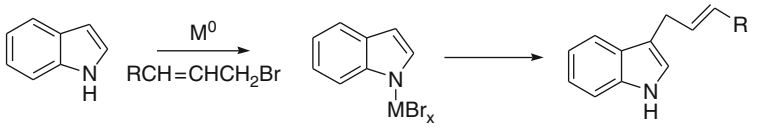


This cyclization has also been done using the TMS-methyl derivative of the carbamate [90]. The reaction is postulated to occur via deprotonation and decomposition of an *N*-trimethylsilylmethyl intermediate at the carbamate group.

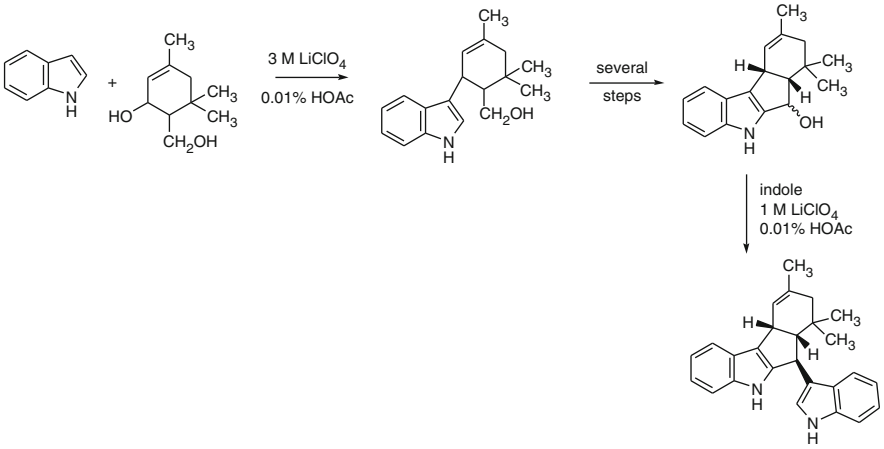


There are also procedures for allylation with halides using zinc [91], gallium or cadmium [92] metal. These reactions are thought to proceed through a metallated indole formed in situ. Consistent with this interpretation, 1-methylindole does not react. With the gallium reagent, 3-methylindole gives the 2-allyl product.

Substituted allylic and propargyl systems react similarly. No examples of allylic "inversion" are reported.

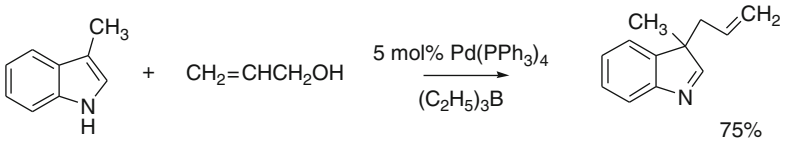


Allylation can be done with allylic alcohols and Lewis acids. An example is the reaction of allylic alcohols in the presence of $LiClO_4$, originally developed by Grieco and coworkers and applied to the synthesis of yuehchukene [93]. The alkylation was done using 3 M $LiClO_4$ in ether containing a trace of acetic acid and proceeded in 82% yield. The subsequent cyclization to C-2 was done at the aldehyde oxidation level and is an example of intramolecular carbonyl addition (see Sect. 5). The introduction of the second indole ring was done by alkylation by the reactive indole-2-carbinol group in the intermediate.

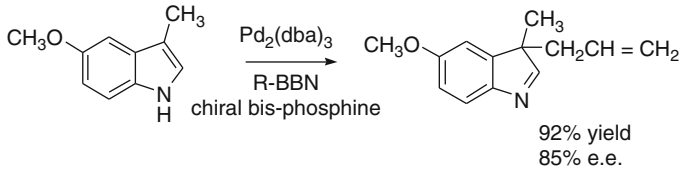


4.2.2 Palladium-Mediated Electrophilic Allylation

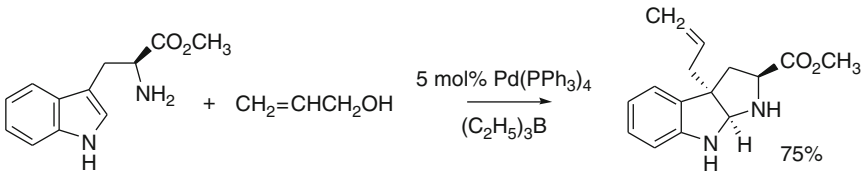
Allylic alcohols can also allylate indole in the presence of triethylborane and a Pd catalyst [94]. This system is capable of allylating a number of nucleophiles and is believed to proceed through a π-allylic-Pd intermediate. The borane functions as a Lewis acid, activating the allylic alcohol towards oxidative addition [95]. With unsymmetrical alcohols, a mixture of the allylic regioisomers is observed. The reaction proceeds satisfactorily with both electron-releasing and electron-withdrawing C-ring substituents. With 3-methylindole the indolenine is isolated.



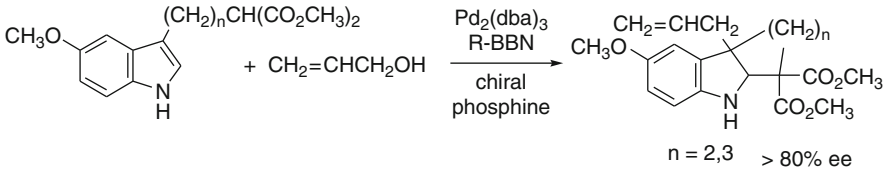
The Pd-catalyzed allylation becomes enantioselective when conducted with chiral phosphine ligands [96].



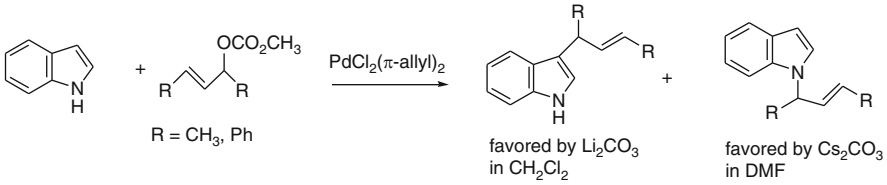
These conditions can also be used in combination with nucleophilic trapping.



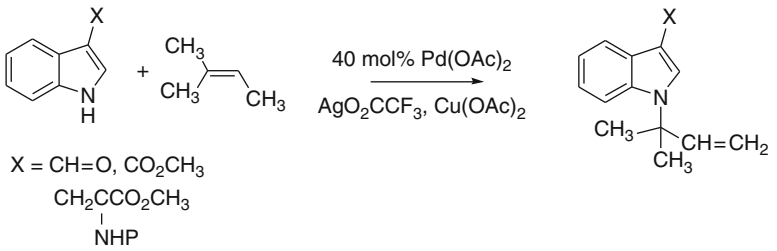
The reaction is applicable to other 3-substituted indoles and has also been used to effect cyclization with nucleophilic groups including hydroxy, carbamate and malonate esters.



Allylic carbonates have also been used successfully in Pd(II)-catalyzed allylation reactions [97]. The regioselectivity of the reaction is somewhat sensitive to the base and solvent used. With more polar solvents (DMF, THF) and stronger base (Cs_2CO_3) N-1 allylation is dominant while Li_2CO_3 in CH_2Cl_2 gives mainly C-3 substitution.

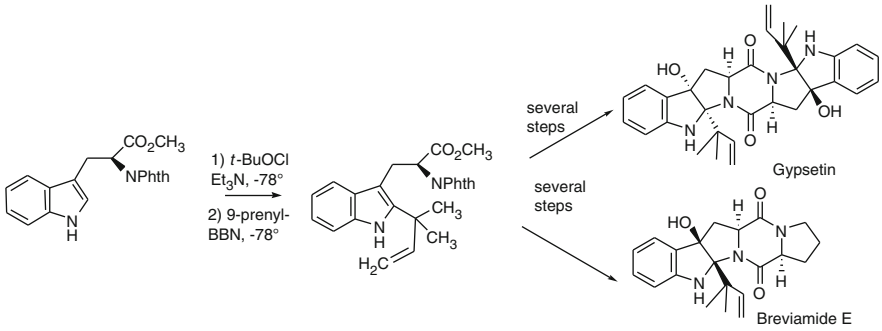


1-(*tert*)-Prenylindoles can be prepared by Pd-mediated reactions using 2-methylbutene as the source of the prenyl group [98]. These reactions presumably involve an allylic-Pd species generated from the alkene.

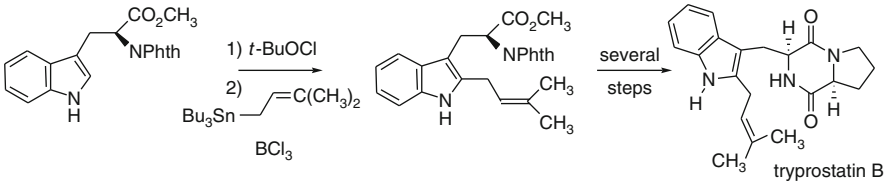


4.2.3 Allylation Induced by Electrophilic Addition

Danishefsky and coworkers developed a method for introducing the *tert*-prenyl group at the indole C-2 position based on C-3 chlorination followed by nucleophilic delivery of the *tert*-prenyl group from a borane [99]. The intermediate was used in synthesis of gypsetin and breviamide E, both of which contain the 2-(*tert*-prenyl) substituent.



A related method provided access to 2-prenylindoles, presumably through an inverted allylic borane, and was applied to the synthesis of tryprostatin B [100].



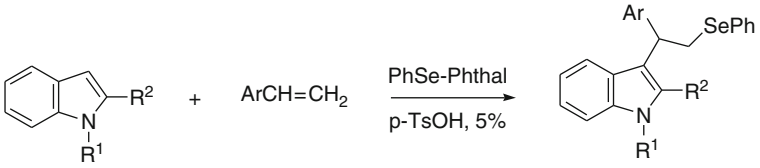
The *tert*-prenylation method has subsequently been applied by several groups to the synthesis of other natural products [101, 102], and was also successfully applied to an indole without a 3-substituent [103].

4.2.4 Enzymatic Prenylation

Prenylated indole derivatives are formed by fungi, especially *Aspergillus, Claviceps* and *Penicillium* species [104]. Extensive work has been done on the enzymes and mechanism of prenylation. Several of the gene systems that code for prenylation have been identified and overexpressed in *Escherichia coli* or *Saccharomyces cerevisiae*. Some of the systems are selective for the C-4 or C-7 positions on the indole ring, while others are specific for N-1 or C-2. Mechanistic studies indicate that the enzymes function by generating a carbocation-phosphate ion pair that can be captured by indole, a mechanism that is parallel to direct chemical allylation [105]. The enzymes sometimes exhibit fairly broad substrate acceptability. For example, the C-4 synthase from *Aspergillus fumigatus* accepts tryptophan analogs such as indole-3-propanoic acid and 2-amino-4-(3-indolyl)butanoic acid (homotryptophan). C-Ring substituted analogs are also accepted, opening the possibility of chemoenzymatic synthesis [106–108].

4.3 Alkylation by Electrophilic Alkene Activation

Alkenes are potential sources of electrophiles for alkylation of indoles, but require selectivity for activation of the alkene over attack on the indole ring. In one example, Zhao et al. found the indole could by alkylated by styrenes in the presence of *N*-phenylselenylphthalimide [109].

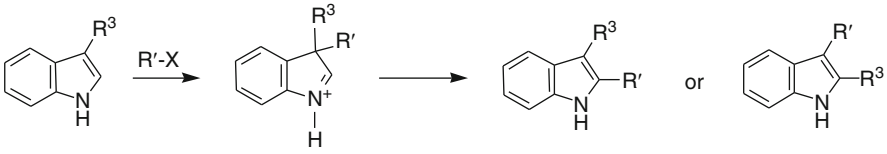


4.4 Intramolecular Alkylation

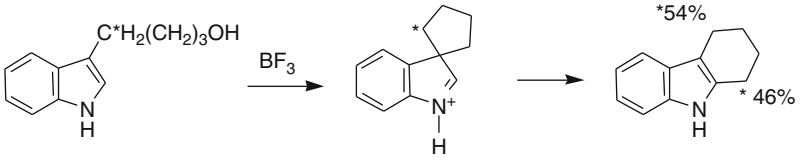
Intramolecular alkylation can be accomplished by generating an appropriate electrophilic site. Because of the availability of 3-substituted precursors, most examples involve cyclization at the 2-position, designated herein as [3-2]. However, [2-3] and [1-2] cyclizations are also common. The ergot alkaloids, as well as other natural products, have been obtained by [3-4] cyclization.

4.4.1 Ipso Substitution at C-3

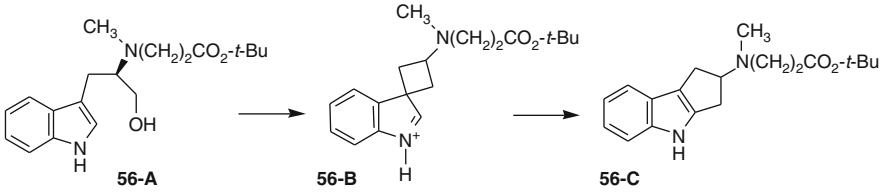
Because of the enhanced reactivity of the 3-position, *ipso* substitution is sometimes observed with 3-substituted indoles. The mechanism is initial attack at C-3, followed by migration to C-2. If the original C-3 substituent is capable of migration, this opens the possibility for a rearrangement.



The existence of this process was first conclusively demonstrated by Jackson, Naidoo and Smith in 1968 [110]. They showed that tritiated 4-(3-indolyl)butanol cyclized by BF_3 gave 46 ± 2% labeling adjacent to C-2, indicating that most (if not all) of the cyclization occurred through a *spiro* intermediate.

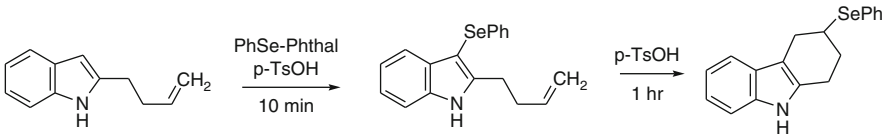


Another example was provided in 1993 by Ganesan and Heathcock [111]. Tosylation of the enantiomerically enriched alcohol **56-A** gave a racemic cyclization product **56-C**. The most likely explanation is the formation of an achiral intermediate **56-B**, the product of *ipso* substitution.

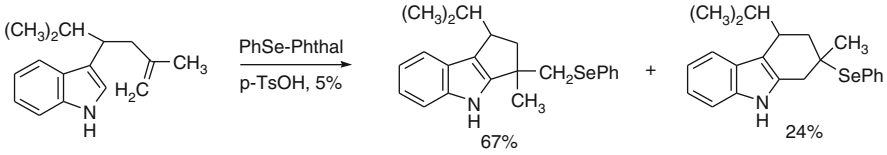


4.4.2 Intramolecular Alkylation by Activation of Double Bonds

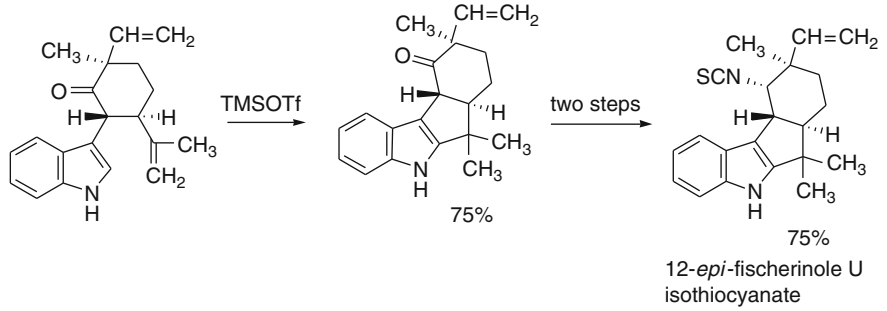
Zhao and coworker applied the selenylation-alkylation to intramolecular cases [109]. With 2-(3-butenyl)indole, the 3-phenylselenenylation product was observed to be an intermediate. This transformation evidently occurs by C-3 protonolysis, followed by formation of the stable cyclization product.



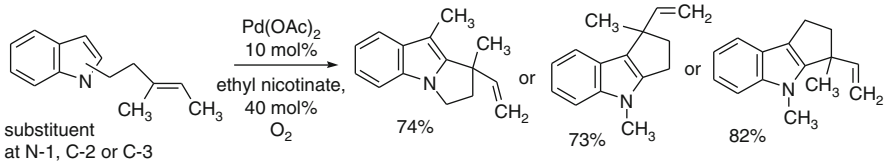
These same reaction conditions led to two isomeric products in the case of a 3-substituted indole.



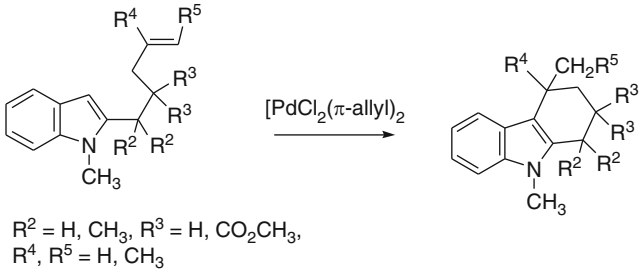
Baran and Richter used an intramolecular alkylation induced by TMSOTf in the synthesis of 12-*epi*-fischerindole U isothiocyanate [112].



A number of procedures for Pd-mediated intramolecular alkylations of indole have been reported. Ferreira and Stoltz reported examples of [1-2], [2-3], and [3-2] cyclizations using 10 mol % $Pd(OAc)_2$ in the presence of pyridine ligands. Using the 3-methylpent-3-enyl substituent in each case, cyclopenta-indoles were formed. The 3-(4-methylhex-4-enyl), substituent generated a tetrahydrocarbazole [113].

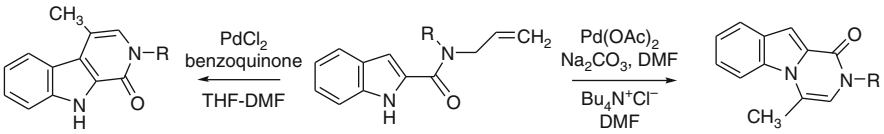


1-Methyl-2-(pent-4-enyl)indole and several substituted analogs are cyclized by $[PtCl_2(\pi-allyl)_2]_2$. The stereochemistry of the reaction is consistent with electrophilic attack on the indole by the Pt-complexed alkene [114].



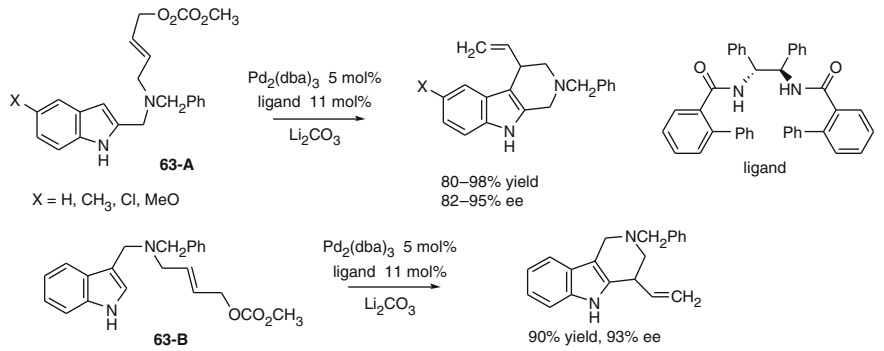
R^2 = H, CH_3, R^3 = H, CO_2CH_3,
R^4, R^5 = H, CH_3

N-Allyl amides of indole-2-carboxylic acid can be cyclized to either N-1 or C-3, depending on the conditions used. The C-3 cyclization occurs with $PdCl_2$-benzoquinone, while $Pd(OAc)_2$ in the presence of Na_2CO_3 and quaternary ammonium salts gives the N-1 cyclization product [115].

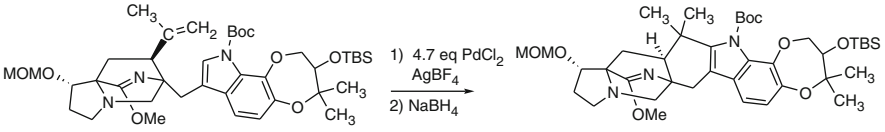


R = Me, allyl, Ph, c-C_6H_{11}

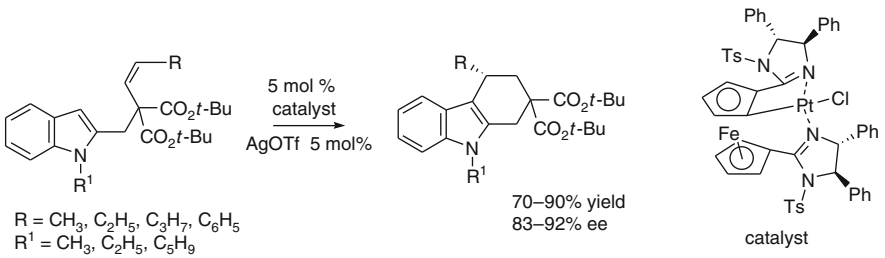
Intramolecular cyclizations of both the [2-3] and [3-2] patterns have been carried out with allylic carbonates. Thus both **63-A** and **63-B** gave good yields and enantioselectivity under the influence of Pd-catalysis [116].



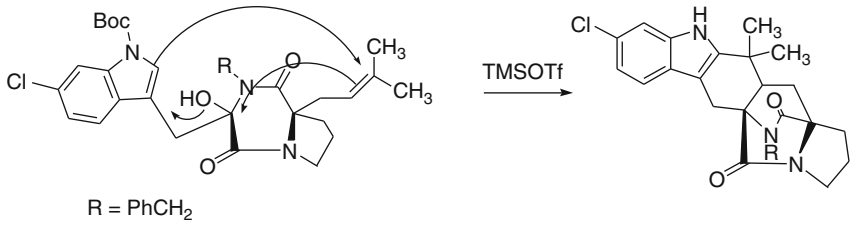
Sensitivity of protecting groups to acid prompted the use of Pd-mediated alkylation in the course of synthesis of parherquamide A [117].



Alkenes have also been activated by a chiral platinum catalyst [118].



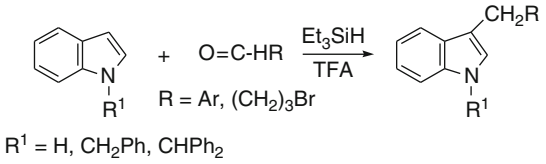
A tandem alkylation originating at a carbinol amide was used in the synthesis of the enantiomer of malbrancheamide B [119].



5 Alkylation by Carbonyl Compounds

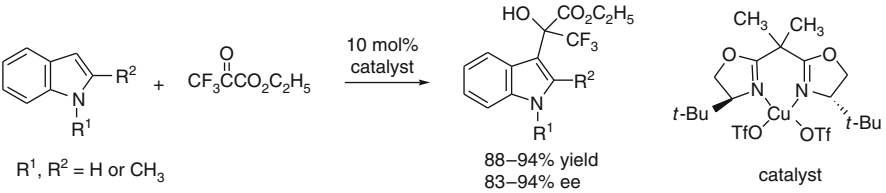
5.1 Indol-3-yl Carbinols

The acid-catalyzed alkylation of indoles by carbonyl compounds is complicated by the fact that the resulting indol-3-yl carbinols are usually reactive under these conditions. The most common outcome is the formation of *bis*-indolylmethanes, as is discussed in the next section. In some cases, the carbinol intermediates can be diverted to alkylation by reductive trapping using triethylsilane-TFA. This reaction gives good yields of 3-benzyl indoles and there are a few examples of 3-alkylation using N-substituted indoles [120].

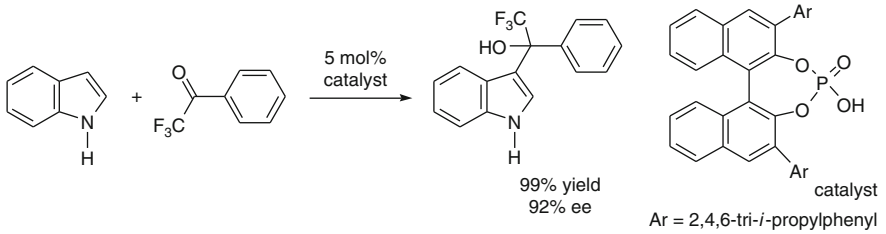


These conditions were used to prepare a series of potential COX-2 inhibitors [121].

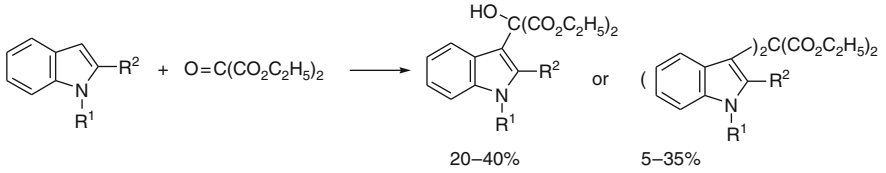
The presence of a strongly electron-attracting group, such as trifluoromethyl can both enhance the reactivity of the carbonyl group and stabilize the carbinol. As a result, such compounds have been the most successful in giving the carbinol product. One of the first successful enantioselective alkylation reactions was carried out using 3,3,3-trifluoropyruvate esters [122].



The same substituent effect is present with trifluoromethyl aryl ketones. *N,N,N′N′*-Tetramethyl-N″-(*t*-butyl)guanidine was an effective catalyst for reaction with trifluoromethyl ketones [123]. The reaction can be done enantioselectively using 3,3′-*bis*-(2,4,6,-tri-*i*-propyl-phenyl)BINOL [124].

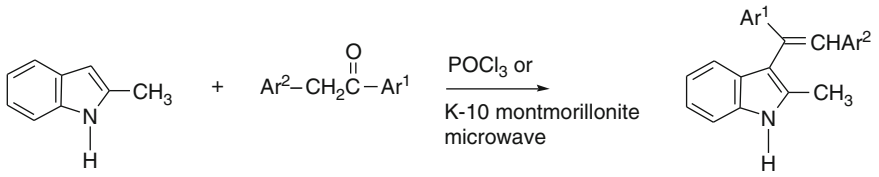


A similar substituent effect operates in the reaction of indole with diethyl ketomalonate conducted by microwave irradiation on montmorillonite K-10 clay [125]. Indole, its 1-methyl and 2-methyl derivatives, along with C-ring analogs, gave mixtures of both the 3-carbinol and *bis*-indol-3-yl products.



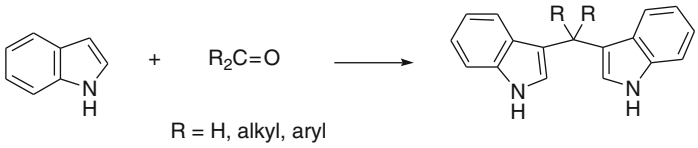
3-Methylindole gave only the C-2-carbinol. These results are consistent with the ester substituents slowing the rate of reaction of the carbinol.

Occasionally, under special circumstances, the intermediate carbinols can be diverted to other products. For example with aryl benzyl ketones, dehydration occurs on reaction with $POCl_3$ or on montmorillonite K-10 clay [126].



5.2 *Bis-Indolylalkanes and Related Compounds*

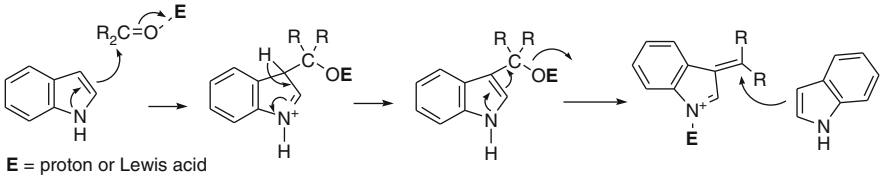
The reaction of indole and its alkyl derivatives with carbonyl compounds under acidic conditions usually forms *bis*-(3-indolyl)methanes.



In recent years, this reaction has been reported using a wide-ranging group of catalysts. Many of the methods were designed to use inexpensive or environmentally benign materials. The catalysts reported to give good results include sulfonic acids [127–130], sulfonic acid ion exchange resins [131, 132], $KHSO_4$ [133], solid-supported acids [134, 135], sulfamic acid [136, 137], ammonium salts [138], triphenylphosphonium perchlorate [139], $LiClO_4$ [140], copper salts [141–143], Lewis acids [144–154], lanthanide salts [155, 156], ferric sulfonates [157], ceric ammonium nitrate [158], zinc oxide [159], heteropoly acids [160–163], montmorillonite K-10 clay [164, 165], and zeolites [166–168]. $FeCl_3$ has been used under solvent-free conditions with microwave irradiation [145]. The ionic liquids bmim (1-butyl-3-methylimidazolium) BF_4 and PF_6 effect reaction with aromatic and aliphatic aldehydes, as well as cyclic ketones [169]. Lanthanides have been used in conjunction with ionic liquids [170]. Some of these catalysts can achieve selective reaction of aldehydes in preference to ketones [171–174].

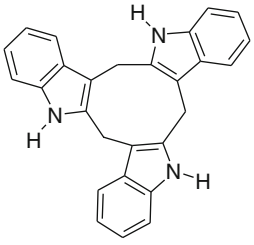
Few of these methods have been investigated in detail in terms of mechanism, but it seems likely that protic and Lewis acids are able to catalyze both the initial

addition step and the elimination step, and, perhaps, the conjugate addition step. In fact, the reaction with aromatic aldehydes can be carried out without a specific catalyst in methanol. The reaction can also be done in water if a surfactant is present to dissolve the indole. No reaction occurs in aprotic organic solvents [175].



Somewhat less clear is the nature of catalysis by halogens and positive halogen compounds, such as I_2 [176, 177], NBS [178], tetra-*N*-butylammonium tribromide [179], and hexamethylenetetramine–bromine complex [180]. These compounds would be expected to react with indoles by halogenations, generating the hydrogen halide as a by-product. Another halogenated catalyst, 2,4,6-trichlorotriazine, is believed to function by generation of HCl in the presence of moisture [181].

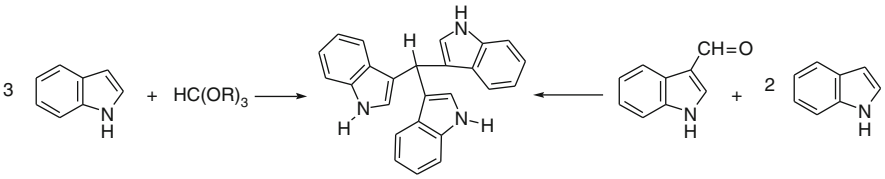
Some of the interest in *bis*-indolylmethanes comes from the purported biological activity of trimeric and tetrameric analogs. A cyclic trimer derived from indole-3-methanol has attracted attention in connection with the antitumor activity associated with vegetables of the species *Brassica*. The chemical lability of indole-3-methanol and its condensation products are the source, however, of considerable complication in interpreting the metabolism of these compounds [182, 183]. Under acidic conditions, indole-3-methanol is converted to the trimer, but also to the *bis*-(3′-indolyl) methane and an isomer [184–186]. The trimer is reported to be an estrogen receptor agonist and to stimulate the function of an estrogen-dependent cell line (MCF-7) [187].



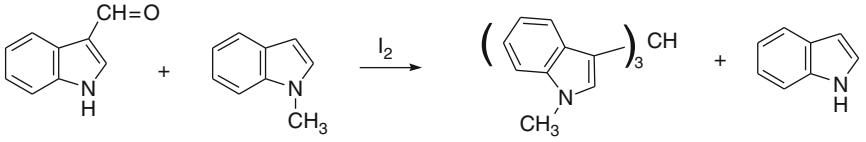
1-Substituted analogs are converted to these cyclic trimers in fair yield by *p*-toluensulfonic acid in CH_2Cl_2 [188, 189]. The trimer is also formed under basic condition from 3-(trimethylammonio-methyl)indole [190]. This method also gives rise to some of the isomeric tetramer.

5.3 *Tris-Indolylalkanes*

There are two general routes to *tris*-(3-indolyl)methanes. One is reaction of the indole with an orthoformate ester [191, 192]. The second method is reaction of the indole and an indole-3-carboxyaldehyde with an acidic catalyst [193]. Only the latter method can be applied to unsymmetrical *tris*-(3-indolyl)methanes.



The kinds of catalysts that have been used for these reactions are similar to those for *bis*-(3-indolyl)methanes [194–201]. In one study, I_2 was found generally superior to Lewis acids [202]. This same study found evidence of redistribution in the case of unsymmetrical *tris*-indolylmethanes. Specifically, reaction of indole-3-carboxaldehyde with 1-methylindole gave only the *tris*-(1-methyl-3-indolyl) methane and gave indole as a by-product, suggesting thermodynamic control and enhanced stability of the 1-substituted trimer.



6 Alkylation by Conjugate Addition

The conjugate addition of indoles to electrophilic alkenes has been known for many years with early examples including methyl vinyl ketone [203] and nitroethylene [204]. A range of new catalysts have been explored. These include a variety of protic and Lewis acids. There has also been exploration of various supported catalysts. Both protic and Lewis acids have also been used in conjunction with ionic liquids, usually imidazolium salts. Many of these studies have been carried out with 1,3-diarylpropen-1-ones as the reactants, but some also include enones such as methyl vinyl ketone and cyclic enones. Chiral catalysts can give enantioselective additions. Much of the work with chiral catalysts has been summarized by Bandini, Melloni, Tommasi and Umani-Ronchi [205]. For the most part, the successful reactions have used either enones or nitroalkenes. There are few reports, for example, of addition to acrylate esters.

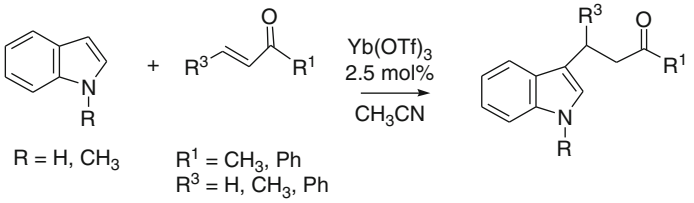
6.1 Catalysts for Conjugate Addition

6.1.1 Protic Acid

Triflic acid (0.1–1.0 mol % in water) catalyzed conjugate addition to a variety of enones, including methyl vinyl ketone, 4-phenylbut-3-en-2-one, cyclopentenone, and cylohexenone [206]. Among other protic catalysts, polyvinylsulfonic acid gives 70–90% yields for various substituted indoles, including the 1-methyl and 2-methyl derivatives, but fails with the less reactive 5-nitroindole [207]. Amberlyst sulfonic acid resins catalyzed the addition of 2-methylindole to cyclohexenone and several aryl enones [208]. Silica-supported $NaHSO_4$ gave good results with several β-unsubstituted enones, as well as β-aryl derivatives [209].

6.1.2 Lewis Acids

The first systematic investigation of Lewis acid-catalyzed additions of indole to enones used $Yb(OTf)_3$. The enones examined included methyl vinyl ketone, pent-3-en-2-one, 4-phenylbut-3-en-2-one and cyclohexenone, all of which gave good yields. The β,β-disubstituted systems 4-methylpent-3-en-2-one and 3-methylcyclohex-2-enone gave lower yields [210].



Among other Lewis acids, $InCl_3$ [211], $SbCl_3$ [212], $CuBr_2$ [213] and $GaCl_3$ [214] have been reported to give good yields with 1,3-diarylpropenones. $InBr_3$ gave good results with β-methyl, β-aryl and cyclic enones [215]. GaI_3 gave good yields with methyl vinyl ketone and 4-methyl-3-penten-2-one, as well as various β-aryl enones [216]. $Y(Tf)_3$ gave good results with a variety of enones, including methyl vinyl ketone and cyclohexenone [217]. $Bi(NO_3)_3$ gave good results with β-methyl, α,β -dimethyl, and β-aryl enones [218]. $Bi(OTf)_3$ is one of the few catalysts reported to be successful for reactions with acrylate esters and acrylonitrile as well as with enones [219]. $ZrOCl_2$, 2 mol %, mixed with the neat reactants, gave good yields for methyl vinyl ketone [220].

A catalyst consisting of 20% $ZnBr_2$ on $Ca_{10}(PO_4)_6F_2$, fluoroapatite, gave 90% yields with several β-unsubstituted enones, but β-aryl reacted more slowly, although good yields were obtained in most cases [221]. Dry montmorillonite K-10 clay gave good results when one equivalent of ethanol was added and the

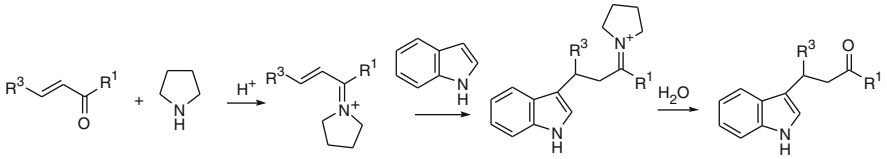
reaction run in nitromethane [222]. K-10 clay exchanged with FeO also gave good results [223].

When carried out in the presence of excess indole, conjugate addition can be followed by *bis*-indolylmethane formation at the remaining carbonyl group. This was observed, for example, with $Zr(OTf)_4$ [224].

Products of this type can also be formed as unwanted by-products under other conditions.

6.1.3 Iminium Ions

Another mechanism for catalysis of conjugate addition is via iminium salts. This reactivity has been exploited for several enantioselective catalysts (see Sect. 6.2). A simple example is provided by the use of pyrrolidine salts [225].

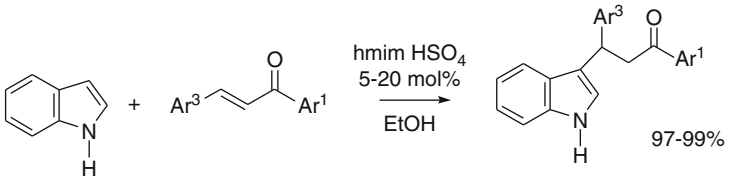


6.1.4 Halogens

Another interesting catalyst is molecular iodine. In ethanol, 10 mol % I_2 catalyzes addition of indole to various 1,3-diaryl propenones in good yield [226]. When I_2 is used in a solid equimolar mixture with the indole and enones, it provides >70% yields with indole and C-ring analogs [227]. Even the relatively unreactive 5-cyanoindole reacts well. 3-Methylindole give 2-substituted products, but the yields are lower. The catalysis is attributed to I_2 acting as a Lewis acid, since HI did not appear to be effective under these conditions. A combination of $CeCl_3.7H_2O$ and NaI, used at 30 mol % and adsorbed on silica, also catalyzes indole conjugate addition to enones [228]. In DMSO, this reagent combination resulted in conjugate addition and also subsequent formation of *bis*-(indol-3-yl adducts at the carbonyl group [229]. Also interesting is the use of 20% of nitrosonium tetrafluoroborate in ether, which is reported to give very good yields of the alkylation products with 1,3-diarylpropenones [230].

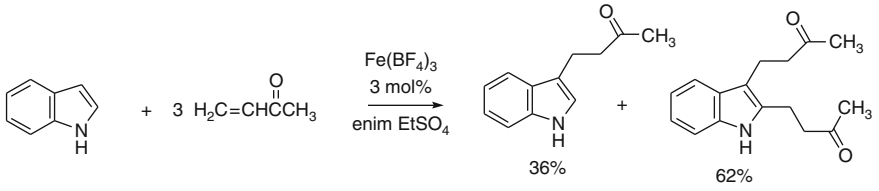
6.1.5 Ionic Liquids

Ionic liquid catalysts have been found to give good results with 1,3-diarylpropenones. The 1-hexyl-3-methylimidazolium acid sulfate, hmin, gave 97–99% yields [231]. These conditions gave equally good results with 2-methylindole, but the yield was much lower (46%) for 1-methylindole.



4-(Pyridinium)butanesulfonic acid tosylate, also is a good catalyst for these reactions [232]. Ionic liquids have also been used in conjunction with solid silica supports. A combination of silica-bound sulfonic acid and the ionic liquid 1-butyl-3-decylimidazolium SbF_6 gave good yields with a variety of enones, including methyl vinyl ketone [233]. Another successful catalyst used a silica-bound imidazolium-butanesulfonic acid [234]. Chiral D-camphorsulfonic acid used in conjunction with 1-butyl-3-methylimidazolium bromide (bmim Br) gave excellent yields with 1,3-diarylpropenones, but the ee was in the 20–30% range in most cases [235].

Lewis acids have also been used in conjunction with ionic liquids. Iron salts were used in either acetonitrile or ionic liquids and gave comparable yields with methyl vinyl ketone. When the enone was used in threefold excess a considerable amount of the 2,3-dialkylation product was obtained [236].



$Cu(OTf)_2$ in the ionic liquid bmim BF_4 gave good yields with methyl vinyl ketone, cyclohexenone and β-aryl enones [237]. Use of bmim BF_4 with $PdCl_2$ was also found to give good yields with β-aryl enones [238].

6.1.6 Ultrasonic and Microwave Radiation

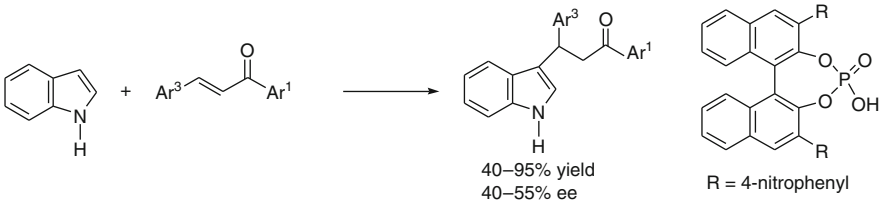
The effects of ultrasonication and microwave radiation have also been examined. *p*-Toluenesulfonic acid under ultrasonic irradiation gave good yields with various 1,3-diarylpropenones [239]. Other conditions that are reported for

1,3-diarylpropen-1-one include $KHSO_4$ [240] or ceric ammonium nitrate [241] with ultrasound. Microwave irradiation of solid mixtures of the indole, enone and 10 mol % SmI_2 gave good yields for methyl vinyl ketone, cyclohexenone and several β-aryl enones [242].

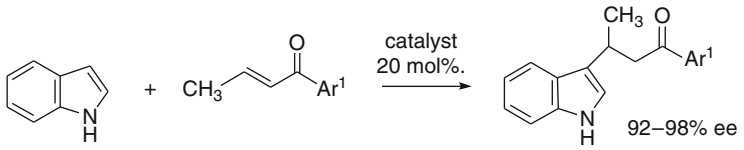
6.2 *Enantioselective Conjugate Addition to Enones*

6.2.1 Protic and Lewis Acid Catalysts

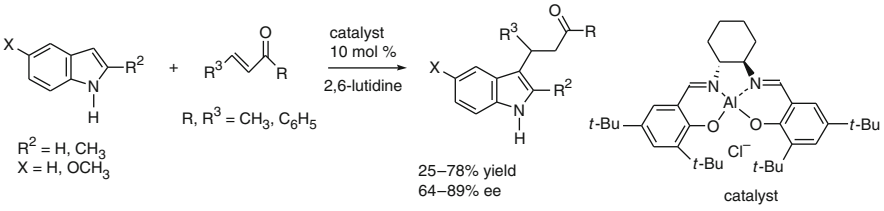
Several chiral catalysts for conjugate addition have been explored, including both protic and Lewis acids. 3,3′-*bis*-(4-Nitrophenyl)-BINOL-phosphoric acid gives 40–98% yields and 40–55% ee with β-aryl enones [243].



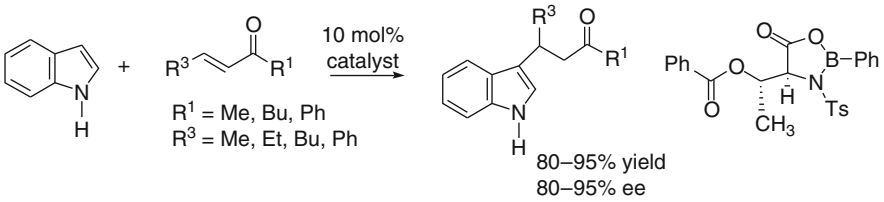
A combination of 3,3′-dibromoBINOL and $Zr(O\text{-}t\text{-}Bu)_4$ gives ee in the range of 92–98% for 1-aryl-but-3-en-1-ones [244].



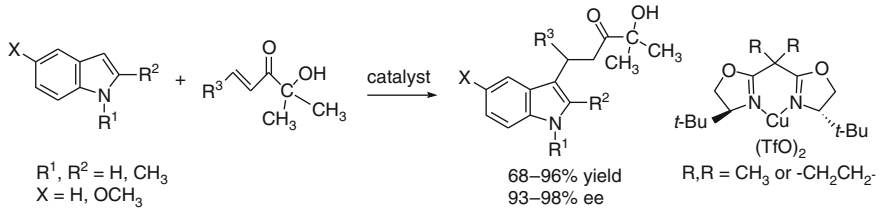
The group of Bandini and Umani-Ronchi investigated aluminum-salen complexes and found that enantioselectivity was promoted by amine bases, 2,6-lutidine being particularly effective. The optimized conditions gave 80–90% ee with several 1-aryl-but-2-en-1-ones [245, 246].



Another chiral catalyst that was examined is an oxazaborolidinone derived from *allo*-threonine. The reaction proceeded in 80–95% yield and 80–95% ee. These conditions were applicable to both 1- and 2-methyl indole, as well [247].

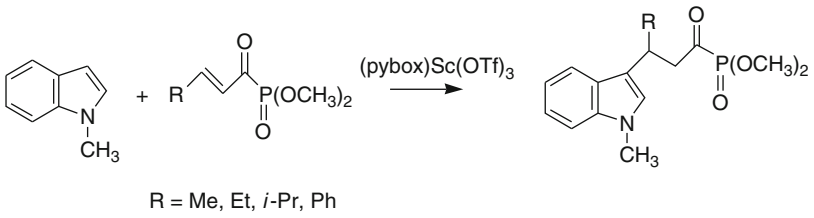


A series of α-hydroxy enones gave good results with a *t*-butyl BOX catalysts or its cyclopropyl analog [248].



Combinations of *bis*-oxazolines with $Cu(OTf)_2$ were also effective for enones having dimethyl phosphonate substituent groups [249].

Enantioselective alkylation occurs with alkenoylphosphonates [250]. The preferred catalyst is a Sc(III)pybox triflate. *N*-Substituted indoles give somewhat higher enantioselectivity than indole itself. The acyl phosphonate adducts are reactive acylating agents and can be readily converted to esters or amides.

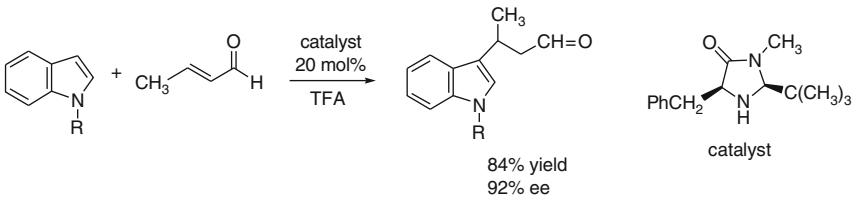


α,β-Unsaturated acylimidazoles show similar reactivity and can also be converted to a variety of derivatives by substitution, including aldehydes and ketones, as well as esters and amides [251].

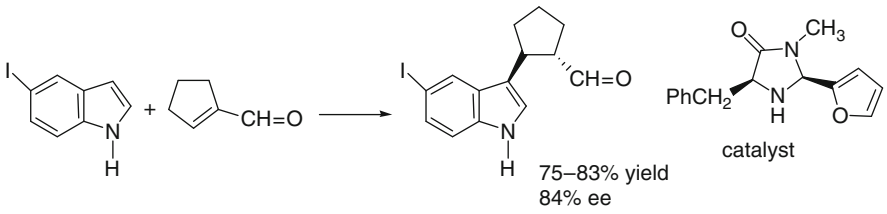
6.2.2 Iminium Ion Catalysts

In addition to chiral acids, amines and amine salts have been used to catalyze conjugate addition. These catalysts presumably function by formation of iminium

derivatives of the enones. Austin and MacMillan used a modified imidazolone catalyst in reactions of 1-substituted indoles with crotonaldehyde and other propenals [252]. At low temperature, 80–90% ee could be achieved using the TFA salt of the catalyst. These conditions also proved to be applicable to indole and C-ring substituted analogs.



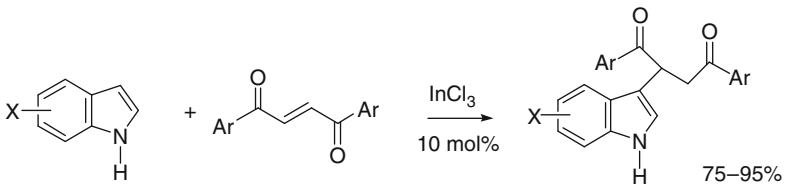
An application of this methodology is found in the synthesis of a drug candidate. In this case a modified imidazolone that gave the desired enantioselectivity with cyclopentene-1-carboxyaldehyde was used [253].



Iminium intermediates are presumably also involved in reactions catalyzed by chiral amines [254] and amine salts derived from cinchona alkaloids [255].

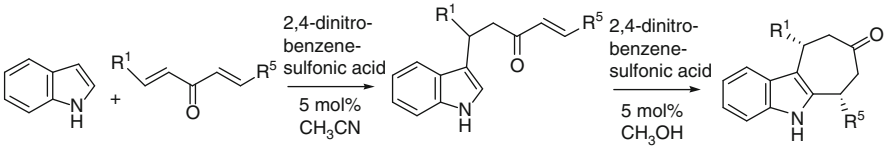
6.3 *Reactions with Enediones and Dienones*

Indoles react with 1,4-diarylbut-2-en-1,4-diones under the influence of $InCl_3$ to give conjugate addition. The 1,5-dione adducts can then be cyclized to furans and other heterocyclic derivatives [256].

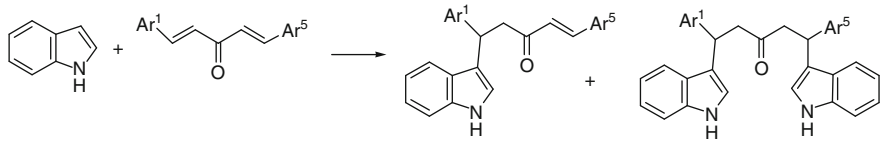


The reactions of indole with 1,5-disubsituted pentan-1,4-dien-3-ones has also been examined. With $R^1 = CH_3$ and $R^5 =$ phenyl, the reaction occurs preferentially

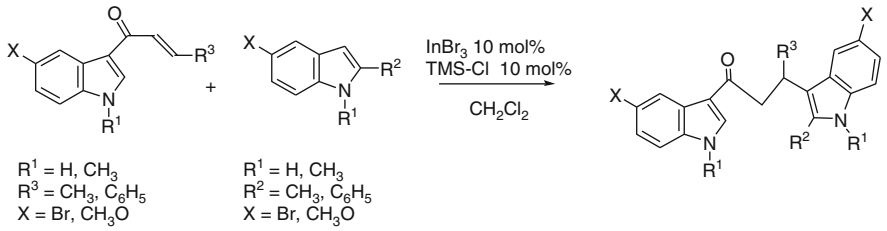
at the methyl-substituted position. The initial adducts can be isolated but undergo cyclization on heating [257]. The cyclization product shows a preference for the *cis*-isomer ranging from 9:1 to as high as 23:1.



The reaction of indole with 1,5-diaryl penta-1,4-dien-3-ones has been examined using both I_2 [258] and $AlCl_3$ [259] in conjunction with ultrasonic irradiation. Both sets of conditions give mixtures of mono- and *bis*-indole adducts. Another catalyst studied for this reaction is $RuCl_3$, which at a 2:1 indole ratio gives the *bis*-(3-indolyl) adducts [260].

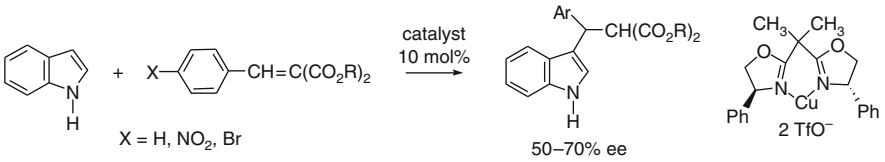


Conjugate addition has also been carried out with 1-(3-indolyl) enones. The reactivity of these compounds might be expected to be attenuated somewhat by the donor character of the indole ring, relative to the carbonyl group. Good results were obtained using $InBr_3$-TMS-Cl, both at 10 mol % [261]. These conditions were also successful with *N*-protected (*t*-Boc, TIPS, $PhSO_2$) 3-indolyl enones.

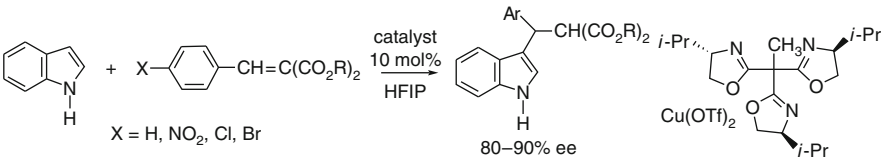


6.4 *Reactions with Alkylidene Malonates*

Among other types of electrophilic compounds that give alkylation of indoles are alkylidene malonate esters. Jorgensen and coworkers observed 50–70% ee using a Cu(BOX) catalyst [262].

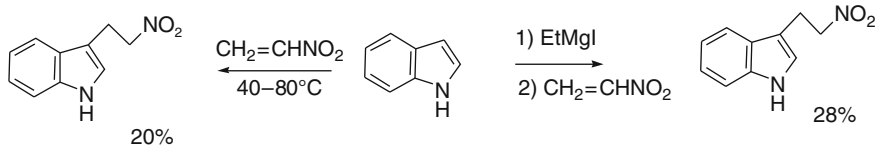


Zhou and Tang were able to obtain 80–90% ee using a *tris*-oxazoline catalyst with $Cu(OTf)_2$ and HFIP as a promoter [263].



6.5 Addition with Nitroalkenes

The reaction of indole or its magnesium salt was first developed by Noland and coworkers [204] and applied to the synthesis of tryptamine [264] and serotonin [265]. The reaction can be done either under thermal conditions or using the magnesium salt.

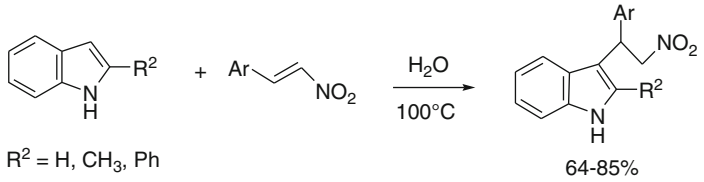


Because of its tendency to polymerize, nitroethylene is a somewhat challenging reactant. When the reaction with indole is conducted at room temperature the yield increases to 80% [266]. Recently, a comparison was done, using β-nitrostyrene, of the Mg salt, thermal and microwave irradiation. The microwave method was found most convenient. These conditions were also applicable to the α-methyl analog [267].

Method	Time	Temp.	Yield
MgI salt	5 min	25	71%
Thermal	48 h	150	80%
Microwave	2 min	?	100%

In recent years many other reaction conditions and catalysts, including chiral catalysts have been examined. The range of catalysts is similar to that for addition to enones. Generally speaking, the nitroalkenes would be expected to be somewhat

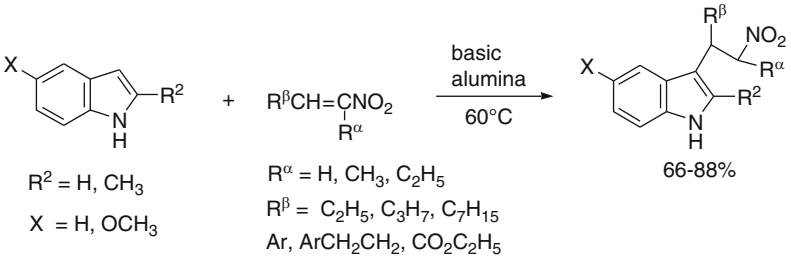
more reactive. Addition of indole to β-aryl nitroalkenes occurs in good yield in water without a catalyst at 100°C [268].



Surfactant-type salts of aluminum [269] and scandium [270] also promote addition in water. A combination of $Sc(OTf)_3$ (5 mol %) with a surfactant that is compatible with super-critical CO_2, promoted reaction in that medium [271].

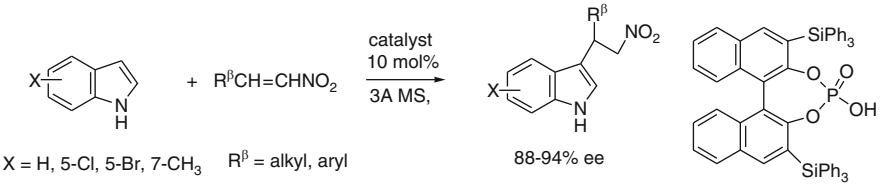
Protic acids that have been used successfully in water include the heteropoly acids $H_3PMo_{12}O_{40}$ and $H_3PW_{12}O_{40}$ [272]. Both H_2SO_4 [273] and $HOSO_2NH_2$ [274] absorbed on silica have been used in solvent-free systems. $NaHSO_4$ supported in silica can be used in acetonitrile [209]. Among the Lewis acid catalysts that demonstrate broad scope in reactivity are $InBr_3$ [275], SmI_3 [276] and $Zn(OAc)_2$ [277]. Other successful supported systems include $CeCl_3/7H_2O/NaI/SiO_2$ [278].

Basic alumina at 60°C gives good results for a number of nitroalkenes.



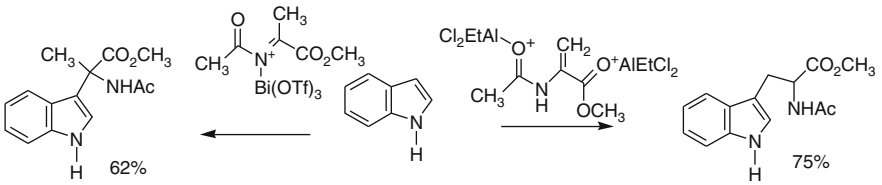
As was the case for addition to enones, several halogen sources including NBS [279] and I_2 [280] can promote conjugate addition to nitroalkenes.

The chiral catalysts that have been used in nitroalkene conjugate additions include *bis*-oxazolines with $Cu(OTF)_2$ [281] or $Zn(OTf)_2$ [282], tridentate *bis*-oxazolines with $Zn(OTf)_2$ [283], mixed thiazoline-oxazolines with $Zn(OTf)_2$ [284], imidazoline-aminophenols with CuOTf [285], *bis*-trifluoromethylsulfonamides [286], binaphthyl sulfonamides [287], binaphthyl imines [288], thioureas [289], and quinolinyl thioureas [290]. A BINOL-phosphoric acid with 3A molecular sieves gave ee values consistently at 90% and above with both β-alkyl and β-aryl nitroalkenes [291].

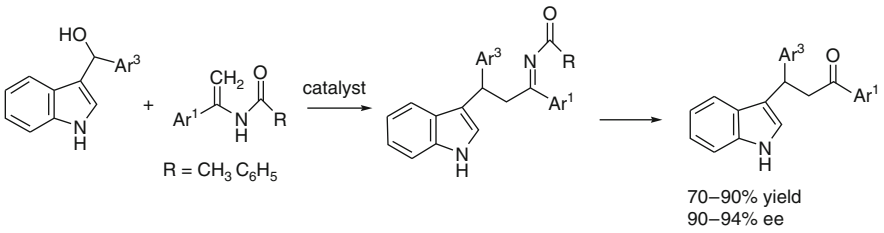


6.6 Other Conjugate Addition Reactions

Piersanti and coworkers explored the effectiveness of a range of Lewis acids in promoting alkylation of indole by methyl α-acetamidoacrylate. This led not only to successful β-addition but also to α-addition (amidoalkylation, see Sect. 7). Ethylaluminum dichloride (two equiv.) and $ZrCl_4$ were the most effective in giving the β-adduct, while several "soft" Lewis acids, of which $Bi(OTf)_3$ was most practical, gave the α-adducts. 1-Methylindole and several C-5 analogs showed the same selectivity [292].

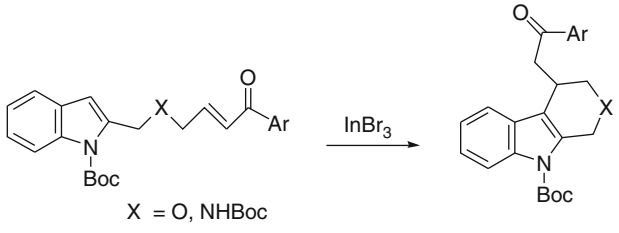


A related reaction involves the use of aryl indole-3-carbinols with enamides. Under the influence of acid catalysts the carbinols generate electrophiles. The adducts hydrolyze to products that are the equivalent of conjugate addition to 1,3-diaryl propenones. These reactions can be done in up to 90% ee with chiral BINOL-phosphoric acid catalysts [293].

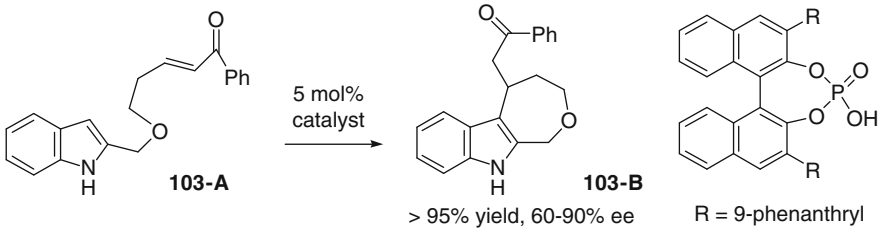


6.7 Intramolecular Conjugate Addition

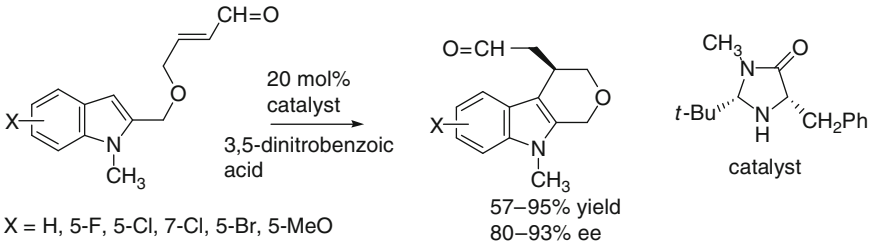
Both β-carbolines and the corresponding oxa analogs have been obtained by $InBr_3$-catalyzed intramolecular addition reactions [294].



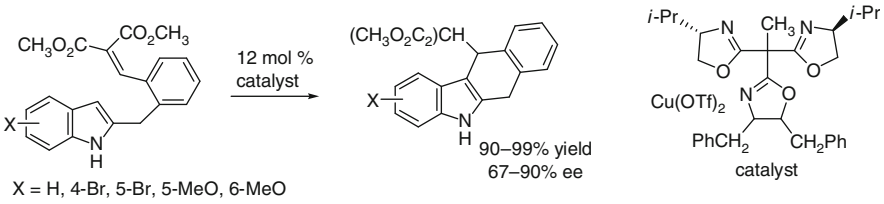
The cyclization of **103-A** exhibits some enantioselectivity when conducted with a BINOL-phosphoric acid [295].



Similar α, β-unsaturated aldehydes have been cyclized by iminium-type catalysis [296].



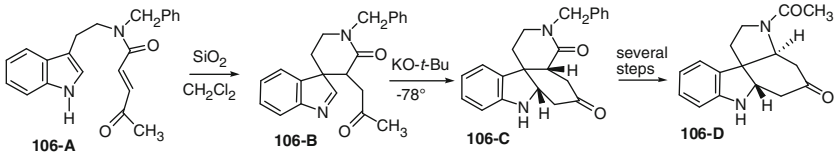
Benzylidene malonate esters have also been subjected to enantioselective cyclization [297].



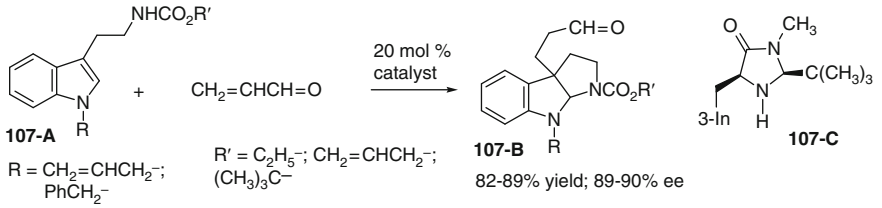
6.8 *Conjugate Addition with Intramolecular Nucleophilic Capture*

As with other electrophilic substitutions, conjugate addition can be used in conjunction with nucleophilic capture of an indolenine intermediate. Marko and coworkers used such a reaction to synthesize a versatile intermediate in alkaloid synthesis [298]. The amide **106-A** cyclized to **106-B**, when exposed to SiO_2 in CH_2Cl_2. The nucleophilic addition was then conducted in a separate step. The

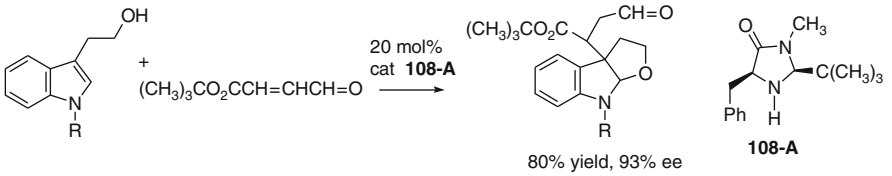
product was taken on to **106-D** by contraction of the C-ring.



Iminium ion catalysts have been used to achieve enantioselective alkylation combined with cyclization. Protected tryptamines react with acrolein under the influence of catalysts **107-C** [299]. Various acroleins with electron-withdrawing substituents at C-3 are also reactive.



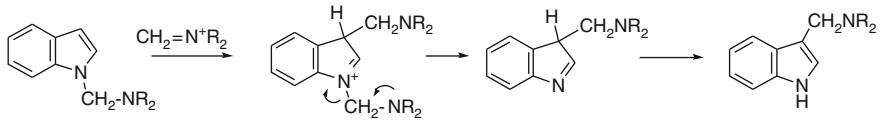
Tryptophols undergo similar reactions.



7 Aminoalkylation (The Mannich Reaction) and Amidoalkylation

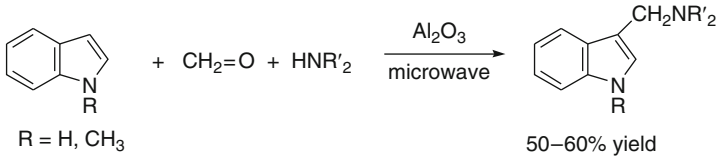
Alkylation by iminium ions, the Mannich reaction, is a mainstay in synthesis of many kinds of indoles. The simplest example, reaction with formaldehyde and dimethylamine, forms gramine, an important synthetic intermediate. This reaction can be conducted to prepare primarily the 1-substituted "isogramine" or the 3-substituted product gramine. Isogramine is formed in aqueous solution, whereas reaction in acetic acid gives gramine [300, 301]. Isogramine is converted to gramine by heating in water or exposure to acid. The mechanism of this isomerization presents a bit of a puzzle, since 1-(aminomethyl)indoles are not easily cleaved by acid. It may be that the 1-alkylation in aqueous solution occurs via an indole anion

as the kinetically preferred nucleophile. In acidic solution, the rearrangement may involve formation of the 1,3-*bis*-substituted indolenine intermediate, and be driven forward by the greater stability of the 3-substituted product.

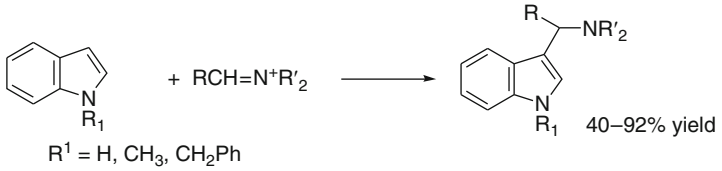


7.1 *Modified Reaction Conditions*

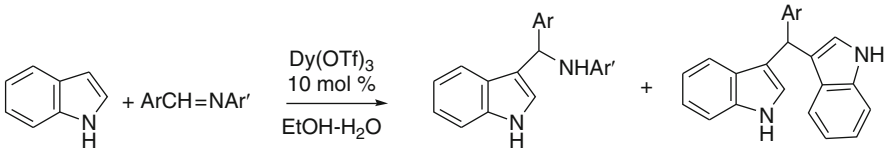
A number of variations in reaction conditions have been explored. Indole and 1-methylindole can be condensed with formaldehyde and secondary amines in the presence of alumina with microwave heating [302].



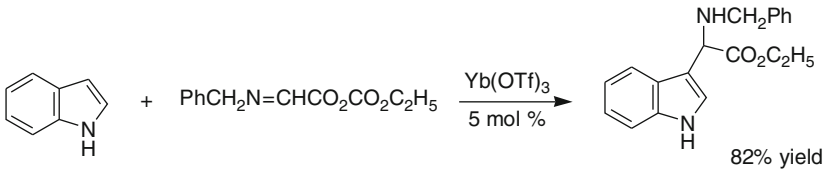
Preformed iminium hydrochloride salts derived from benzaldehyde or isobutyraldehyde give good yields from indole and its 1-methyl or 1-benzyl derivatives [303].



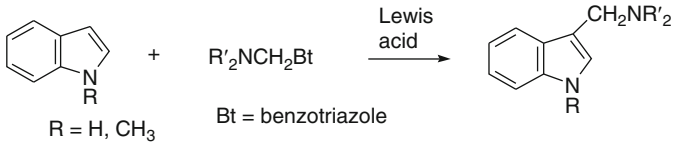
Preformed imines of *bis-C,N*-diarylimines react to give primary amines (60–80% yield), accompanied by small amounts of aryl-*bis*-(indol-3-yl)methanes, in the presence of $Dy(OTf)_3$ or other lanthanide salts [304].



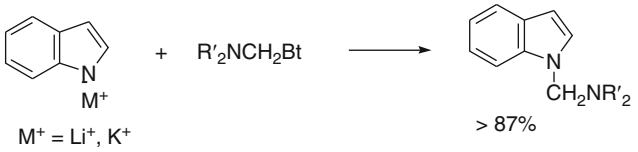
The imine preformed from benzylamine and ethyl glyoxylate alkylates indole, its 1-, and 2-methyl analogs and other derivatives in the presence of catalytic Yb $(OTf)_3$ [305].



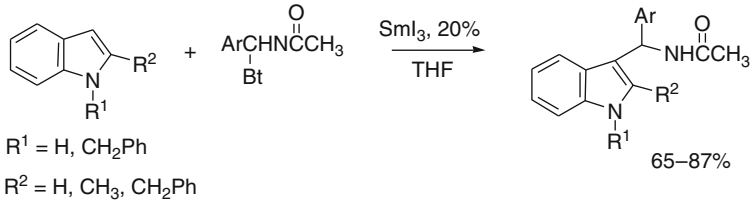
1-(Aminomethyl)benzotriazoles can be used as stable precursors of the iminium ion electrophiles. In the presence of Lewis acids such as $AlCl_3$ or $ZnCl_2$, the 3-(aminomethyl)-indoles are formed. The synthesis is applicable to secondary amines, in which case the $ZnCl_2$ catalyst is best [306].



N-Deprotonated indole anions give the 1-substituted indoles with these reagents [307].



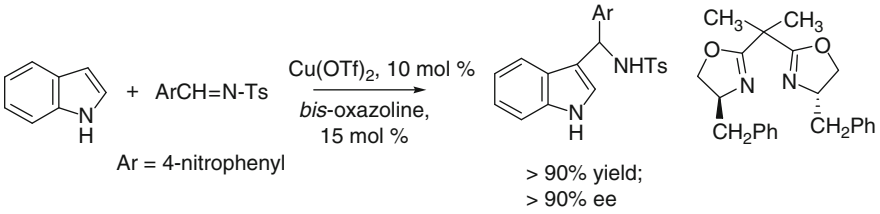
Amidoalkylation has also been carried out using benzotriazole derivatives. The reaction was best done with 20 mol % SmI_3 in THF. These conditions are limited to preparation of α-aryl derivatives [308].



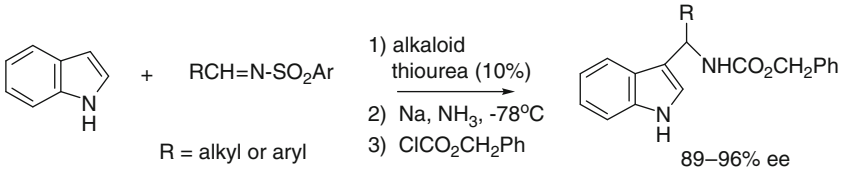
7.2 *Enantioselective Reaction Conditions*

Various chiral catalysts have been explored in the search for enantioselective aminoalkylation. Zhou and coworkers used *bis*-oxazolines with *N*-tosyl-C-arylimines. The best results were obtained with a dibenzyl *bis*-oxazoline in the presence

of $Cu(OTf)_2$. Both yields and ee exceeded 90% in the presence of a fivefold excess of indole [309]. The sulfonyl group is believed to play a critical role in the reactive complex, as the corresponding *N*-phenyl imine gave only racemic product.

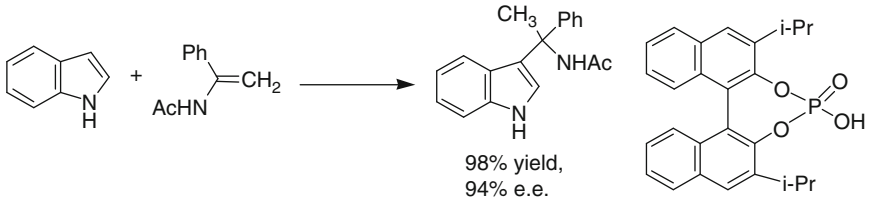


Deng and coworkers used *N*-arenesulfonyl imines and employed modified cinchona alkaloids as the chiral agent. The best catalysts were thiourea derivative of quinidine and quinine. These conditions proved to be applicable to C-alkyl as well as C-aryl imines. The products can be desulfonylated and then isolated as the Cbz derivatives without loss of stereochemical integrity [310].



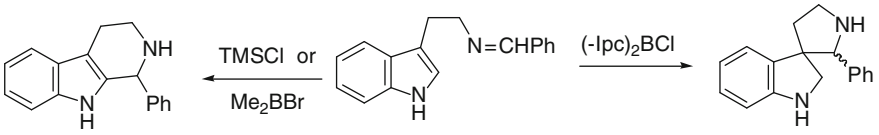
Excellent enantioselectivity has also been obtained using 3,3′-*bis*-(1-naphthyl) BINOL-phosphoric acids [311]. *N*-Tosyl imines of aryl aldehydes were also examined using a binaphthyl Pd(II) carbene complex as the catalyst. Enantioselectivity in the 50–75% range was obtained [312]. Imines formed from α-phenylethylamine and ethyl 3,3,3-trifluoropyruvate give adducts with 85–97% de in the presence of TFA [313]. The chiral auxiliary can be removed by hydrogenolysis.

An enantioselective version of the amidoalkylation reaction has been achieved using α-acetamidostyrene and chiral phosphoric acids. The highest ee was observed with sterically demanding acids. The reaction failed when the indole nitrogen was methylated, suggesting that the hydrogen bond is an important part of the reactive complex [314].

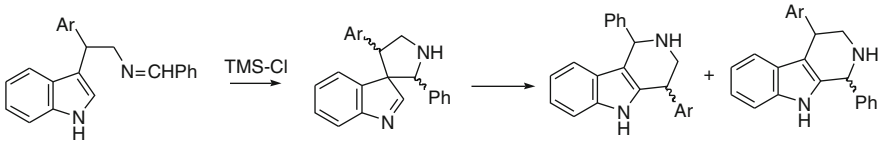


7.3 *Intramolecular Aminoalkylation: The Pictet–Spengler Reaction*

The intramolecular aminoalkylation of tryptamines is an example of the Pictet–Spengler reaction and has been used extensively in the synthesis of indole derivatives, particularly β-carbolines and alkaloids [315]. As with intramolecular alkylation, there is evidence that the Pictet–Spengler reactions can occur by initial attack at C-3 to form a *spiro*-indolenine intermediate [316]. The high migratory tendency of the aminoalkyl group favors its migration to the 2-position [317]. Isolation of the *spiro* structure therefore requires some form of trapping. Hino and coworkers observed reductive trapping when $[(-)\text{Ipc}]_2\text{Cl}$ was used as a Lewis acid in cyclization of *N*-benzylidene tryptamine, whereas other Lewis acids gave the β-carboline [318].

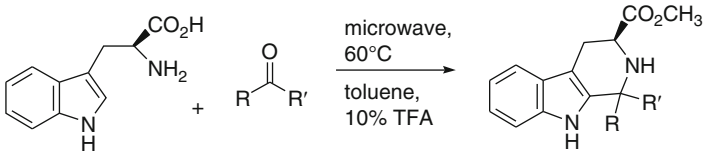


Evidence of the *spiro*-indolenine mechanism also comes from the cyclization of certain α-aryl tryptamines with aromatic aldehydes. In the case of aryl substituents that are particularly electron-rich (3,4-dimethoxy; 3,4-methylenedioxy), isomeric tetrahydro-γ-carbolines resulting from the competing migration of the electron-rich benzyl group predominate in a ratio of about 4:1 [319].



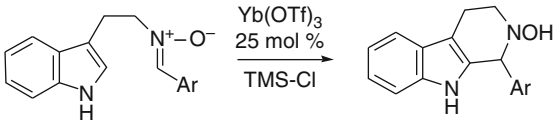
Ar = 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl

Microwave conditions are useful in condensing L-tryptophan with ketones, which react only slowly under conventional conditions [320].



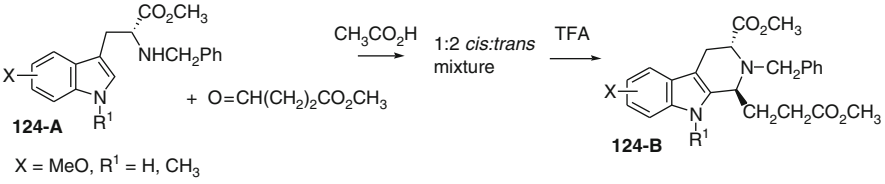
R, R′ = CH_3, C_2H_5, $CH(CH_3)_2$,
Ph, $-(CH_2)_n-$

Nitrones are also satisfactory reactants for Pictet–Spengler cyclization with tryptamine. Among the reagents used for cyclization are $Yb(OTf)_3$-TMS-Cl [321].



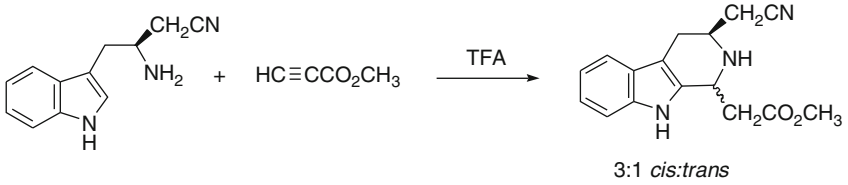
7.3.1 Stereoselectivity in the Pictet–Spengler Reaction

During the 1990s the stereoselectivity of the Pictet–Spengler reaction came into focus and this facilitated its use in stereo-controlled synthesis. Recently, emphasis has turned to the use of versatile intermediates that provide enantioselective synthesis of alkaloids and analogs. One such approach has been developed by Cook and coworkers and used to prepare alkaloids of the ajmaline and sarpagine types [322–326]. The approach is applicable to all of the C-ring methoxy series, as well as to the unsubstituted indoles. The key intermediate is the *trans*-1,3-β-carboline **124-B**, which is prepared from D-tryptophan. The Pictet–Spengler cyclization is followed by a *trans*-selective epimerization at C-1, which is thought to proceed through a C-1-N ionization [327].



Synthetic routes have been developed to several 9-methoxy (indole-4) [328] and 12-methoxy (indole-7) [329] alkaloids, starting with the corresponding D-methoxytryptophan.

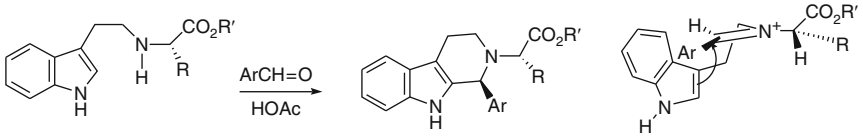
Bailey and coworkers have explored the stereoselectivity of the Pictet–Spengler reaction with L-tryptophan esters [330]. They found that use of TFA could effect kinetically-controlled cyclization. For 1,3-disubstituted β-carbolines, the preference was for the *cis*-1,3 product (diequatorial). For 1,2,3-trisubstituted (*N*-benzyl) analogs, the kinetic preference is for *cis*-1,3-diaxial product. A particularly useful derivative was obtained by converting the ester group to cyanomethyl. Originally the cyanomethyl derivative was cyclized via the enamide prepared from methyl propiolate, and gave a 3:1 *cis:trans* ratio [331].



Later, conditions were found that provided complete stereoselectivity for the *cis*-1,3 β-carboline. The two substituent groups are then used to construct the remainder of the alkaloid skeletons [332].

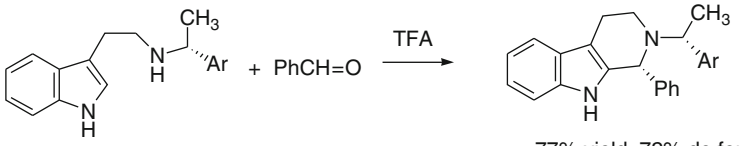
This intermediate was used to prepare several indole alkaloids of the ajmaline-sarpagine group [333]. The method has also been used to synthesize examples of the fumitremorgin group [334]. Lewis has summarized application of these and other methods to alkaloid synthesis [335].

N-(α-Carboxyalkyl)tryptamines can be prepared by alkylation of α-amino acid ester by tryptophyl bromide. The chirality of the amino acid unit directs diastereoselectivity in the range of 70–98% for cyclization with a variety of aromatic aldehydes. The best selectivity is obtained with relatively bulky amino acid substituents, as for valine and isoleucine. The reactions appear to occur under kinetic control and the stereoselectivity is consistent with the sterically preferred Felkin–Ahn transition state [336].



dr = 70:30 - 98.5:1.5

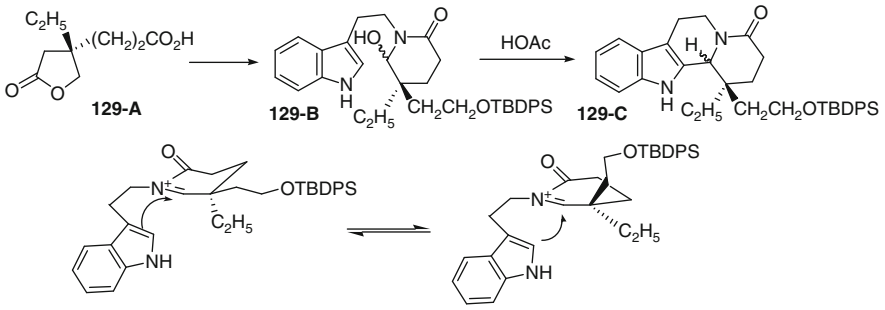
Enantioselective cyclizations have also been achieved using chiral auxiliaries. N^b-Benzyl groups have been used. The α-phenylethyl [337] and α-naphthylethyl [338] groups achieved diastereoselectivity in the 60–80% range in acid-catalyzed reactions with aromatic aldehydes. The diastereomer with *syn* orientation of the phenyl and aryl substituents is preferred and this appears to be the result of thermodynamic control.



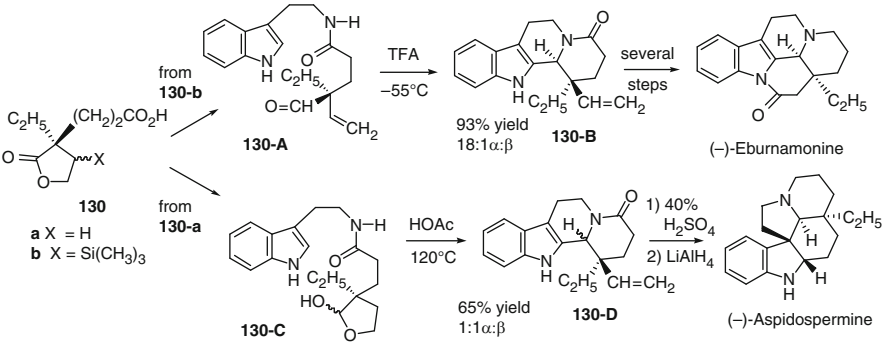
77% yield, 72% de for Ar = Ph
72% yield, 86% de for Ar = naphthyl

Chiral 4-ethyl butyrolactone derivatives can be prepared by carbene insertion reactions. Coupling with tryptamine and oxidation state adjustment gives access to

the carbinolamide **129-B**. This intermediate can be cyclized to a 1:2 mixture of the C-12b-H stereoisomers, which were taken on to (−) eburnamonine and (+)-*epi*-eburnamonine. The cyclization presumably occurs through the acyliminium intermediate and exhibits a rather modest steric discrimination [339].



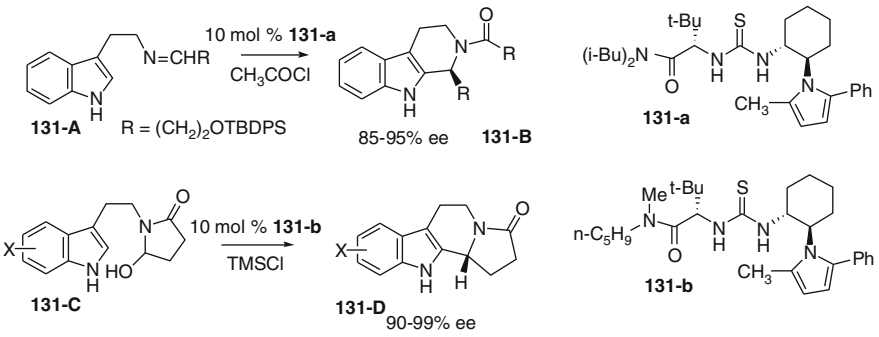
Another route to chiral lactones **130-a** and **130-b** was employed by Schultz and Pettus in the synthesis of (−)-eburnamonine and (−)-aspidospermidine [340]. In the case of (−)-eburnamonine the cyclization was carried out on the aldehyde **130-A,** and yielded the product with 18:1 selectivity for the desired α-stereoisomer. For (−)-aspidospermidine, the cyclization of **130-C** was done in refluxing acetic acid, yielding a 1:1 mixture of stereoisomers. The product was taken on to (−)-aspidospermine by an acid-catalyzed rearrangement (40% H_2SO_4, 100–110°C). The reason for the considerable difference in stereoselectivity of the two Pictet–Spengler cyclizations is not clear.



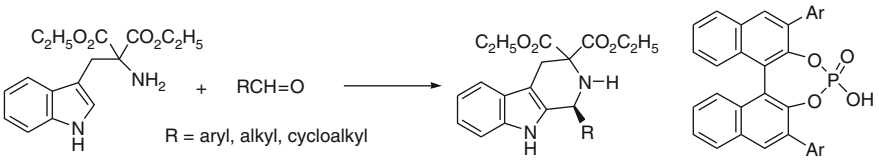
7.3.2 Enantioselective Catalysis of the Pictet–Spengler Reaction

Strictly catalytic enantioselective Pictet–Spengler cyclizations of tryptamine imines have been rather elusive to date. The most successful results were achieved with *N*-acyliminium intermediates and thiourea catalysts. The reactions proceed through

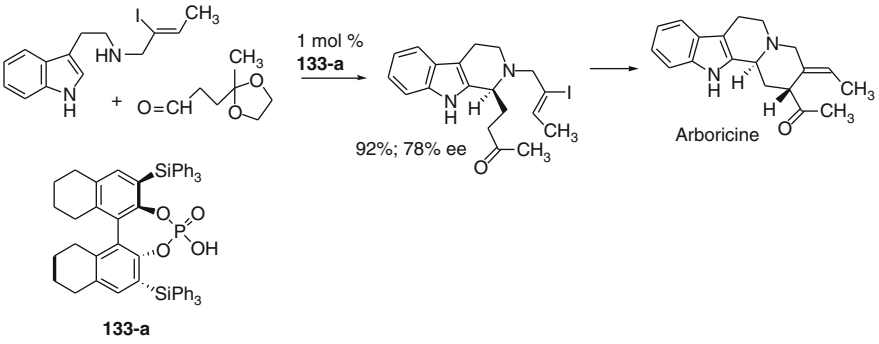
acyliminium ion intermediates generated using acetyl chloride. High enantioselectivity has been found with both acyclic [341] and cyclic [342] acyliminium species using catalyst **131-b**. A β-carboline intermediate **131-B** prepared by this method was used to synthesize (+)-yohimbine [343].



Highly substituted BINOL-phosphoric acids give good (70–95%) enantioselectivity with *bis*-(ethoxycarbonyl)tryptamines but tryptamine itself is unreactive [344].

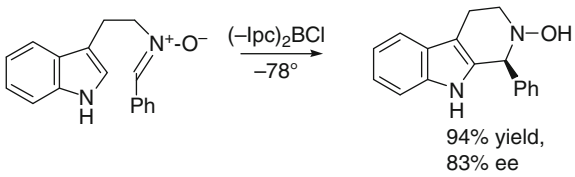


BINOL-phosphoric acids have been used successfully with N-substituted tryptamines [345]. The chiral acid catalysis of the Pictet–Spengler cyclization has been applied to alkaloid synthesis, as in the case of (−)-arboricine [346].



An enantioselective version of the Pictet–Spengler reaction has been achieved using nitrones formed from N^b-hydroxytryptamines by using chiral chloroboranes

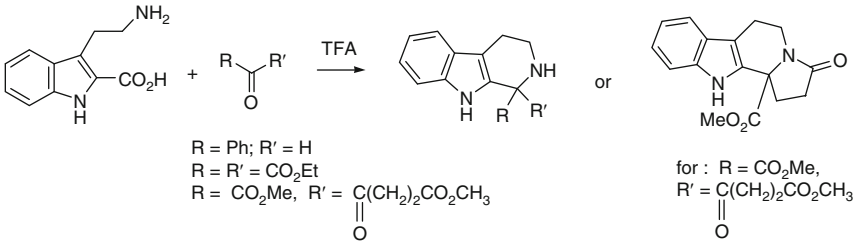
as Lewis acids. High yields and up to 85% ee were obtained using two equiv. of the borane [347].



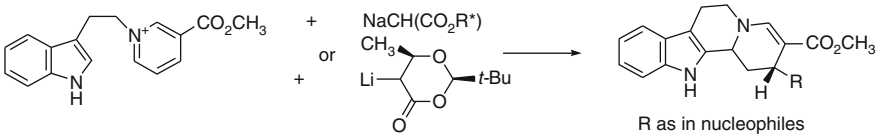
These reaction conditions were also applicable to substituted aryl and alkyl (Me, *t*-Bu) nitrones, although enantioselectivity was reduced for the latter (~40%). Enantioselectivity was also found using chiral *bis*-BINOL-boric acids (two equiv.).

7.3.3 Other Synthetic Applications of the Pictet–Spengler Reaction

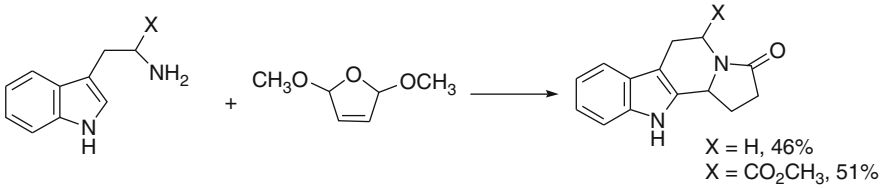
Another version of the Pictet–Spengler reaction uses 2-carboxytryptamines. The reaction is carried out in organic solvent mixtures with TFA as the acid catalyst. The reactions proceed by *ipso* substitution at C-2, followed by decarboxylation. When used with the dimethyl ester of α-ketoglutaric acid, lactams that are useful intermediates in alkaloid synthesis are formed [348].



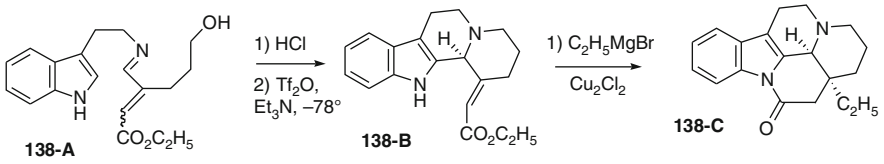
N-(2-Indol-3-ylethyl)pyridinium ions can be converted to iminium ions that undergo cycloaddition by addition of nucleophiles at C-4 of the pyridine ring. Two chiral nucleophiles have been explored. The anions of *bis*-8-phenylmenthyl malonate or 2-(*t*-butyl)-6-methyl-1,3-dioxolan-3-one gave moderate yields, the latter with complete diastereoselectivity. The adduct was taken on to the alkaloids (+)-vallesiachotamine and (−)-isovallesiachotamine [349].



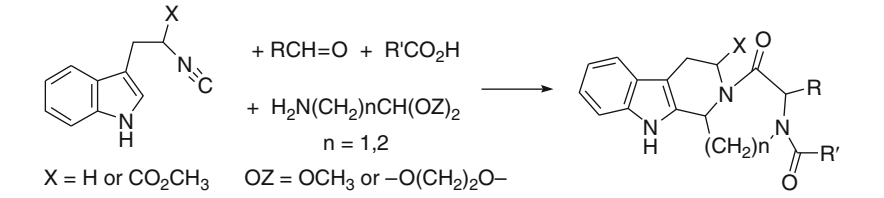
2,5-Dimethoxy-2,5-dihydrofuran serves as a 3-formylpropionate equivalent in Pictet–Spengler reactions with tryptamine and methyl tryptophanate [350].



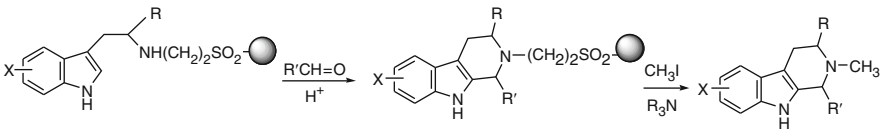
A short synthesis of (±)-eburnamonine, proceeds through the imine **138-A**, which is prepared readily in two steps from dihydropyran, ethyl glyoxylate and tryptamine [351].



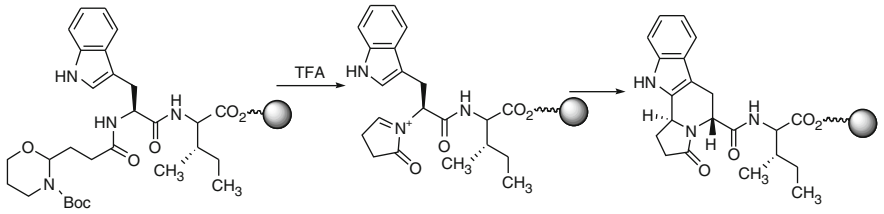
The Pictet–Spengler reaction has been combined with Ugi multi-component chemistry to construct a number of polycyclic indoles. Isonitrile derivatives prepared from tryptamine (or methyl tryptophanate), a carboxylic acid and formaldehyde condense with aminoacetaldehyde diethyl acetal. A few examples employed substituted aldehydes [352].



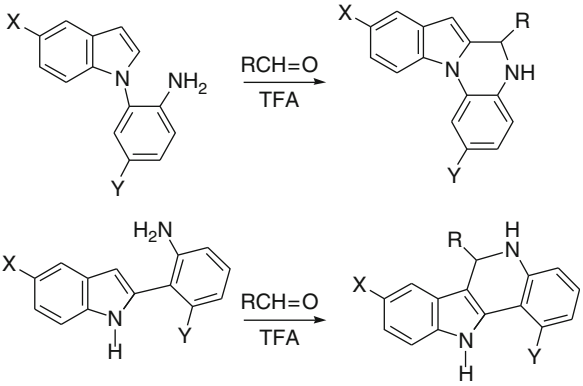
Substituted tryptamines have been used as starting materials in solid-phase synthesis of β-carboline libraries. One strategy for linking to the resin is through vinylsulfonyl groups. The β-carboline and modified analogs can be released by quaternization and elimination [353, 354].



Tryptophan-isoleucine dipeptide linked to PEGA resin was acylated with Boc-protected 3-(1,3-oxazinyl)propanoic acid. Exposure of the material to TFA generates acyliminium ions that cyclize to β-carbolines, with a preference for the *trans*-stereoisomer [355]. The modified dipeptides were cleaved from the resin with a base.



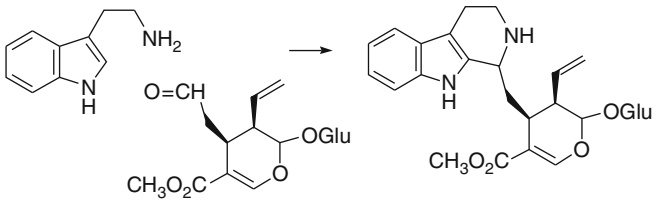
Although the tryptamine-to-β-carboline transformation is the most prevalent example of the Pictet–Spengler intramolecular aminoalkylation reaction in the indole series, it is by no means the only pattern. For example, Kundu and coworkers used 1- and 2-(2-aminophenyl)indoles to form tetracyclic systems by cyclization at C-2 and C-3, respectively [356].



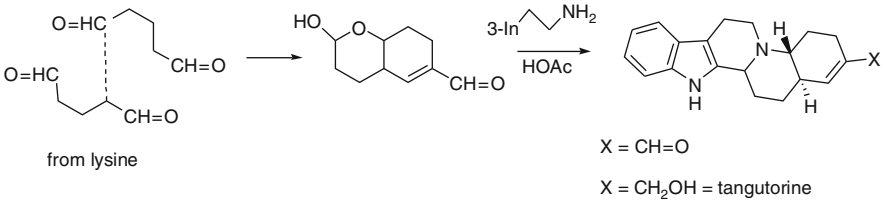
7.3.4 Biological Equivalents of the Pictet–Spengler Reaction

A key step in indole alkaloid biosynthesis is the formation of strictosidine from tryptamine and the aldehyde secologanin [357, 358]. This reaction is catalyzed by the enzyme strictosidine synthase. The crystal structure of the enzyme has been determined and the binding site identified [359]. Site-directed mutagenesis has been used to identify both the active site amino acids and to modify the substrate specificity of the enzyme [360]. The enzymatic mechanism has been compared with the H^+-catalyzed reaction in solution and they appear to be similar, based on

pH dependence and kinetic isotope effects [361]. Computational modeling of the intermediate iminium ion and 2- and 3-(*spiro*-indolenine) substitution intermediates suggests that the cyclization occurs directly at C-2.

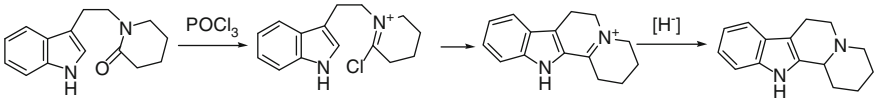


A biological equivalent of a Pictet–Spengler reaction has been proposed to account for the formation of tangutorine, a racemic alkaloid isolated from a *Nitraria* species. Alkaloids in this species appear to be derived from lysine and a dimeric condensation product of glutaraldehyde is a biomimetic analog. When this material was synthesized and allowed to react with tryptamine, a tangutorine structure was obtained and was converted to material identical to the natural product [362].

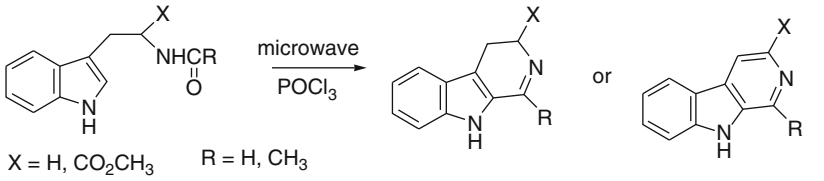


7.4 The Bischler–Napieralski Reaction

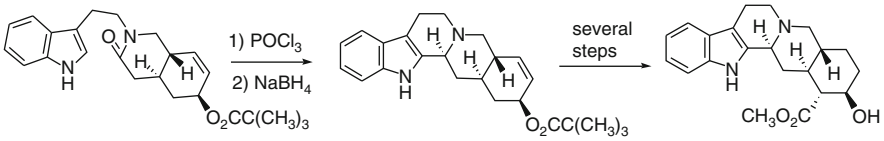
Tryptamine cyclization can also be conducted at the amide oxidation level, which is an example of Bischler–Napieralski reaction. The usual reagent is $POCl_3$, which generates a chloroiminium ion intermediate. The immediate products of cyclization are iminium ions, which are typically then reduced.



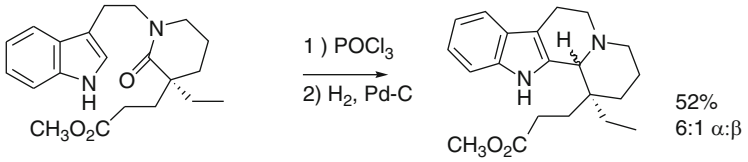
Bischler–Napieralski cyclization of N^b-formyl and N^b-acetyltryptamine has been carried out with microwave heating the reactant and $POCl_3$ adsorbed on silica [363].



As with the Pictet–Spengler reaction, the Bischler–Napieralski cyclization has been used in alkaloid synthesis. For example, a synthesis of yohimbine and related alkaloids began with enantiomerically pure amide [364].



Other examples of alkaloids recently synthesized by Bischler–Napieraski cyclizations include (−)-vincamine [365].

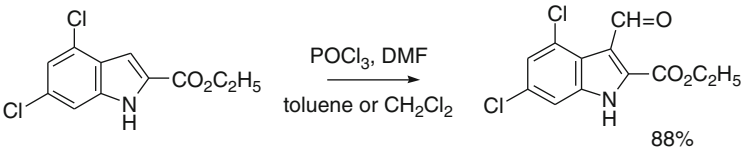


8 Acylation

8.1 C-3 Acylation

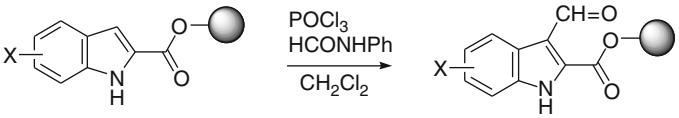
8.1.1 Formylation and Acylation Under Vilsmeier–Haack Condition

The most generally reliable method for acylating indoles in the 3-position is the Vilsmeier–Haack reaction using an amide and $POCl_3$. Many examples of indole acylation under Vilsmeier–Haack conditions are cited in reviews of the reaction [366, 367]. *Organic Syntheses* contains an example of the synthesis of indole-3-carboxaldehyde [368]. The efficiency of the reaction is due to the high reactivity of the indole ring. For the most part, Vilsmeier–Haack conditions give good regioselectivity for the 3-position, even in the presence of an electron-withdrawing substituent at C-2. For example, ethyl 4,6-dichloroindole-2-carboxylate gave the 3-carboxaldehyde in 88% yield on a kilogram scale [369].



In contrast, with 5,7-dimethoxyindole, the activated C-ring competes with the 3-position in acylation reactions and formylation gives a 2:1 mixture of the 3- and 4-products in 99% yield [370]. This reaction can easily be pushed to the 3,4-dialdehyde by warming (93% yield). Acetylation with *N*,*N*-dimethylacetamide gives a similar mixture in somewhat lower yield. A 2-carbomethoxy group shifts the favored position to C-4. 3-Methyl- and 2,3-dimethylindole give the *N*-formyl derivatives as the main products [371].

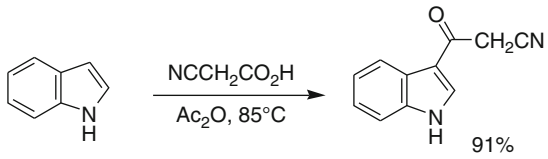
Vilsmeier–Haack formylation was used successfully to formylate a series of indole-2-carboxylic acids bound to Merrifield resin [372].



X = H, 5-NO_2, 5-CH_3O
5-Cl, 4,6-di-Cl

8.1.2 Acylation Using Carboxylic Acids, Anhydrides and Acyl Chlorides

Another indication of the high reactivity of the indole ring toward acylation is its conversion to the 1,3-diacetyl derivative in refluxing acetic anhydride (24 h), and the isolation of 3-acetylindole in 40% yield after hydrolysis of the *N*-acetyl group [373]. A simple procedure for cyanoacetylation of indole and its 1-, 2-methyl and other derivatives has been reported. The indole is added to a warm (85°C) 10:1 solution of acetic anhydride:cyanoacetic acid. The reaction presumably proceeds via the mixed anhydride and the enhanced reactivity of the cyano-substituted group leads to complete selectivity [374].

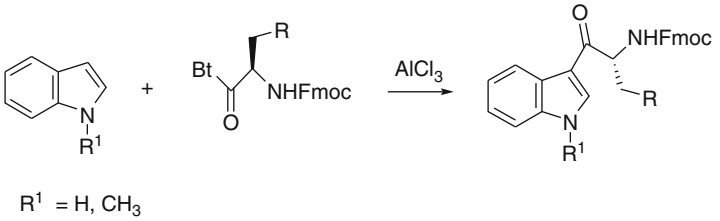


Methanesulfonylacetic acid gives an analogous product (92%), so the process may be general for acetic acids substituted by strong electron-withdrawing groups.

Oxalyl chloride acylates indole to the 3-glyoxyl chloride derivative. This is a very useful reaction because it opens a route to various tryptamine derivatives by $LiAlH_4$ reduction [375]. Condition for very rapid reduction (5 min), have been developed using microwave acceleration and this method is useful in preparing isotopically labeled analogs [376]. The indole-3-glyoxamide structure has emerged as a pharmacophore in its own right. Extensive examinations of these compounds as agonists of the peripheral benzodiazepine receptor have shown nonsedative anxiolytic activity [377–384]. Other series of glyxoxamides proved to be inhibitors of HIV-1 attachment to CD4 cell receptors [385, 386] and antibacterials [387].

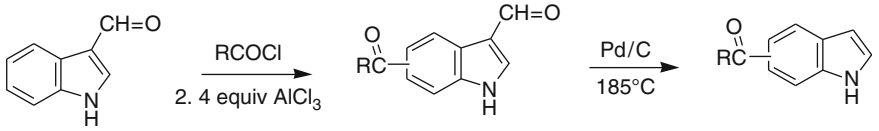
8.1.3 Other Acylating Reagents

Fmoc-protected α-aminoacyl benzotriazoles have been used to acylate 1-methylindole and then converted to short peptides by coupling methods [388].



8.2 C-Ring Acylation

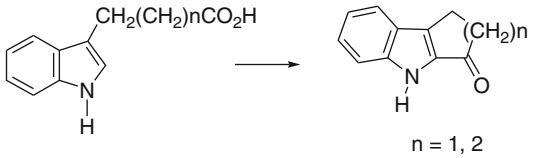
As indicated above, activating substituents can shift acylation to the C-ring. Indoles acylated in the C-ring were obtained by $AlCl_3$-mediated acylation of indole-3-carboxaldehyde, followed by Pd/C catalyzed decarbonylation. The reactions required use of a twofold ratio of the $AlCl_3$, suggesting that the aldehyde is complexed with $AlCl_3$. The product mixtures of 5- and 6-isomers typically favored the former by 3:1, with smaller amounts of the 7-isomer also being formed [389].



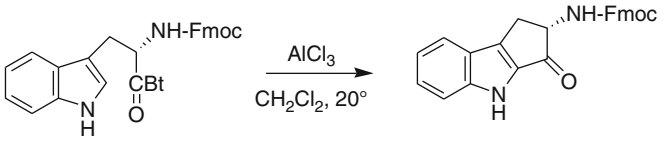
8.3 Intramolecular Acylation

New conditions for intramolecular acylation of indoles have been found in the course of exploration of intramolecular Friedel–Crafts acylation of 3- and

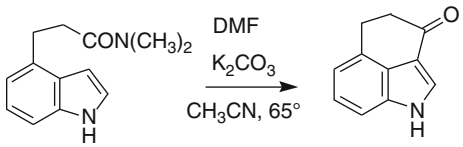
4-(indoly-3-yl)alkanoic acids. 4-(3-Indolyl)butanoic acid is converted to 1-oxo-1,2,3,4-tetrahydrocarbazole in 81% yield using 1 mol % $Bi(NTf)_3$ at 180° [390]. 3-(3-Indolyl)propanoic acid gives the corresponding indanone with $Tb(OTf)_3$ at 250° under sealed tube conditions [391].



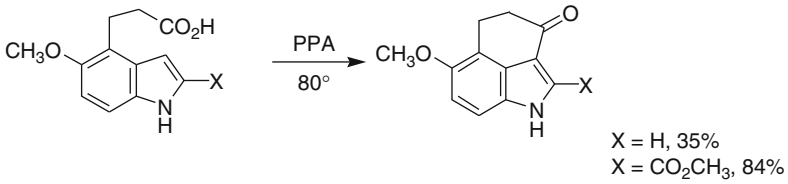
The benzotriazole amide of Fmoc-protected tryptophan is cyclized to the corresponding 2-acyl derivative by $AlCl_3$ [388].



Another area of activity has been the synthesis of the ergot alkaloids, where the c,d-fused ring can be introduced by intramolecular acylation [392]. The [4-3] cyclization has been done under Vilsmeier–Haack conditions by several groups. The most recently optimized conditions report a 74% yield in a reaction system that includes K_2CO_3 [393].

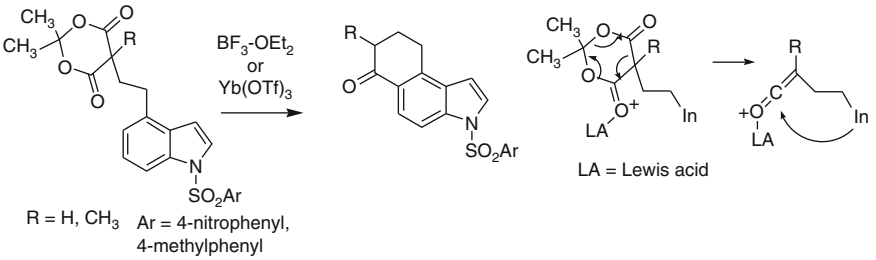


5-Methoxyindole-4-propanoic acid cyclizes to C-3 in 35% yield in PPA at 80°C, while the 2-carbomethoxy derivative gives an 84% yield [394].



Meldrum's acid derivatives have been introduced as readily available precursors for intramolecular acylation. 5-Substituted *N*-(arylsulfonyl)indoles cyclize to C-5 in the presence of BF_3-OEt_2 [395]. Similar cyclizations can also be effected using

$Yb(OTf)_3$. More elaborate structures have also been cyclized. The active acylating agents are presumably ketenes [396].



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Reactions of Indole with Nucleophiles

Tara L.S. Kishbaugh

Abstract While indole naturally tends to act as a nucleophile, there are numerous examples of nucleophilic substitutions as well as nucleophilic additions to the indole ring system.

Keywords Indole · Nucleophilic addition · Nucleophilic substitution

Contents

1 Introduction

Indole is a π-excessive heterocyclic ring system and, as such, it is more likely to act as a nucleophile than as an electrophile. Despite this tendency, there are numerous examples of nucleophilic additions and substitutions on indoles, including a few

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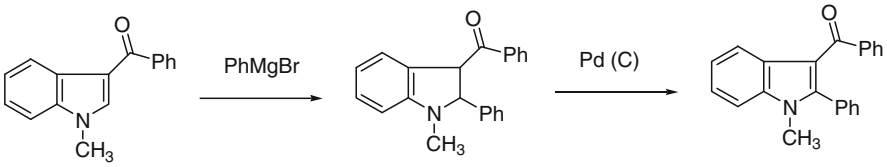
examples described in reviews [1–4]. In fact, the addition of Grignard reagents to indoles was documented as early as 1962, when it was reported that phenylmagnesium bromide adds to 1-methyl-3-benzoylindole (**1**) forming the Michael adduct, 1-methyl-2-phenyl-3-benzoylindoline (**2**), instead of the expected product from addition to the carbonyl [5]. The indoline **2** was treated with palladium on carbon at reflux in *p*-cymene to produce the indole **3** in 33% yield. This example is striking in that the nitrogen is not protected with an electron-withdrawing group, which is often the case in more recent examples.



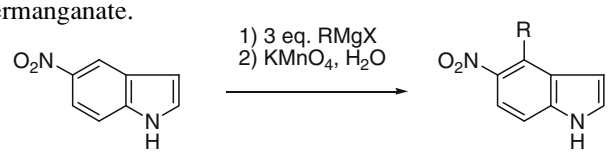
1 **2** (78%) **3** (33%)

Primarily, indole is made more susceptible to participation in nucleophilic substitution or addition reactions by the placement of electron-withdrawing groups (often nitro) at various locations on the ring. While most examples have electron-withdrawing groups at C-2, C-3-, and/or N-1, there are several instances where placement of the electron-withdrawing group on the benzene ring of indole results in nucleophilic addition or substitution at C-4, C-5, C-6, and C-7. One set of indoles that are very reactive to nucleophilic substitution reactions are the *N*-hydroxyindoles. As Somei has recently written a comprehensive review of the chemistry of the hydroxyindoles, this chapter will only mention them briefly [3].

2 Nucleophilic Additions to Indoles

2.1 Nucleophilic Additions to Nitroindoles

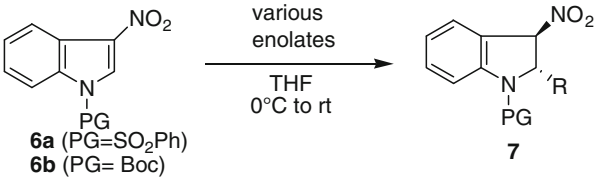
Since the first example of Grignard addition to indoles, many electron-withdrawing groups have been used to activate indole towards nucleophilic additions, but often nitro groups have been the groups of choice. For example, in another early example of nucleophilic additions to indole, Bartoli et al. studied the addition of Grignard reagents to nitroarenes, including 5-nitroindole (**4**) [6]. This results in the alkylation of the adjacent position when the reaction mixture is treated with aqueous potassium permanganate.

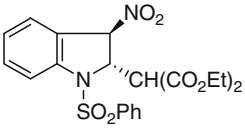
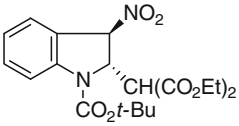
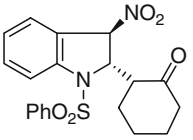
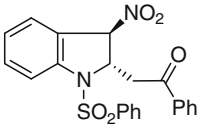


4

5a R = CH_2CH_2Ph (68%)
5b R = n-C_4H_9 (66%)

Table 1 Addition of enolates to form *trans*-2-alkyl-3-nitroindolines



Entry	Product	Yield (%)
1		58
2		64
3		81
4		44

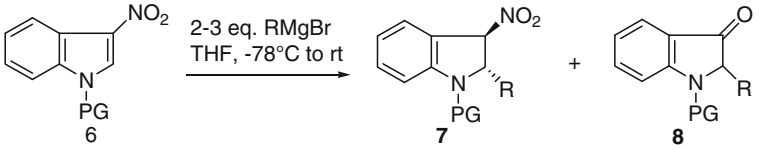
Pelkey and Gribble showed that the enolate of diethyl malonate adds to 3-nitro-1-(phenylsulfonyl)indole (**6a**) at C-2 to form the *trans*-3-nitro-2-substituted indoline **7** [7, 8]. The stereochemistry is confirmed on the basis of coupling constants. Other enolates also add to 3-nitroindoles **6** to form the *trans*-indolines **7** in moderate to good yields [8] (Table 1).

In addition to enolates, Grignard reagents add to 3-nitroindoles **6** to produce the *trans*-2-alkyl-3-nitroindolines **7** in moderate yields [8]. In these examples, the stereochemistry was confirmed by both NMR coupling constants and X-ray crystallography. Indoxyls, which are the result of an in situ Nef reaction, are also isolated in low yields which can be increased to moderate levels (38% of **8** (R = *i*-Pr, PG = SO_2Ph) if reagents such as Ceric Ammonium Nitrate (CAN) are employed to maximize this pathway (Table 2).

2.2 Nucleophilic Additions to α,β-Unsaturated Nitrones

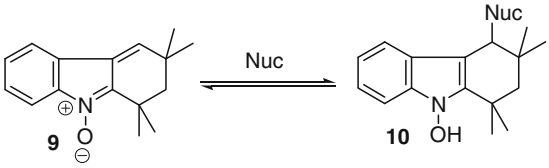
α,β-Unsaturated nitrones based on the indole ring system have been studied for their relevance to the stephacidins and analogs. In a manner similar to the addition

Table 2 *trans*-Indolines and indoxyls produced from addition of Grignards to 3-nitroindoles



Entry	R	PG	Indoline **7** (% yield)	Indoxyl **8** (% yield)
1	Me	SO_2Ph	30	Trace
2	Et	SO_2Ph	41	14
3	Vinyl	SO_2Ph	65	–
4	i-Pr	SO_2Ph	46	13
5	i-Pr	Boc	44	31
6	Vinyl	Boc	78	–

Table 3 Equilibrium ratio of nitrone: hydroxyindoles upon treatment with nucleophiles



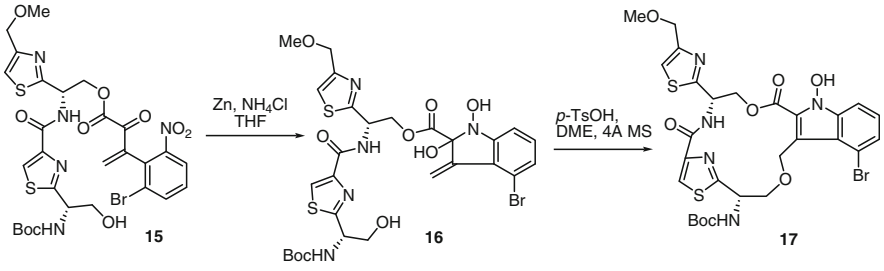
Entry	Nuc	Ratio (**9:10**)
1	Methanol	1:2
2	Sodium methoxide	1:100
3	*p*-Methoxybenzenethiol	0:100
4	Thiophenol	1:9

of Grignard and alkyl lithium reagents to the nitrone tautomer of *N*-hydroxyindole [9], these α,β-unsaturated nitrones undergo Michael addition by a variety of nucleophiles [10–12]. For example, while they were studying routes to avrainvillamide and stephacidin B (a dimer of avrainvillamide), Myers and Herzon found that 3-alkylidene-3*H*-indole-1-oxides undergo reversible nucleophilic addition by alcohols and thiols in the presence of a base but do not react with a variety of nitrogen nucleophiles (such as *n*-propylamine, formamide, 2-pyrrolidine, etc.) [12]. Moreover when they studied the generality of this experiment by adding nucleophiles to nitrones derived from condensation of *E*-cinnamaldehyde and *N*-phenylhydroxylamine, the nucleophilic addition product was not observed, which indicated the rearomatization of the indole product **10** must be important energetically. A question that remains is whether this functionality and reactivity towards nucleophiles is important in the biological activity, namely antiproliferative and antimicrobial activity, of avrainvillamide and its analogs (Table 3).

Nicolaou et al. used the reactivity of α,β-unsaturated nitrones towards nucleophiles to create libraries of compounds relevant to the construction of a model

system for Nocathiacin I, a thiopeptide antibiotic isolated from *Norcardia* sp. and the fungus *Amicolaptosis* sp. [10, 11]. The mechanism of addition is either via a S_N2' displacement on **13** or via 1,5-conjugate addition to the α,β-unsaturated nitrones **12**. The intermediates (**12** or **13**) were not isolated but were captured during the tin dichloride reduction of nitro ketoester **11** in the presence of nucleophiles. A variety of *N*-hydroxyindoles (**14**) were accessible using these conditions. Nitro ketoesters with other substituents (fluorine, ethers, and cyano) were all tolerated with little change to the yield. Primary and secondary alcohols as well as thiols added in good yields (37–87% and 57–75%, respectively), although phenols reacted as carbon nucleophiles. Secondary amines and aniline were not as successful; the yields of nitrogen nucleophiles were modest. However, a number of silyl enol ethers, as well as silanes and stannanes, added to the α,β-unsaturated nitrone in moderate to high yields (31–75%, 20–61%, and 25–63%, respectively). By increasing the number of equivalents of the nucleophile from 1 to 5, the yields can be increased (50–75%) but increasing beyond five equivalents no longer improves the yield. Regardless, the yields are still good even with just one equivalent (Table 4).

This reaction was also studied with a more complicated nitro ketoester starting material [10]. In this example, the nucleophilic addition occurs intramolecularly to form a 15-membered macrocycle. Zinc/ammonium chloride reduction to form the hydroxyindole **16** followed by cyclization provided a better yield of 17 (40% over both steps) than the direct tin dichloride reduction of 15 to macrocycle 17 (10%).

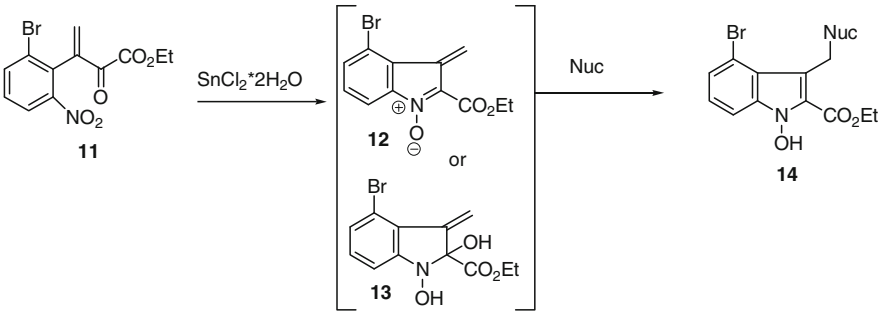


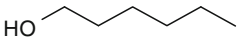
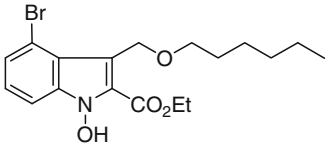
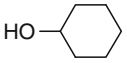
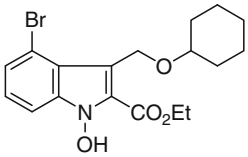
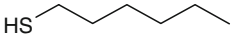
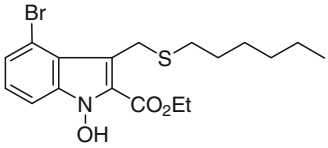
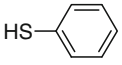
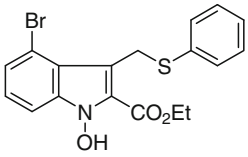
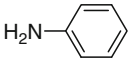
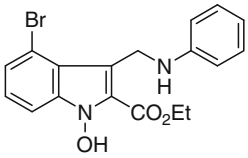
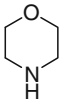
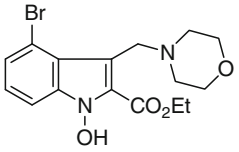
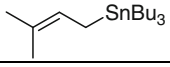
2.3 *Pummerer Reactions to Create Spiro-Indolenines*

Feldman et al. has recently demonstrated the utility of the Pummerer reaction for a controlled oxidative cyclization onto both indole and imidazole rings to produce indolenines and imidazolines [13–20]. There are two possible mechanisms for this reaction, shown in Scheme 1: an additive pathway, where the nucleophile adds to C-3 (path B); or a vinylogous pathway (path A). The question of the mechanism has been studied but neither pathway can be confidently rejected [19].

Asymmetric Pummerer reactions with chiral sulfinates have been moderately successful but avoid pathway A, or more specifically, an achiral thionium ion, although

Table 4 Select examples demonstrating the breadth of *N*-hydroxyindoles possible from reductive cyclization and nucleophilic addition to α,β-unsaturated nitrones



Entry	Nucleophile	Product	Yield (%)
1			54
2			41
3			75
4			68
5			18
6			27
7			62

(*continued*)

Table 4 (continued)

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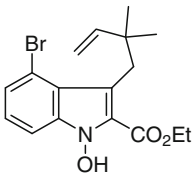
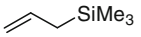
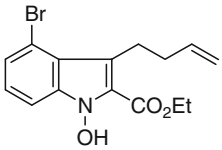
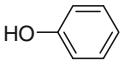
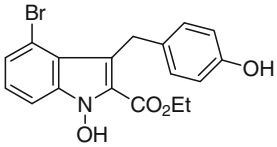
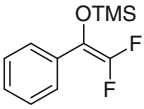
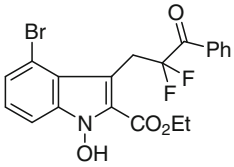
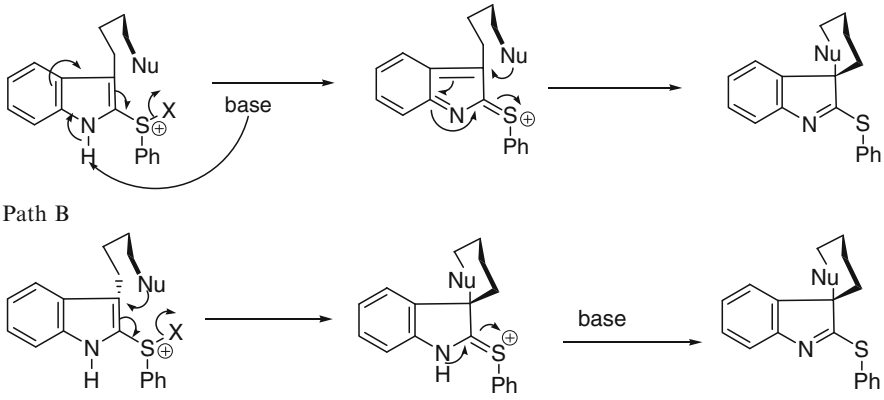
			
8			57
9			40
10			50



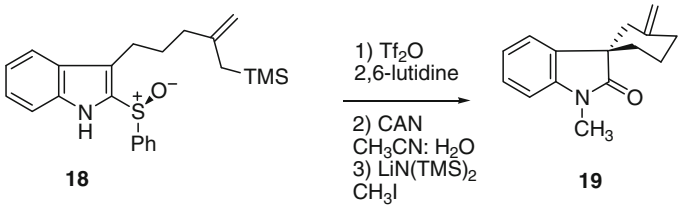
Scheme 1 Possible mechanisms for the Pummerer cyclization to form spiro-indolenines

a tight ion-pair might impart from stereocontrol [19]. Following pathway B, the additive pathway, it should be possible for the chiral sulfur to impart chirality to the newly forming spirocenter. The conversion of chiral indole-2-sulfoxides

(**18, 20**) to spirocyclic indolenines and then to oxindoles (**19, 21**) has been studied. Solvent viscosity and polarity seemed to impact both yield and enantiomeric excess, with toluene being the best choice for silane **18,** while ether is the better solvent for the silylenol ether **20**. Lowering the temperature below −78°C simply stopped the reaction from proceeding for silane **18,** but for the silylenol ether **20**, the enantiomer excess was enhanced with a modest to moderate decrease in yield (Table 5).

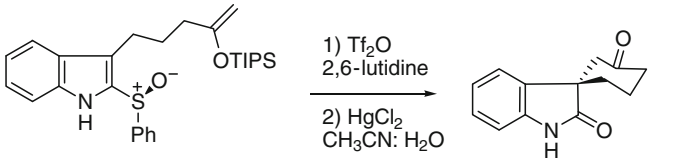
A review of the Pummerer reaction describes much of the breadth of this work [18], but a more recent paper expanded this chemistry to form spirocycles which contain adjacent quaternary carbons [20]. While the test cases (**22** to form the spirocycle **23**) proceeded smoothly, the application to a more complicated structure (**24**), which would be closer to the ring system seen in the natural product, crassanine, demonstrated that a nearby amine would interfere with the addition of the silyl enol ether as a nucleophile. While this precludes the utility of this reaction for the crassanine alkaloids, the unusual ring formed in **25**, a C-3-azetidine spirocyclic indolenine, is found in the chartelline alkaoids.

Table 5 Enantiomeric excess in Pummerer-initiated cyclizations



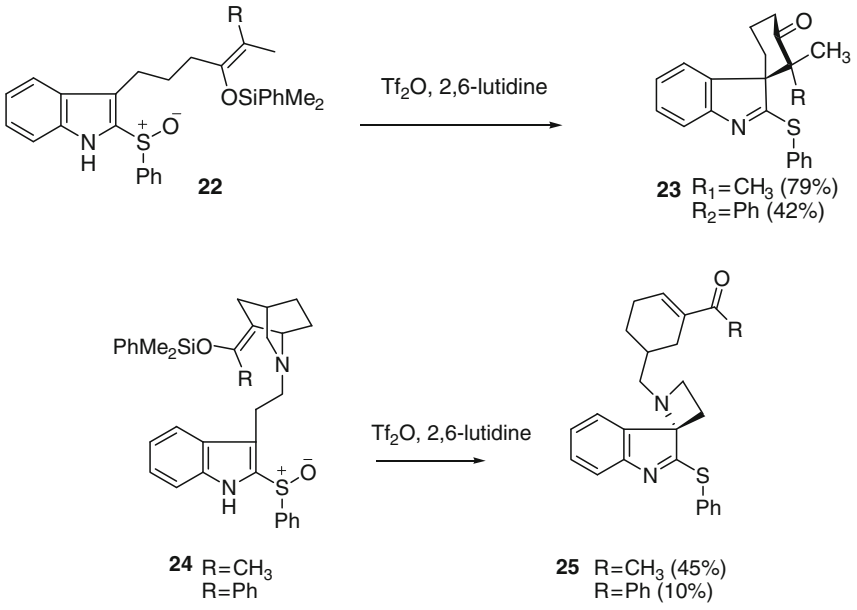
18 **19**

Entry	Solvent	*T* (°C)	% Yield	ee (%)
1	CH_2Cl_2	−78	57	38
2	Toluene	−78	41	55
3	Et_2O	−78	39	49
4	Et_2O	−110	NR	



20 **21**

1	CH_2Cl_2	−78	33	43
2	Toluene	−78	33	67
3	Et_2O	−78	60	51
4	Et_2O	−110	58	86



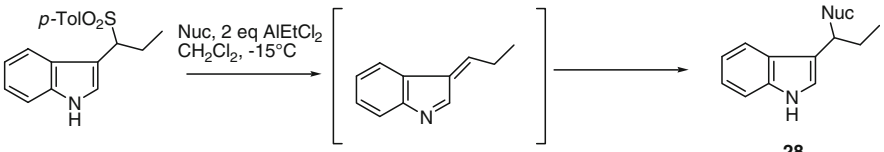
2.4 Addition of Carbon Nucleophiles to Alkylideneindolium Ions

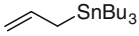
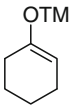
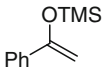
Lewis acids catalyze the elimination of *p*-toluenesulfinic acid from sulfonyl indoles (**26**) or sulfonyl indazoles to generate an imine (**27**), which can then react with nucleophiles such as allyl tin reagents, silyl enol ethers, silyl ketene acetals, and electron-rich aromatics [21]. Optimization of the formation of the imine was done with sulfonyl indazole, allyltributyl tin, and numerous Lewis acids, including $TiCl_4$, $SnCl_4$, $AlCl_3$, and $AlEtCl_2$. Of these, $AlEtCl_2$ showed the highest yields, particularly when 2 equivalents were used (83% yield). The sulfonyl indole **26** and related substrates reacted under these optimized conditions with allyl tin reagents (57–86% yields), silyl enol ethers, and silyl ketene acetals (60–79% yields). This reaction is fairly general in that various substitutions are tolerated including aryl groups and functionalized alkyl groups. Groups placed at C-2 also have nominal impact on the reaction (Table 6).

2.5 Pyridoindole-Based Quinone Methides

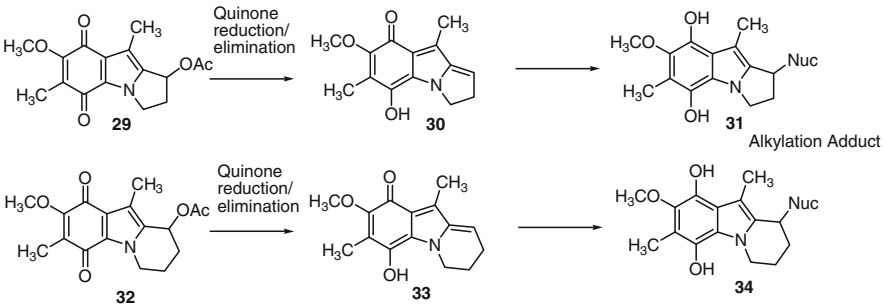
The bioreductive alkylation of quinone natural products is believed to be relevant to their anticancer properties. Pyrrolo[1,2-*a*]indole- and pyrido[1,2-*a*]indole-based quinone methides **30** and **33** were studied for their relative reactivity towards

Table 6 Addition of nucleophiles to alkylideneindolium ions



Entry	Nuc	% Yield
1		72
2		80
3		70

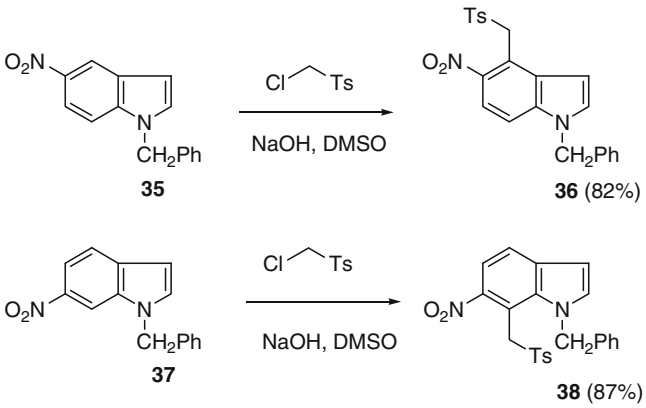
nucleophiles [22]. The methides were generated upon reduction and elimination of leaving groups to form the intermediate, which could then react with nucleophiles to form alkylation adducts **31** and **34**. The kinetic studies indicate that, while the pyridoindole quinone methide **33** forms more easily than the pyrroloindole **30**, it is a poorer bioreductive alkylating agent because of the reversible addition of nucleophiles related to steric congestion. This reactivity is consistent with cytostatic and cytotoxic studies and may explain the prevalence of the pyrrolo[1,2-*a*]indole ring system in naturally occurring bioreductive alkylating compounds, such as the mitomycins.



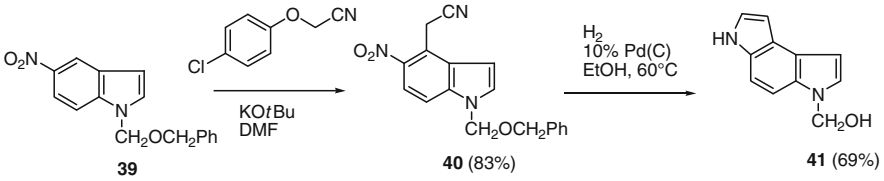
3 Nucleophilic Substitution Reactions of Indole

3.1 Vicarious Nucleophilic Substitutions

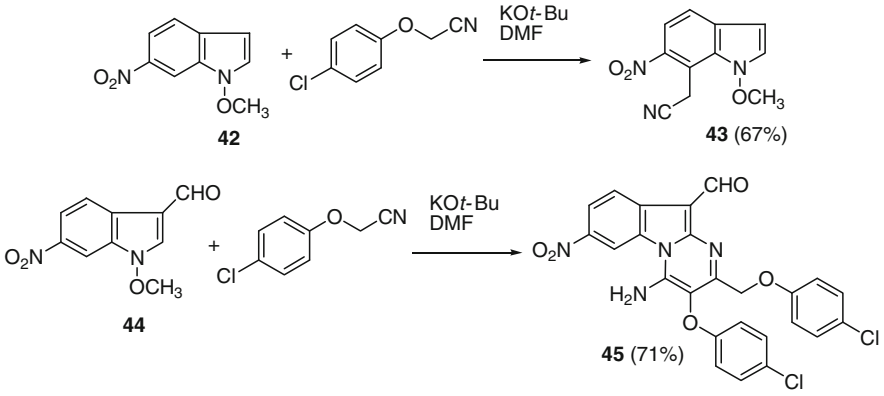
Vicarious nucleophilic substitution (VNS) of hydrogen has successfully installed α-functionalized carbon side chains on nitroindoles [1]. One of the earliest examples of this was the alkylation of 5- and 6-nitroindoles (**35** and **37**) at the 4 and 7 positions, respectively [23]. Makosza and coworkers applied this chemistry to other nitro heteroaromatics, such as thiophene, furan, and pyrrole [24].



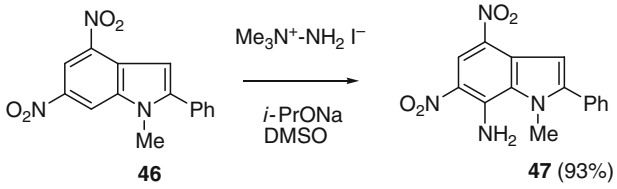
Moreover, a VNS was a key step in the first synthesis of pyrrolo[3,2-*e*]indole – a heterocyclic fragment of the antitumor antibiotic CC_1065. The α-cyano side chain is installed at the C-4 position on *N*-(benzyloxymethyl)-5-nitroindole **39** in good yield [25]. This intermediate (**40**) is then reductively cyclized using Pd(C) to produce the new ring system **41** in 69% yield; however, the protecting group does not remain intact at 65°C. If this reaction is carried out at 45°C, the benzyloxymethyl (BOM) group is left intact, and the pyrrolo[3,2-*e*]indole is isolated in 62%.



Somei demonstrated that the *N*-methoxyindoles **42** and **44** would participate in VNS either adjacent to the 6-nitro at C-7 if no aldehyde were present or at C-3 if the 6-nitro-3-indolecarbaldehyde **44** was the reactant [26]. However in the latter case, the expected product was not obtained, but instead a novel pyrimido[1,2-*a*]indole **45** was formed in 71% yield.



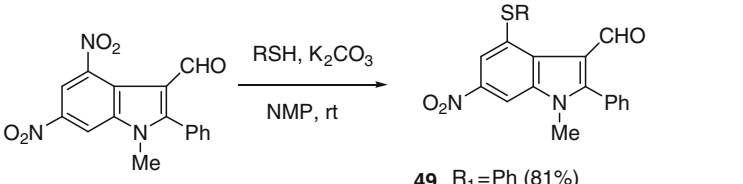
2-Aryl-4,6-dinitroindoles (**46**) have also been explored as substrates for VNS reactions. They can be aminated using 1,1,1-trimethylhydrazinium iodide (TMHI) regioselectively at C-7 [27].

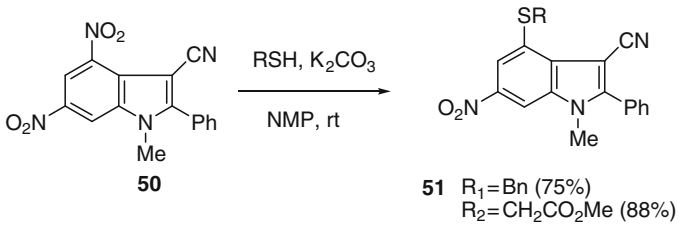


3.2 Ipso Substitution

3.2.1 Ipso Substitution of Nitro Groups

The 2-aryl-4,6-dinitroindoles can be further activated by the placement of an electron-withdrawing substituent at C-3; the resulting indoles (**48** and **50**) will undergo nucleophilic substitution of the 4-nitro group with sulfur nucleophiles but not with other nucleophiles such as sodium azide or phenol [28].

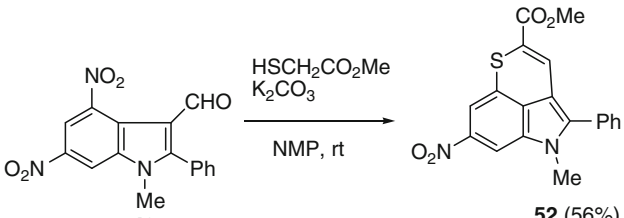




50

51 R_1=Bn (75%)
R_2=CH_2CO_2Me (88%)

When dinitroindole **48** is treated with methyl thioglycolate, the initial substitution product undergoes cyclization to form a thiopyrano[4,3,2-*c*,*d*]indole **52**, which has structural similarity to the natural antibiotic chuansinmycin [28].

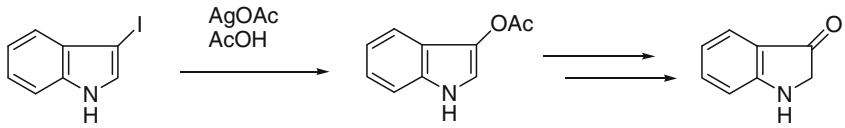


48

52 (56%)

3.2.2 Ipso Substitution of Halogens

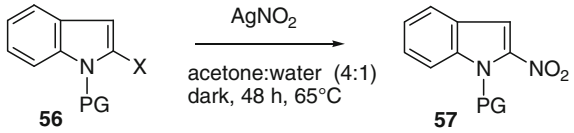
There are limited examples of S_NAr displacements of haloindoles. The simplest example is the *ipso*-displacement of iodine from 3-iodoindole (**53**) when the latter is treated with silver acetate in acetic acid. 3-Acetoxyindole (**54**), a valuable intermediate in the synthesis of indoxyl (**55**), is produced in 28% yield [29].



53 **54**(28%) **55**

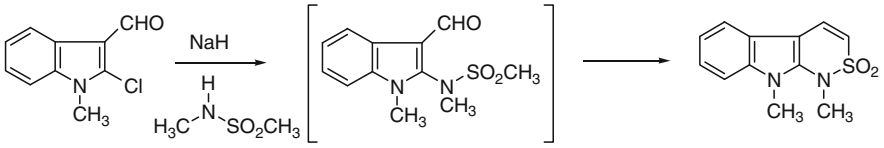
In a similar manner, Gribble demonstrated a convenient preparation of 2-nitroindoles **57** from the corresponding 2-iodo- and 2-bromoindoles **56** and silver nitrite, while the 3-iodoindoles failed to undergo reaction to produce the 3-nitroindoles [30] (Table 7).

Table 7 Nitration of haloindoles

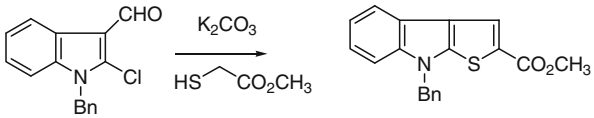


Entry	X	PG	Yield (%)
1	I	CO_2Et	52 (33% recovery of starting material)
2	Br	CO_2Et	63(20% recovery of starting material)
3	I	Boc	57%

Often in this style of reaction, a C-2 halogen is activated by the presence of an electron-withdrawing group at C-3, such as an aldehyde, a nitro, or a sulfone. The earliest examples are low-yielding reactions involving the displacement of the chlorine from **58** with anilines and sulfonamides [31]. In these, the adduct, such as **59**, often cyclized by addition to the aldehyde yielding fused indoles, such as the 1,9-dihydrothiazino[3,4-*b*]indole **60** or the thieno[2,3-*b*]indole **62**.

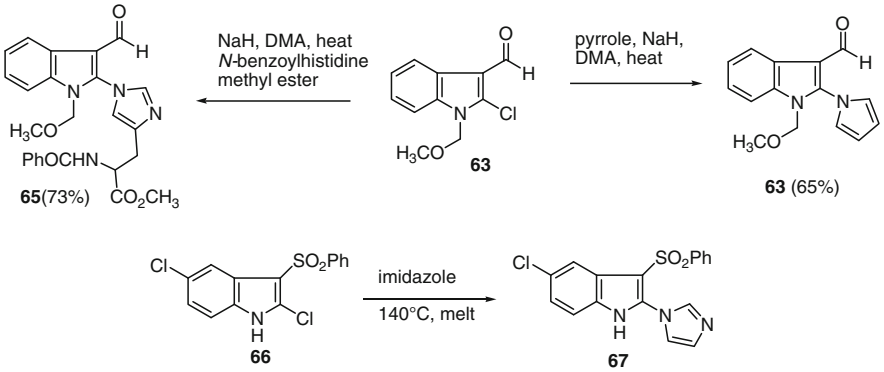


58 **59** **60** (30%)

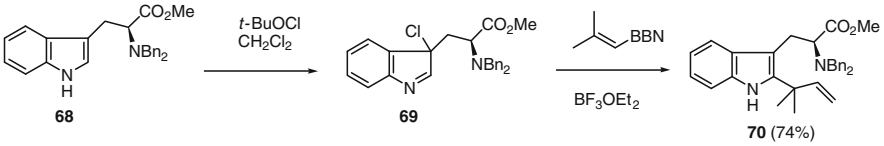


61 **62** (79%)

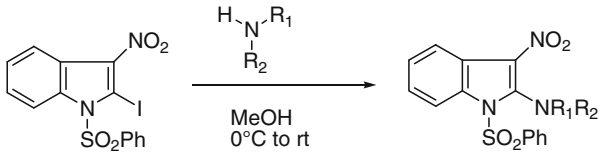
More promising results came from the reaction of 2-chloro-1-(methoxymethyl) indole-3-carbaldehyde (**63**) with a variety of nucleophiles, including pyrrole, indole, and imidazole. This chemistry was used for the synthesis of the unusual Trp-His fragment of Moroidin (**65**) [32]. Moreover, 2,5-dichloroindole-3-sulfone also undergoes nucleophilic replacement of the chlorine atom with imidazole to form a bioesteric analog (**67**) of L-737,126 (not shown), which inhibits HIV-1 reverse transcriptase [33].



Danishefsky and coworkers utilized a nucleophilic displacement of chloride to synthesize 2,3-disubstituted indoles and, more specifically, to realize the total synthesis of gypsetin (not shown) [34, 35]. Tryptamine derivative **68** is transformed into chloroindolenine **69** by *t*-butyl hypochlorite. The chloroindolenine **69** undergoes attack at C-2 by various nucleophiles, including indole, to produce, after tautomerization, the 2,3-disubstituted indoles (22–79%). The addition of a Lewis acid, BF_3–OEt_2 was found to be necessary for high yields for reagents other than prenyl-9-BBN.

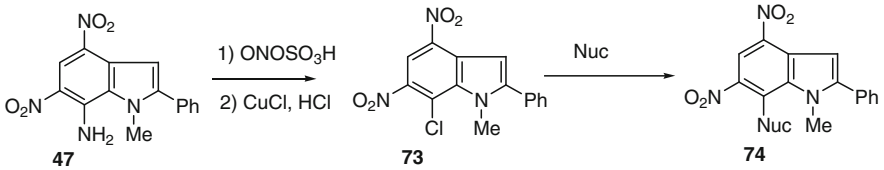


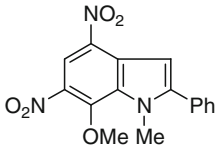
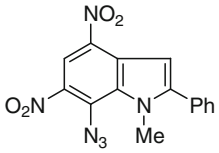
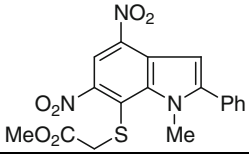
Some more recent examples of nucleophilic displacement of halide involve activation by nitro groups; for example, 2-iodo-3-nitro-1-(phenylsulfonyl)indole **71** yields 2-amino-3-nitroindoles **72** in good yields when treated with secondary amines, but fails to undergo S_NAr with sodium azide, phenol, and ammonia [36].



72 (R_1, R_2=Me; 90%)
(R_1, R_2= Et; 78%)
(R_1, R_2= Bn; 91%)
(R_1, R_2= $-(CH_2)_4$; 83%)
(R_1, R_2= $-(CH_2)_5$; 81%)
(R_1, R_2= $-(CH_2)_2O(CH_2)_2-$; 96%)
(R_1, R_2= $-(CH_2)_2N(CH_3)(CH_2)_2-$; 80%)
(R_1=H, R_2=cyclohexyl; 43%)

Table 8 Nucleophilic displacement of chloride on 4,6-dinitroindoles

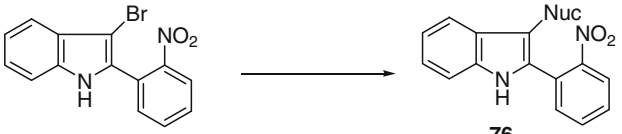


Entry	Reaction conditions	Product	Yield (%)
1	NaOMe, MeOH, 60 °C		80
2	NaN_3, DMF, 20 °C		88
3	$HSCH_2CO_2Me$, MeOH, Et_3N, 20 °C		80

The 7-amino-4,6-dinitro-2-phenylindole **47**, itself prepared by VNSH of indole, can be diazotized and transformed into the chloride **73,** which can undergo ipso-displacement with a number of N-, O-, and S- nucleophiles in high yields [37] (Table 8).

A recent article describes the displacement of bromine from indoles by nucleophiles under phase-transfer-catalyzed conditions [38]. 2-Substituted indoles were brominated using *N*-bromosuccinamide (NBS) in dimethylformamide (DMF); the resulting 3-bromo-2-substituted indoles were treated with nitrogen, sulfur, and oxygen nucleophiles under a variety of methods. The best method consisted in heating the mixture of 3-bromoindole, such as **75,** and nucleophile in acetonitrile, with powdered potassium hydroxide and dibenzo-18-crown-6. Under these conditions, the thiol nucleophiles provided moderate yields (52–80%), but the nitrogen and oxygen nucleophiles required longer reaction times at reflux. In fact, the amines had the highest success when they were used as the solvent (22–60%). The groups examined at C-2 included pyridine, ethoxycarbonyl, phenyl, and 2-aminophenyl, as well as the 2-nitrophenyl seen in **75** (Table 9).

Table 9 Phase transfer catalyzed nucleophilic displacement of bromide



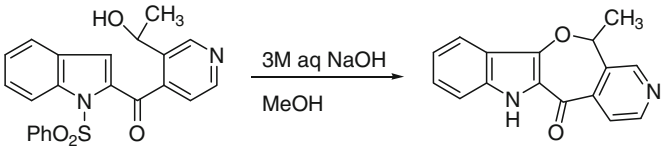
75 **76**

Entry	Nucleophile	% Yield
1	*p*-Methoxyphenol	40
2	*p*-Methoxyphenylthiol	76
3	*p*-Methylphenylthiol	74
4	Pyrrolidine	40
5	Aniline	30
6	Morpholine	60

3.3 S_N2'

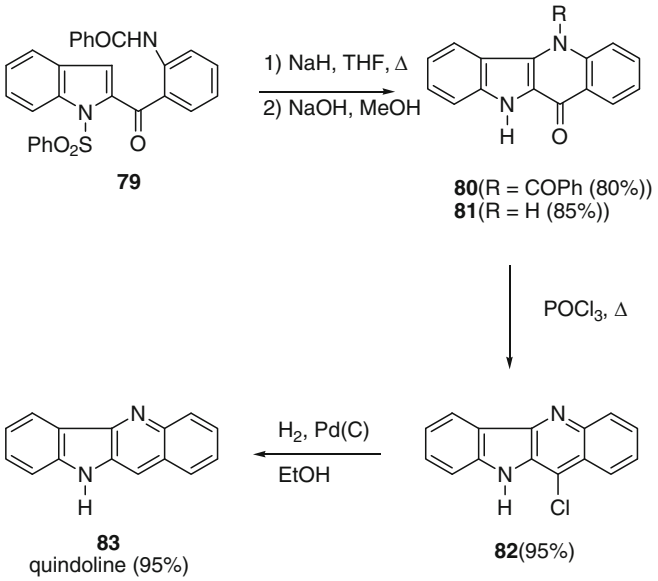
3.3.1 S_N2' at C-3

Electron-withdrawing groups at C-2 have been successful in activating indoles for nucleophilic substitution chemistry. For example, loss of phenylsulfinate with the intramolecular addition of heteroatom nucleophiles to the C-3 position of indole has been demonstrated as early as 1977 [39]. This example involved the intramolecular attack of an alcohol onto C-3 of **77** with the concomitant loss of phenylsulfinate to produce a pyrido[4′,3′:5,6]oxepino[3,2-*b*]indole **78**.

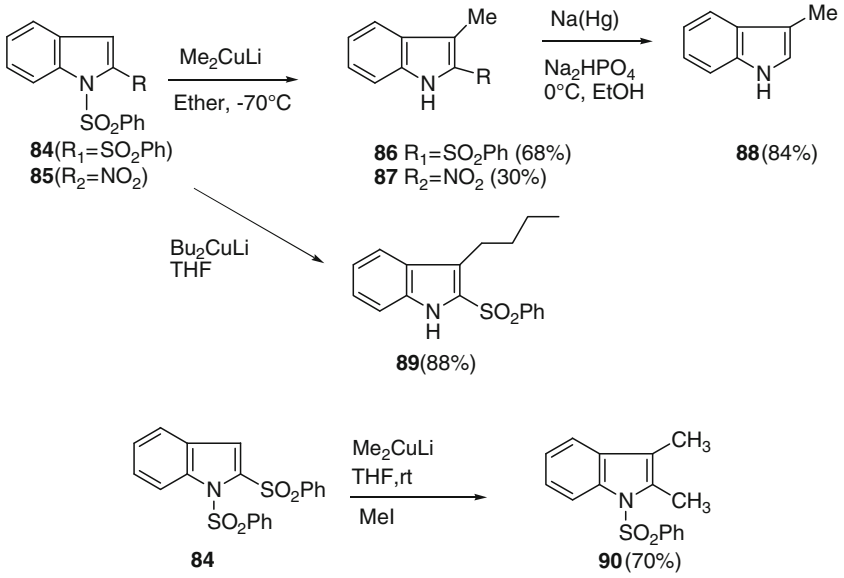


77 **78** (83%)

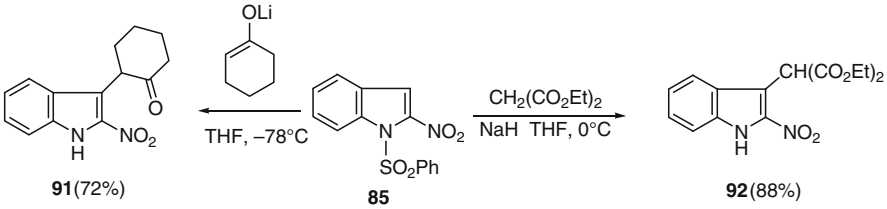
Joule then expanded this chemistry to include intramolecular cyclizations of amines [40]. In the presence of sodium hydride, the amide **79** underwent addition to C-3. Expulsion of phenylsulfinate and tautomerization yielded the ketone **80** in 80% yield. Deprotection with sodium hydroxide yielded the free amine **81** in 85% yield. Reactions of this style provided access to the alkaloids, hydroxycryptolepine, cryptolepine, and quindoline (**83**).

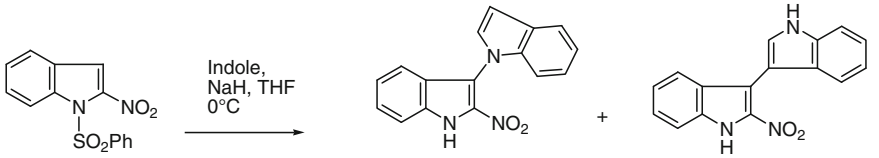


In a similar fashion, Pelkey et al. demonstrated that 1,2-bis(phenylsulfonyl) indole (**84**) would undergo nucleophilic addition by methyl cuprate to form 3-methyl-2-(phenylsulfonyl)indole (**86**) [41]. The phenylsulfonyl group can be removed by treatment with sodium–mercury amalgam to produce skatole (**88**). Other simple cuprates such as butyl cuprate add to **84** to form 3-butyl-2-(phenylsulfonyl)indole (**89**) [8]. The presumed intermediate with a C-2 anion could be trapped by addition of methyl iodide shortly after the addition of methylcuprate to **77** to yield 2,3-dimethyl-1-(phenylsulfonyl)indole (**90**) in 70% yield [8].

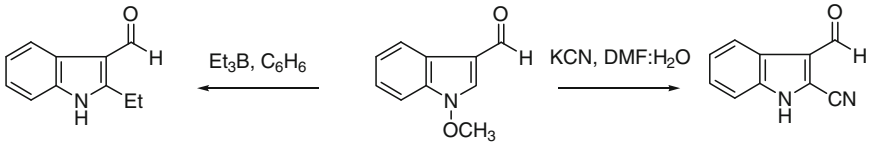


While the 2-nitroindole **85** reacted with dimethyl cuprate in a manner analogous to **84**, the yield was rather low [41]. Addition of other nucleophiles, such as enolates, to 2-nitroindole **85** results in the isolation of 3-substituted-2-nitroindoles (**91** and **92**) in much higher yields. Moreover, if indole is treated with sodium hydride followed by 2-nitroindole **85,** a mixture of bis-indoles (**93** and **94**) is isolated.





Phenylsulfonyl was not the only indole nitrogen-protecting group shown to produce such results in nucleophilic substitution chemistry. 1-Methoxyindole-3-carbaldehyde (**95**) undergoes nucleophilic attack followed by loss of methoxide to form the 2-substituted indolecarbaldehydes, such as **97** in 44% yield, with 49% of the starting material recovered [42]. The presence of the formyl group at C-3 is necessary for a good yield of the adduct, and so is the methoxy on the nitrogen; indole-3-carbaldehyde does not react with nucleophiles even under forcing conditions. 1-Methoxyindole (**98**) and KCN produce only 2% of 2-cyanoindole (**99**), with 48% recovery of the starting material, while the indole-3-carbaldehyde **95** reacts with KCN in 98% yield.



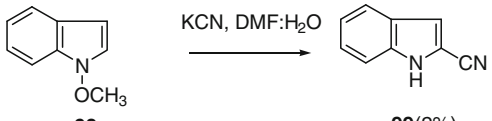
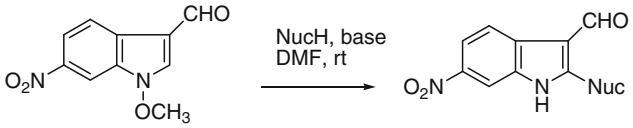


Table 10 Addition of nucleophiles to 1-methoxy-6-nitro-3-indolecarbaldehyde

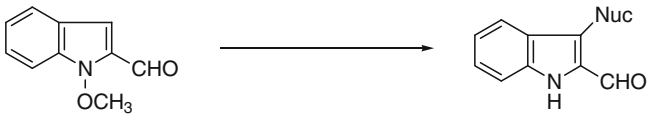


44 **100**

Entry	Nucleophile	Yield (%)
1	Pyrrole	98
2	Indole	96
3	Piperidine	92
4	*N*-Acetyl-L-cysteine	73
5	Dimethyl malonate	92

When 1-methoxy-3-indolecarbaldehyde is further activated by a nitro group at C-6, numerous nucleophiles (carbon, oxygen, sulfur, and nitrogen-centered) add in the presence of strong bases (NaH, KH, KO*t*-Bu) at C-2 with loss of the methoxy to form 2-substituted-6-nitro-3-indolecarbaldehdyes **100** [26]. While nitrogen nucleophiles, such as pyrrole, indole, piperidine, etc. add cleanly to C-2, tertiary amines such as 1,4-diazabicyclo[2,2,2]octane (DABCO) attack the methyl group of the *N*-methoxy to provide the *N*-hydroxyindole indole (Table 10).

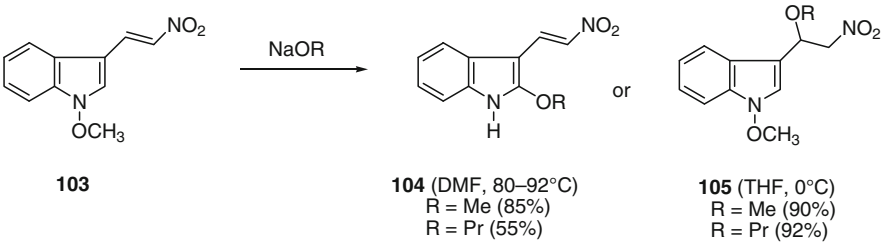
The indole-2-carbaldehyde **101** reacts with sulfur, oxygen, and nitrogen nucleophiles with loss of the methoxy-protecting group to produce the 3-substituted indole-2-carbaldehydes **102** in good yields [42].



101 **102**

Conditions	**Nuc**	**Yield**
$NaSCH_3$, MeOH, Δ	SCH_3	73%
$NHMe_2$, MeOH, Δ	NMe_2	90%
KOPh, *t*-BuOH, Δ	OPh	44%

To further probe the scope of this chemistry, Somei and coworkers studied the reaction of 1-methoxy-3-(2-nitrovinyl)indole (**103**) with nucleophiles [43]. In this substrate, there are two possible sites for the nucleophile to attack. Dipolar aprotic solvents such as DMF or hexamethylphosphoramide (HMPA) encourage attack of the nucleophile at C-2 with concomitant loss of methoxide to form **104**. Use of tetrahydrofuran (THF) results in Michael addition of the nucleophile to the β-carbon of the nitrovinyl side chain to produce **105**.

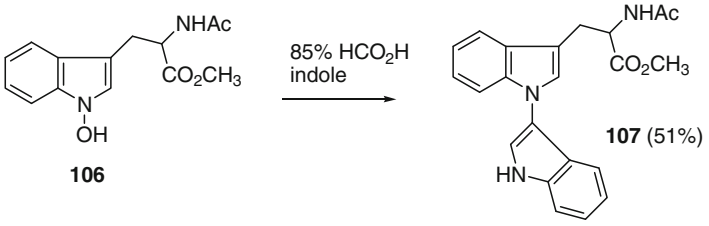


103

104 (DMF, 80–92°C)
R = Me (85%)
R = Pr (55%)

105 (THF, 0°C)
R = Me (90%)
R = Pr (92%)

Somei et al. have also shown that nucleophilic additions occur on the indole nucleus of 1-hydroxyindole and 1-hydroxytryptophan residues in the presence of 85% formic acid [3]. For example, indole displaces the hydroxyl group from (DL)-1-hydroxytryptophan methyl ester (**106**) to provide the 1-(indol-3-yl)indole **107** in 51% yield. When other nucleophiles such as phenol, naphthol, and pyrrole are used, a more complicated mixture of products is isolated.



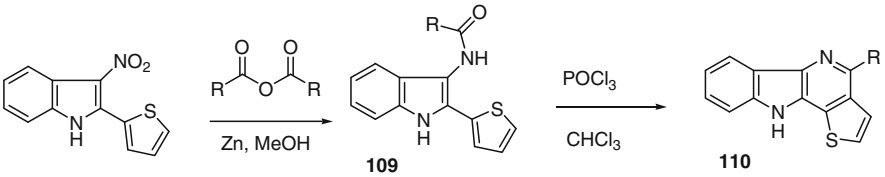
106

107 (51%)

3.3.2 S_N2' at C-3

While Grignards and enolates added to 3-nitroindole **6** to produce *trans*-2 substituted-3-nitroindolines, heteroaryl lithium compounds cause the phenylsulfinate to be lost in an S_N2' manner to form 2-substituted-3-nitroindoles **108** in moderate to good yields [44]. Reductive acylation of the 2-heteroaryl-3-nitroindoles **108** (Ar = thiophene) followed by Bischler–Napieralski reaction produces the δ-carbolines **110** in high yields (Table 11).

Heteroaryl lithiums were prepared by various methods: direct lithiation or lithium–halogen (Br or I) exchange.

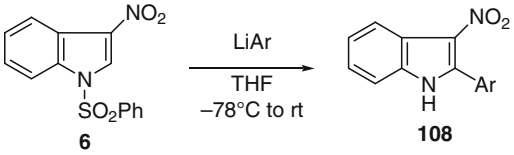


108

109
R_1=Me (96%)
R_2= Ph (94%)

110
R_1=Me (81%)
R_2= Ph (88%)

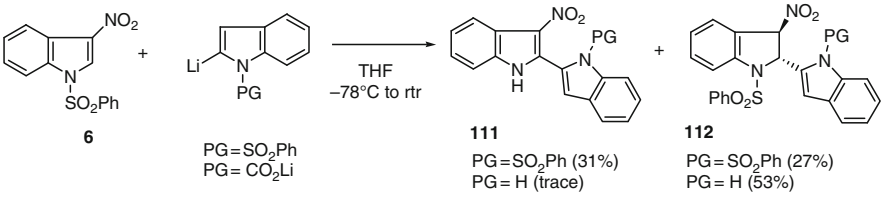
Table 11 Addition of heteroaryl lithiums to 3-nitroindole 6



6 **108**

Entry	Aryl	Yield (%)
1	2-Thiophene	60
2	2-Furan	64
3	1-Boc-2-pyrrole	58
4	1-Methyl-2-imidazole	79
4	2-Thiazole	86
5	2-Pyridine	67
6	3-Pyridine	61
7	Phenyl	75

N-protected indolyl lithium nucleophiles produced mixtures of the substitution and addition products (**111** and **112**) depending on the protecting groups used.



6

PG = SO_2Ph
PG = CO_2Li

111

PG = SO_2Ph (31%)
PG = H (trace)

112

PG = SO_2Ph (27%)
PG = H (53%)

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Metalation of Indole

Erin T. Pelkey

Abstract Metalation reactions involving indoles (and indolines) is reviewed (through 2009). The most common mode of metalation is lithiation. Other metals that have been used, either through direct metalation of indole or through transmetalation, include magnesium, zinc, tin, and boron. This monograph is divided into three sections: metalation directed by a nitrogen functionality, directed ortho metalation by substituents not located at nitrogen, and halogen–metal exchange. All of the sections are organized by the location of the metalation event. The review will have a primary focus on the seminal papers that contributed to the development of metalation reactions and a secondary focus on applications of metalation reactions used in the synthesis of complex indoles including indole natural products.

Keywords Directed ortho metalation · Halogen–metal exchange · Indole · Lithiation

Contents

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1 Introduction

Metalation reactions, either by direct proton abstraction (usually protons directly adjacent to heteroatoms), directed ortho metalation (DOM), or halogen–metal exchange, are extremely useful for the conversion of simple indole starting materials into complex indole products. The indole ring system is prevalent in biochemical systems (e.g., tryptophan, melatonin, and serotonin), medicinal chemistry in the form of drugs (e.g., tadalafil, sumatriptan, fluvastatin, vincristine, and indomethacin) and biologically active molecules (e.g., staurosporine and ellipticine), and complex targets that helped inspire major advances in synthetic chemistry (e.g., strychnine, reserpine, and ibogamine). Due to the ubiquitous nature of the indole ring system, it is not surprising that a significant portion of the seminal work in the field of metalation reactions has been accomplished in the context of indoles. The research groups that have significantly advanced the field of indole metalation include Sundberg, Gribble, Snieckus, Katritzky, Iwao, Kondo, Sakamoto, Amat, Bosch, and Bergman; their work, along with many others, will be presented throughout the monograph. DOM methodology (including indoles) has been reviewed by Beak and Snieckus [1–3], while the use of metalated heterocycles (including indoles) was reviewed recently by Chinchilla and colleagues [4]. Katritzky and Rewcastle reviewed the generation of carbanions in heterocyclic nitrogen systems and this included a significant section on indoles [5].

A timeline that describes some of the major advancements in indole metalation chemistry appears below (Fig. 1). Gilman reported perhaps the earliest metalation of an indole-containing ring system in the literature in 1936, and this work involved the selective lithiation of carbazole and *N*-ethylcarbazole (**1**) at C4 [6]. In 1953, Shirley demonstrated that the treatment of *N*-methylindole (**2**) with *n*-butyllithium led to selective metalation at C2 [7], adjacent to the nitrogen heteroatom as observed previously in other five-membered ring heterocycles [8]. In the search for a removable *N*-protecting group, which would allow for the preparation of 2-substituted *N*-unsubstituted indoles, Sundberg surveyed lithiation reactions of

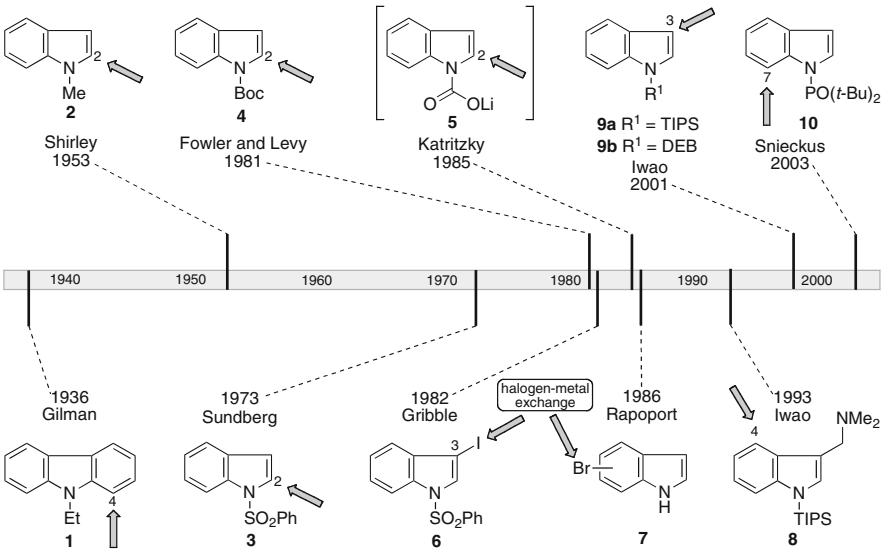


Fig. 1 Timeline of selected advances in indole metalation

simple indoles containing different *N*-protecting groups [9, 10]. They found that *N*-(phenylsulfonyl)indole (**3**) led to selective C2-lithiation and overall was the best substrate. Consequently, the phenylsulfonyl protecting group has become the most common indole-protecting group for selective C2 metalation of indole. In the search for an acid-labile *N*-protecting group capable of directing lithiation, Fowler and Levy found that *N*-(*tert*-butoxycarbonyl)indole (**4**) was also selectively lithiated at C2 [11]. Katritzky used CO_2 as a temporary *N*-protecting group in the synthesis of 2-substituted indoles [12, 13]; this method has subsequently found wide applicability. Gribble demonstrated the first example of metalation at C3 using a halogen–metal exchange reaction with 3-iodo-1-(phenylsulfonyl)indole (**6**) [14]. They also investigated the generation of a 2,3-dilithioindole intermediate via a double halogen–metal exchange reaction with a 2,3-diiodoindole. Rapoport reported the use of halogen–metal exchange reactions of bromoindoles **7** for the functionalization of the benzene part of the indole ring system [15]. Iwao demonstrated the first C4-selective lithiation of the indole ring by treating gramine derivative **8** with *t*-BuLi [16]. Iwao also found *N*-protecting groups, triisopropylsilyl (TIPS) [17] and 2,2-diethylbutanoyl (DEB) [18], that promoted the direct C3-lithiation of indoles **9**. Finally, Snieckus discovered a nitrogen-protecting group, di-*tert*-butylphosphinoyl, which promoted the selective C7-lithiation of indole **10** [19].

Metalated indoles are extremely useful intermediates in synthesis. Either by choice of different *N*-protecting groups, by the use of directed ortho metalating groups, or by halogen–metal exchange reactions, metalation is possible at every position within the indole framework. To name just a few reaction manifolds, metalated indoles can undergo electrophilic substitution, transmetalation, and/or cross-coupling reactions allowing for the synthesis of a variety of highly

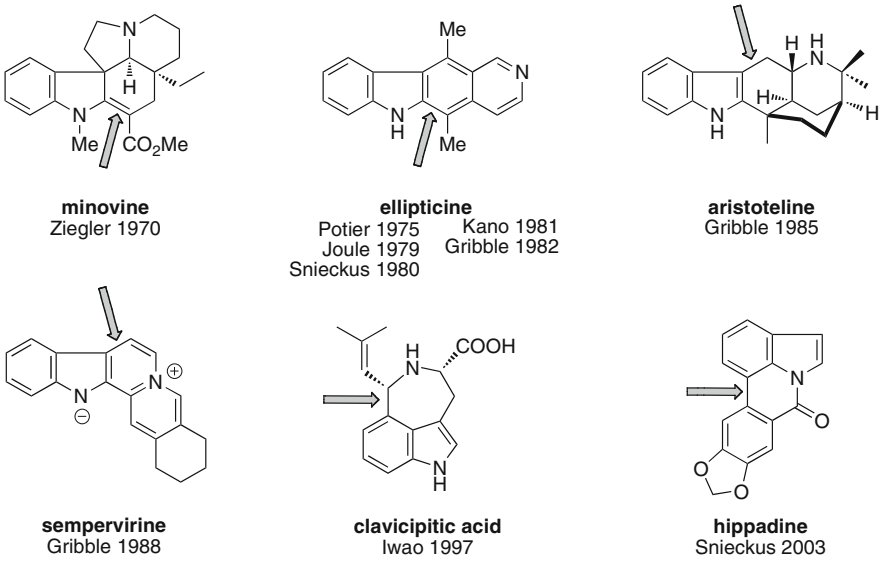


Fig. 2 Selected indole natural products

functionalized indoles including indole natural products. Examples of natural products that have been prepared using indole metalation chemistry appear below (Fig. 2). Completed targets include minovine [20, 21], ellipticine [22–30], aristoteline [31], sempervirine [32], clavicipitic acid [33, 34], and hippadine [19]; the location of the C–C bonds formed via metalated indole intermediates is indicated by the arrows.

This monograph will discuss the two major methods for indole metalation: (1) hydrogen–metal exchange (deprotonation) facilitated by nitrogen-based groups and carbon-based groups; and (2) halogen–metal exchange. Each section will discuss the key contributions that drove methodology development forward and will provide examples of important applications including those related to the total synthesis of natural products.

2 Metalation Directed by Nitrogen Functionality

Treatment of *N*-substituted indoles with strong bases can lead to selective deprotonation at C2, C3, or C7 depending on the nature of the nitrogen-protecting group. Most substitution patterns give selective metalation at C2. In fact, lithiation of *N*-(substituted)indoles is one of the premiere methods for preparing 2-substituted indoles. This section is organized by both the location of the metalation and also by the type of group substituted at nitrogen.

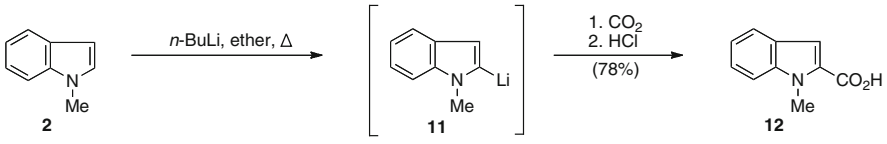
2.1 C2-Lithiation of N-Methylindoles

The C2-lithiation of simple indoles was first investigated by Shirley and Roussell in 1953 [7]. An attempted lithiation of *N*-lithioindole (double lithiation of indole) failed to yield any C-substituted products. On the other hand, treatment of *N*-methylindole (**2**) with *n*-butyllithium gave 2-lithioindole **11** as evidenced by quenching with CO_2, which gave indole-2-carboxylic acid **12** (Scheme 1). The methyl group serves as a non-removable nitrogen substituent. This reaction worked with a variety of electrophiles including *p*-chlorobenzaldehyde, benzophenone, α-naphthyl isocyanate, quinoline, and methyl tosylate. In addition, treatment of *N*-phenylindole with a large excess of *n*-butyllithium followed by CO_2 led to products arising from metalation at both 2-position of the indole ring along with 2′-position of the phenyl ring.

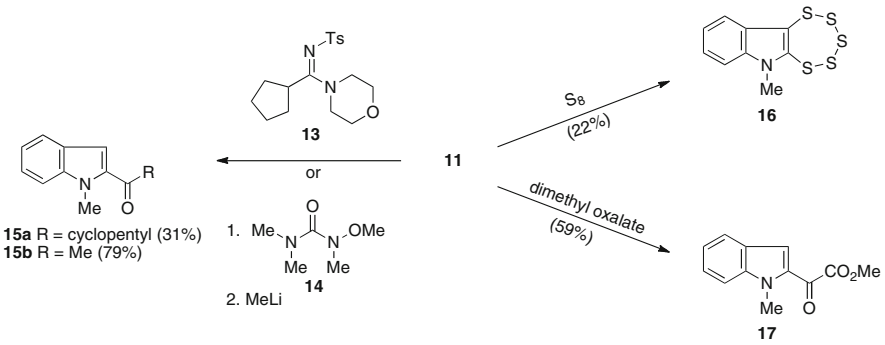
Since this first report, groups have mostly followed the original reaction conditions (*n*-BuLi in ether) to generate **11** for use as a nucleophile and no systematic study has been undertaken. In a series of papers regarding the generation of indolyl-2-borates, Ishikura used *tert*-butyllithium as a base to form **11** [35–43]. In addition, Caixach showed that *N*-methylindole (**2**) was not lithiated by treatment with lithiocyclohexylisopropylamide [44]. This result might not be too surprising after Fraser and co-workers measured the pKa of **2** in THF to be 38.1 using ^{13}C spectroscopy [45]. Recently, Mulvey studied the direct magnesiation of **2** with $(TMEDA)_2Na_2MgBu_4$; a similar reagent was used in the direct zincation of **2** [46].

Over the years, **11** has been treated with many different electrophiles leading to the formation of *N*-methyl-2-substituted indoles (Scheme 2); the electrophiles studied include: acetylpyridines [47], ketones [48], 1-chloro-2-(*N*,*N*-dimethylamino)ethane [49], pyridinecarboxaldehydes [50], iodine [51], amidines (e.g., **13** giving 2-ketoindole **15a**) [52], *N*-methoxyurea **14** (followed by methyllithium giving 2-acetylindole **15b**) [53], furanoses [54], nitrilimines [55], enaminoketones [56], sulfur (giving pentathiepino[6,7-*b*]indole **16**) [57], *bis*-epoxides [58], and bicyclic aminals [59]. Some indole natural products contain an *N*-methyl group, and thus **11** can serve as a viable building block in total synthesis. For example, Ziegler and Spitzner generated **11** at the outset of their total synthesis of minovine (Fig. 2) [20, 21]. An inverse addition of **11** to an ethereal solution containing a large excess of dimethyl oxalate provided the corresponding indole-2-glyoxylate **17**.

Lithioindole **11** and structurally related derivatives have been transmetalated with a variety of metals. Bergman treated **11** with copper(I) bromide which gave the



Scheme 1 C2-lithiation of *N*-methylindole



Scheme 2 Treatment of **11** with selected electrophiles

stable indolyl copper **18a** [51]. Treatment of **18a** with iodobenzene gave *N*-methyl-2-phenylindole **19**. Modifying the reaction conditions led to homocoupled products, 2,2′-biindoles (see also [60]), and cyclotrimerization products, trisindolobenzenes. Kumada formed the indolyl Grignard reagent **18b** by treating **11** with magnesium bromide. Palladium-catalyzed cross-coupling of **18b** with iodobenzene also gave *N*-methyl-2-phenylindole **19** [61]. Labadie converted **11** into stannane **18c** by treatment with tributyltin chloride [62] (see also the work of Liebeskind [63, 64]). Labadie studied the palladium-catalyzed cross-coupling (Stille reaction) of **18c** with a variety of electrophiles including 4-iodotoluene, which gave the corresponding 2-arylindole **19** (R = Me) in good yield. Similarly generated **18d** was used by Quintard to study ipso nitration reactions [65], by Arnswald to study Friedel–Crafts amidations [66], and by Widdowson to study ipso fluorination reactions [67]. Levy and later Ishikura explored the generation and reactions of a number of 2-indolylborates (e.g., **18e**). Indolylborates can be converted into a variety of functionalized indoles including 2-alkylindoles [68], 2-allylindoles [69], 2-vinylindoles [70], 2,3-disubstituted indoles [38, 71], 2-arylindoles (e.g., **19**) via palladium-catalyzed cross-coupling [35–37], fused indoles [39, 40], and 2-ketopyrroles [41]. Iwasawa treated **11** with triethylborate, which presumably led to boronic acid intermediate **18f** [72]. Subsequent treatment with 2,2-dimethyl-1,3-propanediol followed by a rhodium catalyst and carbon dioxide led to the corresponding indole-2-carboxylic acid. As is the case with many heteroarylboronic acids, **18f** is now commercially available. Nicolaou prepared 6,7-dimethyl-*N*-methylindol-2-yl boronic acid as a building block in a total synthesis of aspidophytine [73]. Kaufmann generated an *N*-methylindol-2-yldiarylborane from **11** for study as fluorescent dyes [74]. Maas generated indolyl zincate **18g** and transformed it into 2-vinylindoles via a palladium-catalyzed cross-coupling reaction [75].

Bisagni and co-workers studied the lithiation of *N*-methyl-5-azaindoles. They found that treatment of the latter with *t*-butyllithium led to selective C2-lithiation [76].

Lithiation reactions involving *N*-methyl-3-substituted indoles are sometimes useful for introducing electrophiles regioselectively to C2. Comins [77] and Adam [78] reported regioselective C2-lithiations of indole substrates containing

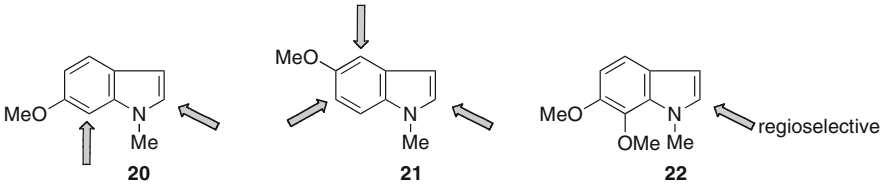


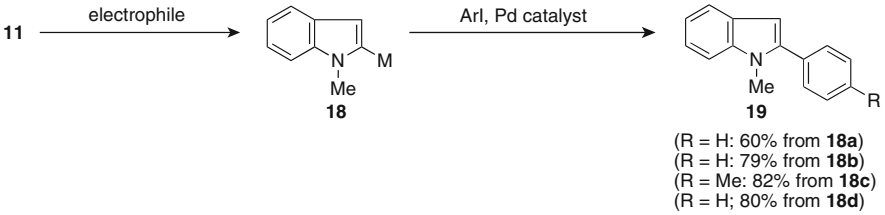
Fig. 3 Methoxy-substituted *N*-methylindoles

3-chloro and 3-vinyl substituents, respectively. On the other hand, lithiation of *N*-methylindoles containing methoxy groups in the benzenoid ring has proven to be unselective (Fig. 3). Lithiation of 6-methoxy-1-methylindole (**20**) led to a mixture of 2-substituted and 7-substituted products [79], while lithiation of 5-methoxy-1-methylindole (**21**) led to a mixture of 2-substituted, 4-substituted, and 6-substituted products [10]. The lack of selectivity is due to the directing effect of the methoxy group [80], whereas the *N*-methyl group is not much more than just a blocking group. Regarding the latter, Sundberg found that using the benzenesulfonyl nitrogen-protecting group led to regioselective lithiation at the C2 position of the indole ring containing a 5-methoxy group [10]. More recently, Nicolaou reported the regioselective C2-lithiation of 6,7-dimethoxy-*N*-methylindole (**22**) for the preparation of the corresponding boronic acid [73]. In that case, the *N*-methyl group was desirable as it was contained in the ultimate natural product target, aspidophytine.

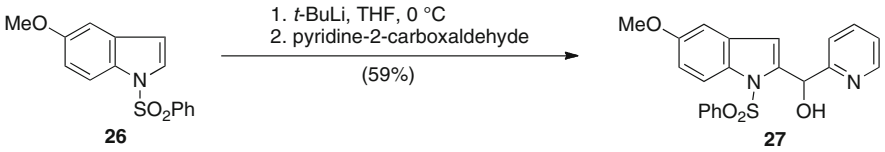
2.2 C2-Lithiation of N*-(Arylsulfonyl)indoles*

To prepare 2-substituted *N*-unsubstituted indoles, Sundberg examined lithiation reactions for several indoles containing different removable *N*-protecting groups [9] as the *N*-methyl group is not readily removable. They assessed six different leaving groups by treating indole substrates **3** and **23** with *t*-butyllithium, quenching with D_2O, and measuring deuterium incorporation at C-2 (Table 1) in the form of **25**; both the methoxymethyl (entry 1) and benzenesulfonyl (entry 4) substrates were successfully lithiated. The benzyloxymethyl (entry 2) and benzyl (entry 3) substrates suffered from lithiation in the methylene portion of the benzyl moiety. Lithiation of the silyl-protected indoles (entries 5–6) led to 2-silylindoles via a rearrangement. The benzenesulfonyl group proved to be the protecting group of choice as it can readily be removed by treatment with mild base; consequently, benzenesulfonyl-protecting group has become the most common indole-protecting group for selective C2 metalation of indole. The use of metalated sulfonamides (including indoles) in synthesis has been reviewed by Familoni [81].

Table 1 Transmetalation of lithioindole **11**



Entry	Base (to generate **11**)	Electrophile	M	Product	Ref.
1	*t*-BuLi	CuBr	Cu	**18a**	[51]
2	*t*-BuLi	$MgBr_2$	MgBr	**18b**	[61]
3	*n*-BuLi	Bu_3SnCl	$SnBu_3$	**18c**	[62–64]
4	*n*-BuLi	Me_3SnCl	$SnMe_3$	**18d**	[65–67]
5	*n*-BuLi or *t*-BuLi	Et_3B	Et_3BLi	**18e**	[35–38, 68–71]
6	*n*-BuLi	$B(OEt)_3$	$B(OH)_2$	**18f**	[72]
7	*t*-BuLi	$ZnCl_2$	ZnCl	**18g**	[75]



Scheme 3 Regioselective lithiation of methoxy-substituted indole

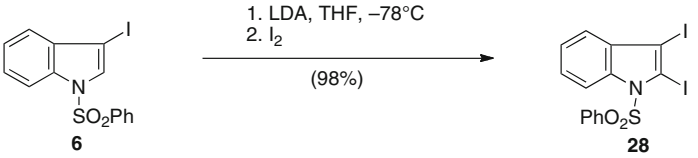
An advantage of the benzenesulfonyl group is that it allows for the regioselective generation of 2-lithioindole derivatives containing methoxy groups and other potential directing groups in the benzenoid ring. For example, Sundberg treated 5-methoxyindole **26** with *tert*-butyllithium followed by pyridine-2-carboxaldehyde which gave **27** in moderate yield (with no trace of products derived from lithiaton of the benzene ring as had been observed with the corresponding *N*-methylindole substrate) (Scheme 3) [10]. Others have observed regioselective transformations in similar systems containing methoxy groups [30, 79, 82–90], benzyloxy groups [91–95], halides [82, 96–99], and a cyano group [100].

Sundberg reported the dilithiation of **3** when treated with 2.2 equivalents of *tert*-butyllithium at −5°C. Trapping with trimethylsilyl chloride gave a product containing two silyl groups [101]. Kondo reported a problem with lithiation in the arylsulfonyl ring upon treatment of **3** with *tert*-butyllithium, but this could be alleviated using LDA [102]; later, Kondo reported that the dilithiation reaction could also be suppressed using mesityllithium as the base [103].

As the benzenesulfonyl group is electron-withdrawing, there is a wide range of bases that can be used to generate lithio intermediate **24**. Shortly after Sundberg's publication in 1973 [9], Grethe [104] and Joule [105] used *n*-BuLi, while Kano

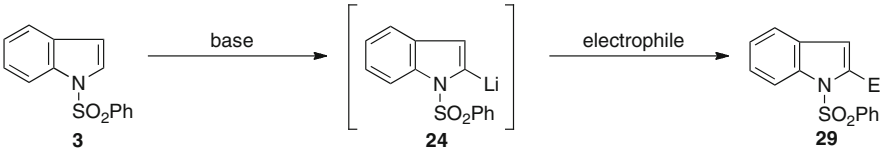
[106] and Gribble [14] used LDA. Other bases that have been used to generate **24** and structurally related analogs include *sec*-butyllithium [107–109], phenyllithium [27], lithium hexamethyldisilazane (LiHMDS) [110], lithium tetramethylpiperidide (LiTMP) [86, 88], and lithium cyclohexylisopropylamide [44]. LDA has become the base of choice for the generation of **24**. One advantage that LDA offers over alkyllithium bases is functional group tolerance. For example, Gribble treated with 3-iodoindole **6** with LDA followed by iodine which gave 2,3-diiodoindole **28** (Scheme 4) [14].

A wide range of electrophiles have been introduced to the C2 position of the indole ring system via lithio intermediate **24**. Electrophiles that have been added include the following (selected examples shown in Table 2): iodine [111, 112] (entry 1), BrCN [112] (entry 2), benzenesulfonyl chloride [112] (entry 3), DMF [14] (entry 4), trimethylsilyl chloride [113] (entry 5), oxirane [114] (entry 6), ketoesters [115, 116] (entry 7), allylic halides [117] (entry 8), acyclic anhydrides [106, 109] (entry 9), dinitrogen tetroxide [118] (entry 10), heterocylic carboxaldehydes [82, 119, 120], heterocylic carbonyl chlorides [92, 94], hetero cyclic



Scheme 4 Selective C2-lithiation of 3-iodo-(*N*)-benzenesulfonylindole **6** with LDA

Table 2 Generation and reactions of 2-lithio-*N*-(phenylsulfonyl)indole **24**



Entry	Base	Electrophile	E	Product	Yield (%)	Ref.
1	LDA	I_2	I	**29a**	80	[111, 112]
2	LDA	BrCN	Br	**29b**	85	[112]
3	LDA	$PhSO_2Cl$	Cl	**29c**	82	[112]
4	LDA	DMF	CHO	**29d**	50	[14]
5	*t*-BuLi	TMS-Cl	TMS	**29e**	75	[113]
6	LDA	Oxirane	CH_2CH_2OH	**29f**	69	[114]
7	*t*-BuLi	$CHOCO_2Et$	$CH_2(OH)CO_2Et$	**29g**	64	[116]
8	*n*-BuLi	Allyl bromide	$CH_2CH{=}CH_2$	**29h**	74	[117]
9	*s*-BuLi	Ac_2O	Ac	**29i**	76[a]	[109]
10	*t*-BuLi	N_2O_4	NO_2	**29j**	67	[118]

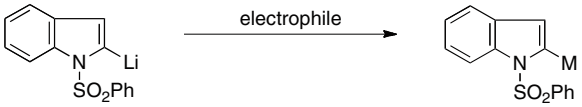
[a]Yield with anhydride improved by inverse addition procedure in many cases

ketones [22, 121, 122], 4,4-dimethoxy-2,5-cyclohexadienones [123], phthalic anhydride [124], pyridine-fused anhydrides [26, 30, 89], ethoxymethylidene Meldrum's acid [125], *t*-butyl isocyanate [32], 1-benzoylpyrrolidin-2-one, sulfinyl aldimines [126], toluenesulfinates [127], tosyl fluoride [128], lactones [25, 129, 130], lactams [131], ketones [132, 133], aldehydes [104, 134, 135], halopyridines [9, 44], oxalates [136], and iodomethane [14, 29]. Gribble reported that 3-lithio-*N*-(phenylsulfonyl)indole, generated via halogen–metal exchange (vide supra) at −100°C, rearranges to form **24** upon warming to room temperature [14].

Lithioindole **24** and structurally related derivatives have been transmetalated with a variety of metals to give important metalated intermediates **30** including indol-2-yl triethylborate **30a** [36, 37, 41, 68, 71], 5-azaindol-2-yl boronic acid [137] related to **30b**, indol-2-yl stannanes **30c** [138, 139] and **30d** [91], other indol-2-yl stannanes [67, 91, 137, 140–145], indol-2-yl coppers [51, 146–148], indol-2-yl zincate **30e** [102, 149–151], and other indol-2-yl zincates [84, 141] (Table 3). Heterocyclic boronic acids tend to be unstable; Burke has developed a method for generating **30b** in situ through use of the corresponding MIDA (*N*-methyliminodiacetic acid) boronate ester [152]. These metalated intermediates **30** are valuable in synthesis since they can be further transformed into 2-substituted indoles and [*b*]-fused indoles via palladium-mediated cross-coupling reactions among other reactions. Caddick has developed an alternate route to indol-2-yl stannanes (e.g., **30d**) using an interesting *ipso* stannylation/detosylation reaction [128, 153].

Joule discovered a novel route to [*b*]-fused indoles via an interesting sequence that involved C2-lithiation of indole, quenching with either lactam [154] or lactone electrophiles [105, 155, 156], and subsequent intramolecular cyclization reactions with consequent loss of the benzenesulfonyl group. Their synthesis of oxepino-fused indole **33** is instructive (Scheme 5) [155]. Treatment of **24** with phthalide (**31**)

Table 3 Transmetalation of 2-lithio-*N*-(phenylsulfonyl)indole **24**



24 **30**

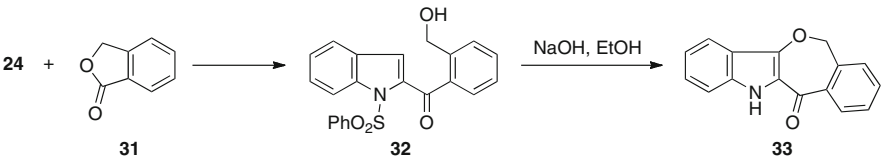
Entry	Base (to generate **24**)	Electrophile	M	Product	Yield (%)	Ref.
1	*n*-BuLi	BEt_3	BEt_3Li	**30a**	–[a]	[36, 37, 41, 68, 71]
2	–	–	$B(OH)_2$	**30b**	–[b]	–
4	LDA	Me_3SnCl	$SnMe_3$	**30c**	83	[138]
4	*t*-BuLi	Me_3SnCl	$SnMe_3$	**30c**	43	[139]
5	LDA	Bu_3SnCl	$SnBu_3$	**30d**	85	[91]
6	LDA	$ZnCl_2$	ZnCl	**30e**	–[a]	[102, 149–151]

[a]Not isolated; used directly in subsequent reactions
[b]Commercially available; no published syntheses found in the primary literature

gave keto alcohol **32**. Mixing **32** with sodium hydroxide gave **33** via an intramolecular cyclization and loss of the benzenesulfinate group.

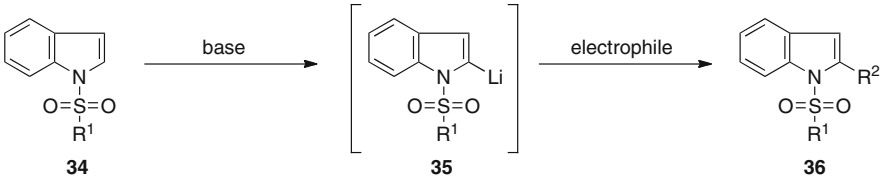
Outside of the prevalent benzenesulfonyl group, the use of other arylsulfonyl groups has been investigated in indole C2-lithiation reactions. Thus, treatment of *N*-arylsulfonylindoles **34** with various lithium bases (as noted) led to 2-lithioindoles **35** and subsequently to 2-substituted indoles **36**. Illustrative examples are shown below (Table 4). Additional studies have also been reported with **34a** [96, 148, 157, 158], the 3-bromo analog of **34a** [159], **34b** [48, 145, 160, 161], a 3-methyl analog of **34b** [162], and an ergot alkaloid derivative of **34c** [163]. In the search for a scalable lithiation procedure, Wu and co-workers found that **34b** could be lithiated with LDA at –25°C in the presence of bis(*N*,*N*-dimethylaminoethyl) ether [96]. Kondo and co-workers studied the use of fluorous-tagged *N*-(arylsulfonyl)indole derivatives [103]. They found mesityllithium to be the best base for the selective α-lithiation of these substrates.

The selective C2-lithiation of 3-substituted-1-(phenylsulfonyl)indoles **37** is a common strategy for the synthesis of 2,3-disubstituted indoles **39**. The bases that have been used to prepare 3-alkyl-2-lithio-*N*-(phenylsulfonyl) indoles **38** include LDA, *n*-butyllithium, *sec*-butyllithium, and phenyllithium



Scheme 5 Joule's synthesis of [*b*]-fused indoles

Table 4 Generation and reactions of 2-lithio-*N*-(arylsulfonyl)indoles **35**



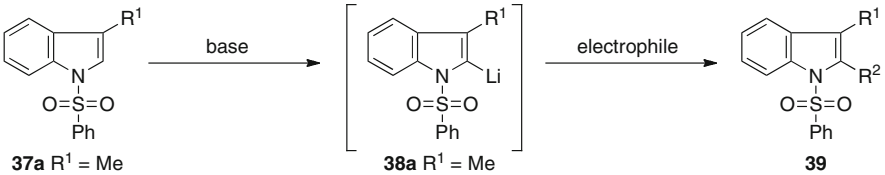
Entry	R^1	SM	Base	Electrophile	R^2	Product	Yield (%)	Ref.
1	*p*-$OMeC_6H_4$	**34a**	LDA	DMF	CHO	**36a**	90	[164]
2	*p*-$OMeC_6H_4$	**34a**	*n*-BuLi	NIS[a]	I	**36b**	60	[141]
3	*p*-MeC_6H_4	**34b**	LDA	Me_3SnCl	$SnMe_3$	**36c**	79	[144]
4	*p*-MeC_6H_4	**34b**	*t*-BuLi	Me_3SnCl	$SnMe_3$	**36c**	–[b]	[143]
5	*p*-MeC_6H_4	**34b**	*t*-BuLi	BtCN[c]	CN	**36d**	43	[165]
6	NMe_2	**34c**	LDA	lactone	lactol	**36e**	91	[130]

[a]*NIS N*-iodosuccinimide
[b]Yield not given; **36c** used without purification
[c]*BtCN* 1-cyanobenzotriazole

(not *tert*-butyllithium). Some straightforward examples are illustrated below (Table 5); Ito contributed additional examples in their preparation of 2-mannosyltryptophans [166, 167]. Much of this work has focused on the preparation of 2,3-disubstituted indoles, substrates that can be transformed into fused indoles [168, 169] including natural product targets such as ellipticine (from **39g**) [27, 29], iboga alkaloids [140], and β-carbolines [170, 171]. Intramolecular cyclizations of 2-lithio-3-substituted indole intermediates have been explored to give [*b*]-fused indoles; the base of choice for the generation of the lithio intermediate is LiHMDS [110, 172, 173].

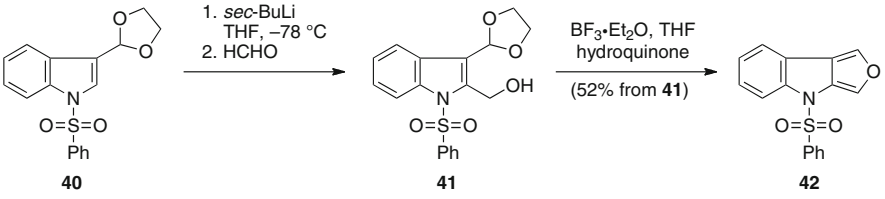
Gribble has reported many examples that involved the generation of lithio intermediate of type **38** that eventually were converted into fused indoles including pyrrolo[3,4-*b*]indoles [107, 108] and furo[3,4-*b*]indoles [27, 29, 176–179]; this work has been reviewed [180]. In some cases, the substituent at C3 was a hydroxyalkyl group or an acetal group; the oxygen heteroatoms in these groups can also participate in stabilizing the lithiated intermediate. A second generation synthesis of furo[3,4-*b*]indole **42** is instructive (Scheme 6) [176]. Treatment of indole **40** with *sec*-butyllithium followed by formaldehyde gave 2,3-disubstituted indole **41**.

Table 5 Generation and reactions of 3-alkyl-2-lithio-*N*-(phenylsulfonyl)indoles **38**



Entry	SM	Base	Electrophile	R^2	Product	Yield (%)	Ref.
1	**37a**	LDA	$(PhCO)_2O$	PhCO	**39a**	50	[24]
2	**37a**	*n*-BuLi	MeS(=O)Cl	S(=O)Me	**39b**	80	[174]
3	**37a**	*sec*-BuLi	Ac_2O	Ac	**39c**	81	[109]
4	**37a**	*sec*-BuLi	$ClC(=O)CO_2Et$	$C(=O)CO_2Et$	**39d**	31	[107]
5	**37a**	LDA	*t*-BuNCO	CONH*t*-Bu	**39e**	68	[175]
6	**37b**	LDA	$(PhCO)_2O$	COPh	**39f**	75[a]	[24]
7	**37b**	PhLi	CH_3CHO	$CH(OH)CH_3$	**39g**	73	[27]
8	**37b**	sec-BuLi	PhCHO	CH(OH)Ph	**39h**	63	[108]

[a]Yield of this transformation with the pyridine analog, isonicotinic anhydride, was also 75%



Scheme 6 Synthesis of furo[3,4-*b*]indole **42**

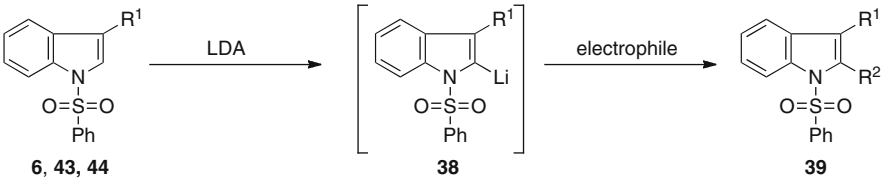
Exposure of **41** to boron trifluoride etherate led to **42** in 52% yield from **40**. Bergman and Janosik lithiated **40** by treatment with LDA in their synthesis of sulfur- and selenium-substituted indoles [181, 182].

As noted earlier (Scheme 4), 3-iodo-*N*-(phenylsulfonyl)indole **6** was lithiated selectively at C2 (thus avoiding halogen–metal exchange) by treatment with LDA [14, 183–185]. This selectivity has also been observed with 3-bromoindole **43** [159, 183, 184, 186], functionalized 3-bromoindoles (not shown) [159, 187], and 3-cyanoindole **44** [103, 188]. Examples of the C2-lithiation of these substrates in the synthesis of 2,3-disubstituted indoles **39** are shown below (Table 6).

Merour [137, 190, 191], Dormoy [86], Mahboobi [85], and Bisagni [76] have reported the selective C2-lithiation of various *N*-(phenylsulfonyl)azaindoles using LDA and *n*-butyllithium. The following example with 5-azaindole **45** is illustrative (Scheme 7) [137]. With a 7-azaindole substrate, lithiation also occurred in the arylsulfonyl ring [190].

The C2-lithation of *N*-(arylsulfonyl)indoles has proven to be an important strategy that helped enable the total synthesis of several indole natural products (Figs. 2 and 4). Targets prepared from *N*-(phenylsulfonyl)indole (**3**) include

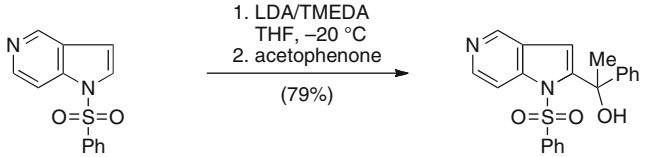
Table 6 Generation and reactions of 3-halo-2-lithioindoles and 3-cyano-2-lithioindoles



6, **43**, **44** **38** **39**

Entry	R^1	SM	Electrophile	R^2	Product	Yield (%)	Ref.
1	I	**6**	$(PhCO)_2O$	COPh	**39i**	79	[189]
2	I	**6**	BrCN	Br	**39j**	80	[184]
3	Br	**43**	PhSSPh	SPh	**39k**	61	[159]
4	Br	**43**	BrCN	Br	**39l**	73	[184]
5	CN	**44**	ICH_2CH_2I	I	**39m**	65[a]	[103]
6	CN	**44**	TsCN	CN	**39n**	77	[188]

[a]Utilized mesityllithium as the base



45 **46**

Scheme 7 Selective C2-lithiation of 5-azaindole

apparacine [146, 147], aspidofractinine [117], cinchonamine [104], desethylcatharanthine [115, 116], ellipticine [22, 25, 26, 30, 89, 122], hyellazole [30, 106, 133], olivacine [121, 122], and sempervirine [32]. Ellipticine has also been prepared from 3-ethyl-*N*-(phenylsulfonyl)indole (**37b**) [24, 29].

2.3 *C2-Lithiation of* N*-(Carboalkoxy)indoles*

The second most used protecting group utilized for preparing 2-substituted *N*-unsubstituted indoles via lithiation chemistry is the acid-labile Boc (*tert*-butoxycarbonyl) group. Fowler and Levy first reported the use of Boc in the generation and reactions of 2-lithiated indoles [11] (Scheme 8). Lithio intermediate **47** was generated by treating Boc-indole **4** with *tert*-butyllithium. Careful quenching with dimethyl oxalate gave 2-methoxalylindole **48a** in 66% yield. The Boc group could be removed by treatment with trifluoroacetic acid or sodium methoxide.

Compound **47** has been generated and used in the synthesis of a variety of 2-substituted indoles **48**. Unlike lithiation of *N*-(phenylsulfonyl)indole **3** [9, 14], lithiation reactions of **4** have not been studied systematically. Nonetheless, selected examples including the corresponding reaction conditions used are given below (Table 7). Silanol **48g** has been generated and exploited by Denmark in cross-coupling reactions [192, 193]. Kline used this chemistry to prepare **48b** en route to a synthesis of 2-iodotryptamine [194]. Additional electrophiles used in reactions with **47** include epoxides (carbohydrates) [166], allylic pivalates [195], and chlorodialkylphosphines [196].

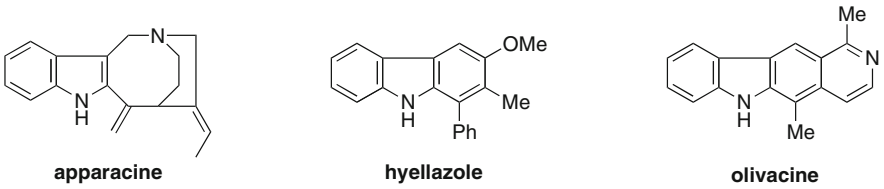
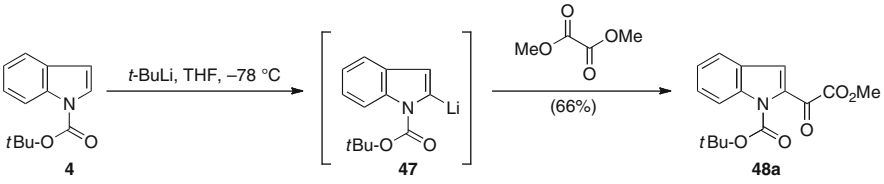
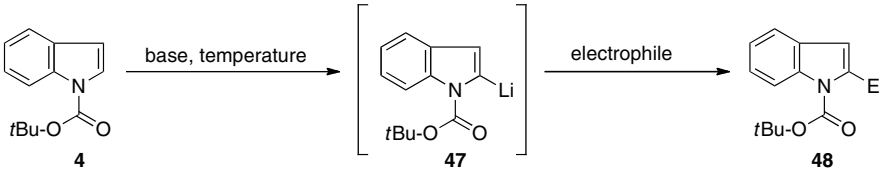


Fig. 4 Additional indole natural product targets synthesized via lithiated indole intermediates



Scheme 8 Selective C2-lithiation of *N*-(*tert*-butoxycarbonyl)indole **4**

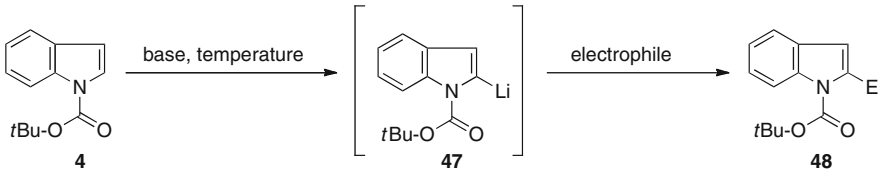
Table 7 Generation and reactions of 2-lithio-*N*-(BOC)indole **47**



Entry	Base	Temp	Electrophile	E	Product	Yield (%)	Ref.
1	*t*-BuLi	–78°C	I_2	I	**48b**	67	[111]
2	*t*-BuLi	–78°C	$ClCO_2Et$	CO_2Et	**48c**	75	[197]
3	*t*-BuLi	–120°C	N_2O_4	NO_2	**48d**	78	[118]
4	*n*-BuLi	–78°C	SO_2Cl_2	SO_2Cl	**48e**	–[a]	[198]
5	*n*-BuLi	–65°C	$ClPOMeN(iPr)_2$	P(=O)HOMe	**48f**	45	[199]
6	LDA	0°C	$SiMe_2Cl_2$	$SiMe_2OH$	**48g**	91	[200]

[a]Not reported

Table 8 Transmetalation of 2-lithio-*N*-(BOC)indole **47**



Entry	Base	Temp	Electrophile	E	Product	Yield (%)	Ref.
1	LiTMP	–78°C	$B(O\text{-}iPr)_3$	$B(OH)_2$	**48h**	65	[223]
2	LiTMP	–78°C	$B(O\text{-}iPr)_3$	$B(OH)_2$	**48h**	94	[205]
3	LDA	0°C	$B(O\text{-}iPr)_3$	$B(OH)_2$	**48h**	96	[200]
4	*t*-BuLi	–78°C	$B(OMe)_3$	$B(OH)_2$	**48h**	69	[224]
5	*t*-BuLi	–78°C	BEt_3	BEt_3Li	**48i**	–[a]	[208]
6	*sec*-BuLi	–[b]	Bu_3SnCl	$SnBu_3$	**48j**	–[b]	[225]
7	*n*-BuLi	–78°C	Bu_3SnCl	$SnBu_3$	**48j**	40	[62]
8	LDA	–78°C	Bu_3SnCl	$SnBu_3$	**48j**	91	[226]
9	*n*-BuLi	–78°C	Me_3SnCl	$SnMe_3$	**48k**	37	[65]
10	LDA	–78°C	Me_3SnCl	$SnMe_3$	**48k**	76	[145]
11	*t*-BuLi	–78°C	$ZnCl_2$	ZnCl	**48l**	–[c]	[102]

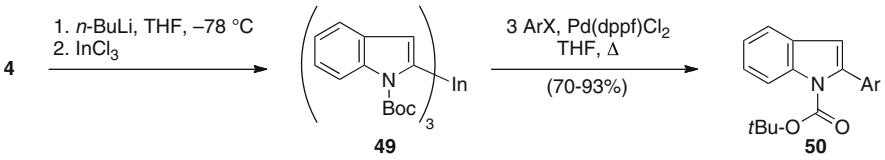
[a]Generated and used directly in a wide variety of reactions
[b]Reported in microfiche
[c]Generated and used directly in Pd-catalyzed cross-coupling reactions

Lithioindole **47** and structurally related derivatives have been transmetalated with a variety of metals to give important metalated intermediates **48h–l**. Examples with the reaction conditions used to generate **47** are given below (Table 8). Vazquez reported a significant advance in the metalation of **4** using LDA under noncryogenic

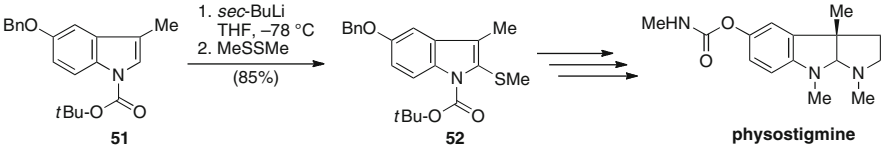
conditions (0°C) [200], and higher yields for the preparation of metalated intermediates seemed to be obtained using LDA. Boronic acid **48h** and functionalized derivatives have been further transformed into the corresponding trifluoroborate salts by treatment with KHF_2 [201–205]. The latter tend to be more stable and useful than boronic acids in palladium-catalyzed cross-coupling reactions. Ishikura and co-workers have explored the chemistry of triethylborate **48i** in great detail [37, 43, 70, 206, 207]; **48i** proved useful in total syntheses of ellipticine [208], yuehchukene [209], and tubifoline [210]. A number of functionalized *N*-(Boc) indole-2-boronic acids [201, 211–215], 2-stannanes [216, 217], 2-zincates [218–220], and a 2-cuprate [221] have been prepared using lithiation chemistry. Daïri and co-workers generated *N*-(methoxycarbonyl)indole-2-boronic acid and used it in a process-quality synthesis of anticancer drug candidate, obatoclax [222].

Sestelo and Sarandeses generated tris(indol-2-yl)indium **49** for use in palladium-catalyzed cross-coupling reactions (Scheme 9) [227]. Lithiation of **4** with *n*-butyllithium followed by treatment with indium trichloride gave **49** which was used directly in palladium-catalyzed cross-coupling reactions leading to 2-arylindoles **50**. These same authors exploited this chemistry to prepare indole-substituted maleimides [228].

The BOC group has enabled the selective C2-functionalization of a wide range of benzenoid-substituted and/or 3-substituted indoles [166, 167, 229–234] [235]. An early example was reported by Castagnoli for the preparation of ethyl 5,6-dimethoxy-3-methylindole-2-carboxylate [236]. Marino lithiated 5-benzyloxyindole **51** with *sec*-butyllithium and quenched the 2-lithio intermediate with dimethyl sulfide giving indol-2-yl sulfide **52** (Scheme 10) [162]. The latter proved to be a useful intermediate in a total synthesis of physostigmine. Cook introduced an isopropenyl group to the 2-position of an *N*-(Boc)indole derivative in a sequence that resulted in the total synthesis of tryprostatin A [237]; others have



Scheme 9 Preparation of novel tris(indol-2-yl)indium intermediate **49**



Scheme 10 Selective C2-lithiation of functionalized *N*-(Boc)indole **51**

prepared tryprostatin analogs using lithiation chemistry [221, 229]. Selective C2-lithiation of *N*-Boc-substituted 5-azaindoles [86] and 7-azaindoles [217] has also been reported.

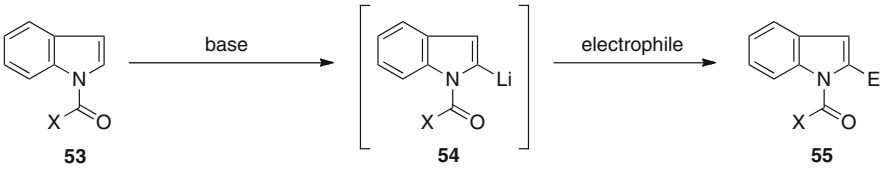
Several protecting groups similar in structure to Boc, other *N*-(carboxy)indoles and *N*-(carbamoyl)indoles, have been investigated in C2-lithiation reactions. Examples of the protecting groups, bases, and electrophiles that have been used appear below (Table 9).

As mentioned throughout the text, the C2-lithation of *N*-(Boc)indoles has proven to be an important strategy that helped enable the total synthesis of several indole natural products including: physostigmine [162] (Scheme 10) arcyriacyanin A [145], ellipticine [208] (Fig. 2), yuehchukene [209], tubifoline [210], and tryprostatin [237]. Approaches to the *Strychnos* [233] and indolocarbazole alkaloids [203, 204] have also been reported.

2.4 C2-Lithiation of Indole-1-Carboxylic Acids

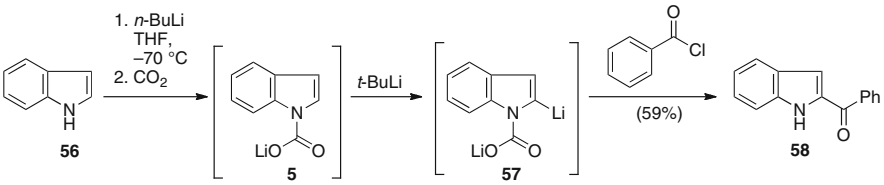
Although the early attempts at the double lithiation of the parent indole ring system failed to produce 2-substituted indoles [7], in 1985, Katritzky invented a sequence that basically accomplished this goal [12]. They used carboxylate as a temporary nitrogen-protecting group, which allowed for the selective C2-lithiation of the indole ring system (Scheme 11). Indole (**56**) is treated with *n*-butyllithium followed by carbon dioxide, which generates lithium indole-1-carboxylate **5**. Subsequent treatment of **5** with *tert*-butyllithium then gave the 2-lithioindole intermediate **57**; quenching the latter with an electrophile (e.g., benzoyl chloride) and work-up then gave 2-substituted indoles (e.g., **58**) after loss of the carboxylate group. This method is advantageous because it does not require extra steps for the introduction

Table 9 C2-lithiation of *N*-(carboxy)indoles and *N*-(carbamoyl)indoles

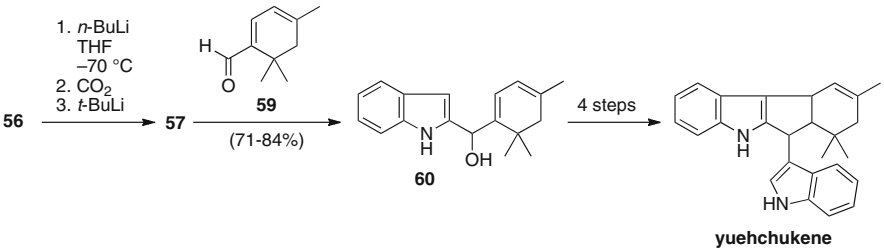


Entry	X	Base	Electrophile	E	Product	Yield (%)	Ref.
1	OMe	LDA	$B(O\text{-}iPr)_3$	$B(OH)_2$	**55a**	70	[222]
2	CEt_3	*sec*-BuLi[a]	$ClCO_2Et$	CO_2Et	**55b**	90	[18]
3	NH*t*-Bu	*t*-BuLi[b]	Me_3SiCl	$SiMe_3$	**55c**	95	[238]
4	NEt_2	*t*-BuLi	Me_3SiCl	$SiMe_3$	**55d**	97	[19]
5	$N(iPr)_2$	BuLi	PCy2Cl	PCy	**55e**	70	[196]

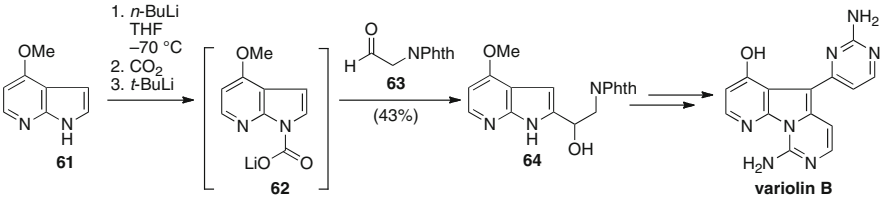
[a] *t*-BuOK was also added; otherwise, lithiation primarily occurred at C3
[b] 2.2 equivalents of *t*-BuLi



Scheme 11 Katritzky method for preparing 2-substituted indoles



Scheme 12 Using Katritzky method in total synthesis of yuehchukene



Scheme 13 Using Katritzky method in total synthesis of variolin B

and removal of indole-protecting groups. Katritzky has also written a review on indole-1-carboxylic acids [239].

The above reaction sequence (Scheme 11), sometimes called the Katritzky method, has been exploited by a number of research groups for the preparation of 2-substituted *N*-unsubstituted indoles [83, 102, 130, 218, 240–245]. Gribble and Bergman used this chemistry to prepare 2-bromoindole and 2-iodoindole [246–248]. Bergman and Janosik further explored this sequence to prepare indol-2-yl sulfides and selenides [57, 249, 250]. Hudkins has used this chemistry to prepare 2-hydroxyalkylindoles en route to indolocarbazole derivatives [251, 252]. The first step in Bergman's short total synthesis of yuehchukene used the Katritzky method and aldehyde **59**, which gave 2-(hydroxyalkyl)indole **60** (Scheme 12) [253, 254].

The Katritzky method has also proven useful in the functionalization of azaindoles. Alvarez and co-workers have used the Katritzky method to synthesize variolin B starting with 7-azaindole **61** (Scheme 13) [255–257].

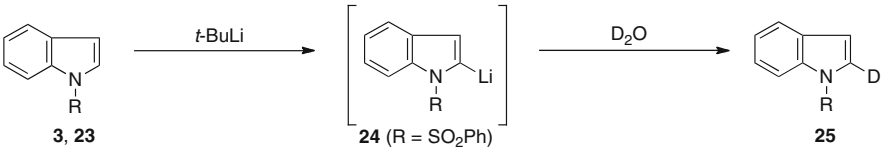
2.5 C2-Lithiation of Other N-(Substituted)indoles

The most common indole nitrogen-protecting groups used in C2-lithiation reaction sequences are benzenesulfonyl and *tert*-butoxycarbonyl (Boc). Additional protecting groups that have been examined, some of which have already been mentioned, include benzyl (Table 10, entry 3), *p*-methoxyphenyl (PMP) [258], trimethylsilylethoxymethyl (SEM) [36, 62, 259–261], methoxymethyl (MOM) [9, 102, 170–172, 262–265] (Table 10, entry 1), diethylbutanoyl (DEB) (Table 9, entry 2), carbamoyl derivatives (Table 9, entries 3–5), diethoxymethyl (DEM) [266–268], (dimethylamino)methyl (isogramine) [269–271], methoxy [272], methoxymethoxy [273], and 2-oxazolinyl [274]. Examples of the C2-lithiation of indole substrates not mentioned prior are given below (Table 11).

Sundberg found that *N*-benzyl-substituted indoles are not suitable substrates for C2 metalation due to competitive metalation at the benzyl methylene [9]. On the other hand, metalation at C2 is possible with *N*-benzylindoles with the presence of an additional directing group at C3 (vide infra) [23]. Additionally, Snieckus reported a tandem DOM/cyclization sequence involving an *N*-benzylindole substrate, which gave tetracyclic indole derivatives [23]. More recently, Sanz reported a tandem halogen–metal exchange/C2-lithiation of *N*-benzylindole **68** (Scheme 14) [276]. Trapping dilithio intermediate **69** with ethyl benzoate gave tetracyclic indolo[1,2-*b*]isoquinoline **70**.

Very few examples of C2-lithiation reactions involving *N*-arylindoles are known [258]. In the search for new indolyl phosphine ligands (e.g., **72**) for palladium-catalyzed amination reactions, mono-lithiation and di-lithiation reactions involving *N*-arylindoles have been used (Scheme 15). Beller reported the synthesis of indolyl ligand **72a** using a mono-lithiation of *N*-phenylindole (**71a**) [277], whereas Nifant'ev used a dilithiation of **71b** under much colder conditions to give bis(phosphine)indole **72b** [278].

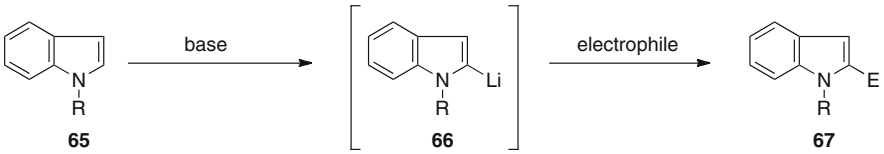
Table 10 Lithiation of different *N*-substituted indoles



Entry	Substrate	R	Solvent	D incorporation at C2 (%)
1	**23a**	CH_2OCH_3	Ether	95
2	**23b**	CH_2OCH_2Ph	Ether	30
3	**23c**	CH_2Ph	THF	15
4	**3**	SO_2Ph	THF	86
5	**23d**	$Si(CH_3)_3$	TMEDA[a]	0
6	**23e**	$Sit\text{-}Bu(CH_3)_2$	THF	0

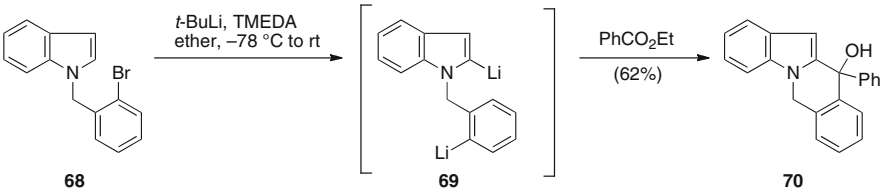
[a]*TMEDA* tetramethylenediamine

Table 11 C2-lithiation of various *N*-(substituted)indoles

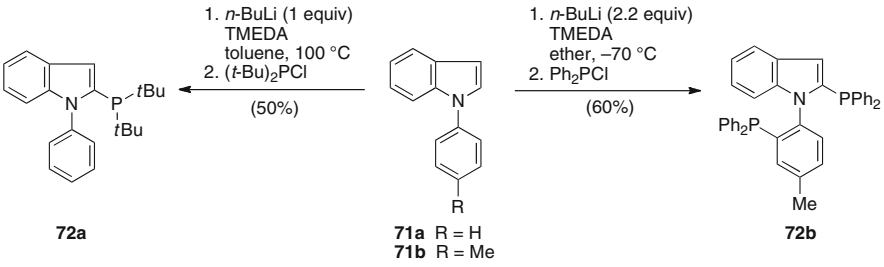


Entry	R	Base	Electrophile	E	Product	Yield (%)	Ref.
1	SEM	*n*-BuLi	Bu_3SnCl	$SnBu_3$	**67a**	77	[62]
2	MOM[a]	*t*-BuLi	PhNMeCHO	CHO	**67b**	53	[275]
3	DEM	*t*-BuLi	Me_3SiCl	$SiMe_3$	**67c**	82	[267]
4	CH_2NMe_2	*n*-BuLi	Ph_2CO	$CHOHPh_2$	**67d**	85	[270]
5	OMe	*n*-BuLi	I_2	CHO	**67e**	73	[272]
6	OCH_2OMe	*n*-BuLi	Me_2NCHO	CHO	**67f**	96	[273]
7	2-(oxazolinyl)	*n*-BuLi	MeI	Me	**67g**	31	[274]

[a]Starting material = **23a**

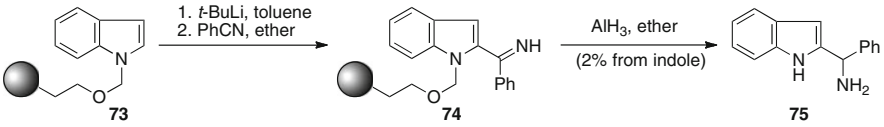


Scheme 14 Tandem halogen–metal exchange/C2-lithiation



Scheme 15 Lithiation reactions involving *N*-(aryl)indoles **71**

Ruhland reported a novel solid-phase C2-lithiation of the indole ring [279] using a linker that resembled the MOM-protecting group (Scheme 16). Lithiation of resin-bound indole **73** was accomplished by treatment with *tert*-butyllithium in toluene followed by quenching with benzonitrile. Reductive cleavage of **74** then gave amine **75** in an overall yield of 2%, proof of principle that this type of transformation is possible.



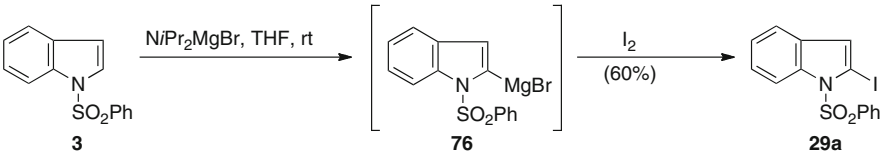
Scheme 16 C2-lithiation of a resin-bound indole derivative

2.6 C2 Metalation with Other Metals

Thus far, all of the metalation reactions of indole discussed have involved lithium–hydrogen exchange (lithiation) using organolithium and bulky lithium amide bases. In recent years, there has been an increase in interest in finding milder, non-lithium bases to effect the metalation of aromatics and heteroaromatics; this topic was reviewed by Mulvey in 2009 [280]. In 1996, Kondo and Sakamoto reported one of the first metalations (metal–hydrogen exchange) of the indole ring that involved a non-lithium base [281]. They achieved the C2-metalation of indole using magnesium bases. For example, they treated *N*-(phenylsulfonyl)indole (**3**) with magnesium diisopropylamide (generated from diisopropylamine and an alkyl Grignard reagent) which gave indol-2-yl Grignard reagent **76**; quenching with iodine then gave 2-iodoindole **29a** (Scheme 17). Following the precedent of Dinsmore in the magnesiation of pyrroles [282], de Koning prepared **29a** (in an improved 79% yield) using a catalytic amount of amine and a stoichiometric amount of the Grignard reagent to generate the magnesium amide base.

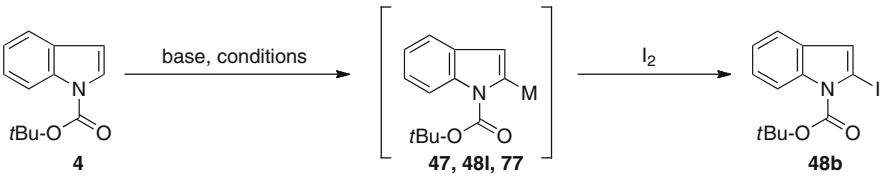
Additional metals that have been used in novel, direct metalation reactions of indole include aluminum [283, 284], copper [285], and zinc [220]. To compare the different conditions that have been explored, different syntheses of *N*-(*tert*-butoxycarbonyl)-2-iodoindole (**48b**) are compared below (Table 12). From **4, 48b** was prepared using different direct metalation methods followed by quenching with iodine; the highest yielding conditions involved the cupration chemistry.

Given the importance of arylboronic acids and arylboronates, Ishiyama and co-workers developed a direct C2-borylation of indole using iridium catalysis [286–289]. Treatment of indole (**56**) with pinacolborane (**78**), iridium catalyst **79**, and 4,4′-di-*tert*-butylpyridine (**80**) in hexane gave indol-2-ylborane **79** in 73% yield (Scheme 18) [288]. Nishida published a similar method using an iridium catalyst and an imine complex [290]. Multiple groups have reported that the iridium-catalyzed borylation with 2-(substituted)indoles led to C7-borylation [291, 292]. Maleczka and Smith reported that the iridium-catalyzed borylation of **4** gave the corresponding indol-3-ylborane [293]; whereas Ishiyama and co-workers also observed 3-borylation with an *N*-(trialkylsilyl)indole substrate [289]. Finally, Snieckus reported an *ipso*-borylation/desilylation produced indol-2-ylboranes [294, 295].



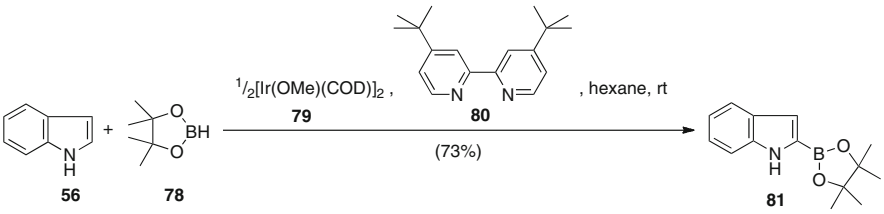
Scheme 17 Direct magnesiation of *N*-(phenylsulfonyl)indole **3**

Table 12 Comparison of different direct metalation reactions



Entry	Base	Conditions	M	Metalated indole	Yield (%)	Ref.
1	*t*-BuLi	THF, –78°C	Li	**47**	67	[111]
2	$(NiPr_2)_2Mg$	THF, rt	Mg[a]	**77a**	52	[281]
3	LiTMP, $ZnCl_2$•TMEDA	THF, rt	ZnCl	**48l**	67	[220]
4	$(i\text{-}Bu)_3Al(TMP)Li$	THF, –78°C	$Al(i\text{-}Bu)_3Li$	**77b**	64	[283]
5	$MeCu(TMP)(CN)Li_2$	THF, –40°C	$Cu(Me)(CN)Li_2$	**77c**	88	[285]

[a]Presumably, di-indol-2-ylmagnesium intermediate is generated by treatment of **4** with $(NiPr_2)_2Mg$



Scheme 18 Direct borylation of indole

2.7 C3-Lithiation

The direct C3-lithiation of the indole ring has been observed with *N*-(trialkylsilyl) indoles although it took some time for this to be realized. In their original 1973 paper, Sundberg reported that the attempted C2-lithiation of *N*-(trialkylsilyl)indoles **23d** and **23e** failed and instead led to products where the silyl group had migrated [9]. Klingebiel later reported that the treatment of 1-(di-*tert*-butylfluorosilyl)indole

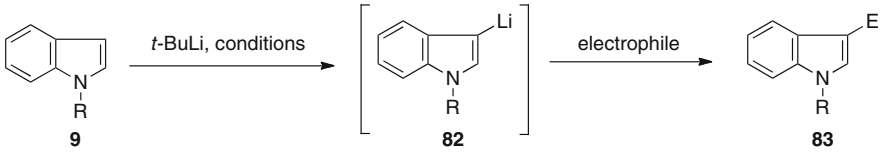
with *tert*-butyllithium led to C3-lithiation as ascertained by the 1,3-disilylindoles obtained upon quenching with fluorotrialkylsilanes [296]. This result was explored further by Iwao using *N*-(triisopropylsilyl)indole (**9a**) [17]. Treatment of **9a** with *tert*-butyllithium in the presence of TMEDA, followed by quenching with electrophiles, led to the formation of 3-(substituted)indoles **83** (Table 13, entries 1–4) in good yields. Although C2 is more acidic than C3 in *N*-(substituted)indoles (by approximately 4 pKa units as measured for indole **2** [297]), the triisopropylsilyl-protecting group blocks reactivity at C2 and also itself is not subjected to transfer. This C3-selectivity was later exploited by Satoh in reactions between *N*-(silyl) indoles and alkylidene carbenoids [258].

Iwao also observed direct lithiation at C3 with *N*-(2,2-diethylbutanoyl)indole **9b** (Table 13, entries 5–8) [18]. The yields obtained with the DEB-protecting group were somewhat lower than those obtained with the TIPS-protecting group. The optimal reaction conditions included hexane as the solvent; much lower yields were obtained when the reactions were run in ether. When superbase was used (*sec*-BuLi + *t*-BuOK), lithiation of **9b** occurred preferentially at C2.

2.8 C7-Lithiation

Although most *N*-(substituted)indoles are selectively lithiated at C2, a few protecting groups have been found to selectively direct lithiation at C7 even in the absence of groups at C2. Iwao found that the DEB (2,2-diethylbutanoyl) group directed lithiation to C7 [18]. This reaction was synthetically useful for 3-(substituted)indole

Table 13 Direct C3-lithiation of *N*-(triisopropylsilyl)indole **9a** and *N*-(2,2-diethylbutanoyl)indole **9b**



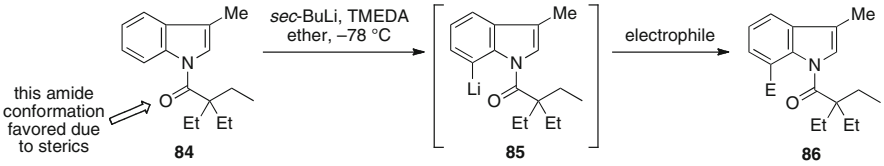
Entry	R	SM	Electrophile	E	Product	Yield (%)	Ref.
1[a]	$Si(iPr)_3$	**9a**	Me_2NCHO	CHO	**83a**	78	[17]
2[a]	$Si(iPr)_3$	**9a**	CO_2	CO_2H	**83b**	88	[17]
3[a]	$Si(iPr)_3$	**9a**	BrF_2CCF_2Br	Br	**83c**	92	[17]
4[a]	$Si(iPr)_3$	**9a**	Me_3SiCl	$SiMe_3$	**83d**	84	[17]
5[b]	$C(=O)CEt_3$	**9b**	Me_2NCHO	CHO	**83e**	49	[18]
6[b]	$C(=O)CEt_3$	**9b**	CO_2	CO_2H	**83f**	51	[18]
7[b]	$C(=O)CEt_3$	**9b**	BrF_2CCF_2Br	Br	**83g**	59	[18]
8[b]	$C(=O)CEt_3$	**9b**	Me_3SiCl	$SiMe_3$	**83h**	58	[18]

[a]Conditions: hexane, TMEDA, 0°C
[b]Conditions: hexane, PMDTA, –78°C

substrates. For example, treatment of **84** with *sec*-butyllithium in the presence of TMEDA under kinetically controlled conditions followed by quenching with various electrophiles gave 7-(substituted)indoles **86** (Table 14). The regioselectivity of the reaction is likely due to the conformation that is preferred for the amide group thus allowing the carbonyl oxygen to directed lithiation to C7. Sakagami used this strategy to prepare 7-geranyl-substituted tryptophan derivatives [221].

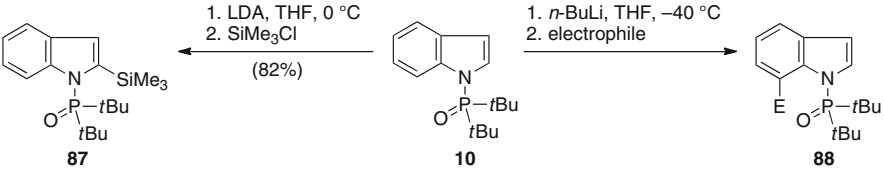
Snieckus identified a second protecting/directing group which allowed for the selective C7-lithiation of indole substrates [19]. Interestingly, the regioselectivity of the lithiation was dependent on the base. Thus, treatment of *N*-(di-*tert*-butylphosphinoyl)indole (**10**) with LDA at 0°C followed by trimethylsilyl chloride gave 2-silylindole **87**. On the other hand, the same reaction with *n*-butyllithium gave the corresponding 7-silylindole **88a**. The scope of this reaction was explored with a few substrates (Table 15). Notably, this C7-lithiation reaction worked in the absence of substituents at both C2 and C3.

Table 14 C7-lithiation of *N*-(2,2-diethylbutanoyl)indole **84**



Entry	Electrophile	E	Product	Yield (%)
1	Me_2NCHO	CHO	**86a**	17
2	CO_2	CO_2H	**86b**	65
3	BrF_2CCF_2Br	Br	**86c**	67
4	Me_3SiCl	$SiMe_3$	**86d**	75
5	$ClCO_2Et$	CO_2Et	**86e**	77
6	PhSSPh	SPh	**86f**	73

Table 15 Selective lithiation reactions of *N*-(di-*tert*-butylphosphinoyl)indole **10**

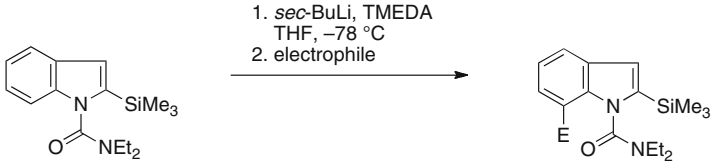


Entry	Electrophile	E	Product	Yield (%)
1	Me_3SiCl	$SiMe_3$	**88a**	72
2	MeI	Me	**88b**	93
3	$BrCH_2CH{=}CMe_2$	$CH_2{=}CMe_2$	**88c**	87
4	Me2NCHO	CHO	**88d**	53
5	$ClPPh_2$	PPh_2	**88e**	44
6	I_2	I	**88f**	78

Another method for achieving C7-lithiation involves blocking the C2 position with a removable group such as trimethylsilyl. After surveying several protecting groups, Snieckus achieved an acceptable yield with the C7-lithiation of *N*-(diethylcarbamoyl)-2-trimethylsilylindole **89**; some of the electrophiles explored are shown below [19] (Table 16).

Perhaps the most common strategy for C7-lithiation of the indole ring involves using *N*-(*tert*-butoxycarbonyl)indoline (**91**). Iwao reported the first lithiation reactions involving **91** in 1992 [298, 299]. Treatment of **91** with *sec*-butyllithium and TMEDA followed by various electrophiles gave 7-(substituted)indolines **92** (Table 17). Additional examples of this reaction have appeared in the literature

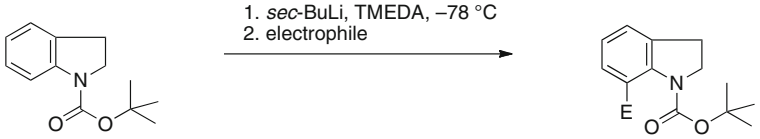
Table 16 Selective lithiation of *N*-(diethylcarbamoyl)-2-(trimethylsilyl)indole **89**



89 **90**

Entry	Electrophile	E	Product	Yield (%)
1	Me_3SiCl	$SiMe_3$	**90a**	82
2	MeI	Me	**90b**	81
3	$BrCH_2CH{=}CMe_2$	$CH_2{=}CMe_2$	**90c**	66
4	Me_2NCHO	CHO	**90d**	40
5	Bu_3SnCl	$SnBu_3$	**90e**	33
6	I_2	I	**90f**	75

Table 17 Lithiation of *N*-(*tert*-butoxycarbonyl)indoline **91**



91 **92**

Entry	Electrophile	E	Product	Yield (%)	Ref.
1	I_2	I	**92a**	59	[298]
2	MeI	Me	**92b**	91	[298]
3	Me_2NCHO	CHO	**92c**	64	[299]
4	Me_3SiCl	$SiMe_3$	**92d**	83	[298]
5	Bu_3SnCl	$SnBu_3$	**92e**	87	[302]
6	$ZnCl_2$	ZnCl	**92f**	–[a]	[303]

[a]**92f** generated and used directly in Pd-catalyzed cross-coupling reactions

[225, 300–303]. Indolines **92** can be converted into the corresponding indoles by oxidation with $Mn(OAc)_3$ [112].

Meyers [304] and Flippin [305] used the indoline C7-lithiation strategy during their respective total syntheses of the pyrrolophenanthridine natural product, oxoassoanine. Overman has used the indoline C7-lithiation strategy with C3-functionalized indolines to prepare a number of complex, indole natural products including: asperazine [306], idiospermuline [307, 308], hodgkinsine [309], quadrigemine C [310], and phenserine [311].

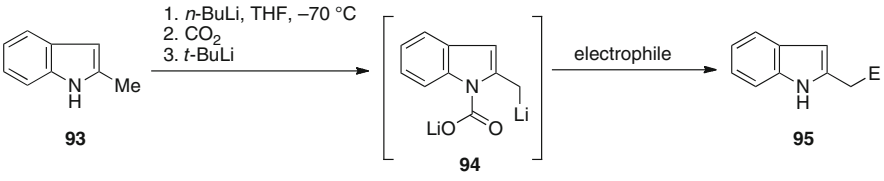
In contrast to the C7-lithiation chemistry, Beak reported that the lithiation of **91** occurred at the 2-position when the reaction conditions included the chiral auxiliary (–)-sparteine [312]. Earlier, Meyers [300] and Albrecht [313] reported the selective C2-lithiation of indoline using aminal and dithiocarbamoyl proecting groups, respectively.

As mentioned in a previous section, the iridium-catalyzed borylation of 2-(substituted)indoles gave 7-(borylated)indoles [291].

2.9 *Lateral Lithiation to a Side-Chain*

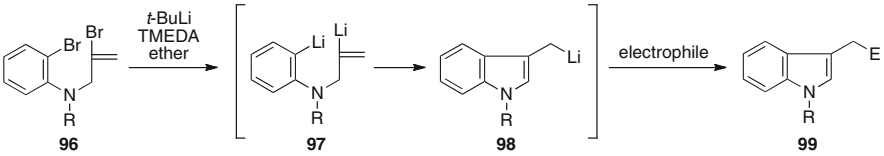
Methyl groups located at the 2-position of indole can be lithiated in the presence of certain nitrogen-protecting groups. This process, known as lateral lithiation, has most often been accomplished using the Katritzky method (in situ protection of the indole nitrogen with carbon dioxide). Katritzky converted 2-methylindole (**93**) into 2-(substituted)indoles **95** via lithio intermediate **94** (Table 18) [13]. The mechanism of this reaction has been studied by Snaith [314]. Amat and Bosch used this chemistry in developing a new approach to the *Strychnos* alkaloids [315]. Bergman

Table 18 Lateral lithiation of 2-methylindole **93**



Entry	Electrophile	E	Product	Yield (%)
1	MeI	Me	**95a**	52
2	$C_6H_{13}I$	C_6H_{13}	**95b**	93
3	Ph_2CO	$C(OH)Ph_2$	**95c**	67
4	*t*-BuNCO	CONH*t*-Bu	**95d**	61
5	CO_2	CO_2H	**95e**	70

Table 19 De novo generation of 3-lithiomethylindoles **97**



96 **97** **98** **99**

Entry	R	SM	Electrophile	E	Product	Yield (%)
1	CH_2Ph	**96a**	Me_3SiCl	$SiMe_3$	**99a**	65
2	CH_2Ph	**96a**	$(PhCH_2S)_2$	SCH_2Ph	**99b**	63
3	Me	**96b**	Me_3SiCl	$SiMe_3$	**99c**	68
4	Me	**96b**	*p*-ClC_6H_4CHO	*p*-$ClC_6H_4CH(OH)$	**99d**	71
5	Me	**96b**	PhNCO	NH(C=O)Ph	**99e**	67

[316] and Junjappa [317] each adapted this chemistry to prepare functionalized carbazoles.

Terashima explored the use of an oxazolinyl group for the lateral lithation of 2-methylindoles [274]. Mérour used a phenylsulfonyl group to direct a lateral lithiation within a 2-methyl-7-azaindole system [191].

Inagaki explored the use of superbase (*n*-butyllithium + *t*-BuOK) to generate the dianion of 2-methylindoles [318] (and other 2,3-dialkylindoles [319, 320]). This provided another method for the functionalization of the 2-methyl group of the indole ring system.

Finally, Barluenga developed a de novo synthesis approach to 3-lithiomethylindole intermediates **97** [321, 322]. Double halogen–metal exchange of dibromoaniline **96** leads to lithio intermediate **98**, which upon quenching with electrophiles gives 3-(substituted)indoles **99** (Table 19).

3 Directed Ortho Metalation

Another method for achieving metalation, via lithium–hydrogen exchange, involves the use of directed metalation groups (DMGs). Substituents such as ethers, alkoxides, halogens, carboxylates, carboxamides, sulfonamides, pyridines, and oxazolines direct metalation (metal–hydrogen exchange) to ortho positions within aromatic systems in a process known as DOM. The DOM reaction has been reviewed by Beak and Snieckus [1–3] and earlier by Gschwend and Rodriguez [8].

The selective C2-, C3-, and C7-lithiation of *N*-(substituted)indoles was covered in the previous section. This section deals with the use of carbon-based substituents to direct metalation throughout the indole ring system.

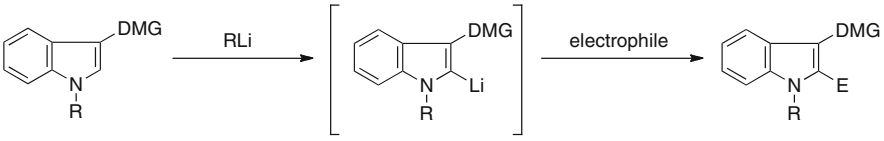
3.1 Directed Ortho Lithiation to C2

The C2-lithiation of indole has been investigated using a number of C3-based DMGs including dimethylaminomethyl (gramine), α-aminoalkoxides, carboxylic acids, carboxamides, α-alkoxyalkyl, and acetals (Scheme 19). Nitrogen-protecting groups are still used in these reactions, and the structure of the protecting group can sometimes alter the regiochemical outcome (C2 vs. C4) of the lithiation reaction.

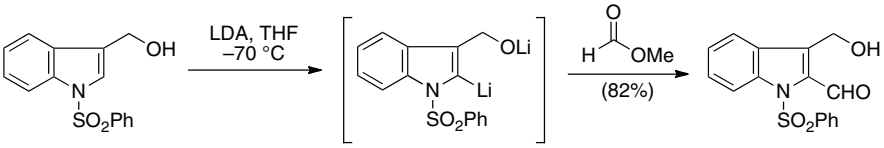
As observed earlier, *N*-(arylsulfonyl)indoles undergo selective lithiation at C2. In an extension, Gribble explored the selective C2-lithiation of 3-hydroxymethyl-*N*-(phenylsulfonyl)indole **100** and related derivatives [27, 29, 177, 178]. In this case, the deprotonated alcohol can be considered a DMG, which helps facilitate lithiation at C2. Treatment of **100** with 2.2 equivalents of LDA followed by methyl formate gave indole-2-carboxaldehyde **102** presumably via dianion intermediate **101** (Scheme 20). Methyl formate was found to give more reliable yields than DMF [29]. This sequence was used by Gribble to prepare a wide range of furo[3,4-*b*] indoles. These types of substrates have also been prepared using acetals [176] (see also [181, 182]) and silyl enol ether groups [179] located at C3.

Comins used their aminoalkoxide methodology [323] to direct C2-lithiation with an indole-3-carboxaldehyde substrate [324]. Kitagaki and Mukai later used the Comins' strategy to prepare a 2-iodoindole-3-carboxaldehyde, a precursor to a 2,3-bis(alkynyl)indole [325]. This strategy was also applied by Comins to direct lateral lithiation onto an *N*-methyl group from an aminoalkoxide generated at C2 [77].

Knight explored the C2-lithiation of indole-3-carboxylic acids [326, 327]. Similar to the reaction with alcohol **100**, two equivalents of LDA were used to generate dianion intermediates which upon quenching with electrophiles gave 2-(substituted)indole-3-carboxylic acids. This strategy was later used by Fisher



Scheme 19 General strategy for directed metalation to C2 from C3-based DMG



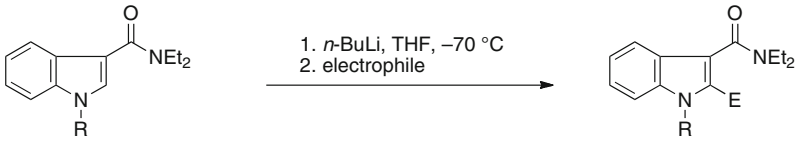
Scheme 20 Directed ortho metalation (DOM) by 3-hydroxymethyl group

and Clark to prepare large quantities of an indole-3-carboxylic acid substrate that showed CNS activity [328].

In the same series of papers, Knight also investigated the selective C2-lithiation of indole-3-carboxamides [326, 327]. In this case, *n*-butyllithium (slight excess) was used as the base instead of LDA. Treatment of indole-3-carboxamides **103** with *n*-butyllithium followed by electrophiles gave 2,3-(disubstituted)indoles **104**. A portion of the results obtained are shown below (Table 20). Snieckus used a directed lithiation of **103c** to prepare the corresponding indole-2-boronic acid, a useful building block for the synthesis of indolocarbazoles [329].

Iwao [16] and Somei [330] investigated the lithiation of gramine derivatives **105** (Scheme 21). Depending on the nitrogen substituent, lithiation can occur at either C2 or C4. With *N*-methylgramine **105a** and *N*-methoxygramine **105b**, lithiation occurs at C2 giving **106a** and **106b** upon quenching with trimethylsilylchloride. On the other hand, with *N*-(triisopropylsilyl)gramine **8**, lithiation occurs preferentially at C4 giving **107**. Trimethylsilyl group also can serve as a block group; lithiation of **106** also gave C4-substituted products via a selective C4-lithiation.

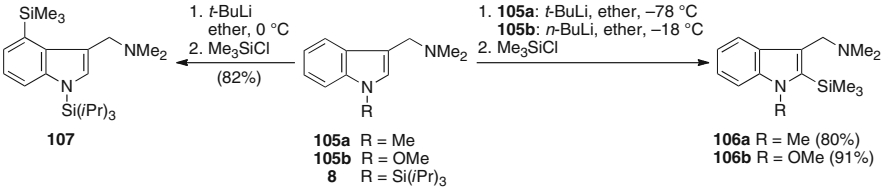
Table 20 Directed ortho metalation (DOM) by 3-carboxamide group



103 **104**

Entry	R	SM	Electrophile	E	Product	Yield (%)	Ref.
1	CH_2OMe	**103a**	MeI	Me	**104a**	91	[327]
2	CH_2OMe	**103a**	PhCHO	CH(OH)Ph	**104b**	86	[327]
3	CH_2OMe	**103a**	PhCOMe	CMe(OH)Ph	**104c**	26	[327]
4	SO_2Ph	**103b**	MeI	Me	**104d**	75	[327]
5	SO_2Ph	**103b**	PhCHO	CH(OH)Ph	**104e**	70	[327]
6	SO_2Ph	**103b**	PhCOMe	CMe(OH)Ph	**104f**	0	[327]
7[a]	Me	**103c**	$B(OMe)_3$	$B(OH)_2$	**104g**	59	[329]

[a]Utilized *sec*-BuLi/TMEDA for deprotonation



107

105a R = Me
105b R = OMe
8 R = Si(*i*Pr)$_3$

106a R = Me (80%)
106b R = OMe (91%)

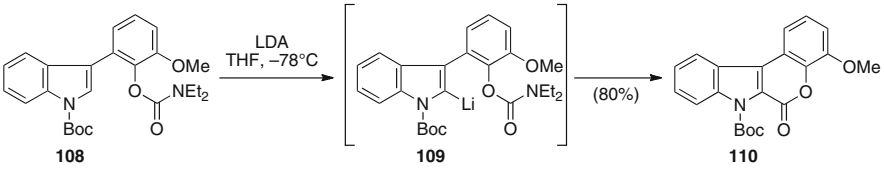
Scheme 21 Regioselective lithiation of gramines

Snieckus has investigated the directed remote lithiation of indoles at C2 in the context of preparing fused heterocycles [23, 224]. The synthesis of indolo[2,3-*c*]benzo[*e*]pyran-6-one **110** is illustrative (Scheme 22) [224]. Treatment of **108** with LDA led to the formation of **110** via cyclization of lithio intermediate **109**. Bisagni used a similar sequence to prepare benzo[*f*]indolo-6,11-quinones [331].

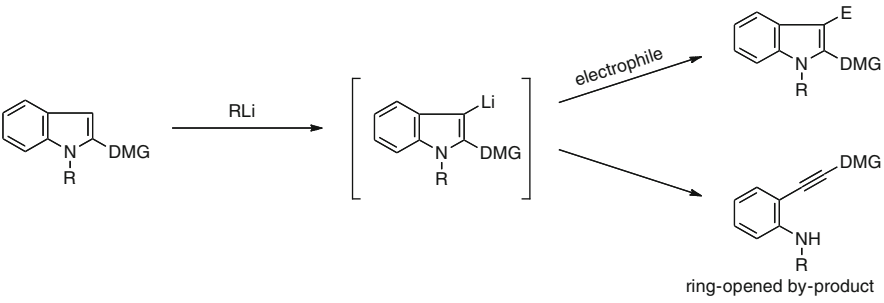
3.2 Directed Ortho Lithiation to C3

The C3-lithiation of indole has been investigated using a number of C2-based DMGs including pyridyl, α-aminoalkoxides, carboxylic acids, and carboxamides (Scheme 23). In some cases, the 3-lithio intermediates give products derived from ring opening reactions rather than 3-substitution; this is dependent upon electronic factors regarding the nitrogen substituent and the DMG.

Gribble was the first to investigate the use of a C2-based DMG (pyridyl) to direct lithiation to the C3 position of the indole ring [332]. Treatment of 2-pyridylindole **111** with *n*-butyllithium followed by quenching with electrophiles gave 2-pyridyl-3-(substituted)indoles **113** in moderate yields via lithio intermediate **112** (Table 21); **112** proved to be unexpectedly stable and only underwent ring fragmentation upon heating to 50°C. Gribble used this strategy in the synthesis of the zwitterionic natural products flavopereirine [333] and sempervirine [32]. More recently, Lipinskia followed this strategy to prepare sempervirine analogs [334].

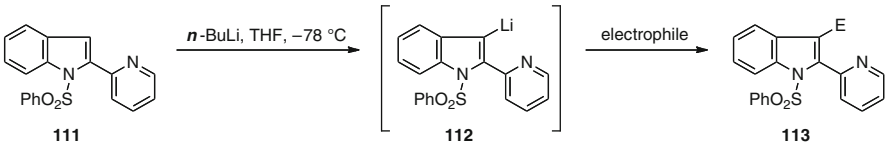


Scheme 22 Directed remote C2-lithiation leading to fused indoles

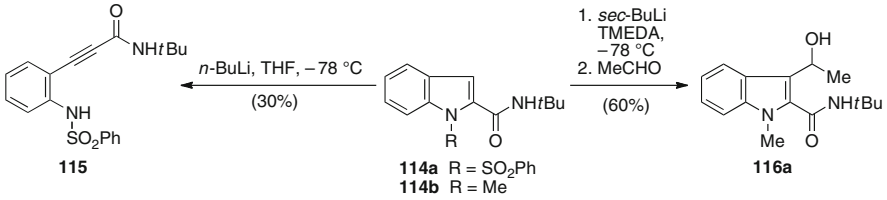


Scheme 23 General strategy for directed metalation to C3 from C2-based DMG

Table 21 Directed ortho metalation (DOM) by a C2-pyridyl substituent



Entry	Electrophile	E	Product	Yield (%)
1	MeI	Me	**113a**	74
2	CO_2	CO_2H	**113b**	58
3	Me_3SiCl	$SiMe_3$	**113c**	51
4	MeCHO	CH(OH)Me	**113d**	68
5	$ClCO_2Et$	CO_2Et	**113e**	55

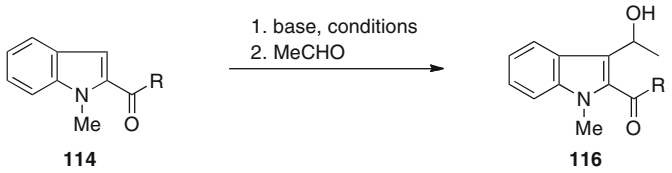


Scheme 24 Lithiation of indole-2-carboxamides **114**

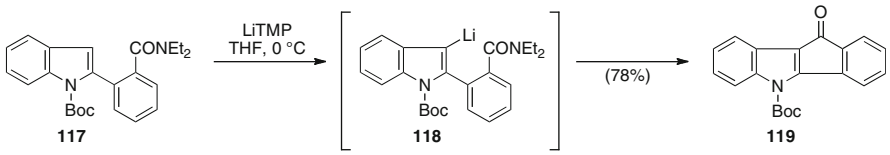
Gribble also explored the lithiation of indole-2-carboxamides [332] (Scheme 24). In this case, the nature of the protecting group altered the reaction outcome. With *N*-(phenylsulfonyl)indole-2-carboxamide **114a**, treatment with *n*-butyllithium led to alkyne **115**. Replacing the phenylsulfonyl group with a methyl group averted the ring fragmentation. Treatment of (*N*)-methylindole-2-carboxamide **114b** with *sec*-butyllithium and TMEDA (*n*-butyllithium failed to generate C3-anion) followed by acetaldehyde gave 2,3-di(substituted)indole **116a**. Rubiralta also reported a ring fragmentation with an *N*-(phenylsulfonyl)indole containing a dithianyl side-chain at C2 [113].

Pujol has examined carboxylic acids (Table 22, entry 5) [335], carboxamides (Table 22, entries 2–3) [335], and hydrazinecarbonyls (Table 22, entry 4) [336] as directing groups for the selective C3-lithiation of indole. The different protecting groups (including the one result from Gribble) are compared below. The best result was obtained using an *N*-ethylcarboxamido group. Interestingly, lithation of indole-2-carboxylic acid failed to yield any product. On the other hand, lithiation of *N*-(methoxymethyl)indole-2-carboxylic acid with *sec*-butyllithium in the presence of HMPA successfully gave C3-substituted indoles [337].

Table 22 Comparing C2-DMGs



Entry	R	SM	Base, conditions	Product	Yield (%)	Ref.
1	NH*t*Bu	**114b**	*sec*-BuLi, TMEDA	**116a**	60	[332]
2	NHEt	**114c**	*t*-BuLi, TMEDA	**116b**	100	[335]
3	NEt_2	**114d**	*t*-BuLi, TMEDA	**116c**	70	[335]
4	$NHNMe_2$	**114e**	*t*-BuLi, TMEDA	**116d**	78	[336]
5	OH	**114f**	*t*-BuLi, TMEDA	**116e**	0	[335]



Scheme 25 Directed remote C3-lithiation leading to fused indoles

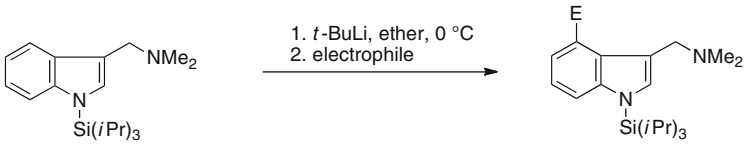
Snieckus reported a directed remote lithiation at C3 of the indole ring system [295]. Treatment of 2-arylindole **117** with LiTMP led to fused indole **119** via 3-lithioindole intermediate **118** (Scheme 25).

3.3 Directed Ortho Lithiation to C4 from C3

Directed lithiation of gramine derivatives is one of the best methods for preparing 4-(substituted)indoles. Iwao has investigated the selective C4-lithiation of gramine derivatives in great detail. The most common substrate for C4-lithiation is *N*-(triisopropylsilyl)gramine **8** [16]; the triisopropylsilyl group serves to block C2-lithiation. Lithiation at C2 can also be blocked using removable trimethylsilyl-protecting groups (e.g., **106**) [16, 330]. A survey of the electrophiles introduced to C4 using this chemistry appears below (Table 23).

Gramines **120** can be transformed into many interesting indole products. The dimethylamino group can be replaced in two steps by quaternization with methyl iodide followed by treatment with fluoride in the presence of nucleophiles (elimination–addition) [342]. Waldmann converted **120e** and **120f** into the

Table 23 Selective C4-lithiation of gramine



Entry	Electrophile	E	Product	Yield (%)	Ref.
1	Bu_3SnCl	$SnBu_3$	**120a**	78	[16]
2	PhSSPh	SPh	**120b**	70	[16]
3	I_2	I	**120c**	58	[16]
4	Me_2NCHO	CHO	**120d**	57	[16]
5	MeI	Me	**120e**	69	[338]
6	EtI	Et	**120f**	62	[338]
7	$ZnCl_2$	ZnCl	**120g**	–[a]	[102]
8	Me_2C=CHCHO	CH(OH)=CMe_2	**120h**	82	[33]
9	$(SiMe_3)_2O$	OH	**120i**	64	[339]
10	Cl_3CCl_3	Cl	**120j**	66	[339]
11	$BrCH_2CH_2Br$	Br	**120k**	56	[339]
12	CBr_4	Br	**120k**	60	[340]
13	MeCHO	CH(OH)Me	**120l**	70	[340]
14	H_2C=CHCHO	CH(OH)=CH_2	**120m**	80	[340]
15	$Me_3SiCH_2N_3$	NH_2	**120n**	79	[341]

[a]Zincate **120g** was generated and used directly in Pd-catalyzed cross-coupling reactions leading to 4-arylindoles

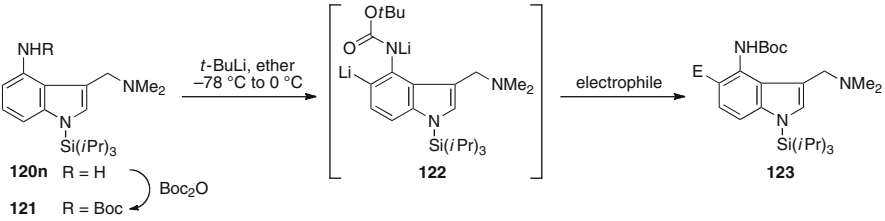
corresponding tryptophan derivatives [338]. Iwao prepared **120h** en route in a total synthesis of clavicipitic acids [33, 34]. Iwao also used this C4-lithiation methodology with 6-methoxy-*N*-(triisopropylsilyl)gramine during a total synthesis of the makaluvamines [343] and also veiutamine [344]. Kirk used the methodology to prepare 4-fluoroserotonin and 4-fluoromelatonin [345].

Pérez-Castells found that treatment of *N*-(triisopropylsilyl)-3-methoxymethylindole also gave 4-(substituted)indoles although the yields tended to be lower than the corresponding gramine derivatives [340].

3.4 Directed Ortho Lithiation in Benzenoid Ring

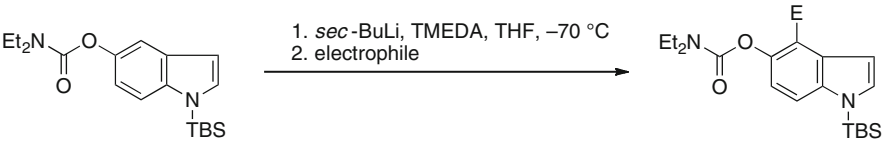
Carboxamides, carbamates, and halogens have served as DMGs for lithiation in the benzenoid portion of the indole ring. In an extension of the C4-lithiation chemistry, Iwao transformed 4-aminogramine **120n** into carbamate **121**, which then underwent selective lithiation at C5 (Table 24) [341]. Treatment of **121** with three equivalents of *t*-butyllithium followed by various electrophiles gave 3,4,5-(trisubstituted)indoles **123** via dianion **122**. This chemistry was also investigated

Table 24 Synthesis of 3,4,5-(trisubstituted)indoles **122**



Entry	Electrophile	E	Product	Yield (%)
1	MeI	Me	**123a**	91
2	Cl_3CCCl_3	Cl	**123b**	83
3	BrF_2CCBrF_2	Br	**123c**	81
4	Me_2NCHO	CHO	**123d**	82
5	PhCHO	CH(OH)Ph	**123e**	81
6	*t*-BuNCO	C(=O)NH*t*Bu	**123f**	65

Table 25 Selective C4-lithiation of indole 5-*O*-carbamates **124**



Entry	Electrophile	E	Product	Yield (%)
1	MeI	Me	**125a**	99
2	Me_2NCHO	CHO	**125b**	96
3	$ClCO_2Et$	CO_2Et	**125c**	43
4	I_2	I	**125d**	79
5	Cl_3CCCl_3	Cl	**125e**	90

with the corresponding 6-methoxyindole derivatives [341] and fused indole derivatives [346].

Snieckus reported the selective C4-lithiation of indole 5-*O*-carbamate **124** [3, 347, 348]. Treatment of **124** with *sec*-butyllithium and TMEDA followed by electrophiles gave 4,5-(disubstituted)indoles **125** (Table 25) [347]. Unexpectedly, the lithiation of 3-substituted derivatives of **124** led to C6-lithiation as demonstrated by formylation at C6 upon quenching with DMF.

Dodd explored the metalation of *N*-sulfonamidoindole-5-carboxamides [349]. Metalation at the 2-position was blocked by incorporation of a trimethylsilyl group (or by utilizing the corresponding indoline derivative). Treatment of protected

indole-5-carboxamide with *sec*-butyllithium followed by electrophiles gave products derived from C4-lithiation.

Tois investigated the solid-phase lithiation of resin-bound indole-5-carboxamides. The reactions led to the mixtures of products derived from C4- and C6-lithiation [350].

Schlosser investigated the use of halogens (fluorine and chlorine) as DMGs in the benzenoid portion of indole rings [351, 352]. This chemistry was used to introduce halogens at all possible positions C4 through C7.

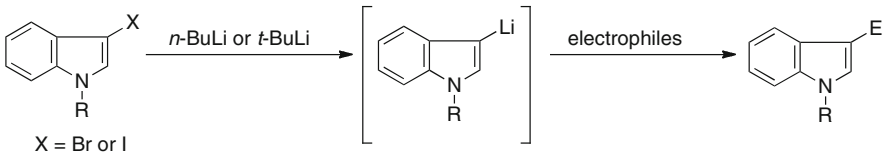
4 Halogen–Metal Exchange

The final method for generating metalated indoles that will be covered in this monograph involves halogen–metal exchange processes. Halogen–metal exchange, most often halogen–lithium exchange, is an excellent method for controlling the regiochemistry of metalation and is particularly useful for metalating sites that are typically unreactive. Halogen–metal exchange is one of the best methods for the regiocontrolled preparation of 3-(substituted)indoles from 3-haloindoles (Scheme 26). Reviews of the halogen–metal exchange reactions have been published by Parham [353] and more recently by Lete [354].

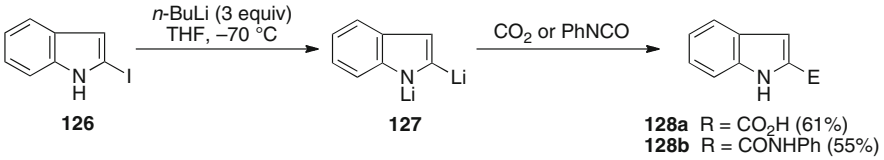
4.1 Halogen–Lithium Exchange at C2

Likely due to the propensity for most *N*-(substituted)indoles to undergo selective hydrogen–lithium exchange at C2, there have only been a few reports involving halogen–lithium exchange at C2. Often, these are found in the context of groups that could activate other positions to lithiation [355–358]. One example of a simple 2-(substituted)indole substrate undergoing halogen–metal exchange was reported by Kaufmann [74]. They reported the conversion of 2-iodo-*N*-methylindole into an indol-2-ylborane via 2-lithioindole **11** generated by iodine–lithium exchange.

Herbert reported modest success in the generation of double anion **127** by treatment of 2-iodoindole (**126**) with *n*-butyllithium [359] (Scheme 27). Quenching with **127** with different electrophiles (two shown) then gave 2-(substituted)indoles

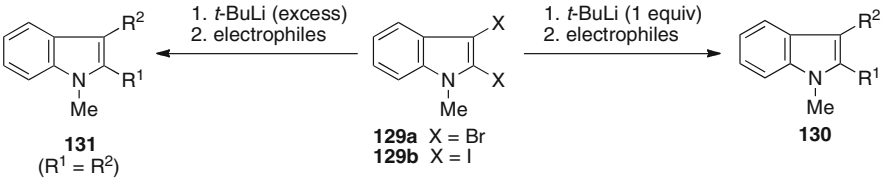


Scheme 26 Halogen–metal exchange involving 3-haloindole substrates



Scheme 27 Generation and reactions of 1,2-dilithioindole **127**

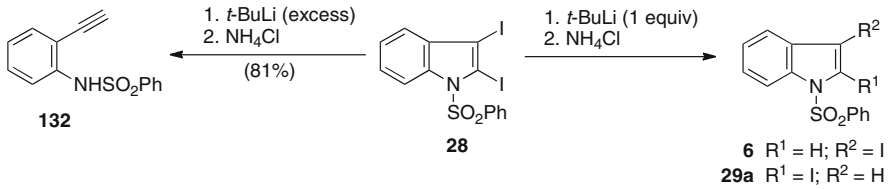
Table 26 Halogen–metal exchange reactions of 2,3-dihalo-*N*-methylindoles



Entry	SM	Electrophile	R^1	R^2	Product	Yield (%)	Ref.
1	**129a**	NH_4Cl	H	Br	**130a**	99	[246]
2	**129a**	Me_2NCHO	CHO	Br	**130b**	86	[246]
3	**129a**	MeI	Me	Br	**130c**	97	[246]
4	**129b**	CO_2	CO_2H	Br	**130d**	85	[246]
5	**130c**	Me_2NCHO	Me	CHO	**130e**	88	[246]
6	**129b**	NH_4Cl	H	H	**2**	99	[248]
7	**129b**	Me_2NCHO	CHO	CHO	**131a**	82	[248]
8	**129b**	$ClCO_2Me$	CO_2Me	CO_2Me	**131b**	75	[248]
9	**129b**	CO_2	CO_2H	CO_2H	**131c**	66	[248]
10	**129a**	$[C_7H_7]^+BF_4^-$	Br	C_7H_7	**130f**	56	[360]
11	**129b**	$[C_7H_7]^+BF_4^-$	I	C_7H_7	**130g**	54	[360]

128. Much earlier, Shirley and Roussell had failed in attempt to generate **127** by treating indole (**56**) with excess *n*-butyllithium [7].

Gribble has explored halogen–metal exchange reactions of 2,3-dihaloindole substrates **129** (Table 26). Treatment of 2,3-dibromo-*N*-methylindole (**129a**) with one equivalent of *tert*-butyllithium followed by different electrophiles gave 3-bromo-2-(substituted)indoles **130** [246]. Subsequent treatment of **130d** with additional *tert*-butyllithium then allowed for replacement of the C3 bromine atom (Table 26, entry 5). With 2,3-diiodo-*N*-methylindole (**129b**), only dilithiation reactions were studied [248]. Treatment of **129b** with excess *tert*-butyllithium followed by different electrophiles gave 2,3-(disubstituted)indoles **131**. Interestingly, Yamamura later reported conflicting results regarding mono-halogen–metal exchange reactions with both **129a** and **129b** [360] (Table 26, entries 9–10). Treatment of either **129a** or **129b** with one equivalent of *tert*-butyllithium followed by quenching with tropylium ion led to products derived from the selective lithiation–halogen exchange at C3 and not C2. Both reports show compelling



Scheme 28 Halogen–metal exchange reactions of 2,3-diiodo-*N*-(phenylsulfonyl)indole (**28**)

evidence for their results; Gribble prepared known materials whereas Yamamura obtained X-ray crystal structures. In addition, Yamamura followed a different route to prepare the regioisomers [360].

Compared to **129**, halogen–metal exchange with 2,3-diiodo-*N*-(phenylsulfonyl) indole (**28**) was more complicated [361] (Scheme 28). Treatment of **28** with one equivalent of *tert*-butyllithium followed by ammonium chloride led to a (undetermined) mixture of 2-iodo-*N*-(phenylsulfonyl)indole (**29a**) and 3-iodo-*N*-(phenylsulfonyl)indole (**6**). On the other hand, mixing **28** with excess *tert*-butyllithium led to alkyne **132** via a facile ring fragmentation.

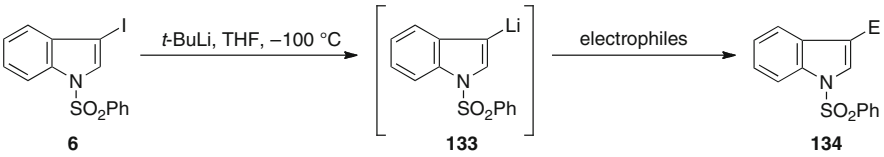
4.2 Halogen–Lithium Exchange at C3

Halogen–lithium exchange at the C3 position has been thoroughly explored and developed. Gribble reported the first example in 1982 with 3-iodo-*N*-(phenylsulfonyl)indole (**6**) [14]. Treatment of **6** with two equivalents of *tert*-butyllithium at –100°C led to the formation of unstable 3-lithioindole intermediate **133**. Quenching **133** at low temperatures (usually –100°C) gave 3-(substituted)indoles **134** (Table 27). During the synthesis of isoellipticine and 6-methoxyisoellipticine, Gribble generated **133** (and the 6-methoxy analog of **133**) and quenched with 3,4-pyridinedicarboxylic acid anhydride giving a ketoacid intermediate en route to a total synthesis of ellipticine [173].

There is one major drawback with using **133**. At temperatures above –100°C, 3-lithioindole **133** rearranges to 2-lithioindole **24** as evidenced by the formation of 2-methyl-*N*-(phenylsulfonyl)indole upon quenching with 2-iodomethane [14] (see also [363]). This rearrangement spurred the search for alternatives.

A major advance came from Amat and Bosch in 1994 [364]. They showed that halogen–lithium exchange reactions of 3-bromo-*N*-(*tert*-butyldimethylsilyl)indole (**135**) gave 3-lithioindole intermediate **136**, which did not suffer ring fragmentation or rearrangement to the corresponding 2-lithioindole intermediate (even at room temperature). Since then, a number of reports have used this transformation for the preparation of 3-(substituted)indoles **137**, and selected results are summarized below (Table 28). The silyl-protecting group can be conveniently removed

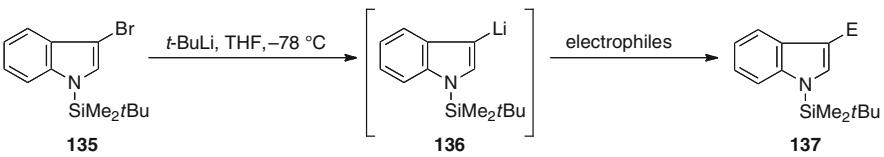
Table 27 Halogen–metal exchange reactions of 3-iodo-*N*-(phenylsulfonyl)indole (**6**)



Entry	Electrophile	E	Product	Yield (%)	Ref.
1	MeI	Me	**134a**	62	[14]
2	$ClCO_2Et$	CO_2Et	**134b**	51	[14]
3	PhCHO	CH(OH)Ph	**134c**	89	[14]
4	Me_2NCHO	CHO	**134d**	71	[14]
5	PhSSPh	SPh	**134e**	84	[14]
6	$SiMe_3Cl$	$SiMe_3$	**134f**	76	[14]
7[a]	Oxirane	CH_2CH_2OH	**134g**	87	[31]
8[a]	$B(OMe)_3$	$B(OH)_2$	**134h**	47	[362]
9[a]	$B(OiPr)_3$	$B(OH)_2$	**134h**	85	[231]
10	$ZnCl_2$	ZnCl	**134i**	–[b]	[102]
11	Me_3SnCl	$SnMe_3$	**134j**[c]	85	[144]

[a]Prepared by halogen–metal exchange of 3-bromo-*N*-(phenylsulfonyl)indole
[b]Zincate **134i** was generated and used directly in Pd-catalyzed cross-coupling reactions leading to 3-arylindoles
[c]**134j** = *N*-(toluenesulfonyl)-3-(trimethylstannyl)indole which was prepared by halogen–metal exchange of 3-bromo-*N*-(toluenesulfonyl)indole

Table 28 Halogen–metal exchange reactions of 3-bromo-*N*-(*tert*-butyldimethylsilyl)indole (**135**)



Entry	Electrophile	E	Product	Yield (%)	Ref.
1	MeI	Me	**137a**	95	[364]
2	EtI	Et	**137b**	96	[373]
3	$ClCO_2Et$	CO_2Et	**137c**	84	[364]
4	CO_2	CO_2H	**137d**	94	[364]
5	PhCHO	CH(OH)Ph	**137e**	67	[364]
6	Me_3SnCl	$SnMe_3$	**137f**	94	[364]
7	$ZnCl_2$	ZnCl	**137g**	–[a]	[150, 374]
8	$B(OMe)_3$	$B(OH)_2$	**137h**	–[b]	[371]

[a]Zincate **137g** was generated and used directly in Pd-catalyzed cross-coupling reactions leading to 3-arylindoles
[b]Boronic acid **137h** was generated and used directly in Pd-catalyzed cross-coupling reaction leading to an imidazole-substituted indole

by treatment with tetrabutylammonium fluoride. Additional examples of this transformation [249, 365–369] including benzene ring functionalized indoles [228, 347, 370, 371] have also appeared in the literature. In addition, *N*-(triisopropylsilyl)-3-bromoindole **83c** [372] and methoxy-substituted derivatives [370] have been investigated and worked well.

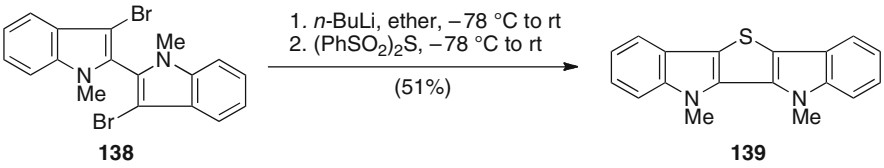
Liu used a double halogen–lithium exchange to prepare diindolo[3,2-*b*:4,5-*b*′] thiophenes (e.g., **139**). For example, treatment of 3,3′-dibromo-2,2′-biindole **138** with *n*-butyllithium followed by quenching with bis(phenylsulfonyl) sulfide gave **139** (Scheme 29) [60].

Halogen–lithium exchange reactions have also been applied to the functionalization of 3-bromo-*N*-(benzyl)indole [375] and an *N*-reverse prenylated 3-bromoindole [376].

4.3 Halogen–Lithium Exchange in Benzenoid Ring

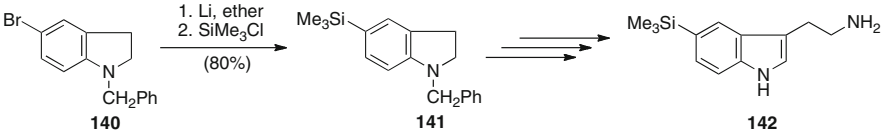
Compared to halogen–lithium exchange at C3, relatively few studies have examined halogen–lithium exchange in the benzenoid moiety of the indole ring. An early example was reported by Zilkha and co-workers with 5-bromoindoline **140** [377]. Treatment of **140** with lithium metal followed by trimethylsilyl chloride gave 5-trimethylsilylindoline **141** (Scheme 30). The latter was converted into a number of indole derivatives including 5-trimethylsilyltryptamine (**142**). Much later, Dodd used a similar reaction to prepare an indoline-5-carboxamide derivative, which was then converted into 4,5-(disubstituted)indoles via DOM [349].

Rapoport developed a method of bromine–lithium exchange involving bromoindoles **7** lacking substitution on nitrogen [15]. The reaction was started by treating



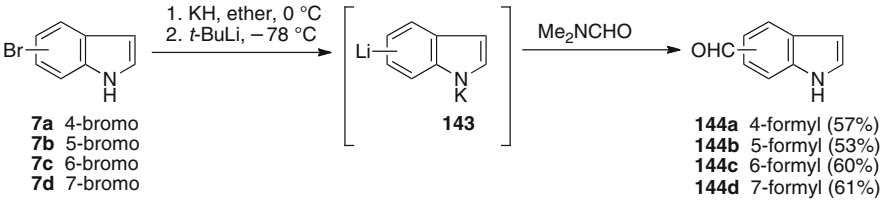
138 **139**

Scheme 29 Double bromine–lithium exchange reaction



140 **141** **142**

Scheme 30 Bromine–lithium exchange of 5-bromo-(*N*)-benzylindoline (**140**)



Scheme 31 Bromine–lithium exchange of bromoindoles **7**

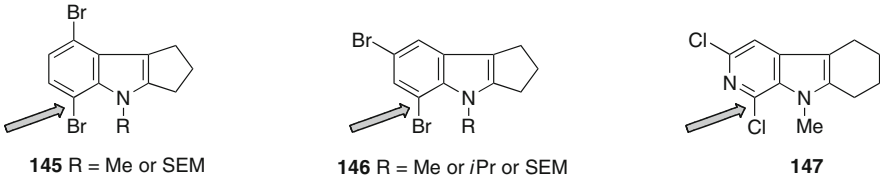


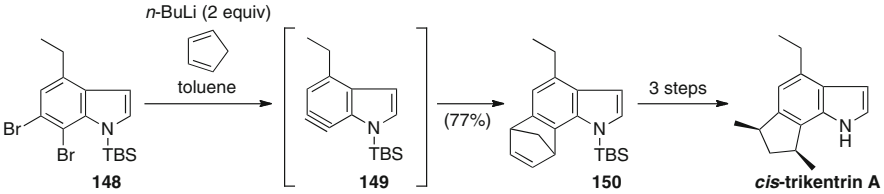
Fig. 5 Regioselectivity of halogen–metal exchange reactions with dihalogenated substrates

the bromoindoles **7** with potassium hydride followed by *tert*-butyllithium to generate dianions **143**. Quenching **143** with dimethylformamide then gave formylindoles **144** (Scheme 31). Weinreb amides were also used as electrophiles which gave ketoindoles. Martin used this method in the synthesis of additional 5-(substituted) indole derivatives [378].

Sauer used bromo–lithium exchange reactions to prepare benzene ring-substituted ergoline derivatives [379]. Andersen used a bromine–lithium exchange reaction to generate 5-lithio-*N*-(4′-fluorophenyl)indole, which was transmetalated to both the corresponding indole-5-zincate and indole-5-stannane [380]. Tois prepared an indole-5-carboxylic acid by bromine–lithium exchange followed by quenching with carbon dioxide [350].

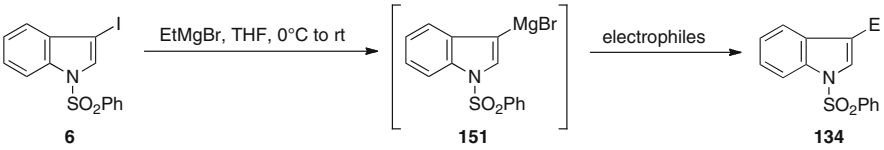
The regioselectivity of bromine–lithium exchange reactions in dibromoindole substrates has been studied by Li [381, 382]. With both 4,7-dibromoindoles (e.g., **145**) [382] and 5,7-dibromoindoles (e.g., **146**) [381], bromine–lithium exchange occurs preferentially at C7 (Fig. 5) upon treatment with *tert*-butyllithium. A similar result was reported recently by Lachance involving the selective chlorine–lithium exchange observed with 6-azaindole **147** [383].

Buszek has used bromine–lithium exchange reactions to generate 4,5-, 5,6-, and 6,7-indolyne derivatives [384–387]. Their total synthesis of *cis*-trikentrin A is illustrative of the power of their methodology (Scheme 32) [386]. Treatment of 6,7-dibromoindole **148** with two equivalents of *n*-butyllithium in the presence of cyclopentadiene gave cycloadduct **149**. The latter was converted into *cis*-trikentrin A in three additional steps.



Scheme 32 Generating a 6,7-indolyne derivative via bromine–lithium exchange

Table 29 Generation and reactions of indol-3-yl Grignard reagent



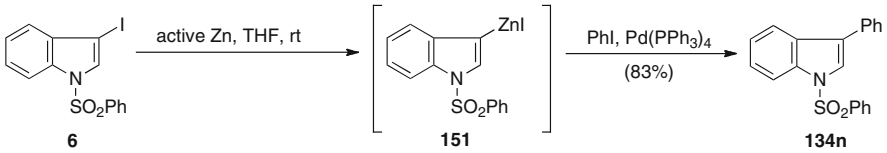
Entry	Electrophile	E	Product	Yield (%)
1	PhCHO	CH(OH)Ph	**134c**	82
2	EtCHO	CH(OH)Et	**134k**	65
3	$[CH_2O]n$	CH_2OH	**134l**	48
4[a]	CO_2[a]	CO_2Me	**134m**	85
5[b]	PhI[b]	Ph	**134n**	50

[a]Intermediate treated with diazomethane to give methyl ester **134m**
[b]Reaction run with $Pd(PPh_3)_4$

4.4 Indolyl Grignard Reagents

Another method used for halogen–metal exchange involves treating haloindoles with Grignard reagents (usually ethylmagnesium bromide or isopropylmagnesium chloride). Sakamoto investigated halogen–magnesium exchange reactions with 3-iodoindole **6** (Table 29) [388]. Treatment of **6** with ethylmagnesium bromide gave indoly-3-yl Grignard **151**; quenching with electrophiles then gave 3-(substituted)indoles **134**. Unlike the corresponding 3-lithioindole intermediate **133**, **151** did not rearrange to form the indol-2-yl Grignard reagent even at room temperature. Sakamoto also investigated the formation of the indol-2-yl Grignard reagent derived from 2-iodo-*N*-(phenylsulfonyl)indole (**29a**) [388] and this also worked well.

The reactions of indolyl Grignard reagents, generated in this fashion, have been explored further by others [389–392]. A regioselective Grignard formation at C2 occurred upon treatment of 2,3-diiodo-*N*-(phenylsulfonyl)indole (**28**) with isopropylmagnesium chloride [393].



Scheme 33 Generation and reaction of indol-3-ylzinc iodide

Indolyl Grignard reagents have also been generated by direct deprotonation with a magnesium base (e.g., iPr$_2$NMgBr) [281] and also by transmetalation of lithioindole intermediate **11** (Table 1, entry 2) [61].

4.5 Halogen–Metal Exchange with Other Metals

In addition to the extensive use of lithium and magnesium, halogen–metal exchange of haloindole substrates has been investigated with zinc, copper, boron, and tin.

Sakamoto reported the generation of indol-3-ylzinc iodide **152** by mixing 3-iodo-*N*-(phenylsulfonyl)indole **6** with active zinc [363] (Scheme 33). Treatment of **152** with iodobenzene and a palladium catalyst provided another route to 3-phenylindole **134n**. Knochel reported the formation of indol-3-ylzincs by treating **6** with iPr$_2$Zn and Li(Acac) [394]. Sakamoto generated indol-2-ylzincates by treating 2-iodo-*N*-(phenylsulfonyl)indole with Me$_3$ZnLi/TMEDA [395].

Finally, a few examples of boron–iodine exchange [396], tin–iodine exchange [137, 397], and copper–iodine (via cuprate) exchange [398, 399] have appeared in the literature. Cupration of 2,3-diiodo-*N*-(phenylsulfonyl) preferentially occurred at C2 [398, 399].

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Metal-Catalyzed Cross-Coupling Reactions for Indoles

Jie Jack Li and Gordon W. Gribble

Abstract Metal-catalyzed cross-coupling reactions for indoles are reviewed. Palladium-catalyzed cross-coupling reactions are the most widely explored and applied of all metal-catalyzed cross-coupling reactions. Applications of Kumada coupling, Negishi coupling, Suzuki coupling, Stille coupling, Sonogashira reaction, the Heck reaction, carbonylation, and C–N bond formation reactions in indoles are summarized. In addition, other transition metal-catalyzed cross-coupling reactions using copper, rhodium, iron, and nickel in indole synthesis are also discussed.

Keywords Copper · Cross-coupling · Heck · Indole · Palladium · Stille · Suzuki

Contents

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1 Introduction

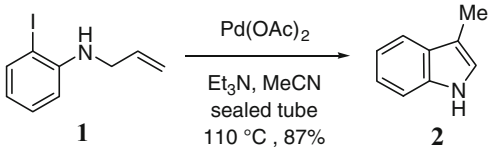
Metal-catalyzed cross-coupling reactions have emerged as an important advancement in organic chemistry during the last few decades. Meanwhile, due to the importance of indoles in medicinal chemistry and many other fields, metal-catalyzed cross-coupling reactions have been extensively applied in the field of indole synthesis. While many books and reviews [1–3] have been published in the field, a book by the authors is solely dedicated to *Palladium in Heterocyclic Chemistry* [4]. In this chapter, we will cover applications of palladium- and other transition metal-catalyzed cross-coupling reactions in indole synthesis and reactions.

2 Palladium-Catalyzed Cross-Coupling Reactions

2.1 Mori–Ban Indole Synthesis

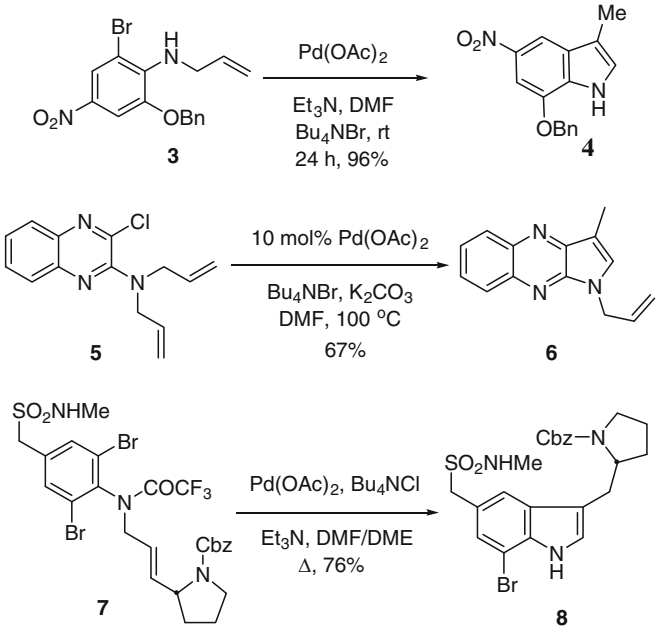
The Mori–Ban indole synthesis [5–12], the intramolecular version of the Heck reaction as applied to the synthesis of indoles, is not a *cross*-coupling reaction per se, but it is covered here due to its importance in assembling the indole core.

The cyclization of *o*-halo-*N*-allylanilines to indoles is a general and efficient methodology. For example [5], the conversion of **1** and **2** can be performed at low temperature, shorter reaction times, and with less catalyst to give 3-methylindole (**2**) in 87% yield.

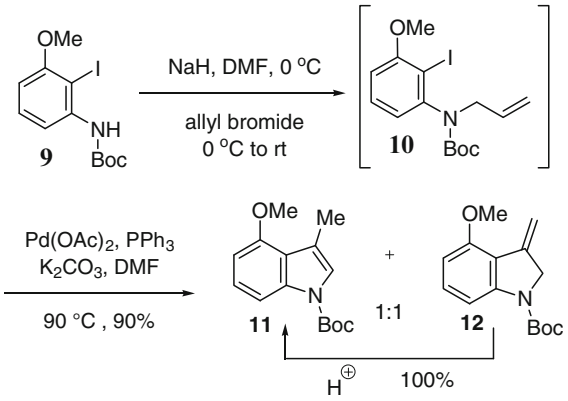


1 **2**

Larock's improved method [13–18], which has been widely adopted, involves catalytic (2%) $Pd(OAc)_2$, *n*-Bu_4NCl, DMF, base (usually Na_2CO_3), 25°C, and 24 h (also known as the "Jeffrey's conditions"). Larock extended his work in several ways, particularly with regard to Pd-catalyzed cross-coupling of *o*-allylic and *o*-vinylic anilides with vinyl halides and triflates to produce 2-vinylindoles. The related "Larock indole synthesis" is discussed separately in the next section. In a program to synthesize CC-1065 analogs, Sundberg prepared indole **4** from *o*-bromo-*N*-allylaniline **3** in excellent yield [19] using the Jeffrey's conditions. Silver carbonate and sodium carbonate were less effective than triethylamine. One of the present authors (JJL) took advantage of the Mori–Ban indole synthesis using the Jeffrey's conditions to prepare a series of quinoxalinyl-pyrrole derivatives such as **6** from chloro-allylamino-quinoxalines such as **5** [20].

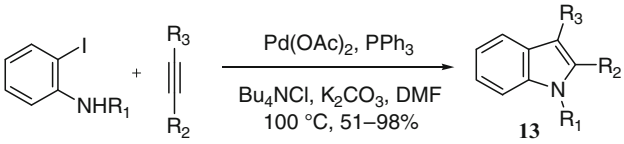


Macor also exploited the Mori–Ban indole synthesis to synthesize several anti-migraine analogs of Sumatriptan and homotryptamines as potent and selective serotonin reuptake inhibitors [21, 22]. Noticeably, the presence of the second bromine (the bromine "passenger") on substrate **7** was not significantly deleterious to the reaction although a small amount of the 7-bromoindole **8** might be sacrificed at the end of the reaction to consume the active palladium catalyst. The approach to 7-bromoindole **8** could provide a general method accessing 7-bromoindoles (a rare class of indole derivatives), which then could be further adapted to the synthesis of more complex 7-substituted indoles.



Recently, Cook's group described their Mori–Ban indole synthesis of substrate **10**, easily assembled from **9** [23]. The intramolecular cyclization gave a 1:1 mixture of indole **11** and *exo*-3-methylene-indoline **12**, which was readily converted to **11** upon treatment with acid. By changing the base from K_2CO_3 to Ag_2CO_3, the Mori–Ban reaction gave *exo*-3-methylene-indoline **12** exclusively in 90% yield.

2.2 *Larock Indole Synthesis*

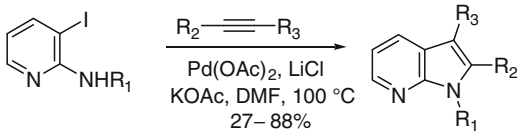


R_1 = H, Me, Ts
R_2, R_3 = *n*-Pr, *t*-Bu, cyclohexyl, TMS, Ph, CH_2OH, C(Me) = CH_2, $(CH_2)_2OH$, CMe_2OH

Larock and coworkers described the one-step Pd-catalyzed reaction of *o*-haloanilines with internal alkynes to give indoles [24, 25]. This excellent reaction, which is shown for the synthesis of indoles **13**, involves oxidative addition of the aryl halide (usually iodide) to Pd(0), *syn*-insertion of the alkyne into the ArPd bond, nitrogen displacement of the Pd in the resulting vinyl-Pd intermediate, and final reductive elimination of Pd(0).

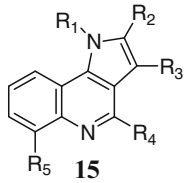
The reaction can be regioselective with unsymmetrical alkynes, and this is particularly true with silylated alkynes wherein the silyl group always resides at the C-2 indole position in the product. This is noteworthy because silyl-substituted indoles are valuable substrates for other chemistry (halogenation, Heck coupling). Gronowitz used the appropriate silylated alkynes with *o*-iodoanilines to fashion substituted tryptophans following desilylation with $AlCl_3$ [26]. Similarly, a series of 5-, 6-, and 7-azaindoles was prepared by Ujjainwalla and Warner from *o*-aminoiodopyridines

and silylated (and other internal) alkynes using $PdCl_2$dppf [27, 28]. Yum and coworkers also used a Larock indole synthesis to prepare 7-azaindoles **14** [29, 30] and, from 4-amino-3-iodoquinolines, pyrrolo[3,2-*c*]quinolines **15**, which have a wide spectrum of biological activity [30].



14

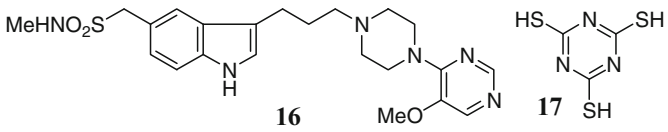
R_1 = Me, Bn, H, *p*-MeOBn
R_2 = TMS, Ph, Pr
R_3 = CH_2OH, CH_2CH_2OH, Me, Ph, Pr



15

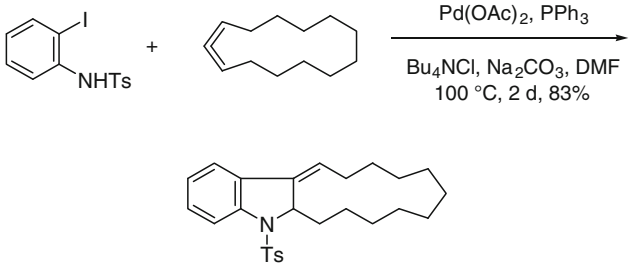
R_1 = aryl, Bn, *n*-Bu
R_2 = TMS, Ph, *n*-Pr
R_3 = Me, CH_2OH, CH_2CH_2OH, *n*-Pr
R_4 = H, Me
R_5 = OMe, OCF_3

The Larock synthesis was used by Chen and coworkers to synthesize the 5-(triazolylmethyl)tryptamine MK-0462, a potent 5-HT_{1D} receptor agonist, as well as a metabolite [31, 32]. The reaction was carried out on a 25-kg scale. Larock employed his methodology to prepare tetrahydroindoles [33], and Maassarani used this method for the synthesis of *N*-(2-pyridyl)indoles [34]. The latter study features the isolation of cyclopalladated *N*-phenyl-2-pyridylamines. Rosso and coworkers have employed this method for the industrial scale synthesis of an antimigraine drug candidate **16**. In this paper, removal of spent palladium was best effected by trimercaptotriazine (**17**), although many techniques were explored [35].



16 **17**

Larock found that allenes (1,2-dienes) undergo Pd-catalyzed reactions with *o*-iodoanilines to afford 3-alkylidene indolines, including examples using cyclic dienes, e.g., to give **18** [36], and ones leading to asymmetric induction, e.g., to give **19** [37, 38]. The highest enantioselectivities ever reported for any Pd-catalyzed intramolecular allylic substitution reactions were observed in this study. Mérour modified this reaction for the synthesis of 7-azaindolinones, following ozonolysis of the initially formed *exo*-methylene-indoline [39].



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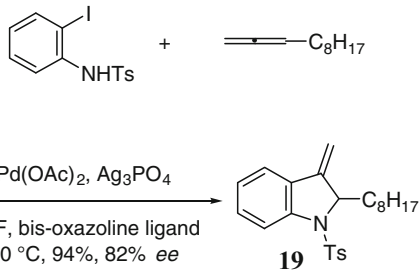
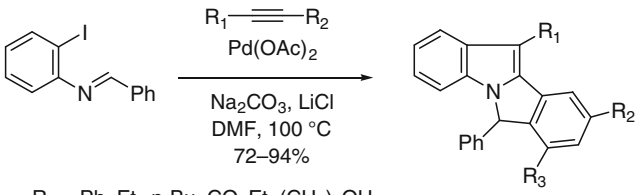


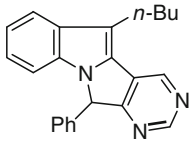
19

Prior to his work with internal alkynes, Larock found that *o*-thallated acetanilide undergoes Pd-catalyzed reactions with vinyl bromide and allyl chloride to give *N*-acetylindole and *N*-acetyl-2-methylindole each in 45% yield [40]. In an extension to reactions of internal alkynes with imines of *o*-iodoaniline, Larock reported a concise synthesis of isoindolo[2,1-*a*]indoles **20** and **21** [41, 42]. The regioselectivity was excellent with unsymmetrical alkynes.

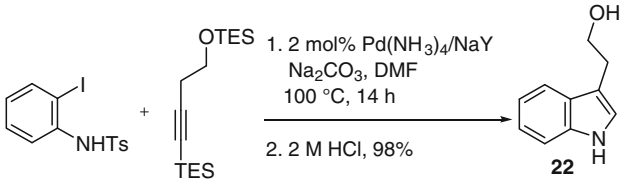


R_1 = Ph, Et, *n*-Bu, CO_2Et, $(CH_2)_4OH$
R_2 = H, Me,CF_3
R_3 = H, OMe, CO_2Et

20

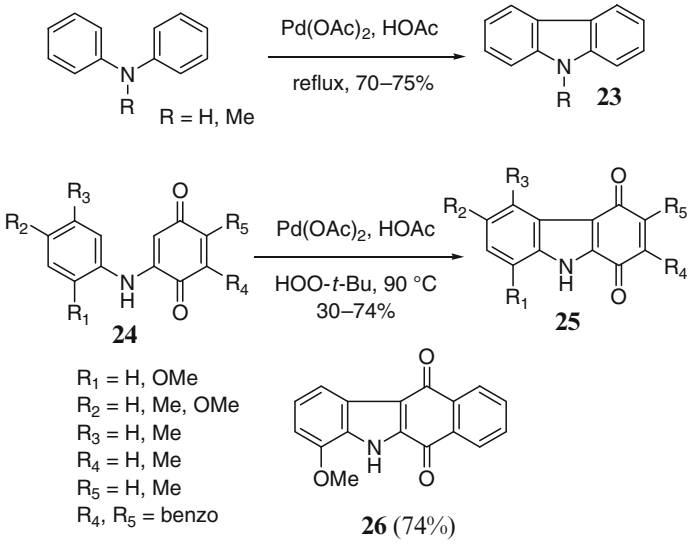


21 (93%)



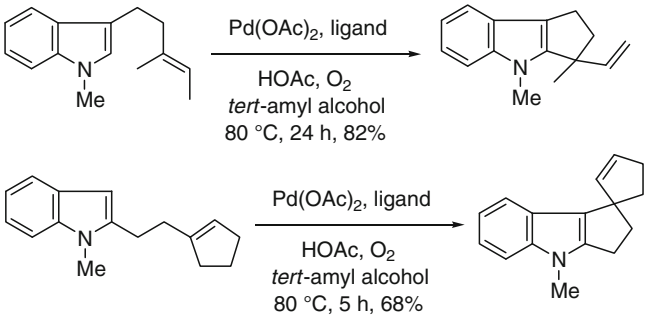
In 2009, Djakovitch et al. described the first heterogeneous ligand- and salt-free Larock indole synthesis [43]. For instance, indole **22** was assembled in high yield under these conditions compared to the traditional homogeneous Larock indole synthesis conditions.

2.3 *Oxidative Coupling*

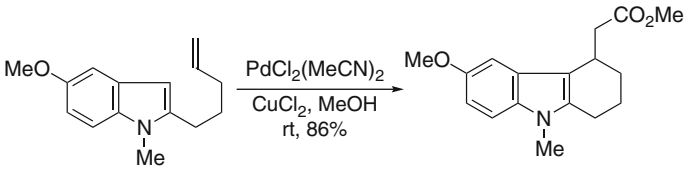


Most of the early applications of palladium to indole chemistry involved oxidative coupling or cyclization using stoichiometric Pd(II). Åkermark first reported the efficient oxidative coupling of diphenylamines to carbazoles **23** with $Pd(OAc)_2$ in refluxing acetic acid [44]. The reaction is applicable to several ring-substituted carbazoles (Br, Cl, OMe, Me, NO_2), and 20 years later Åkermark and colleagues made this reaction catalytic in the conversion of arylaminoquinones **24** to carbazole-1,4-quinones **25** with *tert*-butylhydroperoxide or oxygen as the oxidant [45]. This oxidative cyclization is particularly useful for the synthesis of benzocarbazole-6, 11-quinones (e.g., **26**).

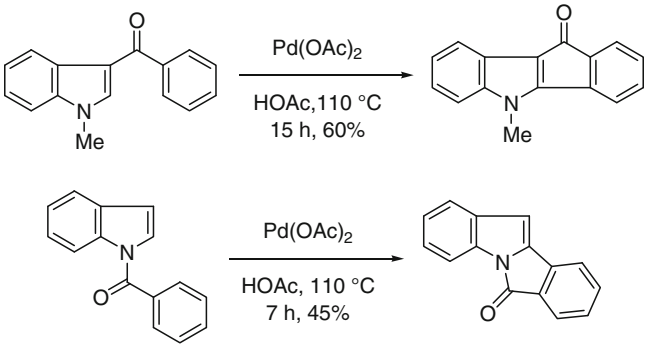
Stoltz has reported the first oxidative indole annulations that are catalytic in palladium, and two examples are illustrated below [46]. The ligand is ethyl nicotinate.



A similar Pd-catalyzed cyclization–carboalkoxylation of several alkenyl indoles has been described by Widenhoefer, one of which is shown [47].

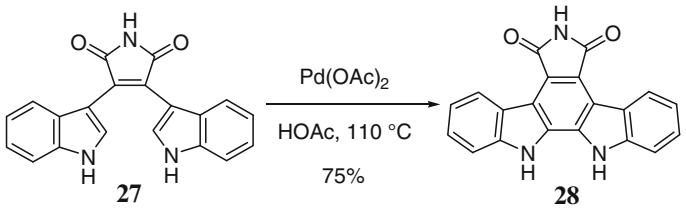


In a series of papers, Itahara established the utility of $Pd(OAc)_2$ in the oxidative cyclization of *C*- and *N*-benzoylindoles, and two examples are shown [48–50]. Itahara also found that the cyclization of 3-benzoyl-1,2-dimethylindole proceeds to the C-4 position (31% yield) [48]. Under similar conditions, both 1-acetylindole and 1-acetyl-3-methylindole are surprisingly intermolecularly arylated at the C-2 position by benzene and xylene (22–48% yield) [51, 52].



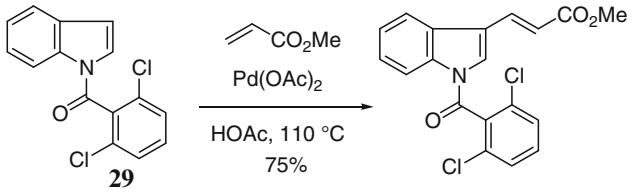
Hill described the $Pd(OAc)_2$-oxidative cyclization of bisindolylmaleimides (e.g., **27**) to indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles (e.g., **28**) [53], which is the core ring system in numerous natural products, many of which have potent protein kinase activity [54]. Other workers employed this Pd-induced reaction to prepare

additional examples of this ring system [55, 56]. Ohkubo found that $PdCl_2$/DMF was necessary to prevent acid-induced decomposition of benzene-ring-substituted benzyloxy analogs of **27**, and the yields of cyclized products under these conditions are 85–100% [55].



27 **28**

Intermolecular Pd oxidative couplings with indoles are well established, although initial results were unpromising. For example, Billups found that indole reacts with allyl acetate (Pd(acac)/Ph_3P/HOAc) to give a mixture of 3-allyl-(54%), 1-allyl-(7%), and 1,3-diallylindole (11%) [57]. Allyl alcohol also is successful in this reaction but most other allylic alcohols fail. Likewise, methyl acrylate reacts with *N*-acetylindole ($Pd(OAc)_2$/HOAc) to give only a 20% yield of methyl (*E*)-3-(1-acetyl-3-indolyl)acrylate and a 9% yield of *N*-acetyl-2,3-bis-(carbomethoxy) carbazole [58]. Itahara improved these oxidative couplings by employing both *N*-(2,6-dibenzoyl)indoles (e.g., **29**, **30**) and *N*-(phenylsulfonyl)-indole as substrates [59]. Reaction occurs at C-3 unless this position is blocked. The coupling can be made catalytic using AgOAc or other reoxidants [59]. Some examples are shown below and *E*-stereochemistry is the major or exclusive isomer. Acrylonitrile also reacts with **29** under these conditions (52%; $E/Z = 3/1$) [59], and methyl vinyl ketone, ethyl (*E*)-crotonate, and ethyl α-methyl acrylate react with *N*-(phenylsulfonyl)indole under these oxidative conditions [60]. Interestingly, an *N*-indole 2-pyridylmethyl substituent leads to C-2 alkenylation with methyl acrylate, acrylonitrile, and phenyl vinyl sulfone under typical conditions ($Pd(OAc)_2$, $Cu(OAc)_2$, HOAc, dioxane, 70°C) [61].



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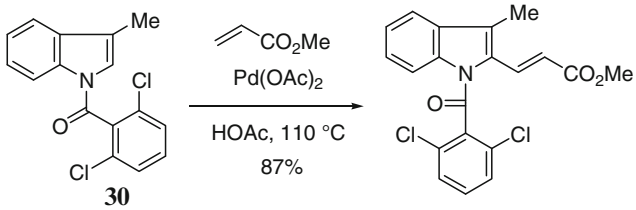

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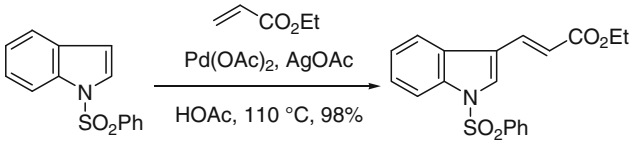
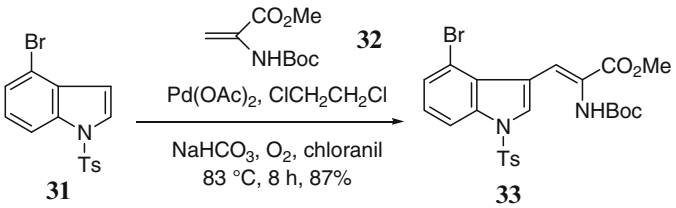
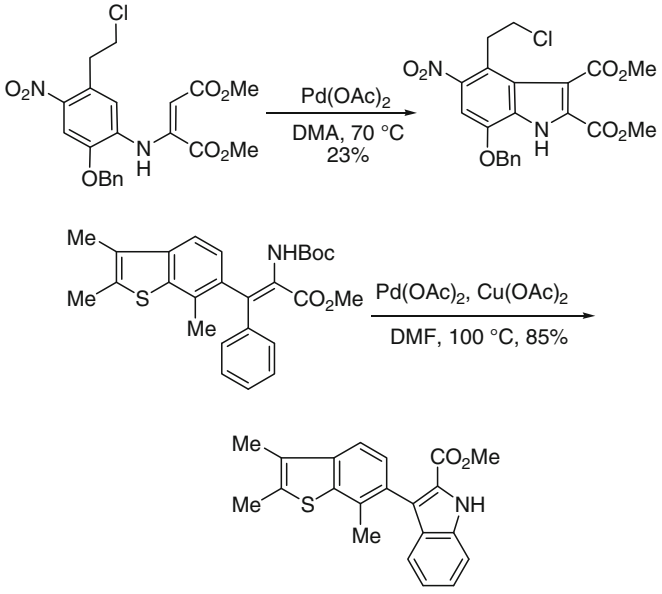


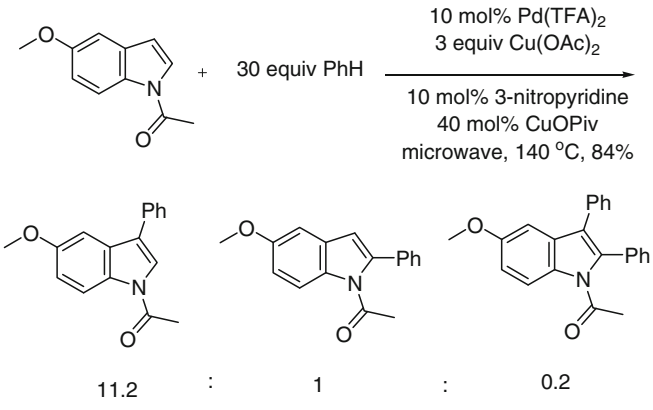
Hegedus found that 4-bromo-1-(4-toluenesulfonyl)indole (**31**) reacts with methyl acrylate to form the C-3 product in low yield under stoichiometric conditions [62]. Yokoyama, Murakami and coworkers also utilized **31** in total syntheses of clavicipitic acid and costaclavine, one key step of which is the oxidative coupling of **31** with **32** to give dehydrotryptophan derivative **33** [63, 64]. The use of chloranil as a reoxidant to recycle Pd(O) to Pd(II) greatly improves the coupling over earlier conditions [65, 66]. For example, chloranil was more effective than DDQ, MnO_2, Ag_2CO_3, $Co(salen)_2/O_2$, and $Cu(OAc)_2$. In the absence of chloranil the yield of **33** is 31%.



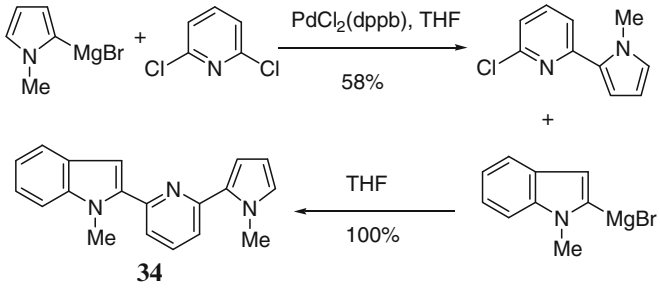
The palladium-catalyzed C-3 alkylation of indoles via nucleophilic allylic substitution on allylic carbonates and acetates has been described [67, 68]. Two clever indole ring syntheses involving oxidative cyclization are illustrated below [69, 70].



In 2007, Fagnou reported a remarkable catalytic cross-coupling of unactivated arenes onto indoles via oxidative oxidation [71]. Using $Cu(OAc)_2$ as the oxidant and 3-nitropyridine as the additive, C–H activation was accomplished via the S_EAr mechanism. As a consequence, 3-acylindole was phenylated predominantly at the C-3 position although small amount of C-2 phenylated was observed as well.



2.4 *Kumada Coupling*

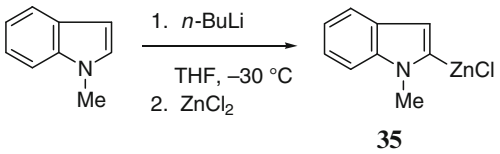


Of all the palladium-catalyzed coupling reactions, the Kumada coupling has been applied least often in indole chemistry. However, this Grignard-Pd cross-coupling methodology has been used to couple 1-methyl-2-indolylmagnesium bromide with iodobenzene and α-bromovinyltrimethylsilane to form 1-methyl-2-phenylindole and 1-methyl-2-(1-trimethyl-silyl)vinylindole in 79% and 87% yields, respectively [72, 73]. Kumada constructed the tri-heterocycle **34** using a tandem version of his methodology [74].

Kondo employed the Kumada coupling using the Grignard reagents derived from 2- and 3-iodo-1-(phenylsulfonyl)indole to prepare the corresponding phenyl derivatives in 50% yield [75]. Widdowson expanded the scope of the Kumada coupling and provided some insight into the mechanism [76].

2.5 *Negishi Coupling*

Although the Negishi coupling has been less frequently used in indole synthetic manipulations than either Suzuki or Stille couplings, we will see in this chapter that Negishi chemistry is often far superior to other Pd-catalyzed cross-coupling reactions involving indoles. One of the first such examples is Pichart's coupling of 1-methyl-2-indolylzinc chloride (**35**) with iodopyrimidine **36** to give **37** [77].



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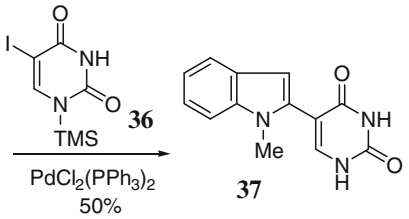
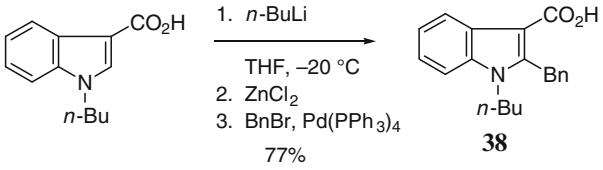


37

Danieli extended the Pd-catalyzed coupling of 2-indolylzinc chlorides to a series of halopyridin-2-ones and halopyran-2-ones [78]. This Negishi coupling is more efficient than a Suzuki approach but not as good as a Stille coupling. An example of the latter will be shown in Sect. 2.7. These workers also generated zinc reagents from 5-iodopyridin-2-one and 5-bromopyran-2-one but Negishi couplings were sluggish. Since direct alkylation of a 2-lithioindole failed, Fisher and coworkers utilized a Negishi protocol to synthesize 2-benzylindole **38** as well as the novel CNS agent **39** [79].



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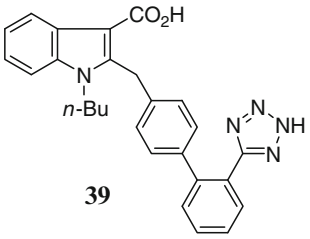
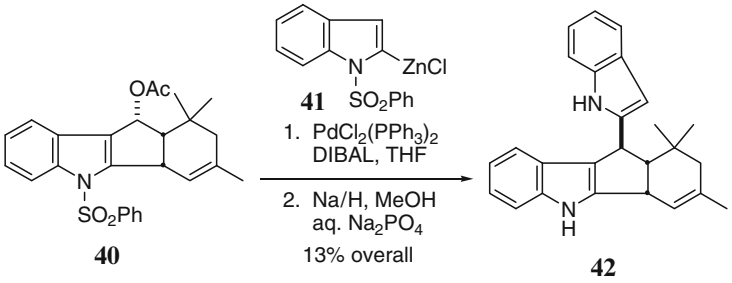
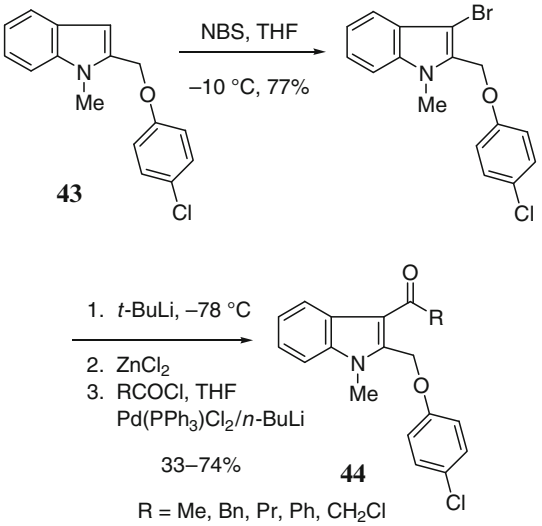


39

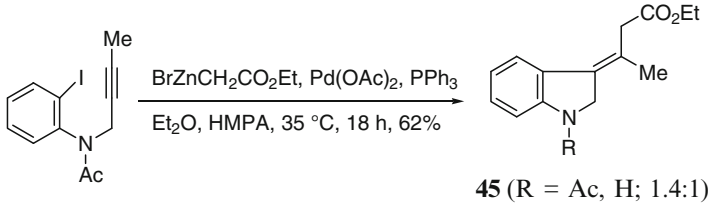
Cheng and Cheung also employed a 2-indolylzinc chloride **41** to couple with indole **40** in a synthesis of "inverto-yuehchukene" **42** [80]. Other Pd catalysts were no better in this low-yielding process.



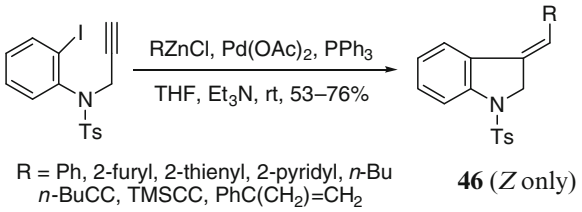
Negishi methodology can also be used to achieve the 3-acylation of indoles. Thus, Faul used this tactic to prepare a series of 3-acylindoles **44** from indole **43** [81]. Indole **43** could also be iodinated cleanly at C-3 with *N*-iodosuccinimide (78%).



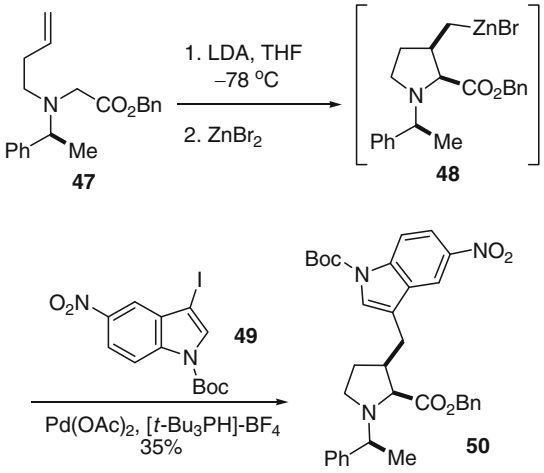
Grigg employed organozinc chemistry to construct 3-alkylidenedihydroindoles such as **45** via a tandem Pd-catalyzed cyclization-cross-coupling sequence [82]. A similar route to such compounds was reported by Luo and Wang; e.g., **46** [83].



45 (R = Ac, H; 1.4:1)

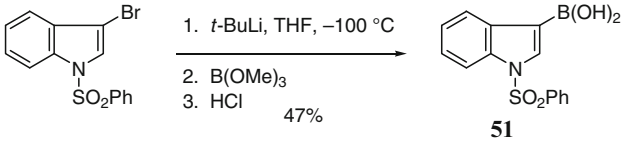


Karoyan et al. accomplished an asymmetric synthesis of prolino-homotryptophan **50** via amino-zinc-ene-enolate cyclization of **47** followed by transmetalation of the cyclic zinc intermediate **48** with indolyliodide **49** [84]. The use of a Pd catalyst derived from Fu's [*t*-Bu_3PH]-BF_4 was required to avoid the undesired β-hydride elimination. Proline chimeras such as **50** are useful tools for medicinal chemistry and/or biological applications.



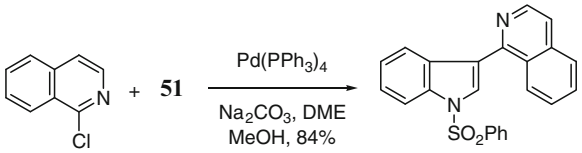
2.6 *Suzuki Coupling*

Two reviews were published in 2001 and 2002, respectively, on the Suzuki coupling of indoles by Ishikura [85, 86].



Although the first report of an indoleboronic acid was by Conway and Gribble in 1990, this compound (**51**) was not employed in Suzuki coupling, but rather it was utilized en route to 3-indolyl triflate [87].

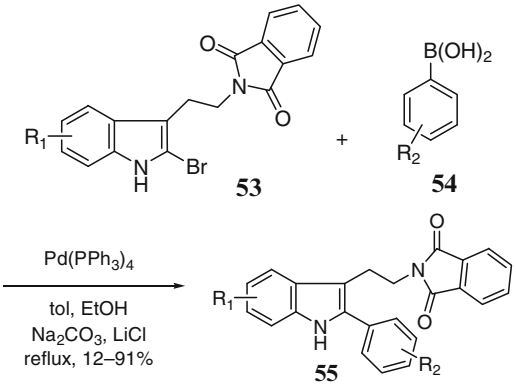
In the intervening years, indoleboronic acids substituted at all indole carbon positions have found use in synthesis. For example, Claridge and coworkers employed **51** in a synthesis of isoquinoline **52** under standard Suzuki conditions in high yield [88]. Compound **52** was subsequently converted to the new Pd-ligand 1-methyl-2-diphenylphosphino-3-(1′-iso-quinolyl)indole.



52

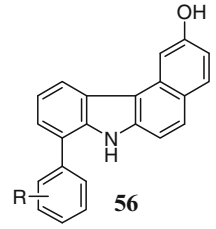
Several groups have reported the synthesis and Suzuki reactions of a *N*-methylindolyl-3-carboxamido-2-boronic acid for the synthesis of benzo[*a*]carbazoles [89], a *N*-Boc-5-sulfonamidoindolyl-2-boronic acid for the synthesis of novel KDR kinase inhibitors [90, 91], indolyl-4-boronic acid in a new synthesis of lysergic acid [92], and 5-, 6-, and 7-indolylboronic acids for the synthesis of aryl-substituted indoles [93, 94]. Carbazole-2,7-bis (boronates) have been employed to construct diindolocarbazoles [95].

The medicinal importance of 2-aryltryptamines led Chu and coworkers to develop an efficient route to these compounds (**55**) via a Pd-catalyzed cross-coupling of protected 2-bromotryptamines **53** with arylboronic acids **54** [96]. Several Suzuki conditions were explored and only a partial listing of the arylboronic acids is shown here. In addition, boronic acids derived from naphthalene, isoquinoline, and indole were successfully coupled with **53**. The C-2 bromination of the protected tryptamines was conveniently performed using pyridinium hydrobromide perbromide (70–100%). Other groups have employed 2- and 5-halotryptamines (and homotryptamines) in Suzuki coupling to prepare novel inhibitors of 15-lipoxygenase [97] and selective 5-HT receptor agonists [98]. 2-Phenyl-5- (and 7-) azaindoles have been prepared via a Suzuki coupling of the corresponding 2-iodoazaindoles [99].



R_1 = H, 5-OBn, 5-OMe, 5-Cl, 5-Me, 6-F, 7-Me
R_2 = H, 2-Me, 3-Me, 4-Me, 3-NO_2, 4-F, 4-Cl, 3-OMe
3,5-diMe, 2,4-diCl, 3,5-diOMe, 3,5-diCF_3, 3,5-diCl

Carini et al. converted 8-bromobenzo[*c*]carbazole to the corresponding aryl derivatives **56**, which are selective inhibitors of cyclin dependent kinase 4 [100], and Nicolaou employed a 4-bromoindole to craft **57** in a model study towards the synthesis of diazonamide A [101].



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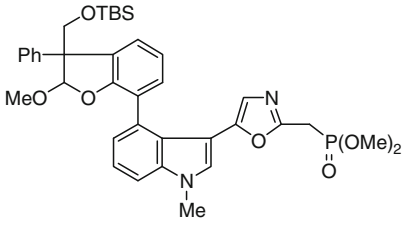
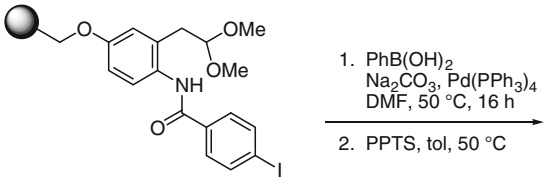


57

Abell utilized a Suzuki cross-coupling reaction on resin **58**. Subsequent acid treatment effected cyclization to indole **59**, which was readily cleaved with amines and alcohols to form potential libraries of amides and esters, respectively [102].



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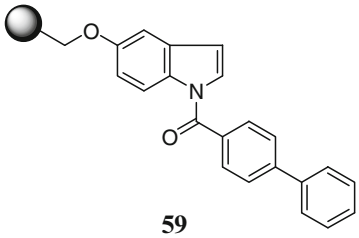
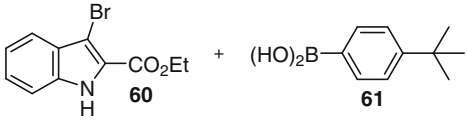
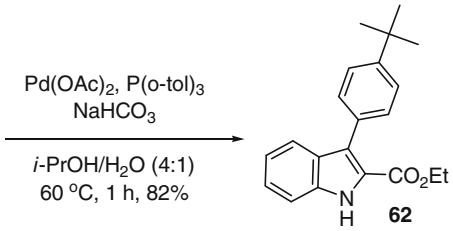


59

A group of process chemists at GSK optimized the Suzuki coupling of indolylbromide **60** with boronic acid **61** to afford a drug intermediate **62** [103]. They performed a screen to choose optimal ligand, solvent and base. In order to remove the residual palladium in isolated product, they treated the reaction mixture with toluene and 20% aqueous $NaHSO_3$ at elevated temperature. The palladium content was lowered from ~8,000 to 100 ppm or less on a 20 L scale.

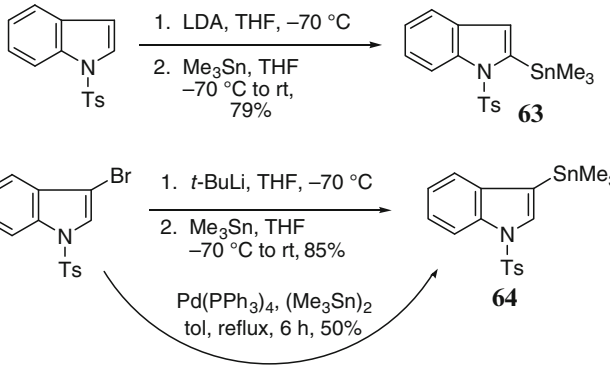


60 **61**

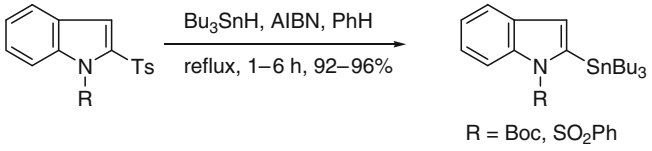


2.7 *Stille Coupling*

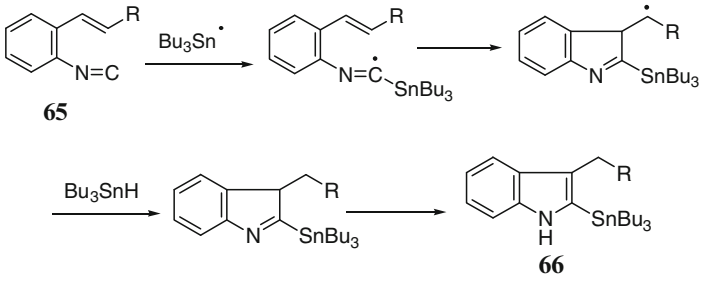
Despite the well-documented toxicity of organotin compounds, the use of these reagents in Pd-catalyzed cross-coupling reactions continues unabated, following the pioneering work of Stille. Indolylstannanes are usually prepared either by treating the appropriate lithioindole with a trialkyltin halide or by halogen-tin exchange with, for example, hexamethylditin. Typical procedures for the generation of (1-(4-toluenesulfonyl)indol-2-yl)trimethylstannane (**63**) and (1-(4-toluenesulfonyl)indol-3-yl)trimethylstannane (**64**) are illustrated [104, 105]. Bosch described an excellent route to the *N*-TBS-3-trimethylstannylindole [106].



The indolyltributylstannanes, which are more robust than their trimethylstannyl counterparts, are prepared similarly [107, 108]. Labadie and Teng synthesized the *N*-Me, *N*-Boc, and *N*-SEM (indol-2-yl)tributylstannanes [108], and Beak prepared the *N*-Boc trimethyl- and tributyltin derivatives in high yield [107]. Caddick and Joshi found that tributylstannyl radical reacts with 2-tosylindoles to give the corresponding indole tin compounds as illustrated [109].

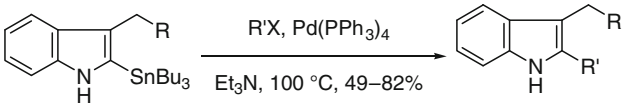


Fukuyama devised a novel tin-mediated indole ring synthesis leading directly to 2-stannylindoles that can capture aryl and alkyl halides in a Pd-catalyzed cross-coupling termination reaction [110–112]. The presumed pathway is illustrated and involves initial tributylstannyl radical addition to the isonitrile **65**, cyclization, and final formation of stannylindole **66**.



65 **66**

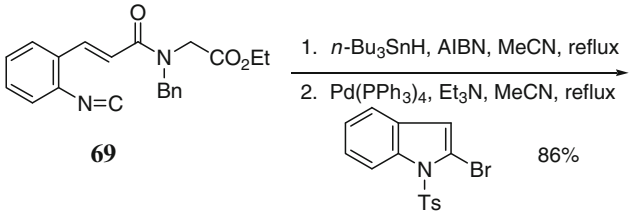
Moreover, the in situ reaction of **67** under Stille conditions affords a variety of coupled products **68**, which have been employed in a synthesis of (−)-vindoline [113].



67 **68**

R = CO_2Me, CH_2OTHP, *n*-Bu
R' = Ph, 4-Ac-Ph, Bn, 1-cyclohexenyl, 1-hexenyl
X = Br, I, OTf

The potential power of Fukuyama's method is illustrated by the synthesis of biindolyl **70** which was used in a synthesis of indolocarbazoles [111, 112]. The isonitriles (e.g., **69**) are generally prepared by dehydration of the corresponding formamides with $POCl_3$.



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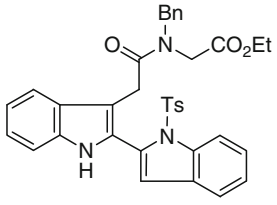
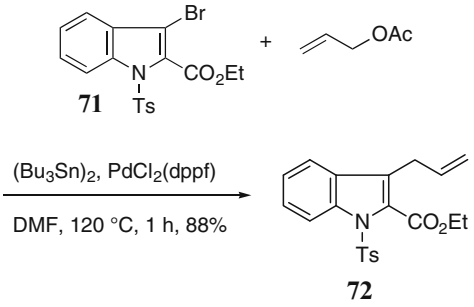
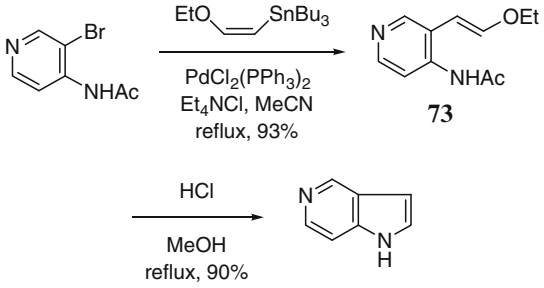


70

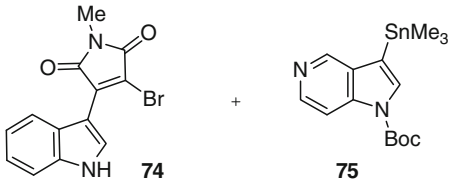
Murakami generated 3-tributylstannylindoles in situ (but also isolable) using 3-bromoindole **71**, allylic acetates and carbonates, and hexamethyl tin [114, 115]. A typical procedure is illustrated for the synthesis of **72**. The corresponding 5-bromo analog is allylated to the extent of 59%. 3-Stannylindoles couple smoothly in tandem fashion with 2,3-dibromo-5,6-dimethylbenzoquinone under Stille conditions [116].

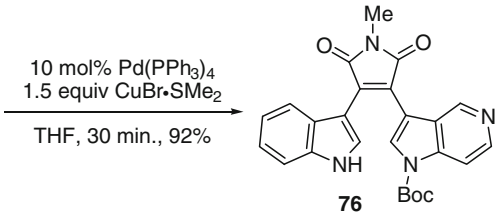


Halonitropyridines were particularly attractive as coupling partners with tributyl-2-ethoxyvinyltin and precursors to azaindoles. Although the (*Z*)-isomer of **73** is obtained initially, it isomerizes to the (*E*)-isomer which is the thermodynamic product. This strategy represents a powerful method for the synthesis of all four azaindoles (1*H*-pyrrolopyridines) [117]. In fact, this method, starting with 2, 6-dibromoaniline, is one of the best ways to synthesize 7-bromoindole (96% overall yield) [118].



Mérour synthesized novel 5-azaindolocarbazoles as cytotoxic agents and Chk1 inhibitors [119]. Therefore, the Stille coupling between monobromoindolylmaleimide **74** and trimethylstannyl-1-Boc-5-azaindole **75** gave adduct **76** in 92% yield. When the corresponding less toxic 3-tributylstannyl-1-Boc-5-azaindole instead of **75** was used, only 36% yield was obtained.



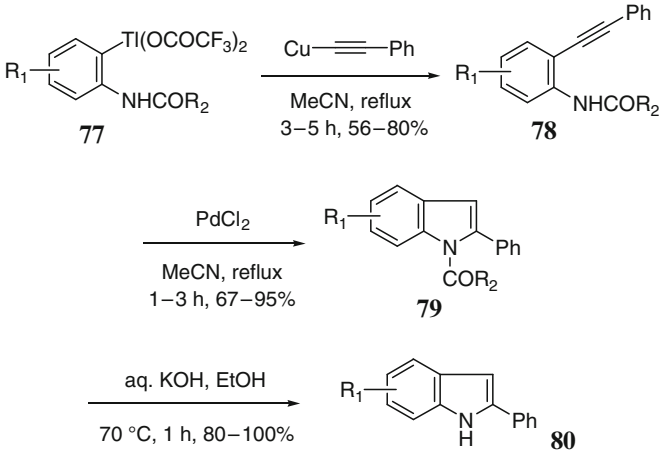


76

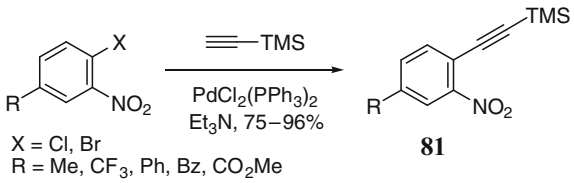
2.8 *Sonogashira Coupling*

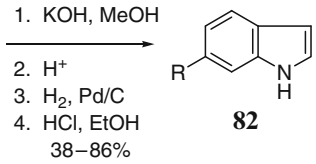
The Sonogashira coupling is the Pd-catalyzed coupling of aryl halides and terminal alkynes [120], which, in the appropriate cases, can be followed by the spontaneous, or easily induced, cyclization to an indole ring. It is a sequel to the Castro acetylene coupling and subsequent cyclization to indoles in the presence of copper [121–124]. For example, Castro and coworkers found that copper acetylides react with *o*-iodoaniline to form 2-substituted indoles often in high yield. In the intervening years, the Pd-catalyzed cyclization of *o*-alkynylanilines to indoles has become a powerful indole ring construction.

Yamanaka and coworkers were the first to apply the Sonogashira coupling reaction to an indole synthesis when they coupled trimethylsilylacetylene with *o*-bromonitrobenzene [$PdCl_2(Ph_3P)_2/Et_3N$]. Treatment with NaOEt/EtOH gives *o*-(2,2-diethoxyethyl)nitrobenzene (39% overall), and hydrogenation and acid treatment affords indole (87%, two steps) [125–127]. The method is applicable to a variety of ring-substituted indoles and, particularly, to the synthesis of 4- and 6-azaindoles (pyrrolopyridines) from halonitropyridines. Taylor coupled thallated anilides **77** with copper(I) phenylacetylide to afford the corresponding *o*-alkynylanilides **78**. In the same pot, catalytic $PdCl_2$ is then used to effect cyclization to *N*-acylindoles **79** [128]. Hydrolysis to the indoles **80** was achieved by base.

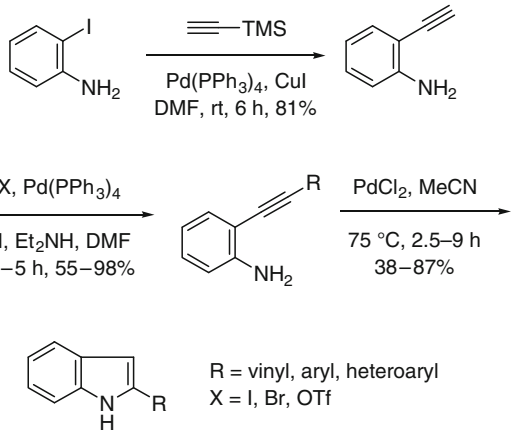


Tischler and Lanza effected coupling of several substituted *o*-chloro- and *o*-bromo-nitrobenzenes with trimethylsilylacetylene to give the *o*-alkynylnitrobenzenes **81** [129]. Further manipulation affords the corresponding indoles **82** in good to excellent yield.



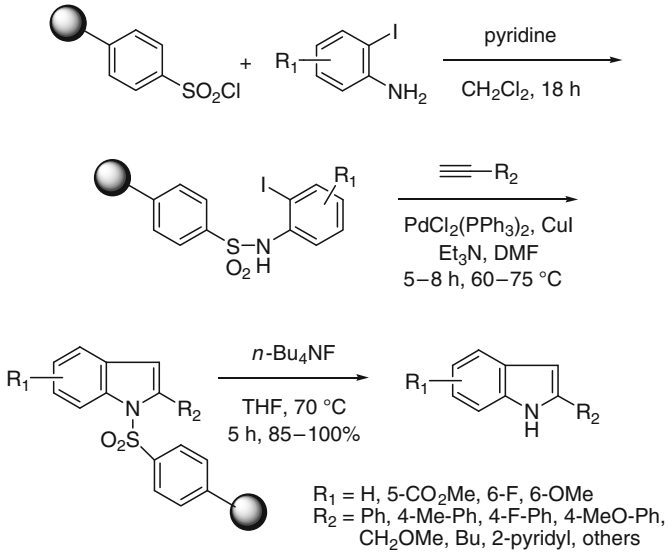


The combination of Pd-catalyzed coupling of terminal acetylenes with *o*-alkynylanilines or *o*-alkynylnitrobenzenes followed by base or CuI cyclization to an indole has been used in many situations with great success. Arcadi employed this methodology to prepare a series of 2-vinyl-, 2-aryl-, and 2-heteroarylindoles from 2-aminophenylacetylene and a subsequent elaboration of the acetylenic terminus. A final Pd-catalyzed cyclization completes the scheme [130].

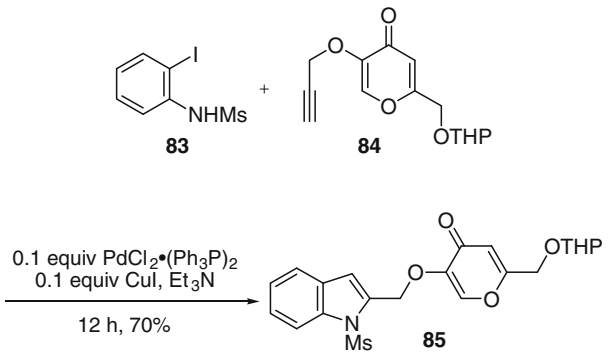


A new, water soluble palladium catalyst was used in the Sonogashira reaction ($Pd(OAc)_2$ triphenylphosphine–trisulfonate sodium salt) [131], and several groups adapted the Sonogashira coupling and subsequent cyclization to the solid-phase synthesis of indoles. Bedeschi and coworkers used this method to prepare a series of 2-substituted-5-indolecarboxylic acids [132]. Collini and Ellingboe extended the technique to 1,2,3-trisubstituted-6-indolecarboxylic acids [133]. Zhang and

coworkers used the solid phase to prepare a series of 2-substituted-3-aminomethyl-5-indolecarboxamides, and, by manipulation of the resin-bound Mannich reaction intermediates, to synthesize 3-cyanomethyl-5-indole-carboxamide and other products of nucleophilic substitution [134]. This research team also employed a sulfonyl linker, as summarized below, to provide a series of substituted indoles [135, 136]. The advantages of this particular approach are that the sulfonyl linker is "traceless", since it disappears from the final indole product, and the polystyrene sulfonyl chloride resin is commercially available.



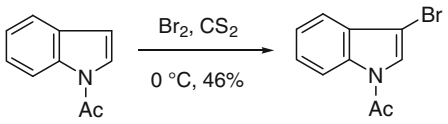
Pirrung carried out a Sonogashira coupling between phenyliodide **83** and alkyne **84** [137]. With *N*-methanesulfonyl protection, the coupling product spontaneously cyclized to the indole and **85** was obtained in 70% yield.



2.9 Heck Coupling

The incredibly powerful and versatile Heck coupling reaction has found enormous utility in indole ring synthesis and in the elaboration of this important heterocycle. Due to the enormity of this topic the section is divided into Heck reactions of indoles; the synthesis of the indole ring as developed by Hegedus, Mori–Ban, and Heck; and the Larock indole ring synthesis.

Both inter- and intramolecular Heck reactions of indoles have been pursued and these will be considered in turn. Appropriately, Heck and coworkers were the first to use Pd-catalyzed vinyl substitution reactions with haloindoles [138]. Thus, 1-acetyl-3-bromoindole (**86**) gave a 50% yield of 3-indolylacrylate **87**. A similar reaction with 5-bromoindole yielded (*E*)-methyl 3-(5-indolyl)acrylate (53% yield), but 3-bromoindole gave no identifiable product.



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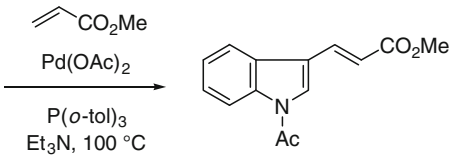
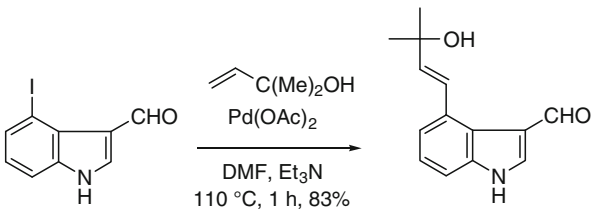


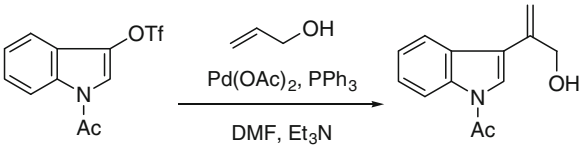
87

Somei carried out the Heck reactions of haloindoles with allylic alcohols. For example, reaction of 4-iodo-3-indolecarboxaldehyde with 2-methyl-3-buten-2-ol afforded alcohol **88** in high yield [139]. This could be subsequently transformed to (±)-6,7-secoagroclavine. Interestingly, the one-pot thallation–palladation protocol failed in this case.



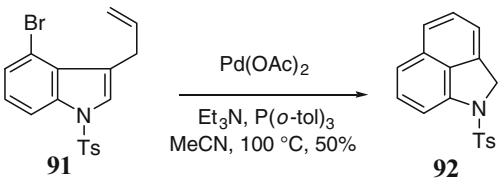
88

Mérour and Gribble have independently explored the Heck reactions of indolyl triflates with allylic alcohols and other substrates [140–142]. For example, reaction of triflate **89** with allyl alcohol gives the rearranged allylic alcohol **90** [140].

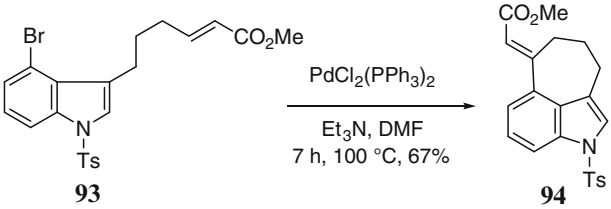


89 90

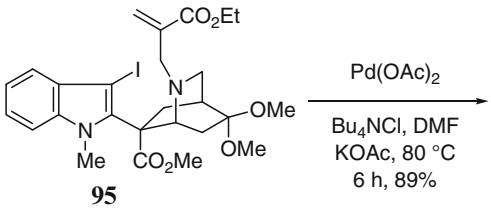
The intramolecular Heck reaction as applied to indoles has led to several spectacular synthetic achievements. Both Hegedus and Murakami exploited intramolecular Heck reactions to synthesize ergot alkaloids. In model studies, Hegedus noted that 3-allyl-4-bromo-1-tosylindole (**91**) cyclizes to **92** in good yield [62, 143, 144], and Murakami's group observed that, for example, **93** cyclizes to **94** [145]. Roberts effected similar cyclizations leading to 7- and 8-membered ring tryptophan surrogates [146, 147], and Snieckus used similar intramolecular Heck reactions to prepare *seco*-C/D ring analogs of Ergot alkaloids [148].



91 92



93 94



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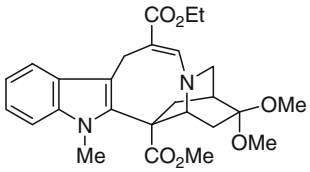
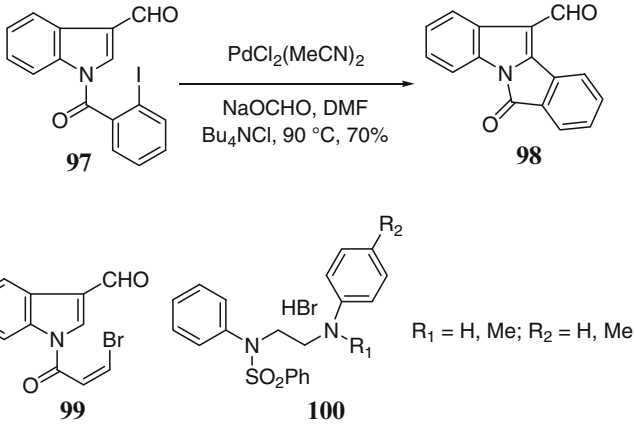


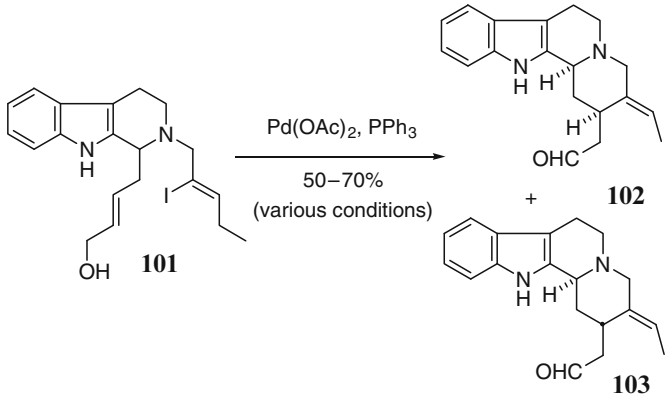
96

In his synthetic approaches to iboga alkaloids, Sundberg pursued several Heck cyclization strategies but found the best one to be **95** and **96** [149].

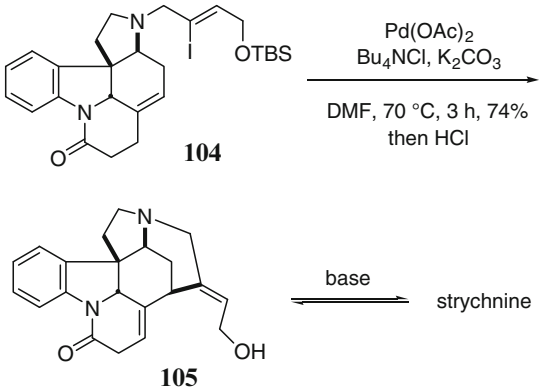
Kraus found that a Pd-catalyzed cyclization is superior to those involving tin-initiated radical cyclizations in the construction of pyrrolo[1,2-*a*] indoles such as **98** [106]. The bromide corresponding to **97** cyclizes in 48% yield, and *N*-(2-bromo-1-cyclohexenecarbonyl)indole-3-carboxaldehyde cyclizes in 60% yield. In contrast, the corresponding radical reactions afford these products in 35–53% yields. Substrate **99** failed to cyclize under these Heck conditions, as did **100** as reported by Srinivasan [107]. However, radical cyclization of **100** did afford the desired 3, 4-benzocarbolines.



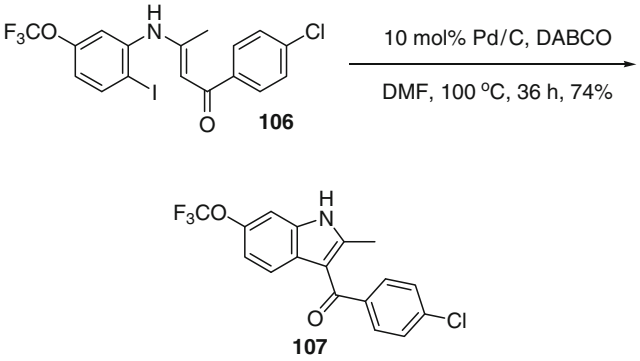
Rawal applied the Heck cyclization in elegant fashion to the construction of indole alkaloids. His route to geissoschizine alkaloids features a novel ring D formation, **101**, **102**, and **103** [150]. Whereas classical Heck conditions favor the isogeissoschizal (**103**) product, the "ligand-free" modification of Jeffrey favors the geissoschizal (**102**) stereochemistry.



Following the application of a Heck cyclization to a concise synthesis of the *Strychnos* alkaloid dehydrotubifoline [151, 152], and earlier model studies [153], Rawal employed a similar strategy to achieve a remarkably efficient synthesis of strychnine [154]. Thus, pentacycle **104** is smoothly cyclized and deprotected to isostrychnine (**105**) in 71% overall yield.



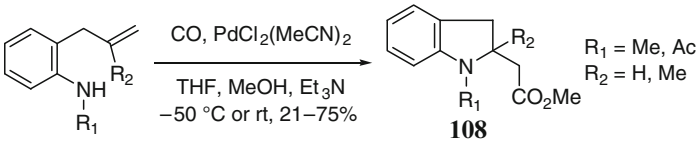
Enamine **106** underwent an intramolecular Heck reaction using palladium on charcoal to afford benzoyl indole **107** in 74% yield after crystallization from heptane/EtOAc [155]. Benzoyl indole **107** is an intermediate for a Merck PPARγ modulator.



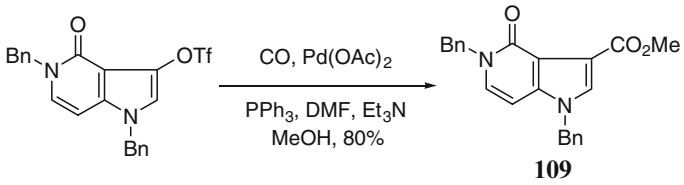
2.10 Carbonylation

The insertion of carbon monoxide into σ-alkylpalladium(II) complexes followed by attack by either alcohols or amines is a powerful acylation method. This carbonylation reaction has been applied in several different ways to the reactions and syntheses of indoles. Hegedus and coworkers converted *o*-allylanilines to indoline

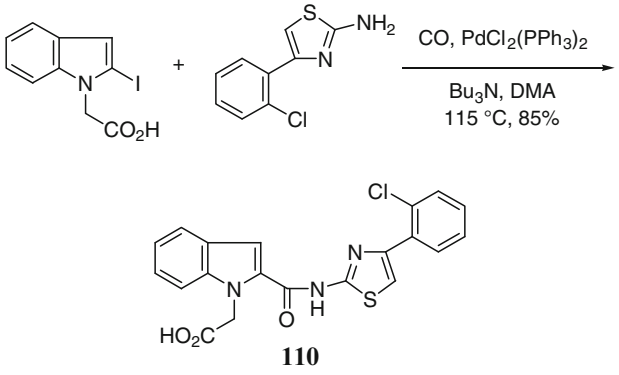
esters **108** in yields up to 75% [156]. In most of the examples in this section, CO at atmospheric pressure was employed.



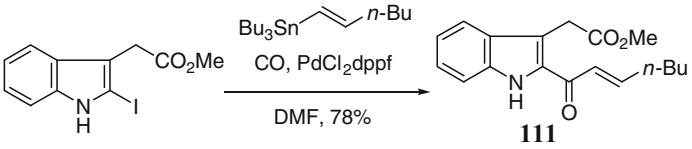
Edstrom expanded his studies on the carbonylation of pyrroles to the methoxycarbonylation of 5-azaindolones leading to **109** [157, 158].

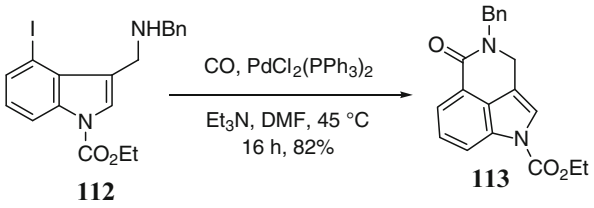


Herbert and McNeil have shown that the appropriate 2-iodoindole can be carbonylated in the presence of primary and secondary amines to afford the corresponding 2-indolecarboxamides in 33–97% yield. Further application of this protocol leads to amide **110**, which is a CCK-A antagonist (Lintitript) [159].



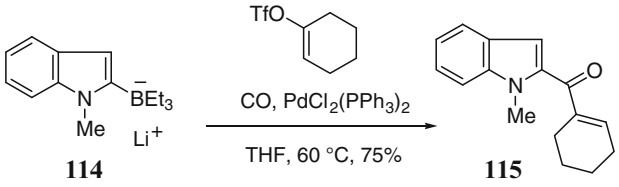
Fukuyama employed a vinyltin derivative in the carbonylation of 3-carbomethoxymethyl-2-iodoindole to afford **111** [111]. Buchwald effected the carbonylation of 4-iodoindole **112** to give lactam **113** [160].





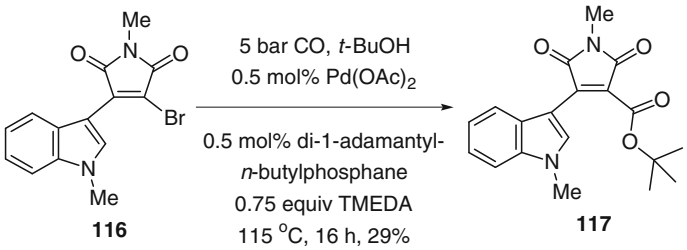
112 **113**

Ishikura has adapted his Pd-catalyzed cross-coupling methodology involving indolylborates to include carbonylation reactions. For example, **114** was treated with enol triflates in the presence of CO and Pd to give 2-acylindoles such as **115** [161].



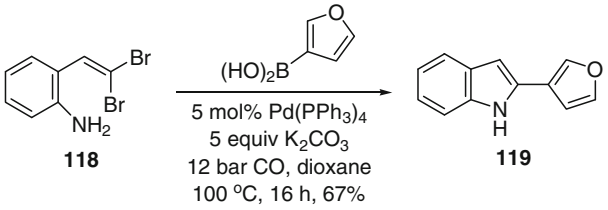
114 **115**

In 2008, Beller and coworkers reported catalytic and stoichiometric synthesis of novel 3-aminocarbonyl-,3-alkoxycarbonyl-, and 3-amino-4-indolyl-maleimides [162]. For instance, *t*-butyl ester **117** was prepared in 29% yield from 3-bromo-4-indolyl-maleimide **116** under the palladium-catalyzed carbonylation conditions using *t*-butanol as the solvent and TMEDA as the base.



116 **117**

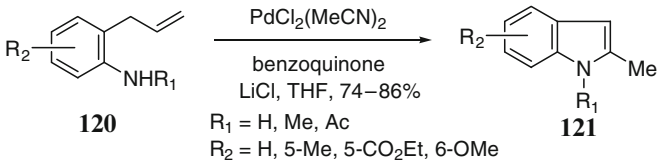
A 2009 paper described a palladium-catalyzed domino-C,N-coupling/carbonylation/Suzuki coupling reaction was used provide an efficient synthesis of 2-aroyl-/heteroaroylindoles [163]. For instance, 2-*gem*-dibromovinylaniline **118** and 3-furyl-boronic acid under carbon monoxide afforded 3-furylindole **119** in 67% yield.



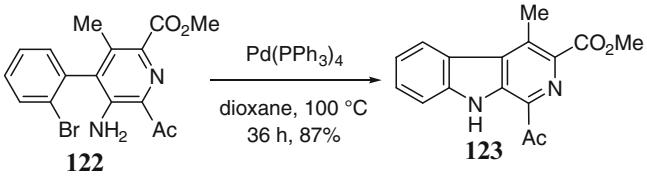
118 **119**

2.11 C–N Bond Formation

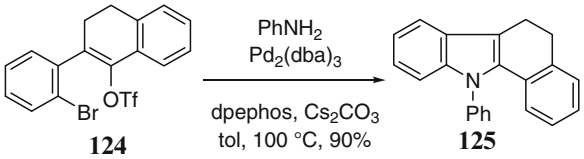
Hegedus conducted the Pd-induced amination of alkenes [164] to an intramolecular version leading to indoles from *o*-allylanilines and *o*-vinylanilines [165, 166]. One of the original examples from the work of Hegedus are shown below. The Hegedus indole synthesis can be stoichiometric or catalytic and a range of indoles was synthesized from the respective *o*-allylanilines in modest to very good yields (31–89%) [167].



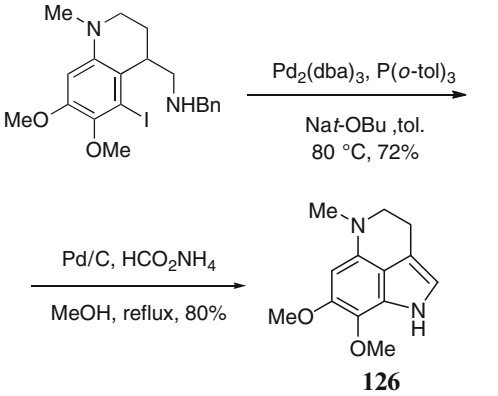
Boger and coworkers were the first to report the intramolecular amination of aryl halides in their synthesis of lavendamycin [168–170]. Thus, biaryl **122** is smoothly cyclized under the action of palladium to β-carboline **123**, which comprises the CDE rings of lavendamycin.



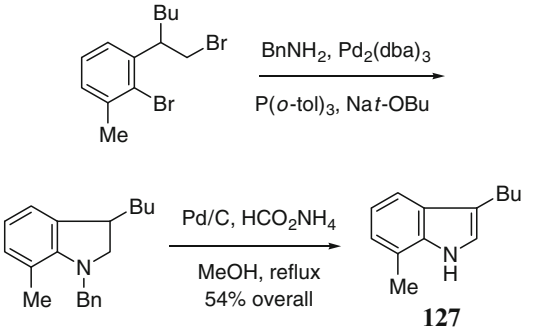
Similarly, carbazoles can be synthesized via a double *N*-arylation of primary amines [171, 172], and comparable tactics lead to indoles, as shown for **124** and **125** [173].



Buchwald parlayed the powerful Hartwig–Buchwald aryl amination technology [174–186] into a simple and versatile indoline synthesis [187]. For example, indole **126**, which has been employed in total syntheses of the marine alkaloids makaluvamine C and damirones A and B, was readily forged via the Pd-mediated cyclization shown below [187]. This intramolecular amination is applicable to the synthesis of *N*-substituted optically active indolines [188, 189]. and *o*-bromobenzylic bromides can be utilized in this methodology, as illustrated for the preparation of **127** [190, 191].



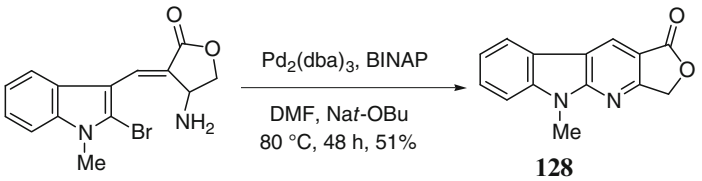
126



127

Snieckus and coworkers applied the Hartwig–Buchwald amination to the synthesis of *o*-carboxamido diarylamines, which can be elaborated to oxindoles [192]. Dobb synthesized α-carboline **128** via an intramolecular amination protocol [193]. These α-carbolines (pyrido[2,3-*b*]indoles) have been found to be modulators of the $GABA_A$ receptor, and this ring system is found in several natural products (grossularines, mescengricin). Snider achieved a similar cyclization of a 2-iodoindole leading to syntheses of (−)-asperlicin and (−)-asperlicin C as illustrated for the model reaction giving **129** [194]. The requisite 2-iodoindole was readily synthesized by a mercuration sequence [$Hg(OCOCF_3)_2$, KI/I_2/82%].

Recently, Lautens engineered a silver-promoted domino Hartwig–Buchwald amination/direct arylation: access to polycyclic heteroaromatics [195]. From substrate **130**, a unique a hetero-pentacycle **131** was assembled with a seven-membered ring as its core.



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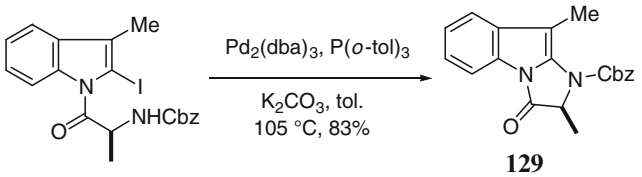
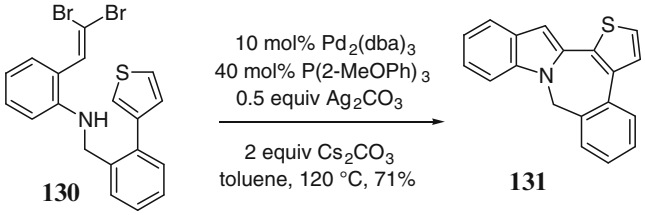
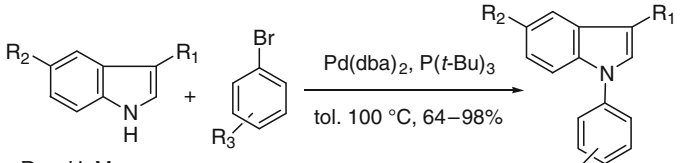


129



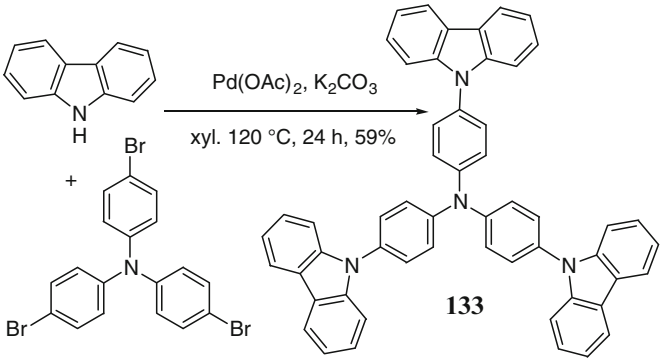
130 **131**

The Buchwald–Hartwig aryl amination methodology cited above in this section was engaged by Hartwig and others to synthesize *N*-arylindoles **132** [196, 197]. Carbazole can be *N*-arylated under these same conditions with *p*-cyanobromobenzene (97% yield). Aryl chlorides also function in this reaction. The power of this amination method is seen by the facile synthesis of tris-carbazole **133** [198].



132

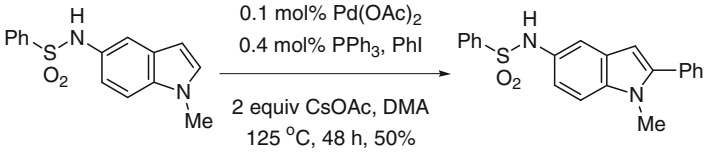
R_1 = H, Me
R_2 = H, OMe
R_3 = H, 4-OMe, 2-Me, 4-F, 4-Me, 4-CN, 4-Ph, 4-CHO, 4-CF_3, 4-$CONEt_2$



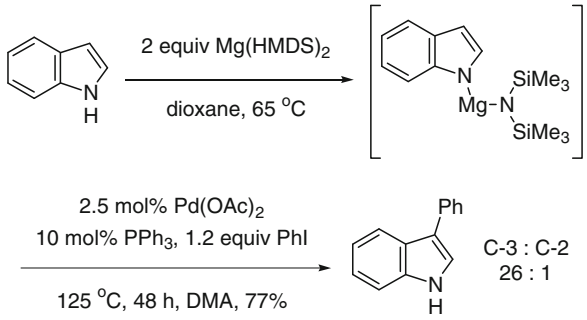
133

2.12 Direct Arylation

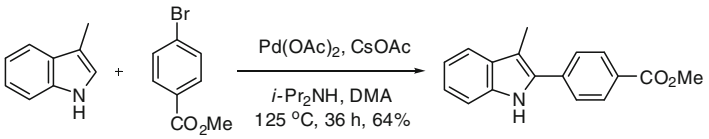
Although palladium-catalyzed cross-coupling reactions provide an efficient entry to *C*-arylated indoles, these reactions require the preparation of functionalized heteroarenes such as boronates and halides. Therefore, *C*-arylation reactions of azole and related heteroarenes via direct C–H bond functionalization of the parent heteroarenes would be much more favorable. In 2004, Sames reported a selective palladium-catalyzed C2-arylation of *N*-substituted indoles via direct C–H bond arylation [199]. Use CsOAc as the base and low concentration of the substrates proved to be critical for the success of this methodology.



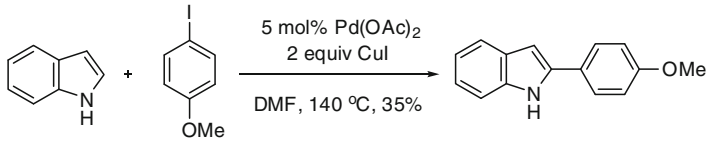
One year later, Sames and coworkers described formation of indole magnesium salts by treatment with either Grignard reagents or Mg(HMDS)2 as a strategy for C-arylation of indoles [200]. As shown in the example below, a 26:1 ratio of C-3/C2 selectivity was achieved using Mg(HMDS)2 to generate the indole magnesium intermediate. It is possible that the bulky trimethyl-silyl group offers the steric shielding from the C-2 position thus resulting in selective C-3 arylation.



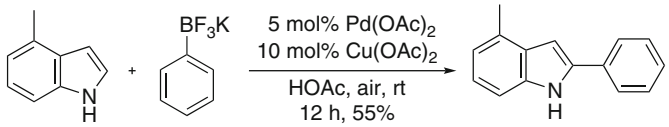
Also in 2007, Sames and coworkers reported that protection of the NH group using N-Mg, N-Zn, or N-SEM could be eliminated when substrate concentration was increased and phosphine ligands removed. Indeed, phosphine ligands inhibit the reaction. Therefore, 3-methylindole (5.0 M) was arylated at C-3 with methyl 4-bromobenzoate in 64% yield when CsOAc was used as the base without the phosphine ligand [201].



At the end of Sect. 2.3 on Oxidative Cyclization, we briefly mentioned Fagnou's remarkable catalytic cross-coupling of unactivated arenes onto indoles via oxidative oxidation using $Cu(OAc)_2$ [71]. Bellina and Rossi described a regioselective direct C-2 arylation free NH of indoles using Pd and Cu catalysts [202]. Unfortunately, the yields were only moderate, ranging from 10 to 53% for different aryl iodides. On the other hand, their direct palladium-catalyzed C-3 arylation had higher yields (53–97%) for free NH indoles with aryl bromides under ligandless conditions [203].



Recently, Zhang and coworkers reported a direct palladium-catalyzed C-2 arylation of indoles with potassium aryltrifluoroborate salts [204]. Remarkably, the direct arylation took place at room temperature when acetic acid was used as the solvent.



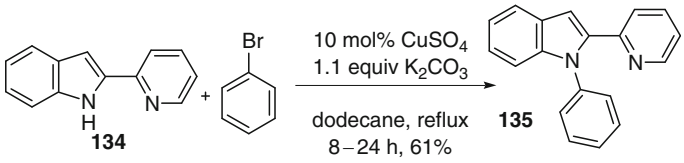
3 Copper-Catalyzed Cross-Coupling Reactions

An excellent review by Djakovitch on transition metal-catalyzed, direct and site-selective N1, C2-, or C3-arylation of indole nucleus was published in 2009 [205].

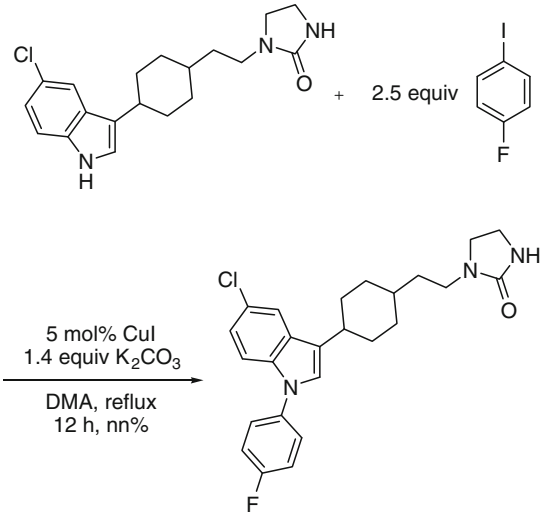
3.1 Selective N1-Arylation

Selective N1-arylation via copper-catalyzed cross-coupling reaction may be achieved under ligand-free conditions or ligand-promoted conditions.

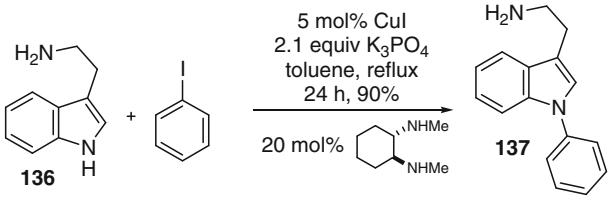
Using a simple ligand-free procedure, Wang et al. prepared the N1-phenylation product **135** from indole **134** using $CuSO_4$ as the catalyst and K_2CO_3 as the base [206].



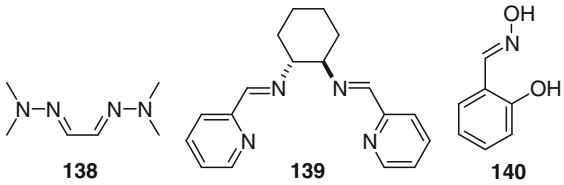
Also under ligand-free conditions, a series of 5-HT_2 antagonists was synthesized using CuI as the catalyst, ZnO as the cocatalyst, and K_2CO_3 as the base [207, 208]. One example is shown below. A remarkable selectivity was achieved for the N1-arylation for the indole NH versus the urea NH of the imidazolidin-2-one moiety.



After Buchwald's report of copper-catalyzed N1 arylation of indoles using *trans*-1,2-cyclohexanediamine (CHDA) as the ligand [209], many diamine and related dinitrogen ligands have been developed. For instance, *trans-N,N′*-dimethyl-1, 2-cyclohexanediamine was a better ligand than CHDA for phenylating indole **136** and **137** [210].

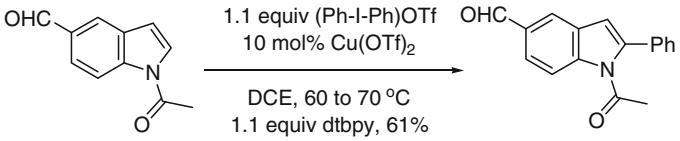


Additional ligands to promote copper-catalyzed N1-arylation of indoles include hydrazones such as **138** [211], Schiff base such as **139** [211], and salicyladoxime **140** [212]. *N*-Hydroxyphthalimide [213] and *L*-proline [214] were also used as ligands for copper-catalyzed N1-arylation of indoles.



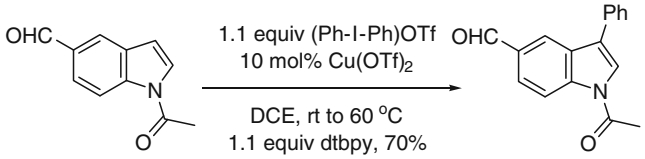
3.2 Selective C2-Arylation

Direct and site-selective C2-arylation of indole nucleus is more challenging than the corresponding N1-arylation. Nonetheless, Gaunt's group achieved such a feat for *N*-acylindoles with aryliodonium salts using $Cu(OTf)_2$ as the catalyst [215]. The mild reaction conditions tolerate a variety of functional groups (dtbpy = 2,6-di-*tert*-butylpyridine).



3.3 Selective C3-Arylation

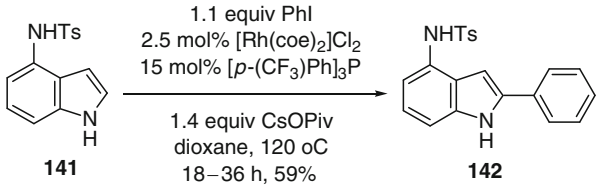
By extenuating the reaction temperatures, Gaunt et al. was able to selectively phenylate C3-position of indole nucleus using aryliodonium salts [215]. At temperatures below 60°C, $Cu(OTf)_2$-catalyzed C3-arylation took place selectively between *N*-acylindoles with aryliodonium salts using dtbpy as the agent to prevent indole dimerization.



4 Rhodium-Catalyzed Cross-Coupling Reactions

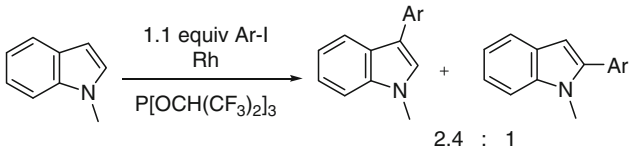
4.1 Selective C2-Arylation

Although there is no report on rhodium-catalyzed selective N1-arylation, Sames described a direct C2-arylation of indoles catalyzed by rhodium complexes [216]. When the rhodium catalyst was mixed with an electron-deficient phosphine ligand, a weak base, and an aryl iodide, a highly electrophilic and reactive Ar–Rh(III) species was generated in situ. The catalyst then promotes the C–H bond activation at the C2 position and arylation would take place selectively at C2 as demonstrated by the transformation of **141** and **142**.



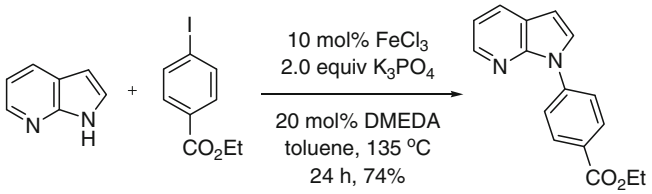
4.2 Selective C3-Arylation

Rhodium-catalyzed selective C3-arylation of indoles was reported by Itami et al. in 2006 [217]. Using a rhodium complex bearing a strong p-accepting phosphine ligand, they achieved a moderate selectivity of 2.4:1 for C3/C2 arylations as shown below.



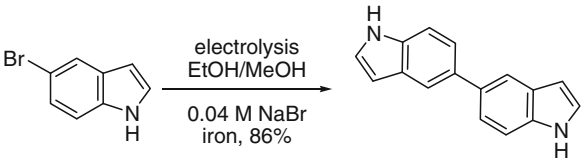
5 Iron-Catalyzed Cross-Coupling Reactions

Iron catalysis is experiencing a renaissance. In 2007, Bolm described a selective N1-arylation using $FeCl_3$ as the catalyst and K_3PO_4 as the base [218]. The coupling reaction was facilitated by the addition of 20 mol% of DMEDA as a chelating agent.

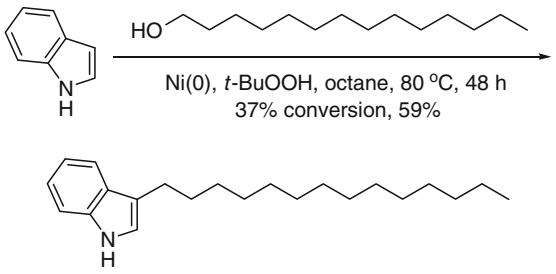


6 Nickel-Catalyzed Cross-Coupling Reactions

Using nickel-2,2′-bipyridine complex as the catalyst, electroreductive coupling of 5-bromoindole gave rise to the bis-indole shown using NaBr as the electrolyte and iron and the sacrificial electrode [219].



A trace amount of nickel metal was able to catalyze the alkylation of indole at the C3-position in the presence of *tert*-butyl peroxide [220]. Mechanistically, the mixture of Ni(0)/*t*-BuOOH was likely to be responsible for oxidizing the primary alcohol to the corresponding aldehyde, which was then added to the C3-position of the indole ring. The resulting alcohol was reduced in situ to give the 3-alkylindole shown below.



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Radical Reactions of Indole

Jeanese C. Badenock

Abstract Radical additions and cyclization reactions continue to play a dominant role in the chemistry of indoles, generating, in many cases, fused derivatives via cascade sequences.

Keywords Cascade sequences · Indole · Manganese(III) acetate · Radical cyclizations · Radical reactions · Tributyltin hydride · Xanthates

Contents

1 Introduction

Radical reactions are now a well-established and commonly used methodology for the synthesis of heterocycles and indoles in particular. Tributyltin hydride mediated radical reactions including additions, substitutions, and cyclizations continue to be

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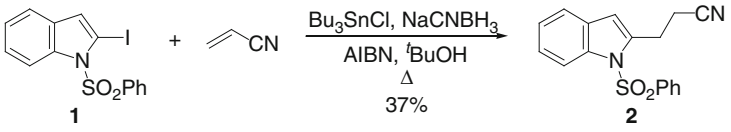
the most well-developed methodology despite tin toxicity and tedious purification protocols. Attempts to circumvent these associated difficulties have seen the development of methods for the in situ generation of Bu_3SnH using Bu_3SnCl under reductive conditions, as well the use of *tris*(trimethylsilyl)silane (TTMSS) as a replacement radical mediator. Other tin-free reagents and conditions utilized with indoles include: triethylborane (Et_3B) using O_2 as an initiator, hypophosphorous acid (H_3PO_2), and *N*-ethylpiperidine hypophosphite (EPHP) [1] in aqueous solvents and the atom transfer and single-electron transfer (SET) agents such as samarium iodide, copper(I) chloride, indium metal, and *tris*(2,2′-bipyridyl)ruthenium dichloride. Additionally, oxidative free-radical reactions using manganese(III) acetate continue to provide more examples of indole derivatives, but these still appear to be confined to the addition of β-dicarbonyl compounds. Xanthate (dithiocarbonate)-based radical chemistry has gained popularity in the last decade, largely driven by the efforts of Zard and coworkers [2–4], and mainly due to the mild and neutral reaction conditions utilized in its use as well as the inexpensiveness of the reagents employed. Additionally, xanthate-generated free radicals have proven to have a longer lifetime and thereby efficiently add to unactivated alkenes. A full account of the chemistry and mechanisms associated with these reagents has already been reported [5, 6] and will only be mentioned briefly here.

2 Intermolecular Radical Reactions

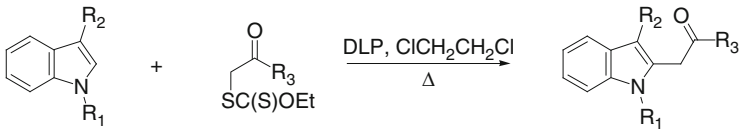
2.1 Radical Addition and Substitution Reactions of Indole

Although examples of intramolecular radical additions and radical cyclizations continue to dominate the literature, there are a few examples of intermolecular additions mainly to the C-2 or C-3 positions of the indole ring. Early examples utilized hydrogen peroxide and $FeSO_4{\cdot}7H_2O$, oxidative free-radical reaction conditions (Mn(III), Fe(II) and Ce(IV)) [7], or photolysis [8], but required a large excess of reagents and suffered from low product yields.

The addition of indol-2-yl radicals, generated from a variety of 2-haloindoles, to electron-deficient alkenes has been reported [9]. In this investigation, in situ generation of catalytic quantities of tributyltin hydride provided the optimal conditions and represents one of the few reports which involve an intermolecular reaction of aryl radicals. A typical example, shown below, between acrylonitrile and *N*-(phenylsulfonyl)-2-iodoindole (**1**) gave a best yield of 37%.

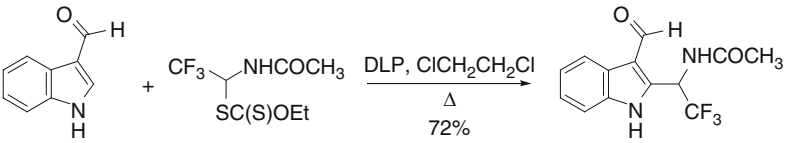


Miranda and coworkers utilized xanthate-mediated radical conditions to add α-acetyl and α-acetonyl radicals to indoles **3a** and **3b**, with good regioselectivity, at the C-2 position [10]. In this case, better yields were observed with indole (**3a**) than with the *N*-benzyl-3-indolecarboxaldehyde (**3b**).



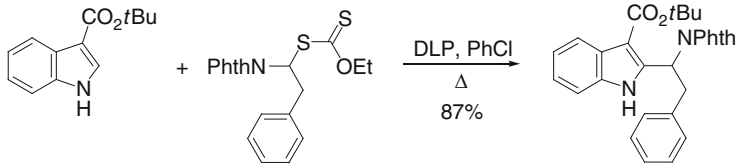
3a: $R_1 = H$; $R_2 = H$ **4a**: $R_3 = OEt$ **5a**: $R_1 = H$; $R_2 = H$; $R_3 = OEt$ (60%)
3b: $R_1 = CH_2Ph$; $R_2 = CHO$ **4b**: $R_3 = CH_3$ **5b**: $R_1 = CH_2Ph$; $R_2 = CHO$; $R_3 = CH_3$ (44%)

Fluorinated groups have also been added to the C-2 position of indoles and pyrroles [11]. Therefore, 3-indolecarboxaldehyde (**6**) was easily transformed into the 2,3-disubstituted indole **7** in 72% yield. Further manipulation of **7** using ethanolic hydrochloric acid resulted in ring closure to give a tricyclic [2,3-*b*]fused indole.



6 **7**

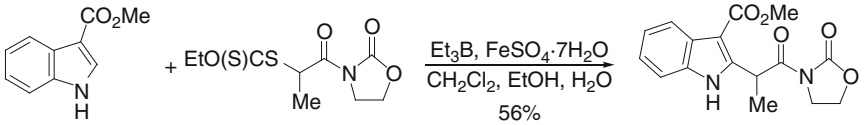
More recently, *S*-phthalimidomethyl xanthates derived from various amino acids have been added to various unactivated alkenes [12]. In particular, ornithine- and phenylalanine-derived xanthates, such as **9**, added effectively to 3-cyanoindole and *t*-butyl 3-indolecarboxylate (**8**) in the presence of stoichiometric amounts of dilauroyl peroxide (DLP) to give the disubstituted indole **10** in 87% yield. Miranda also utilized this methodology recently to synthesize C-2-alkylated tryptamine derivatives en route to azepino[4,5-*b*]indoles [13].



8 **9** **10**

Et_3B and $FeSO_4 \cdot 7H_2O$ have also been used to initiate a xanthate-mediated intermolecular oxidative radical alkylation with moderate success [14]. In this

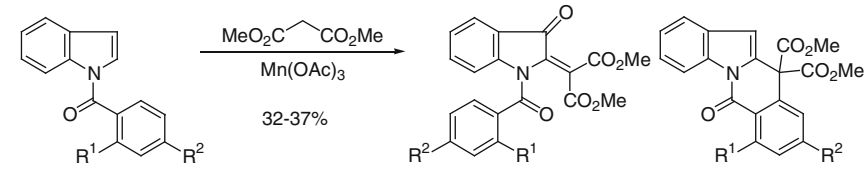
report, isoxazolidinone (**12**) and lactone xanthates were added to 3-carbomethoxyindole (**11**) in yields of 56% and 54%, respectively. The yields obtained upon addition of xanthate **4a** to indole (**3a**) itself under these conditions, however, did not supersede those obtained with DLP (30% vs. 60%).



11 **12** **13**

A synthesis of poly-*N*-vinylindole derivatives has also been reported using xanthate-mediated controlled radical polymerization (RAFT polymerization) [15]. The investigation, which focused on the use of various chain transfer agents, utilized *N*-vinylindole, 2-methyl-*N*-vinylindole and 3-methyl-*N*-vinylindole to synthesize polymers with controlled molecular weights and low polydispersities. The photorefractive properties of these polymers were then further investigated.

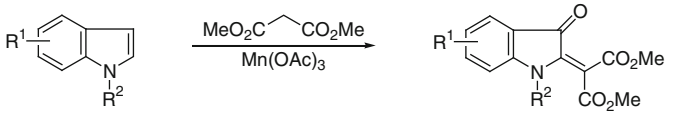
Intermolecular radical addition products were also observed between N-substituted indoles derivatives and 1,3-dicarbonyl compounds under oxidative conditions [16]. In this case, 3-unsubstituted *N*-benzoylindoles **14a–c** bearing methoxy groups at either the *ortho* or *para* positions or both gave the unexpected 3-indolone **15** rather than the tetracyclic **16**, observed in earlier reports, albeit in low yields.



14a: R^1 = H, R^2 = OMe
14b: R^1 = OMe, R^2 = H
14c: R^1 = OMe, R^2 = OMe

15 **16**

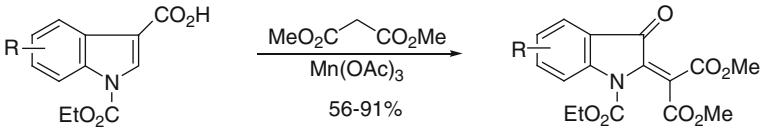
Further investigation of this addition reaction revealed that similar indolones could be obtained when N-protected indoles (**17**) bearing sulfonyl and ethoxycarbonyl groups were treated with dimethyl malonate and manganese(III) acetate. Modest improvement in yield was observed with the carbamate protecting group while the introduction of a substituent on the aryl ring illustrated that both the position and electronic effect were important to the reaction. The best yield (74%) was observed with indoles bearing a 4-methyl group, and a very low yield (10%) was seen with those indoles bearing bromine at the C-5 position.



17

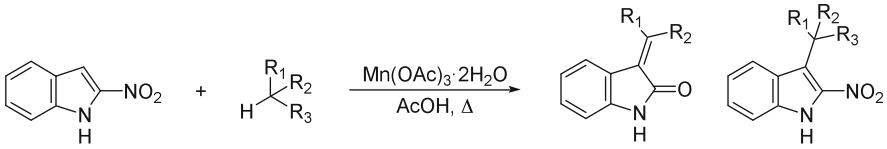
18a: R^1 = H, R^2 = Mes (36%)
18b: R^1 = H, R^2 = Ms (29%)
18c: R^1 = H, R^2 = Ts (25%)
18d: R^1 = H, R^2 = CO_2Et (43%)
18e: R^1 = 4-Me, R^2 = Mes (64%)
18f: R^1 = 4-Me, R^2 = CO_2Et (74%)
18g: R^1 = 5-Me, R^2 = CO_2Et (41%)
18h: R^1 = 5-Br, R^2 = CO_2Et (10%)
18i: R^1 = 4-OMe, R^2 = CO_2Et (34%)

Much improved yields (56–91%) of 3-indolone **20** were obtained when aryl substituted 3-indolecarboxylic acids **19** were subjected to these radical oxidative conditions. However, the treatment of 2-indolecarboxylic acids under identical reaction conditions gave poor yields of the corresponding 2-indolone.



19: R = H, 5-Me, 6-Me, 7-Me, 5-Br, 5-Cl, 5-OMe **20**

Radical addition reactions were also recently added to the repertoire of 2-nitroindole (**21**), previously dominated by nucleophilic reactions [17]. Treatment of the indole with activated methylene compounds such as dimethyl malonate, malonitrile and pentane-2,4-dione in a refluxing solution of $Mn(OAc)_3{\cdot}2H_2O$ in acetic acid gave mainly 2-oxo-indolin-ylidenes **22** after an in situ Nef reaction. The expected 3-subsitiuted 2-nitroinole **23**, however, was only observed with the methine compounds 3-methylpentane-2,4-dione and 5-oxo-4-propionylheptane-nitrile.

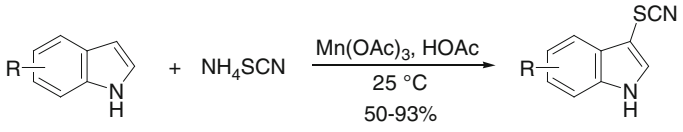


21 **22** **23**

R_1	R_2	R_3	Product	% yield
CO_2Me	CO_2Me	H	**22**	55
COMe	COMe	H	**22**	52
CN	CN	H	**22**	66
COPh	COPh	H	**22**	49
COPh	COMe	H	**22**	67[a]
CO_2Me	COMe	H	**22**	61[a]
CO_2Me	CO_2Me	Me	**23**	53
COEt	COEt	$(CH_2)_2CN$	**23**	48

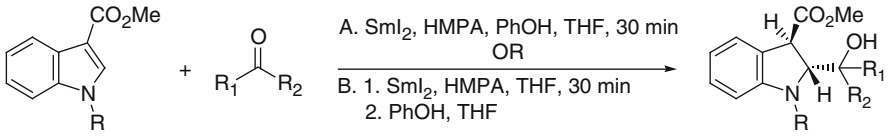
[a]A mixture of *E*- and *Z*-isomers

Zhang's interest in addition of heteroatom radicals to aromatic rings was extended recently to indoles [18]. Using ammonium thiocyanate and manganese (III) acetate in acetic acid at room temperature, a simple intermolecular thiocyanation of the 3-position of a variety of substituted indoles (**24**) was realized. The highest yield of 93% was obtained with 7-methylindole.



24 **25**: R = Me, OBz, Br

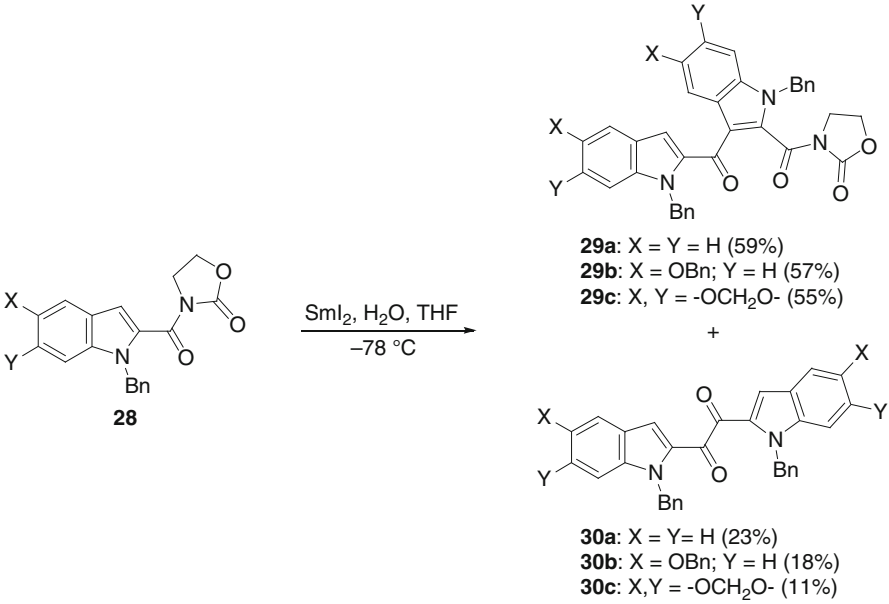
Samarium diiodide-induced intermolecular coupling of aldehydes and ketones to indoles with an electron-withdrawing group at the 3-position of the indole have also been reported [19]. Carbonyl compounds including acetone, acetophenone, benzophenone, pivaldehyde, and isobutyraldehyde added to the C-2 position of the indole to give the thermodynamically stable *trans*-dihydroindole derivatives **27**.



26 **27**

Conditions	R	R_1	R_2	% yield
A	Me	Me	Me	87
A	Boc	Me	Me	76
A	Me	Ph	Ph	<5
B	Me	Ph	Ph	76
A	Boc	*t*-Bu	H	77
A	Boc	*i*-Pr	H	66
A	Me	*i*-Pr	H	69
A	Me	Et	H	-
A	Me	Ph	Me	<5
B	Me	Ph	Me	72

Bisindoles **29** and **30** were also obtained when oxazolidinone derived indoles **28** were treated with samarium iodide (SmI_2), presumably due to the 1,4- or 1,2-addition of the ketyl radical anion to the C–C or C–O double bonds of another equivalent of the indole [20].



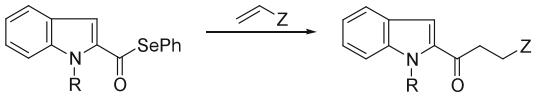
Photochemically-induced addition of difluoromethylene groups to the C-2 position of indole has also been reported [21]. However, conversion of the radical precursor, α,α-difluoro-α-(phenylseleno)acetate, was reported as poor and the resultant yields of the substituted compounds were low.

2.2 Radical Addition Reactions of Indolylacyl Radicals

Over the last decade there has been great interest in the synthesis and use of 2- and 3-indolylacyl radicals generated from seleno esters and glyoxylic acids, fuelled by the work of Bennasar [22]. Early reports from this group outlined the intermolecular addition reaction of such generated radicals to various alkenes and pyridines [23, 24].

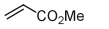
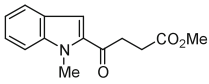
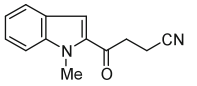
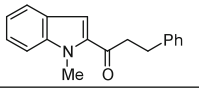
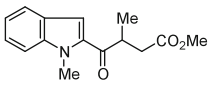
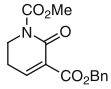
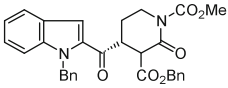
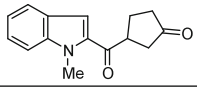
As such, 2-indolylacyl radicals generated from phenyl seleno esters **31**, added to electron-deficient alkenes using typical reductive tin radical conditions and gave decent yields (60–66%) of the addition product **32**. These examples gave no evidence of the products of premature reduction or decarbonylation. Alternatively, alkenes bearing two electron-withdrawing substituents, e.g., dimethyl fumarate generated lower yields of the addition product and gave significant amounts of the reduced 2-indolecarbaldehyde. Cyclic electron acceptors such as cyclopentanone and *N*-tosyl-5,6-dihydro-2(1*H*)pyridone gave satisfactory yields only when

TTMSS or the nonreductive hexabutylditin (n-Bu_6Sn_2) were used as the radical mediator. A few examples are included below.

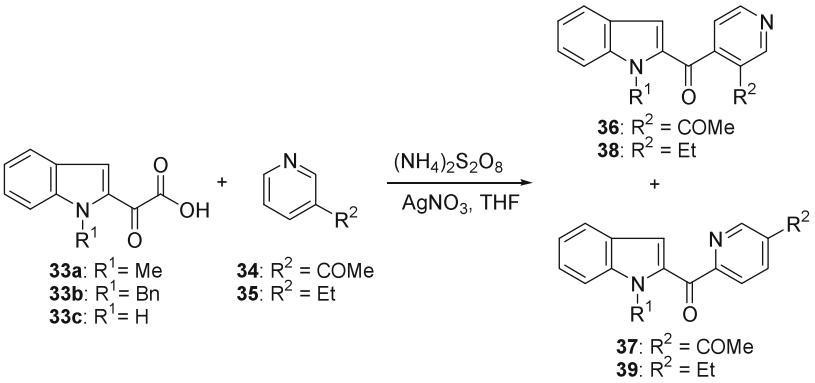


31a: R =Me
31b: R = Bn

32

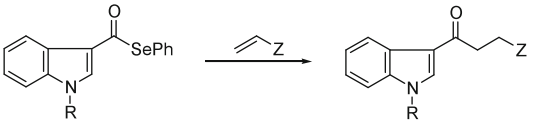
Indole	Alkene	Product	Method	% Yield
31a			n-Bu_3SnH, AIBN, C_6H_6, Δ	62
31a			n-Bu_3SnH, AIBN, C_6H_6, Δ	66
31a			n-Bu_3SnH, AIBN, C_6H_6, Δ	60
31a			n-Bu_3SnH, AIBN, C_6H_6, Δ	54
31b			TTMSS, AIBN,C_6H_6, Δ	58
31a			n-Bu_6Sn_2, hν, C_6H_6, Δ	55

2-Indolylacyl radicals were also generated from indoleglyoxylic acids **33a**,**b** when subjected to Minisci transformation conditions. This sequence involves the decarboxylation of the α-keto acid using $(NH_4)_2S_2O_8$ as the oxidant followed by addition of the resultant acyl radical to aromatic rings: in this case, pyridine derivatives 3-acetylpyridine (**34**) and 3-ethylpyridine (**35**). Examples shown below demonstrated the formation of two regioisomers, whose ratios were determined by ^{1}H NMR of the product mixture, with the best yield (90%) being observed when the *N*-methylindole **33a** was treated with **34**. Solvent changes were also reported as significantly affecting the regioselectivity of the radical addition.



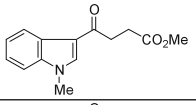
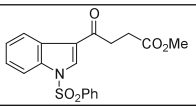
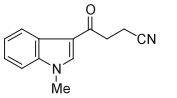
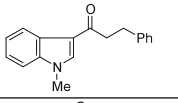
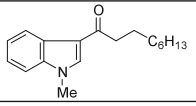
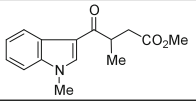
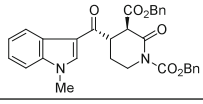
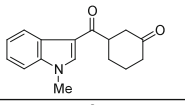
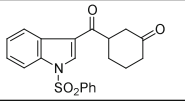
Indole	Pyridine	Products (ratio)	% Yield
33a	**34**	**36a** + **37a** (1:1)	90
33a	**34**	**36a** + **37a** (7:1)	40
33a	**35**	**38a** + **39a** (0:1)	20
33b	**34**	**36b** + **37b** (1:1)	30
33c	**34**	**36c** + **37c** (1:1)	20

In a similar vein, the regioisomeric 3-indolylacyl radicals, generated from seleno esters **40a**,**b**, also reacted with alkenes bearing electron-withdrawing groups such as methyl acrylate (Z = CO_2Me: 82%) and acrylonitrile (Z = CN: 76%) but in higher yields than reported with the 2-indolylacyl radicals [24]. Interestingly, reaction with unactivated alkenes such as styrene (Z = Ph: 50%) and 1-octene (Z = C_6H_{13}: 45%) were also observed, which illustrates the high reactivity of the preformed radical. Additionally, reaction of the seleno ester bearing a methyl group on the nitrogen (**40a**) produced higher yields than those seen with the *N*-(phenylsulfonyl) indole **40b**. The examples shown below were selected for comparative purposes with those seen with reaction of indoles **31**.



40a: R =Me
40b: R = Bn

41

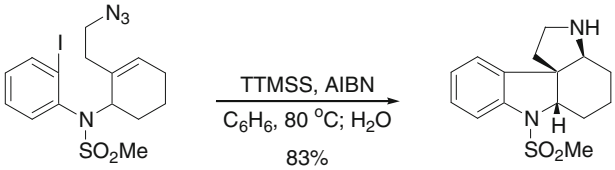
Indole	Alkene	Product	Method	% Yield
40a			*n*-Bu_3SnH, AIBN, C_6H_6, Δ	82
40b			*n*-Bu_3SnH, AIBN, C_6H_6, Δ	55
40a			*n*-Bu_3SnH, AIBN, C_6H_6, Δ	80
40a			*n*-Bu_3SnH, AIBN, C_6H_6, Δ	50
40a			TTMSS, AIBN, C_6H_6, Δ	45
40a			TTMSS, AIBN, C_6H_6, Δ	47
40a			TTMSS, AIBN, C_6H_6, Δ	72
40a			*n*-Bu_3SnH, AIBN, C_6H_6, Δ	76
40b			TTMSS, AIBN, C_6H_6, Δ	35

3 Intramolecular Radical Reactions

As a result of the large number of indole and indoline alkaloids present in the literature, many reports and reviews have emerged demonstrating the capabilities of radical cyclization to furnish fused indole structures [25–30].

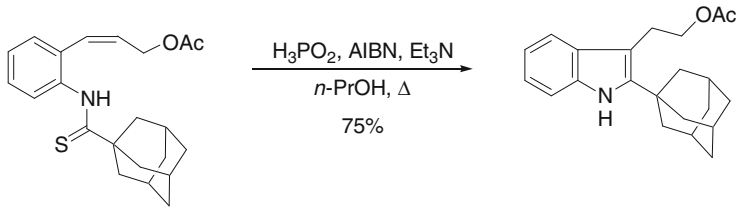
3.1 Synthesis of the Indole Core

In Murphy's approach to the tetracycle core of *Aspidosperma* alkaloids, the tandem cyclization reaction of an iodoazide was investigated [31]. Treatment of **42** with TTMSS and AIBN generated the tetracycle **43** as a single diastereomer. It was suggested that the aryl radical cyclizes in a 5-*exo*-*trig* fashion onto the alkene generating a new radical which subsequently cyclizes onto the azide, forming the desired ABCD rings of the alkaloid. This chemistry was later expanded into a formal synthesis of (±)-aspidospermidine [32].



42 **43**

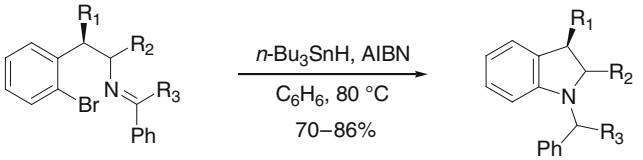
Fukuyama and coworkers gave a full account of the use of hypophosphorous acid in the cyclization of *o*-alkenylthioanilides to generate 2,3-disubstituted indoles [33]. These mild conditions proved quite compatible with a variety of functional groups, e.g., hydroxyl groups, and provided an efficient process for installing bulky groups, such as the adamantanyl and cyclohexyl groups at the C-2 position of the indole [34]. The indole alkaloid (±)-catharanthine was synthesized using this methodology.



44 **45**

N-Substituted indolines have also been synthesized via an uncharacteristic radical addition to the nitrogen terminus of dialkyl ketimines [35]. In this case, intramolecular cyclizations of aryl radicals, generated from a variety of *o*-bromophenethylamine ketimines (**46**) using typical tin hydride conditions, occurred in a 5-*exo* fashion. This result contrasted drastically with the previously observed

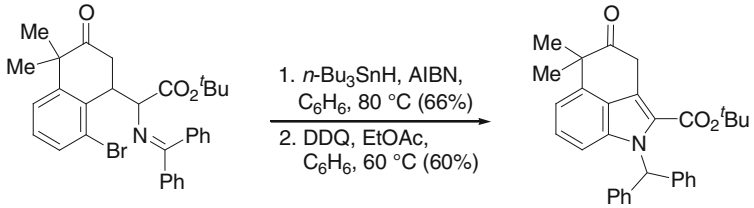
6-*endo* cyclization pathway of similarly constructed aldimines [36–38]. Johnston and coworkers further investigated the scope of this reaction and observed that imines derived from aryl alkyl ketones bearing an electron-withdrawing group (radical-stabilizing groups) were well tolerated (65–90%). Substitution of the phenethylamine backbone allowed for access into 2,3-disubstituted indolines, while the inclusion of a stoichiometric amount of the radical initiator coupled with longer reaction times gave access to indolines generated from α-ketoimines [39].



46
R_1 = H, CH_3, OCH_3
R_2 = H, CH_3
R_3 = CH_3, Ph

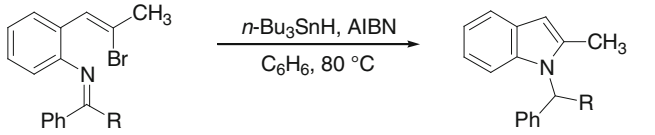
47

An enantioselective α-indoline amino acid protocol was also described using glycinyl imines but with varying loss of enantiomeric purity [40]. More recently, synthetic attempts towards the indole alkaloid ambiguine G, as seen in the synthesis of **49**, have also utilized this chemistry [41].



48 **49**

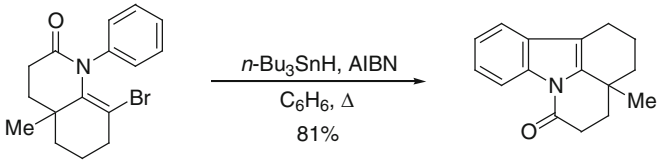
Johnston also explored a radical-mediated vinyl amination strategy in attempts to access pyrrolidinyl enamines [42, 43]. In the example shown below, 2-methyl-*N*-substituted indoles (**51a**,**b**) were also synthesized in decent yield via a 5-*exo*-*trig* cyclization of a vinyl radical to a ketimine nitrogen without evidence of the products of premature reduction.



50

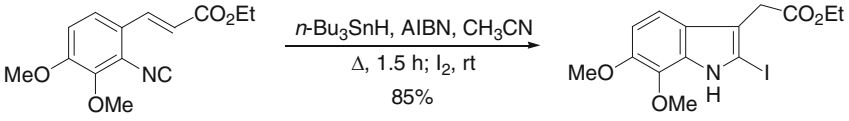
51a: R = CH_3 (64%)
51b: R = Ph (53%)

Throughout the course of their investigation of vinyl radical cyclization using *N*-alkenyl-7-bromo-substituted hexahydroindolinones, Padwa synthesized a pyrido [3,2,1-*jk*]carbazolonone (**53**) in 81% yield as a result of cyclization of the radical onto the benzene ring [44].



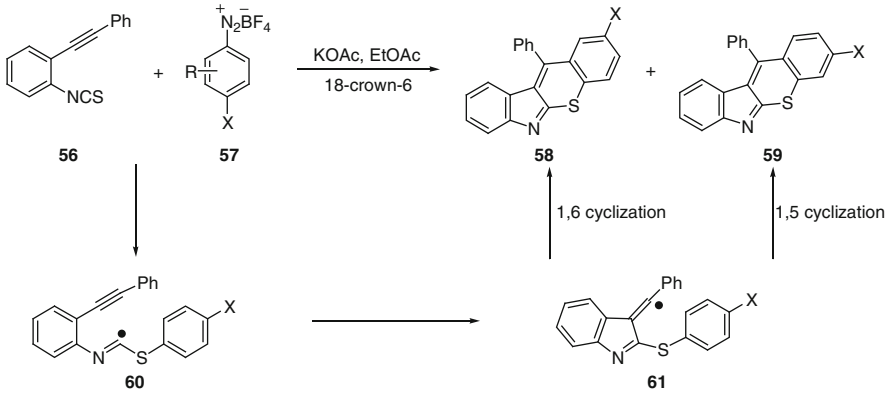
52 **53**

Fukuyama's tin-mediated indole synthesis was also highlighted in the enantioselective total synthesis of aspidophytine [45]. Treatment of the 2-alkenylphenylisonitrile **54** with tributyltin hydride and AIBN in refluxing acetonitrile followed by treatment of the 2-stannyl indole intermediate with iodine gave the expected 2-iodoindole **55**, bearing methoxy groups at C-6 and C-7 of the indole ring, in 85% yield.



54 **55**

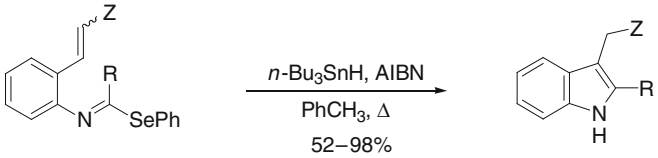
A number of reports have emerged that utilize imidoyl radicals generated using several different protocols in the synthesis of indoles. Rainier used typical tin reduction conditions to achieve cyclization of imidoyl radicals, generated from isocyanides, onto alkynes [46]. Utilizing isothiocyanates however, Nanni and coworkers generated α-(arylsulfanyl)imidoyl radicals (**60**), which underwent a cascade reaction to synthesize a new class of compounds, thiochromeno[2,3-*b*]indoles [47]. This outcome is thought to involve the initial addition of the aryl radical, generated from the corresponding diazonium tetrafluoroborates **57**, to the sulfur atom of the isothiocyanate to give imidoyl radical. Successive cyclization onto the triple bond generates a vinyl radical **61**, which either undergoes a 1,5- or 1,6-cyclization onto the benzene ring. Interestingly, significantly higher yields of **58** and **59** were observed when a methylsulfanyl group was placed *ortho* to the initial aryl radical presumably due to its ability to stabilize this radical and act as a good leaving group in the cyclization.



56 **57** **58** **59** **60** **61**

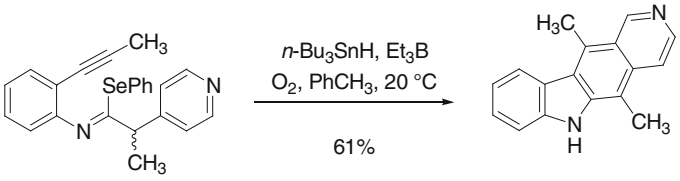
X	R	58 (%)	59 (%)
H	H	50	-
CF_3	H	27	23
Cl	H	27	23
OCH_3	H	20	20
SCH_3	H	8	32
N_3	H	4	40
$C(O)CH_3$	H	2	43
H	*o*-SCH_3	70	-
Cl	*o*-SCH_3	-	70

Bowman's approach to imidoyl radicals commenced with imidoyl selanides [48, 49]. Subsequent cyclization onto electron-deficient α,β-unsaturated esters (Z = CO_2Et) as well as to electron-rich propyl- and phenyl-alkenes (Z = Pr, Ph) gave 2,3-disubstituted indoles in moderate to excellent yields with no evidence of the products of simple reduction.



62 **63**: R = Me, Bn, *p*-Tol, *p*-Cl-C_6H_4

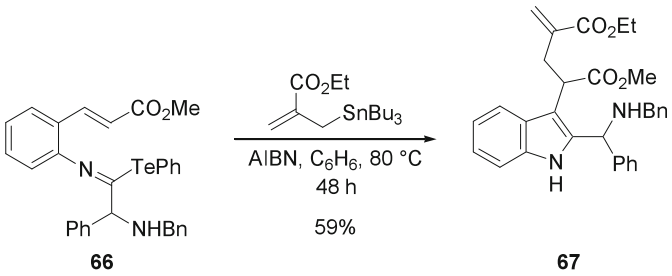
Cascade sequences involving the cyclization of imidoyl radicals onto alkynes and then aromatic rings have been used to synthesize aryl- and heteroaryl-fused [*b*] carbazoles [50]. Optimized conditions used for this sequence involved: the addition of the initiator Et_3B to a deoxygenated solution of Bu_3SnH and the imidoyl selanides, introduction of O_2, stirring for 24 h, deoxygenation, addition of another portion of Et_3B, and then stirring until the selenide was no longer present. This protocol was used to synthesize the anticancer alkaloid ellipticine (**65**) in five steps (19% overall) from ethyl 2-(4-pyridyl)acetate. The final key radical cyclization step in this synthesis is illustrated below.



64 **65**

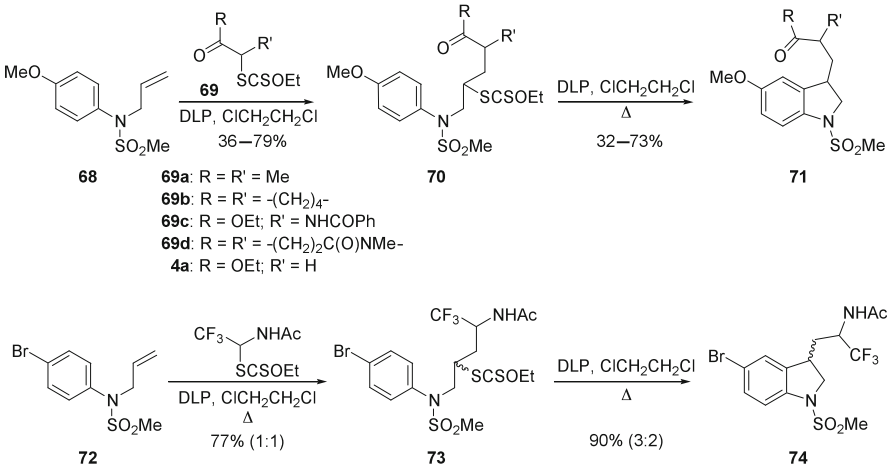
Imidoyl radicals generated from imidoyltellurides have also cyclized under tin hydride conditions to give good yields of 2,3-disubstitued indoles [51]. Generated from 2-alkenylphenylisocyanide and aromatic or aliphatic imines by heating in acetonitrile at 60°C for 10 h, followed by silica gel-induced hydrolysis of the

triethoxysilyl group, the imidoyltellurides were shown to tolerate a wide variety of functional groups and were extended to form more structurally complex indoles such as **67**.



66 **67**

Xanthate-mediated cyclizations have also been used to generate indole and indoline derivatives. In Zard's synthesis of melatonin, the indole nucleus was realized from this protocol [52]. Utilizing the *para*-methoxy *N*-allylaniline **68** as the synthetic precursor, substituted xanthates **69a-d** and **4a** were added using typical conditions seen in an intermolecular addition of this type, i.e., DLP (0.2 equiv.), $ClCH_2CH_2Cl$ under reflux. A smooth intramolecular cyclization of the intermediate xanthates **70**, isolated in yields of 36–79%, occurred using stoichiometric amounts of the peroxide and gave the indolines **71** in fair yield. The conditions utilized for the effective transformation of the indoline to indole were discovered serendipitously and optimized at ten equivalents of 95% H_2SO_4 for 30 min. Cyclizations of this type have also been used to gain access to previously inaccessible trifluoromethylated indolines such as **74**, which was generated as a mixture of enantiomers in 90% yield [53].

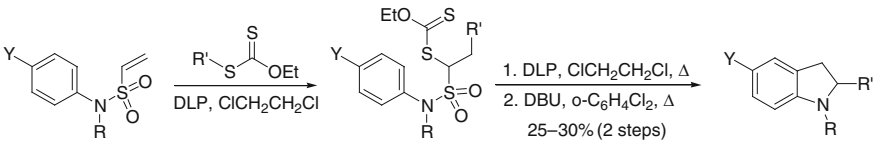


68 **70** **71**

69a: R = R' = Me
69b: R = R' = -$(CH_2)_4$-
69c: R = OEt; R' = NHCOPh
69d: R = R' = -$(CH_2)_2$C(O)NMe-
4a: R = OEt; R' = H

72 **73** **74**

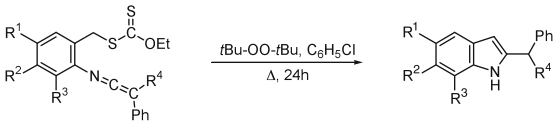
Zard also used a xanthate-mediated radical cascade sequence to synthesize indolines from vinyl sulfanilides in three steps [54]. The initial peroxide-initiated intermolecular addition of the xanthate to the vinyl sulfanilide was followed by an intramolecular cyclization onto the ortho position of the aromatic ring. Further heating with DBU generated the dihydroindole through a base-induced isomerization of the olefinic bond followed by conjugate addition.



75 **76**

77a: R = CH_3; Y = H; R' = CH_2CO*t*-Bu
77b: R = CH_3; Y = H; R' = CH_2COPh
77c: R = CH_3; Y = F; R' = CH_2CN
77d: R = CH_2Ph; Y = H; R' = CH_2CN

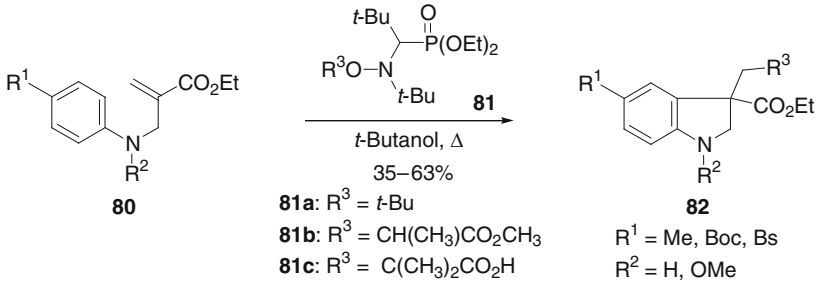
Vidal and coworkers exploited the intramolecular addition of benzylic radicals onto ketenimines to provide a novel route to 2-alkylindoles [55, 56]. Utilizing tin-free conditions – *t*-butyl peroxide in refluxing chlorobenzene for 24 h – ketenimines **78**, bearing a xanthate group, were thought to undergo a 5-*exo-dig* addition of the resulting benzylic radical to the electrophilic central carbon followed by an imine–enamine tautomerism to give indoles in fair yields.



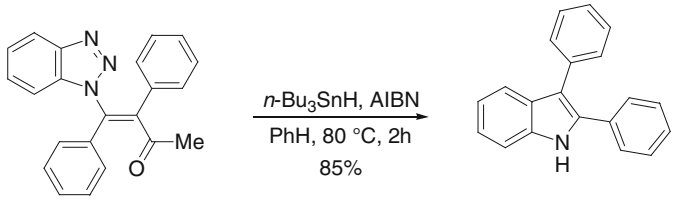
78 **79**

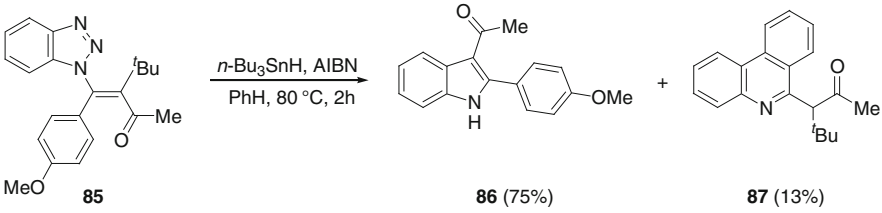
R^1	R^2	R^3	R^4	% Yield
H	H	H	Ph	50
Br	H	H	Ph	24
Cl	H	H	Ph	60
CH_3	H	H	Ph	47
H	NO_2	H	Ph	64
H	H	CH_3	Ph	60
C_6H_4		H	Ph	52
H	H	H	CH_3	44

Alkoxyamine-mediated assembly of indolinones and indolines has been described [57]. This route offered the added benefits of employing tin-free conditions and the possibility of inserting oxygen functionality through trapping with a nitroxyl radical. As such, when unsubstituted or *para*-substituted anilines were treated with three Tordo-type alkoxyamines, **81a–c**, the cyclized indolines were obtained in modest to fair yield.



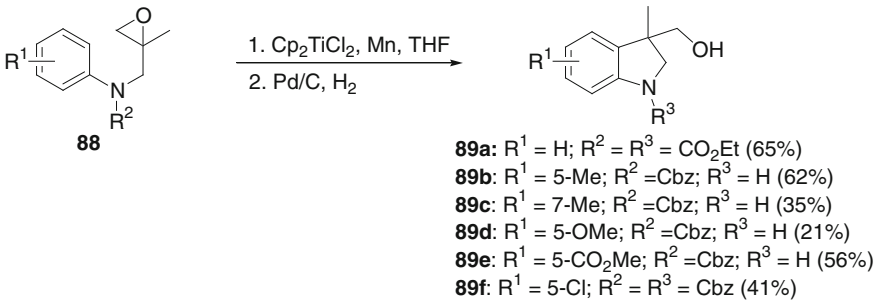
Earlier this year, Kim reported a novel synthesis of 2,3-disubstituted indoles when β-aryl-β-(benzotriazol-1-yl)-α-primary alkyl (or aryl)-α,β-unsaturated ketones were treated with excess *n*-Bu_3SnH [58]. The proposed mechanism begins with the formation of the *O*-stannyl ketyl radical of **83**, which upon loss of nitrogen generates an aryl radical, followed by a 5-*exo*-*trig* cyclization, hydrolysis, and oxidative cleavage to give indole **84**. Interestingly, 3-acyl (or aroyl)-2-alkyl indoles, such as **86**, were isolated when the primary alkyl or aryl groups were replaced by a *t*-butyl group, presumably due to the facile nature of loss of the stabilized *t*-butyl radical. Two examples are seen below.



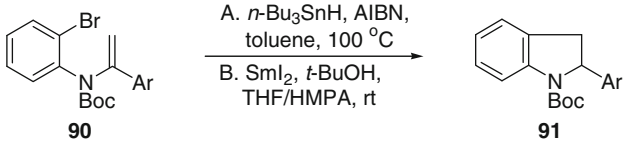


A novel indoline ring synthesis from epoxides using titanocene(III) chloride has also been reported [59]. Using several 1,1-disubstituted epoxides, indolines with a preinstalled quaternary C-3 carbon were obtained in fair to good yields. The proposed mechanism is thought to commence with the titanocene(III) chloride catalyzed ring opening, to generate a β-titanoxy radical, which then cyclizes onto

the aromatic ring in a 5-*exo* fashion. Oxidation and loss of a proton give the observed indolines **89a–f**.

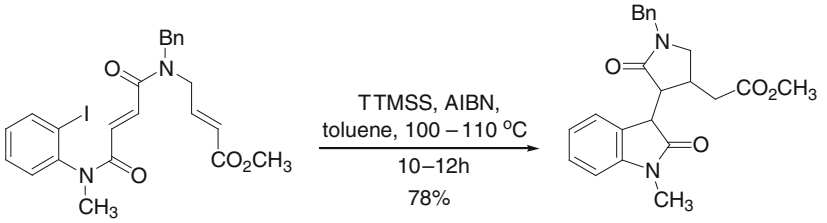


Fluorinated 3-methyleneindolines have also been prepared by tributyltin hydride-promoted radical cyclization of bromoaryl-*N*-propargylcarbamates [60]. These versatile intermediates were then further transformed into 3-functionalized nuclei and side-chain indole derivatives by a simple carbonyl-ene reaction. Fuwa and coworkers recently outlined the synthesis of a number of 2-substituted indolines and indoles using 5-*endo-trig* cyclization strategies [61]. As such, *o*-bromoaniline-derived ene carbamates (**90**) underwent aryl radical cyclization with tributyltin hydride as well as with samarium iodide (SmI_2) in *t*-butanol to give the expected 2-arylindolines **91** in good yield.



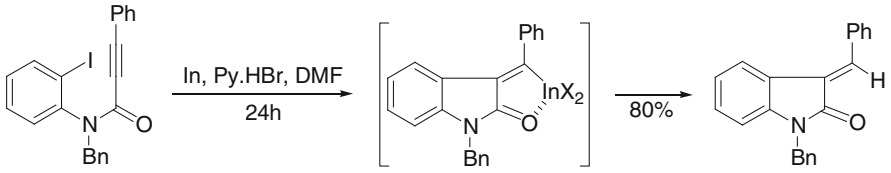
Ar	% Yield under A	% Yield under B
Ph	82	90
p-OMePh	85	86
p-ClPh	62	80
o-MePh	72	63
2-furyl	51	54

Recent syntheses of indol-2-ones (oxindoles) include Chuang's *p*-toluenesulfonyl radical induced cyclization of allylsulfones and the oxidative free-radical reactions of α,α-dimethylsulfonyl substituted anilides [62], the "tin-free" synthesis of 3-aminoindolinones from *O*-benzyl oxime substituted amidocyclohexadienes [63], and Pudlo's 5-*exo-trig*/5-*exo-trig* tandem radical cyclization of acrylamides to give 3-pyrrolidinone substituted oxindoles, shown below [64].



92 **93**

An indium-mediated radical cyclization sequence has been used to synthesize stereoselectively 3-alkylideneoxindoles [65, 66]. The generation of predominantly the *E*-isomer, such as seen with **96** below, is attributed to the strong coordination of the indium to the carbonyl of the oxindole intermediate, and the transformation of various iodo-ynamides to the cyclized oxindoles occurred in good yield. Selective approaches to the *E*- and disubstituted 3-alkylideneoxindoles involving a tandem palladium-catalyzed cross coupling reaction were also highlighted in this report.

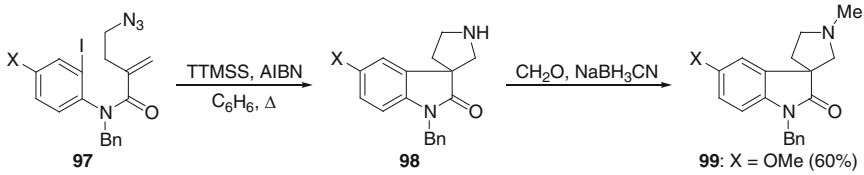


94 **95** **96**

Nicolaou [67, 68] and Fukase [69] have also reported the use of radical cyclization and solid phase methodology to synthesize indoline scaffolds and indol-2-ones.

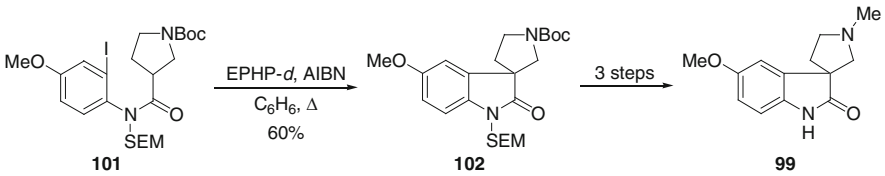
3.2 Synthesis of Spirooxindoles and Spiroindolines

The recent isolation of a number of biologically active, naturally occurring spiropyrrolidinyloxindole alkaloids such as spirotryprostatin A and B – coupled with the discovery of a number of highly active synthetic analogs [70] – has fuelled renewed interest in the development of new approaches to this class of heterocycle. Murphy has utilized his previously established aryl iodoazide tandem radical cyclization strategy to synthesize the alkaloids horsfiline (**99**) [71] and coerulescine (**100**) from **97** [72]. In a newer approach to horsfiline, Murphy observed a radical translocation (1,5-hydrogen atom abstraction) prior to cyclization when iodoamide **101** was treated with the radical precursor EPHP in refluxing benzene [73].

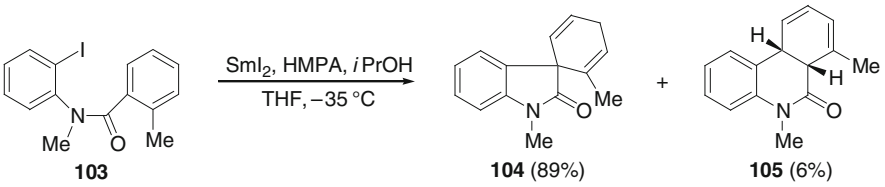


97 **98**

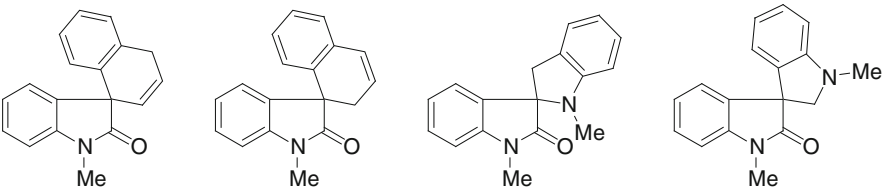
99: X = OMe (60%)
100: X = H (63%)



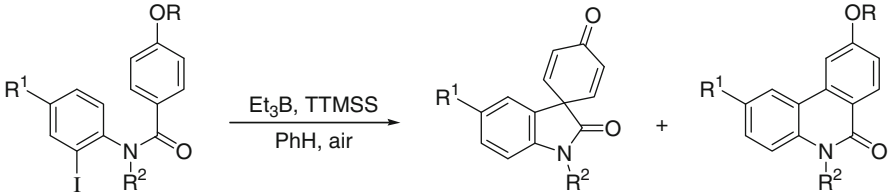
In Tanaka's approach to spirooxindoles, a novel aryl radical cyclization onto an aromatic ring was accomplished using samarium(II) iodide/HMPA and *i*PrOH [74]. As exemplified below, the *o*-methyl-substituted *N*-methylbenzamide **103** generated the spirocycle **104** in 89% yield along with small quantities of the fused tricyclic compound **105**. The proposed mechanism to the spirocycle involves a SET followed by a 5-*exo*-*trig* cyclization onto the benzene ring, a further SET, and finally protonation. The reduced product, which varied in yields depending on the benzamide studied, is thought to occur due to rearrangement of the intermediate spirohexadienyl radical, a SET, and protonation of the resultant anion.



Other aromatic rings that were studied as radical acceptors in this investigation included naphthalene and indole [75]. As such, spirocycles of the type **106**–**109** were synthesized with moderate success when HMPA was replaced with the additive LiBr.



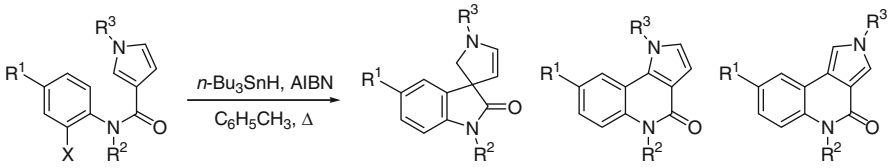
Curran was able to effect a similar cyclization using *para*-substituted benzamides bearing either Boc or methyl groups on the nitrogen [76]. Reaction conditions involving TTMSS and Et_3B in a solution of the amides in benzene at room temperature and open to the air, produced the spirocyclic compounds **111** in yields ranging from 29 to 53%. Cyclizations performed with the TBS- or methyl-protected precursors gave the phenanthridinones (**112**) as the major products.



110 111 112

R^1	R^2	R	111 (%)	112 (%)
H	Me	TBS	13	57
H	Me	Tr	43	-
H	Me	Bz	29	-
H	Me	Me	15	38
Me	Me	Tr	53	0
OEt	Boc	Tr	34	-

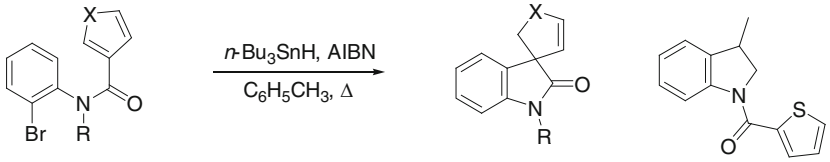
Radical cyclization of pyrrolo-3-carboxamides bearing an electron-withdrawing group on the pyrrole nitrogen, such as *t*-butyl or methyl carbamates, gave spiro-pyrrolodinyloxindoles **114** via a 5-*exo-trig* cyclization onto the C-3 position of the pyrrole ring [77, 78]. In all cases, **115** was isolated, which is the product of either a 6-*endo* cyclization or, more likely, forms via the rearrangement of the intermediate radical after a 5-*exo* cyclization.



113 114 115 116

X	R^1	R^2	R^3	114 (%)	115 (%)	116 (%)
I	CO_2Me	Me	Boc	26	13	5
Br	OMe	Me	Boc	31	18	1
Br	OMe	SEM	CO_2Me	32	15	-

Similar radical cyclizations of other five-membered heterocycles such as furan and thiophene also yielded the expected spirooxindoles as the major product without any evidence of rearrangement [79, 80]. However, when the carboxamide group was substituted with an allyl group, i.e., **117b**, cyclization of the initially formed aryl radical onto the allyl group generated the indoline **119** in 20% yield.

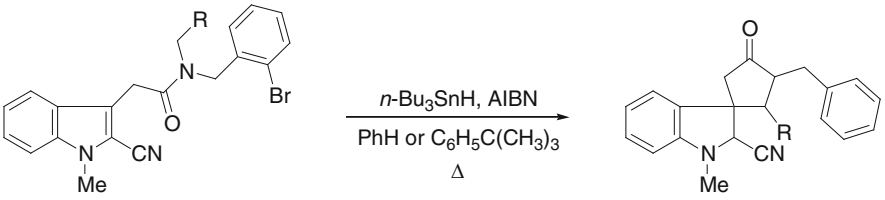


117a: R = Me; X = S
117b: R =CH_2CHCH_2; X = S
117c: R = Me; X = O

118a (76%)
118b (62%)
118c (59%)

119 (20%)

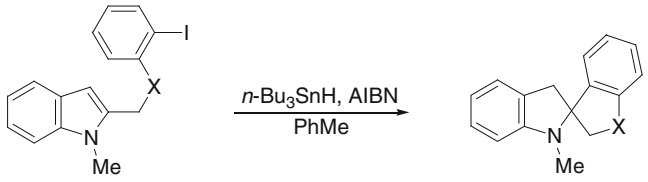
A tandem radical sequence was observed when the indole amide **120** was treated with tributylstannyl radical [81]. The initially formed aryl radical is proposed to undergo a 1,5-hydrogen atom abstraction to form an α-amido radical en route to the cyano spiroindolines **121a** and **121b**. Treatment with potassium *tert*-butoxide and oxygen in THF gave the C-3 spirooxindole in modest yield.



120

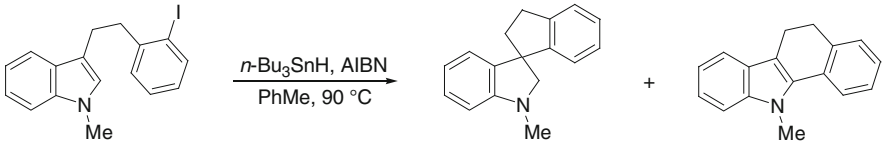
121a: R = H (30%)
121b: R = Me (53%)

Flanagan et al. performed an extensive methodological study of radical cyclization of indoles, and outlined a number of routes to 2- and 3-spirocyclic indoles, benzo[*c*]carbazoles, and fused[1,2-*a*]indoles in fair to good yields [82]. In particular, spirocyclization of the 2-(2-iodophenylethyl)indole (**122a**) occurred by a 5-*exo-trig* pathway to give the 2-spirocycle **123a** as the major product. Introduction of an oxygen in the tether gave increased yields of **123b** (72% vs. 55%). Similar reactivity was observed with the 3-(2-iodophenylethyl)indole **124**; however, an alternative 6-*endo* cyclization generated the benzocarbazole **126** as the minor product.



122a: X = CH_2
122b: X = O

123a: X = CH_2 (55%)
123b: X = O (72%)

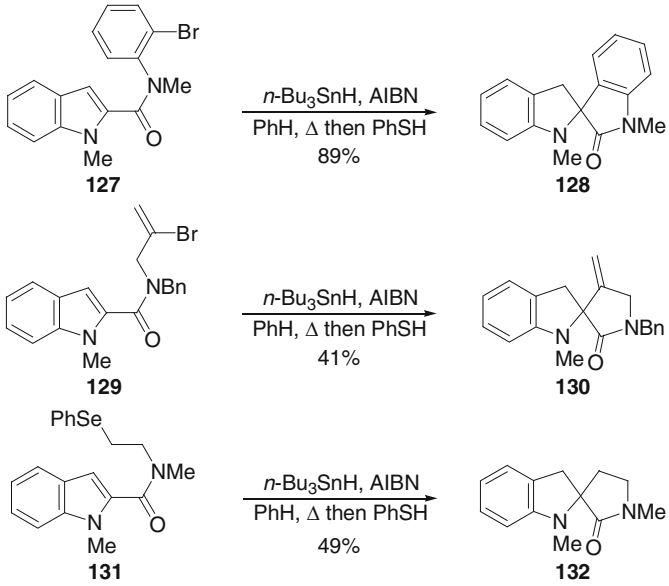


124

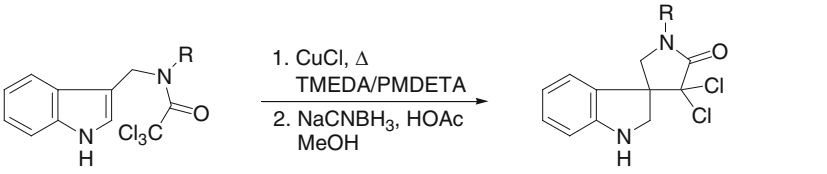
125 (63%)

126 (36%)

A radical *ipso*-type substitution on indoles and benzofurans has resulted in other dearomatized spirocycles [83]. Aryl, vinyl, and alkyl radicals added to the C-2 position of the indole to give novel compounds, **128**, **130**, and **132**, in moderate to excellent yields. In the case of the addition of alkyl radicals, significant amounts of the reduced starting material were also isolated.



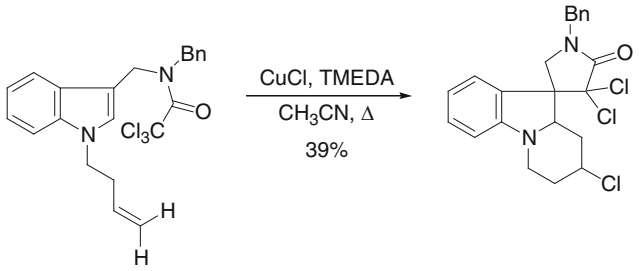
An interesting synthesis of chlorinated spiroindolines using a copper-catalyzed atom transfer radical cyclization has been reported [84]. When trichloroacetamides **133** were treated with copper(I) chloride in the presence of the amine ligands, tetramethylethylene diamine (TMEDA) and pentamethyldiethylene diamine (PMDETA), followed by sodium cyanoborohydride, the spiroindoles **134a–d** were obtained in good yield. The initial dichloro radical undergoes a 5-*exo-trig* cyclization onto the indole C-3 position (Kharasch ring closure). Reduction of the resultant imine – formed due to loss of HCl – occurred in a facile manner.



134a: R = Bn (81%)
134b: R = *i*-Pr (79%)
134c: R = $CH_2P(O)(OEt)_2$ (75%)
134d: R = $CHPhP(O)(OEt)_2$ (57%)

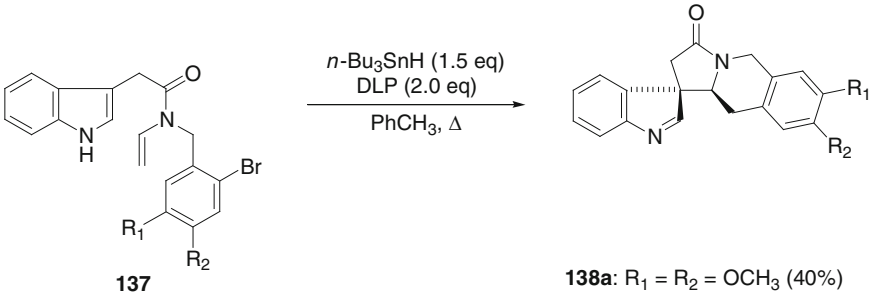
In a more recent elaboration of this work, a domino radical cyclization was observed when a similarly built trichloroacetamide bearing a tethered alkene on the

indole nitrogen was subjected to the previously described conditions [85]. In this case, a 5-*exo-trig*/6-*endo-trig* cyclization sequence was observed and the resultant benzospiro-indolizidinepyrrolidinones, e.g., **136**, were isolated in fair yield.



135 **136**

A recent synthesis of spiroindolenine derivatives has employed a tandem radical-oxidation sequence [86]. Enamides **137** were subjected to a mixture of tributyltin hydride and DLP to produce the corresponding indolenine as a single diastereomer (confirmed from 2D NMR experiments). The mechanism is thought to involve the cyclization of the initial aryl radical to the vinyl group in a 6-*endo* fashion to generate an α-amidoyl radical which is oxidized by DLP to an acyliminum ion prior to cyclization at the C-3 position of the indole ring.



137

138a: $R_1 = R_2 = OCH_3$ (40%)
138b: $R_1 = R_2 = -OCH_2O-$ (40%)
138c: $R_1 = R_2 = H$ (35%)

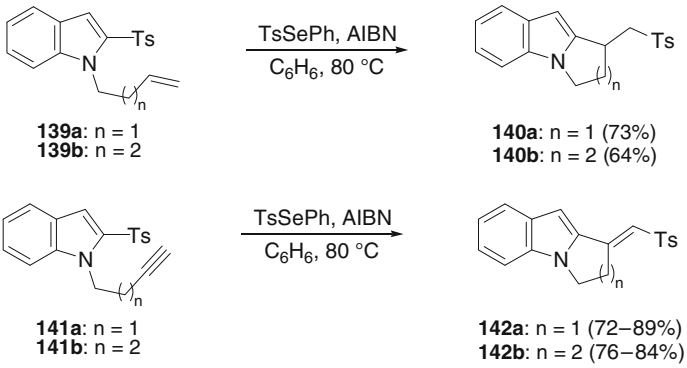
3.3 Synthesis of Indole-Fused Five-Membered and Six-Membered Rings

In most of the examples outlined in this section, the radical cyclizations were accompanied by oxidation to re-establish the aromatic indole nucleus; however, there are some cases where the 2,3-dihydroindoles (indolines) were isolated. It remains unclear which structural features are required in order to facilitate this oxidation especially under reductive tributyltin hydride conditions.

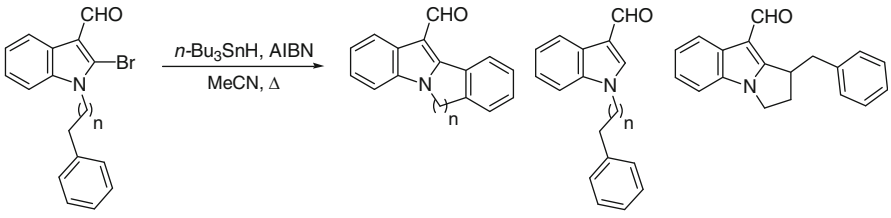
3.3.1 Synthesis of 1,2-Fused Indoles and Indolines

1,2-Fused indoles have been synthesized using various radical strategies. Some of the more renowned works include Ziegler's Photochemically-induced cyclization of alkyl, vinyl, oxiranyl, and aziridinyl radicals [87–89], Chuang's benzenesulfonyl radical induced oxidative cyclization of 1-(4-allylsulfonylbutyl)indole [90], and Moody's tin-mediated cyclization of 1-ω-iodoalkylindoles [91].

Caddick and coworkers have reported [92] the use of Se-phenyl-*p*-toluenesele-nosulfonate (TsSePh) in a perfect combination of their earlier work [93]. Treatment of 1-alkenyl- (**139**) and 1-alkynyl-2-tosylindoles (**141**) with TsSePh (0.25 equiv.) and AIBN (0.1–1 equiv.) in benzene gave the five- and six-membered cyclized indoles (**140** and **142**) in good yields.

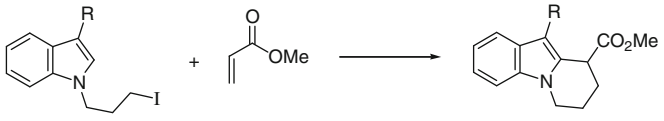


Fiumana and Jones also investigated the annulation reactions of indoles to form fused [1,2-*a*]indoles [94]. In the presence of tributyltin hydride and AIBN in acetonitrile, 1-alkyl-2-bromoindoles **143a–d** underwent smooth cyclization to give tetracyclic indoles **144a-c** as well as the reduced products **145a-d**. In the case of the bromoindole **143d** ($n = 4$), a new tricyclic indole **146** was isolated in 48% yield. It is thought that in this case a 1,5-hydrogen atom abstraction of the initially formed C-2 indole radical is followed by cyclization of the resulting alkyl radical onto the indole C-2 position. Rearomatization of the indole nucleus was observed in all tricyclic products isolated.



Bromide	N	144 (%)	145 (%)	146 (%)
143a	1	25	55	—
143b	2	65	20	—
143c	3	37	32	—
143d	4	—	27	48

Benzindolizidines such as **148** were also accessed through a tandem radical addition–cyclization–oxidation sequence from the reaction of substituted 1-(2-iodoethyl)indoles **147a–e** with methyl acrylate under the nonreductive conditions of hexa(*n*-butyl)ditin [95]. The intermolecular addition of the initially formed primary radical to the double bond of methyl acrylate with concomitant cyclization onto the indole ring is followed by a poorly understood oxidation. In order to overcome some inherent difficulties associated with the use of hexabutylditin, Fenton-type conditions ($FeSO_4$, H_2O_2) were applied to this sequence with some success [96]. Indeed, the expected benzindolizidine derivatives were obtained in better yields than generated previously (30–60%). Under these conditions, methyl radicals generated from DMSO initiate the radical cascade sequence that upon oxidation of the resultant benzylic radical by Fe(III) generates a intermediate carbocation en route to the indole.

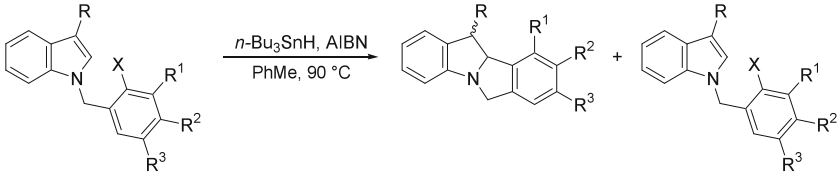


147 **148**

Indole	R	% Yields of 148	
		(n-$Bu_3Sn)_2$, hν, C_6H_6, 80 °C[95]	$FeSO_4 \cdot H_2O$, DMSO, H_2O_2[96]
147a	H	15	30
147b	CHO	45	37
147c	CO_2Me	60	60
147d	$COCO_2Et$	32	35
147e	CN	54	51

Flanagan also observed the formation of fused [1,2]indoles as a result of radical cyclization sequences when *N*-(*o*-halobenzyl)indoles **149** were heated under standard tin hydride conditions [82]. However, in contrast to what was observed by Caddick and Fiumana, dihydroindoles were isolated due to quenching of the intermediate benzyl radical with tributyltin hydride, rather than rearomatization from loss of a hydrogen atom. Consequently, *N*-(*o*-bromobenzyl)indole **149a**

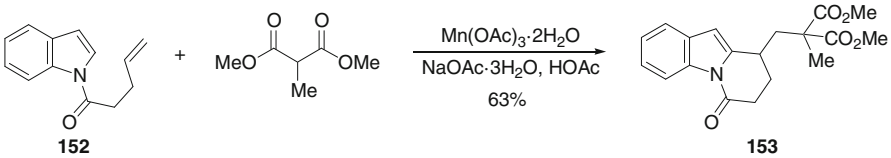
underwent a 5-*exo-trig* cyclization to give the cyclized dihydroindoline **150a** in 32% yield as well as the product from premature reduction (**151a** (43%)). This cyclization was shown to be influenced greatly by the substituents on the arene ring with increased yields being observed when electron-releasing groups such as methoxy were present (80% vs. 32%). Stereochemical correlations between the arene substitution groups and the hydrogen at the C-3 position were also observed and found to follow an obvious sterically-driven pathway. In this case, when *N*-(*o*-halobenzyl)-3-methyl indole derivatives (**149c–g**) were treated under these standard reductive radical conditions, the α-CH_3 product predominated when larger groups were present on the benzene ring.



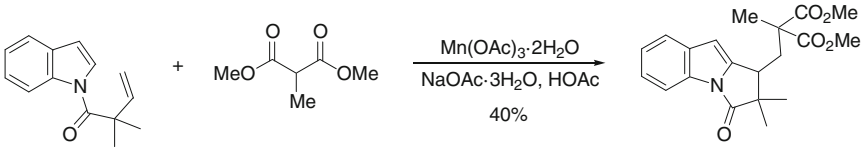
149 150 151

Indole	R	R^1	R^2	R^3	X	150 (%)	151 (%)	α-:β-CH_3
149a	H	H	H	H	Br	32	43	-
149b	H	OCH_3	OCH_3	OCH_3	I	80	<5	-
149c	CH_3	H	H	H	Br	38	11	1:1
149d	CH_3	H	H	H	I	35	16	1:1
149e	CH_3	H	OCH_2O		Br	54	26	3:2
149f	CH_3	H	OCH_3	OCH_3	I	56	30	2:1
149g	CH_3	OCH_3	OCH_3	OCH_3	I	66	10	1:3

Oxidative radical cyclization sequences have also been used to generate 1,2-fused indoles. Treatment of amides **152** and **154** with dimethyl methylmalonate in the presence of manganese(III) acetate and sodium acetate in acetic acid, gave the expected cyclized product in 63% and 40%, respectively [97]. The proposed mechanistic sequence involves the intermolecular addition of the dimethyl methylmalonate radical to the tethered exocyclic alkene followed by cyclization and finally rearomatization. Byers and coworkers also achieved a similar cyclization on the C-2 position of the indole when a 3-acylindole was subjected to these oxidative cyclization conditions.

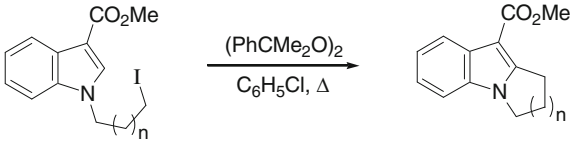


152 153



154 **155**

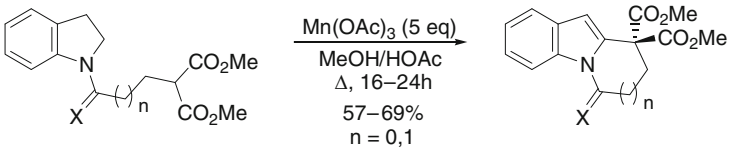
Miranda et al. reproduced Ziegler's [87–89] previously observed cyclization of alkyl radicals, utilizing in this case the tin-free conditions of 1.5 equivalents of dicumyl peroxide (DCP) in refluxing chlorobenzene [98]. The expected 1,2-fused tricyclic indoles **157** were obtained in excellent yield, with a slightly higher yield obtained when a 5-*exo-trig* cyclization followed by rearomatization was performed. The utility of these oxidative conditions was demonstrated with similarly substituted pyrroles, isoquinolin-1-ones, and quinolone derivatives undergoing cyclization in good yield. DCP is thought to generate the very reactive methyl radical, after thermolysis and subsequent fragmentation, which abstracts the iodide to initiate the cyclization. Once addition to the aromatic ring has occurred, the DCP is thought to also function as an oxidant and hence restore the aromatic ring.



147c: n = 1
156: n = 2

157a: n = 1 (90%)
157b: n = 2 (85%)

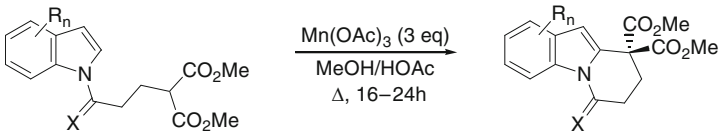
In his investigation into indole alkaloids bearing a 1,2-fused six-membered ring and a quaternary center at C-2 of the heterocyclic core, Kerr and coworkers illustrated that both indolines and indoles undergo intramolecular cyclizations under oxidative radical conditions to give tricyclic indole products [99]. Using five equivalents of $Mn(OAc)_3$ in refluxing methanol or acetic acid, the indolines underwent smooth dehydrogenation and subsequent cyclization in fair yields.



158 X = O; H,H; Ph,H

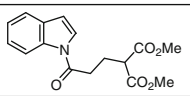
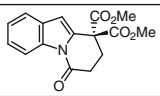
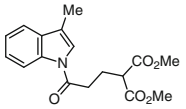
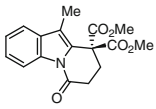
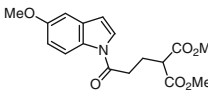
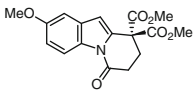
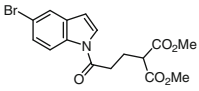
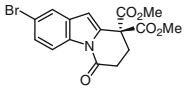
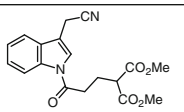
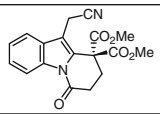
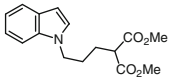
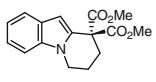
159

N-acyl and *N*-alkyl indoles, with functional groups at C-3 or C-5, produced good yields of the expected tricyclic products with smaller quantities of manganese acetate.

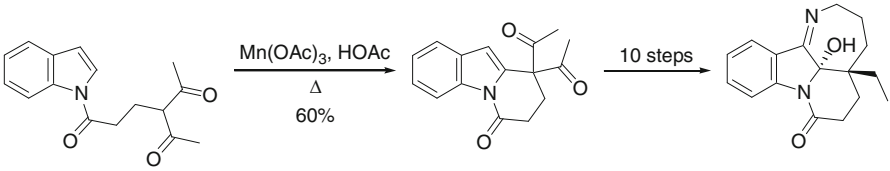


160 X = O; H,H

161

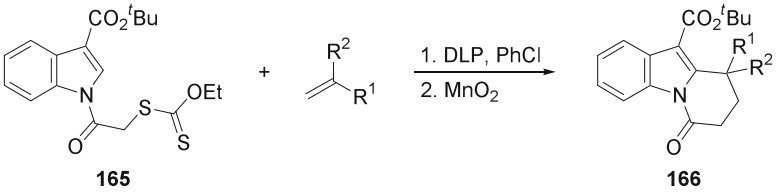
Substrate	Product	% Yield
		74
		82
		74
		68
		72
		67

Further development of this protocol saw advances toward the indole alkaloid tronocarpine and the first total synthesis of mersicarpine (**164**) [100].



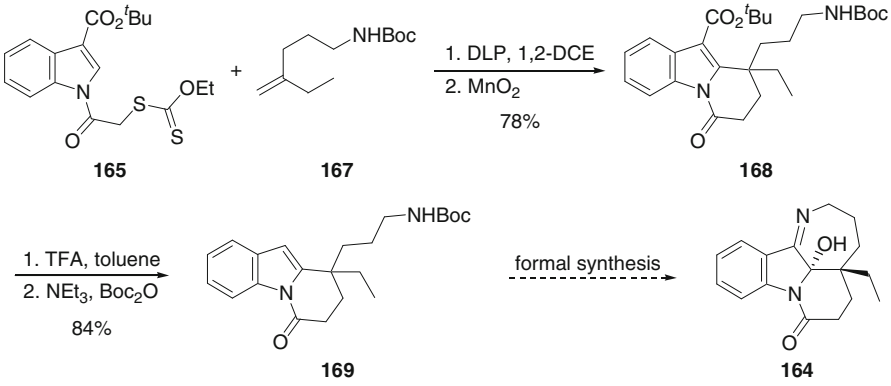
162 **163** **164**

Recently, Zard and coworkers used xanthate chemistry in the development of a more convergent route to mersicarpine (**164**), inspired by Kerr's synthesis. In this report the authors describe the addition of various olefins to indole xanthate **165**, bearing a *t*-butoxycarbonyl group at the C-3 position, to give tricyclic 1,2-fused indoles **166** [101]. Upon addition of a stoichiometric amount of DLP, the acetamide radical, derived from **165**, adds to the olefin (5 equiv.) generating a new radical which cyclizes in a 6-*exo* fashion onto the indole ring. Treatment of the crude reaction mixture with manganese dioxide (10 equiv.) rearomatizes any cyclized dihydroindole compounds formed as a result of premature reduction to generate the final annulated indoles in yields ranging from 44 to 79%.



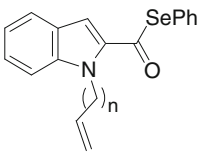
R	R^1	% Yield
CH_2OAc	H	69
$CH(OMe)_2$	H	57
OAc	H	75
$SiMe_3$	H	65
CO_2Me	H	44
CH_2OAc	Me	74
OAc	Me	70
CH_2NHBoc	Me	63
$-(CH_2)_5-$		75
$-(CH_2)_2NBoc(CH_2)_2-$		79

This formal synthesis of mersicarpine generated the key intermediate **169** described in Kerr's paper [100] in four steps from xanthate **165**. The ensuing radical cascade sequence of **165** with olefin **167** generated indole **168**, in 78% yield, which bears the ethyl and protected amino groups necessary for the synthesis of the naturally occurring alkaloid. Deprotection of the *t*-butyl ester and carbamate, decarboxylation, and reprotection of the amine were accomplished in one-pot using trifluoroacetic acid followed by Boc anhydride and triethylamine, and gave 84% of the desired intermediate **169** needed to declare a formal synthesis.

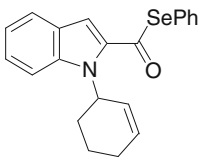


Intramolecular reactions of 2-indolylacyl radicals have also been reported [102]. When subjected to standard reductive tin-hydride conditions, indole seleno esters **170–175**, carrying alkenyl, cyclohexenyl, or tetrahydropyridyl moieties on the nitrogen, generated tri- and tetracyclic indoles resulting from either 5-*exo*- or

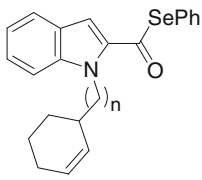
6-*endo-trig* cyclizations. In the example outlined below, the more stable *trans*-fused product **176** was obtained in 75% yield while the spirocyclic compound **177** was only observed in small quantities.



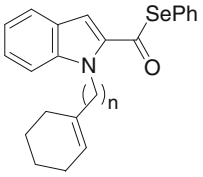
170 (n = 1,2,3)



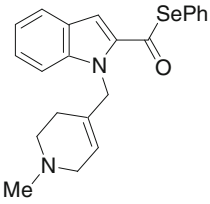
171



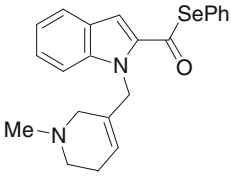
172 (n = 1,2)



173 (n = 1,2)



174



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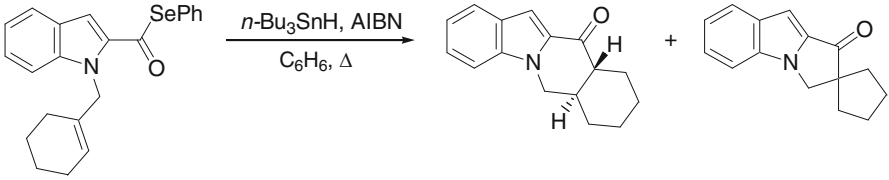
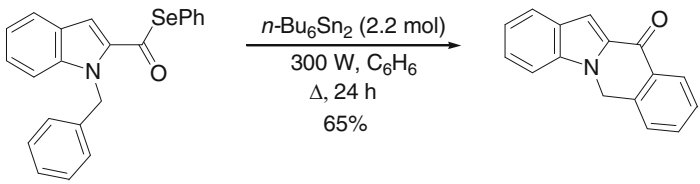


172a

176 6-*endo* (75%)

177 5-*exo* (10%)

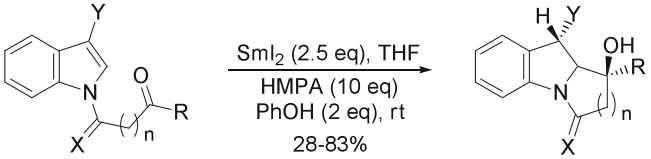
Seleno ester **31b**, which bears a benzyl group on the indole nitrogen, underwent smooth cyclization under nonreductive conditions – hexabutylditin with a 300 W sun lamp – to give the tetracyclic indole **178** in 65% as the sole product [103]. Analogous seleno esters, with 3- or 4-pyridylmethyl moieties attached to the indole nitrogen, also cyclized under similar reaction conditions, but afforded indolo[1,2-*b*] naphthyridinones in considerably lower yields (35% and 15%, respectively) [104].



31b

178

SET agents continue to gain popularity in the radical chemistry sphere, mainly due to their attractive tin-free conditions. As such, indoles bearing alkyl and acyl groups on the nitrogen were treated with samarium diiodide in THF along with excess HMPA and 2.0 equivalents of phenol as a proton source [105]. Cyclization yields were lowest when R = H, which corresponded to literature predictions, while the highest yield of 83% was observed when methyl 1-(4-oxopentyl)-1*H*-indole-3-carboxylate (**179**: Y = CO_2Me; X = H,H; R = Me; *n* = 2) was utilized. The mechanism involves the transfer of an electron from the SmI_2-HMPA complex to the carbonyl to generate a radical anion which cyclizes onto the indole C-2 position via a 5-*exo*- or 6-*exo-trig* pathway, followed by a second electron transfer and subsequent protonation. Experiments conducted in the absence of HMPA with indoles carrying the electron-withdrawing groups at the 3-position of the indole, e.g., methyl 1-(3-oxobutyl)-1*H*-indole-3-carboxylate (**179**: Y = CO_2Me; X = H,H; R = Me; *n* = 1), gave surprisingly higher yields and greater diastereoselectivity.



179

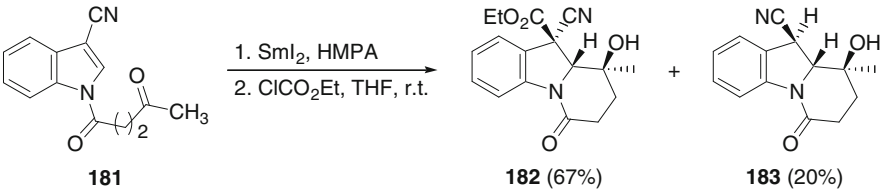
X = O; H,H
Y = H, CO_2Me
R = H, Me

180

n = 1,2

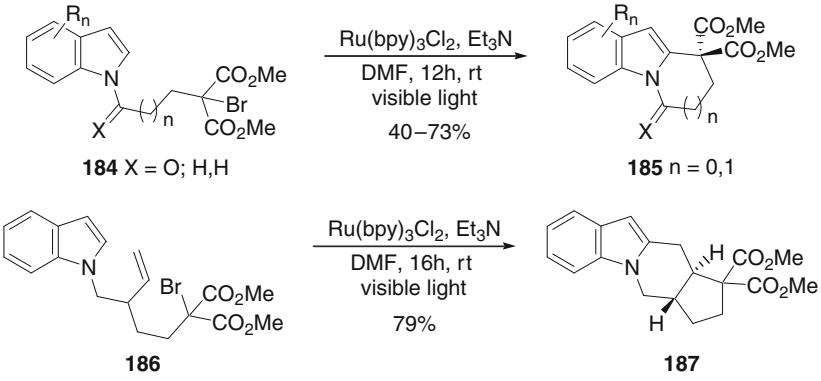
Kise and coworkers recently presented a comparative study to Reissig's 2003 paper outlining electro-reduction conditions used to effect an intramolecular cyclization of 1-indolealkanones and 3-methoxycarbonyl-1-indolealkanones [106]. While obtaining generally comparative yields, some of the stereospecificity observed using SmI_2/PhOH/HMPA in THF was lost when the electro-reduction conditions (Pb cathode undivided cell in isopropanol containing Et_4NOTs as a supporting electrolyte) were employed.

Reissig and coworkers further attempted to trap the intermediate samarium enolate, generated during ketyl cyclizations, with various electrophiles after cyclization [107]. Consequently, 3-cyano and 3-methoxycarbonyl *N*-acylated indole derivates were subjected to SmI_2-induced cyclization conditions followed by treatment with various electrophiles (8 equiv.). The expected polycyclic indoles were produced as single diastereomers in moderate to good yields and in most cases were accompanied by the protonated product. This was explained by a highly ordered cyclic transition state during ketyl radical addition to the indole ring followed by alkylation from the convex face of the molecule. One such example is outlined below.



181 **182** (67%) **183** (20%)

The photoredox catalyst, *tris*(2,2′-bipyridyl)ruthenium dichloride, has also been utilized to effect radical cyclization onto the C-2 position of indoles and pyrroles [108]. The catalyst, upon activation with visible light, acts as a single-electron reductant and generates a reactive alkyl radical by dehalogenation of a carbon–halogen bond. The optimized conditions, $Ru(bpy)_3Cl_2$ (1.0 mol%), Et_3N (2 equiv.) in DMF at room temperature under irradiation by a 14 W household light bulb, generated both five- and six-membered fused 1,2-indoles and tolerated functionality at C-3, C-4, and C-5 inclusive of cyano groups, esters and amides. This methodology was beautifully extended to a cascade sequence which resulted in the formation of the tetracyclic indole **187**, as a single diastereoisomer in 79% yield.

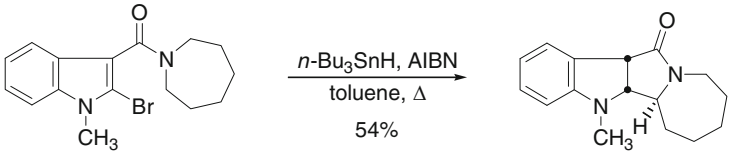


184 X = O; H,H **185** n = 0,1

186 **187**

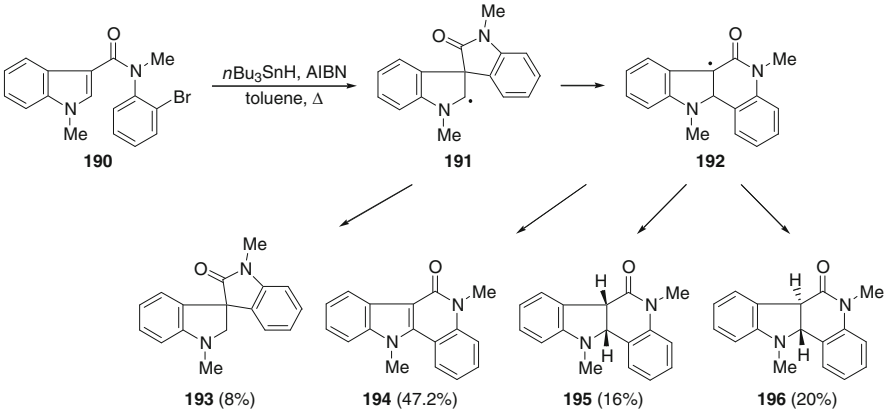
3.3.2 Synthesis of 2,3-Fused Indoles and Indolines

In our own investigation, we were able to synthesize hexahydropyrrolo[3,4-*b*] indoles from 2-bromo-3-carboxamides, for example **188**, in fair yield [109]. This reaction was successful using piperidyl-, azepinyl- and *t*-butylcarboxamides but only gave the product of premature reduction with the corresponding pyrrolidylcarboxamide. We propose a mechanism involving C-2 radical generation, 1,5-hydrogen atom transfer to generate an α-amidoyl radical, and 5-*endo-trig* cyclization to give the isolated dihydroindole with a *cis–trans* stereochemistry as confirmed by X-ray crystallography [110]. Dehydrogenation/oxidation using either DDQ or Pd/C produced the expected indoles.



188 **189**

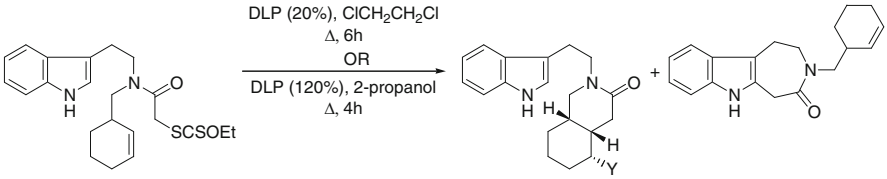
In contrast, Ganguly's investigation of indole-3-carboxamide **190** yielded four compounds with the major product being the fused 2,3-indole **194** [80]. The isolation of the spiro compound **193** indicates that the likely mechanism involves a 5-*exo-trig* cyclization followed by a rearrangement to give the doubly stabilized benzyl radical **192**. This either accepts a hydrogen atom to give the *cis*- or *trans*-dihydroindoline (**195** or **196**) or undergoes oxidation to regenerate the indole ring (**194**).



190 **191** **192**

193 (8%) **194** (47.2%) **195** (16%) **196** (20%)

The tetracyclic core of the berbane and alloyohimbane alkaloids has been accessed using xanthate-based radical chemistry [111]. The precursor xanthate **197** was prepared from tryptamine and then subjected to reflux conditions (1,2-dichloroethane or 2-propanol) in the presence of a catalytic amount of DLP. The resultant piperidones (**198** and **200**) generated via a 6-*exo-trig* cyclization were obtained in reasonable yields and accompanied by azepinone **199**, the product of presumed radical attack on the 2-position of the indole. The alloyohimbane core was finally accessed through reductive Bischler–Napieralski conditions.



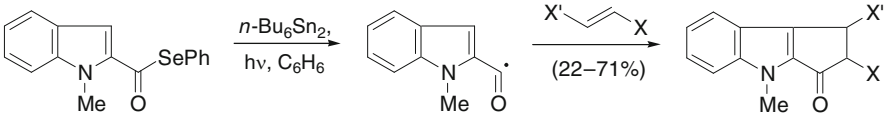
197

198: Y = SCSOEt (48%)
200: Y = H (54%)

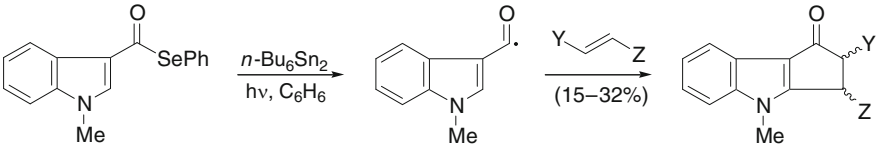
199 (22%)
(24%)

Bennasar extended his research on 2- and 3-indolylacyl radicals to intramolecular cyclizations to yield 2,3-fused indoles [112]. Under nonreductive conditions (n-Bu_6Sn_2, hν), radical **201** underwent a cascade addition–oxidative cyclization sequence with a number of alkene acceptors including dimethyl fumarate (45%), methyl 1-cyclohexenecarboxylate (53%), methyl crotonate (71%), vinyl sulfone (22%), and the α,β-unsaturated lactam ester, 2-oxo-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid dibenzyl ester (41%) to form cyclopenta[*b*]indol-3-ones **202**. Reaction of **201** with acrylonitrile and methyl acrylate, however, generated cyclohepta[*b*]indoles, the products of bis-addition–cyclization sequences.

3-Indolylacylradical **203** exhibited similar reactivity, albeit in a less efficient manner with alkenes, such as methyl crotonate (32%), crotonitrile (20%), 1-octene (15%), and vinyl acetate (15%) to generate cyclopenta[*b*]indol-1-ones **204** after radical addition and cyclization onto the C-2 position of the indole ring [24]. These results contrasted nicely with the observed intermolecular reactions of 2- and 3-indolylacyl radicals generated using tributyltin hydride.

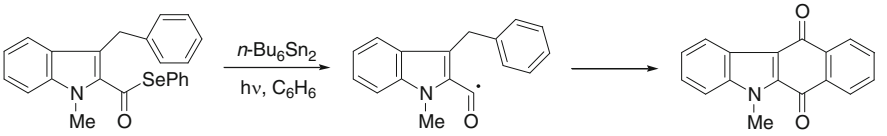


31a **201** **202**

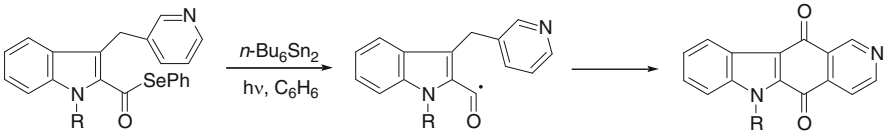


40a **203** **204**

Bennasar also exploited radical cyclization of *N*-alkyl seleno esters **205** and **208** that incorporate benzyl [103] and 3-pyridylmethyl groups [104], respectively, at the C-3 position of the indole ring. Pleasingly, the corresponding 2-indolylacyl radicals underwent the desired cyclization to give the tetracyclic phenyl indolyl ketones **207** and **210**. In the case of *N*-methyl (**208a**: R = Me) and *N*-benzyl seleno esters (**208b**: R = Bn), the cyclizations demonstrated high regioselectivity, adding mainly to the 4-position of the pyridine ring before the final oxidation of the methylene group, which amounts to a formal synthesis of ellipticine (**65**). Much diminished yields of the final quinone were obtained when the indole nitrogen bore the electron-withdrawing methoxymethyl group.



205 **206** **207** (50%)

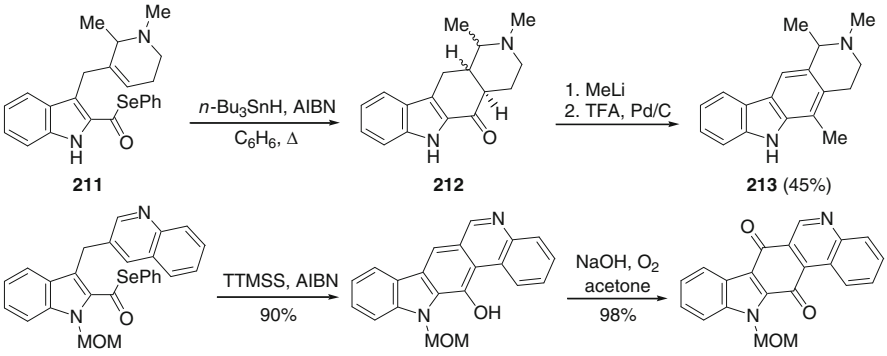


208a: R = Me
208b: R = Bn
208c: R = MOM

209

210a: R = Me (60%)
210b: R = Bn (42%)
210c: R = MOM (10%)

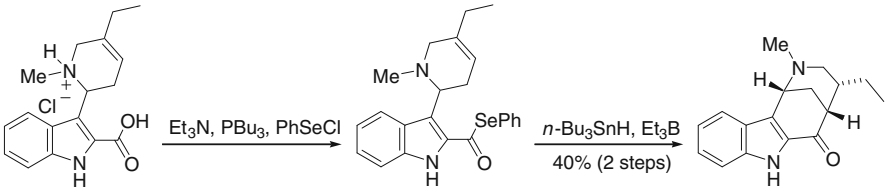
The total synthesis of the pyrido[4,3-*b*]carbazole alkaloid guatambuine (**213**) [113] and a formal synthesis of calothrixin B [114] have also been reported using radical cyclizations of 2-indolylacyl radicals onto 1,2,5,6-tetrahydropyridine and quinoline rings, respectively. In the synthesis of calothrixin, radicals generated from *N*-MOM seleno ester **214** under mild reductive conditions (TTMSS, AIBN, 80°C, 4 h) afforded pentacyclic phenol **215** in 90% yield as the sole product – a sharp contrast to the observed low yields of indole **210c**. Mild basic oxidation converted the phenol into *N*-MOM calothrixin (**216**) in almost quantitative yield.



211 **212** **213** (45%)

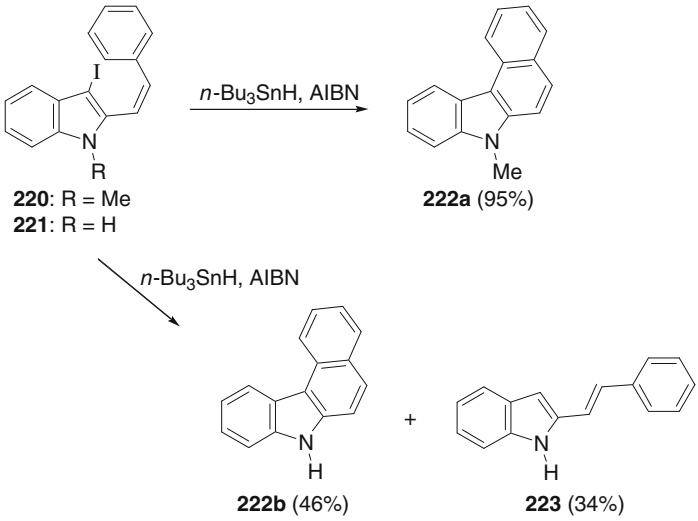
214 **215** **216**

2-Indolylacyl radicals have also been used to access the 1,5-methanoazocino [4,3-*b*]indole system found in the uleine and *Strychnos* alkaloids [115, 116]. In several examples, Bennasar and coworkers utilized tributyltin hydride and Et_3B to affect 6-*exo* and 6-*endo* cyclizations of the radicals, which were derived from the corresponding seleno esters, onto tetrahydropyridine double bonds. The example shown below illustrates the utility of the reaction sequence in the preparation of the uleine alkaloid isodasycarpidone (**219**). As such, seleno ester **218** was synthesized easily from indole and 2-cyanotetrahydropyridine and then further converted to the natural product in fair yield.

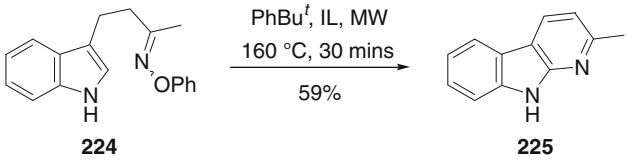


217 **218** **219**

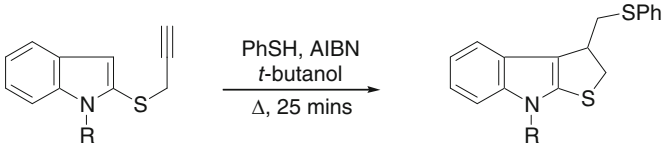
Both 2- and 3-styrylindoles underwent cyclization via a 6-*endo-trig* pathway to yield benzo[*c*]- and benzo[*a*]carbazoles in 58% and 90% yield, respectively, under standard reduction conditions [82]. This contrasted with the observed spiro-compounds that form with the analogous alkanes, devoid of unsaturation in the tether. Interestingly, *N*-methyl-*cis*-3-iodo-2-styrylindole (**220**) also yielded the expected benzocarbazole derivate **222a** in 95% yield while the parent indole **221** only gave a modest yield of carbazole **222b** together with 34% of *trans* 2-styrylindole **223**. This suggested to the authors that isomerization of the alkene competes with carbon–halogen homolysis when the tether is conjugated with the indole ring.



Iminyl radicals, generated by microwave irradiation of *O*-phenyl oxime ethers such as **224**, cyclized onto the indole 2-position to afford indolopyridine derivatives (**225**) [117]. The most likely pathway involves a 6-*endo* cyclization and was further exploited into a formal synthesis of neocryptolepine from gramine in five steps.

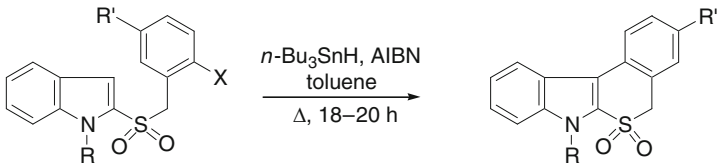


As indole-annulated sulfur heterocycles continue to gain popularity as synthetic targets, Majumdar's approach to trihydrothieno[2,3-*b*]indole [118] and benzo[*c*]thiopyrano[2,3-*b*]indole derivatives [119] is well placed as a viable route. As seen with sulfide **226** and sulfoxide **228**, 5-*endo*- and 6-*endo-trig* cyclizations onto the C-3 position of the ring occurred in fair yields.



226

227a: R = COPh (68%)
227b: R = $COCH_3$ (65%)

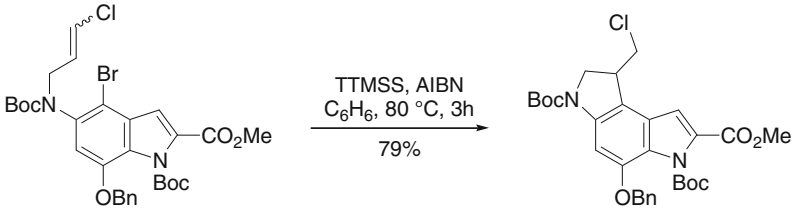


228

229a: R = Me; R' = H (60%)
229b: R = Me; R' = OMe (56%)
229c: R = Et; R' = H (58%)
229d: R = Et; R' = OMe (61%)

3.3.3 Synthesis of Other Five-Membered and Six-Membered Ring Fused Indoles and Indolines

Radicals generated at positions other than C-2 or C-3 of the indole core have been less frequently reported in the literature [120]. A 5-*exo-trig* cyclization resulting in the pyrrolo[3,2-*e*]indole ring system was reported in the synthesis of seco-duocarmycin [121]. This precursor of the natural antibiotic (+)-duocarmycin has presented itself an interesting and promising synthetic target. Hence, the radical precursor, *N*-(3-chloropropenyl)indole **230**, was synthesized in nine steps from 2-methoxy-4-nitroaniline as a mixture of the *E* and *Z* isomers. Generation and cyclization of the C-4 indole radical was then accomplished by treatment with TTMSS and catalytic AIBN to generate the pyrroloindole **231** in 79% yield.



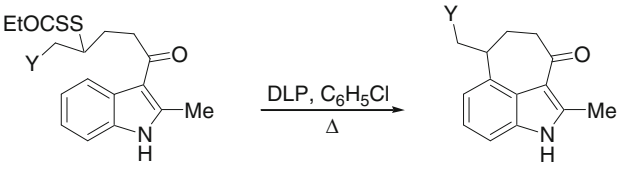
230 **231**

A novel radical pathway to benzocathinones and their derivatives involving cyclizations of halo *N*-aroyl derivatives of carbazoles and β-carbolines has also been reported to proceed in fair to excellent yield [122].

3.4 Synthesis of Indole-Fused Seven-Membered and Eight-Membered Rings

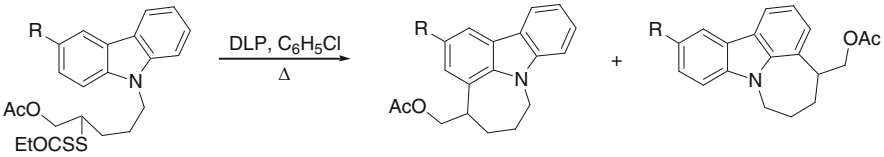
Several new methods have emerged over the last decade to synthesize medium-sized rings and have proved a nice complement to the previously explored methods [123, 124].

Zard utilized xanthate chemistry in his investigation of the construction of seven-membered rings fused to indole ring systems [125]. In this report, he describes the use of stoichiometric amounts of DLP in boiling chlorobenzene to effect cyclization of xanthate **232** onto C-4 of the indole ring. Attempts to extend this methodology to seven-membered rings fused at the nitrogen by utilizing carbazoles **234** gave less regioselective results. In fact only the parent xanthate **234a** (R = H) gave the tetracyclic carbazole **235a** (R = H) as the sole product in 60% yield, while the presence of sulfide and sulfone groups, R = SMe and SO_2Me, respectively, on the benzene ring produced two isomers in approximately equal quantities as a result of annulation to C-1 and C-8 of the xanthate.



232 **233**

Xanthate	Y	233 (%)
232a	OAc	54
232b	Phth	47
232c	CN	48
232d	$(CH_2)_8OAc$	32
232e	CH_2CO_2Et	35

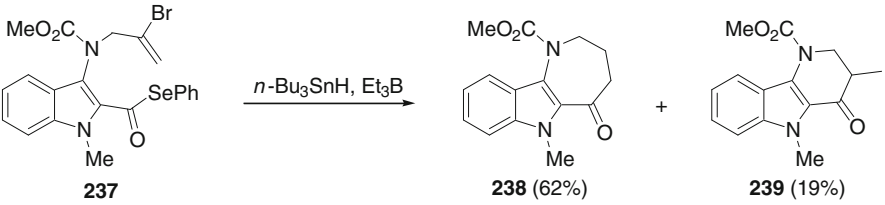


234a: R = H
234b: R = SMe
234c: R = SO_2Me

235a: R = H (60%)
235b: R = SMe (27%)
235c: R = SO_2Me (28%)

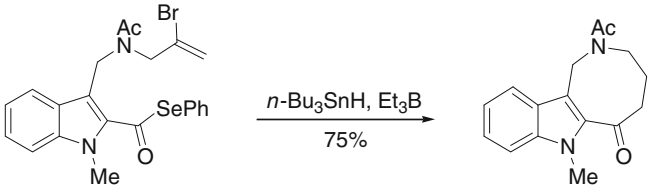
236b: R = SMe (23%)
236c: R = SO_2Me (37%)

Bennasar also recently extended their interest in the cyclization of *N*-alkenyl substituted 2-indolylacyl radicals towards the annulation of larger rings [126]. A 7-*endo*-ring closure was observed when bromovinyl substituted seleno ester **237** was treated with excess tin hydride in Et_3B. In addition to the desired azepino[3,2-*b*] indole **238**, the 6-*exo* cyclization product **239** was observed as the minor product, with both products showing no evidence of the bromine atom in their structures. Previous attempts at this cyclization using a tethered allyl moiety, rather than the 2-bromo-2-propenyl tether, also gave the azepinoindole but only as the minor product.



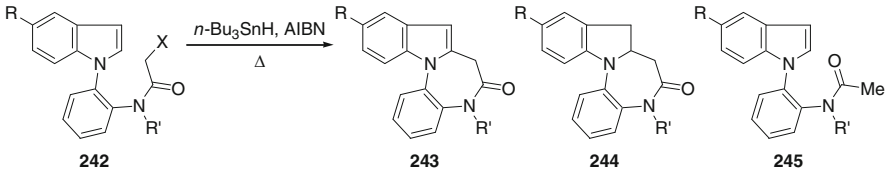
237 **238** (62%) **239** (19%)

Azocino[3,2-*b*]indoles were obtained when seleno ester precursors bearing 3-butenylamino and allylaminomethyl chains on the C-3 position of the indole were subjected to the same reductive radical conditions used previously with indole **237**. Inclusion of a bromine atom on the alkene acceptor gave the most rewarding result (shown below) at a hydride concentration of 0.02 M; yielding 75% of the 8-*endo* product **241**, without the detection of any products, formed as a result of reduction or the alternative 7-*exo* cyclization. This method proved to be a nice complement to the ring-closing metathesis protocol used in this laboratory to effect similar cyclizations and recently resulted in the total synthesis of apparicine [126, 127].



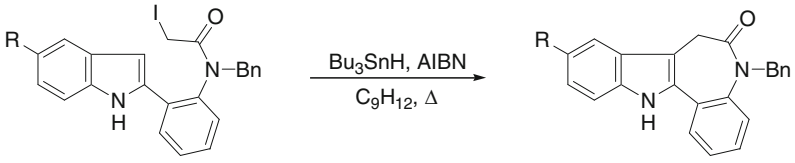
240 **241**

Bremner et al. observed a seldom seen 8-*exo-trig* cyclization with 1-indolylhaloacetamides (Br, I) using tributyltin hydride in the presence of AIBN [128]. In addition to the desired indolo[2,1-*d*][1, 5]benzodiazocine derivative, the dihydroindole-fused analog and some reduced product were obtained in fair yields and confirmed by ^{1}H NMR. The yield of the cyclized product **243**, fused to the *a* side of the indole, was generally increased by the steric bulk of the substituent group on the haloacetamide nitrogen, the boiling point of the solvent used, and the halogen present on the substrate.



R	R′	X	243 (%)	244 (%)	245 (%)
H	Me	I	20	60	20
H	$CH_2C_6H_4$-***p***-OMe	I	13	11	7
H	CH_2Ph	I	25	43	10
H	$CH_2(CH_3)Ph$	I	22	26	
OMe	Me	I	50	-	20
OMe	CH_2Ph	I	25	-	<1
F	Me	I	35	-	17
H	CH_2Ph	Br	54	20	
OMe	Me	Br	24	-	33

Free-radical cyclization has also been used to gain access to the 7,12-dihydro-indolo[3,2-*d*]benzepin-6(5*H*)-one (paullone) system [129]. This novel approach involves the cyclization of *N*-benzyliodoacetamides **246** under standard tin hydride conditions onto the C-3 position of the indole to generate a seven-membered ring on fused to the *b* face of the indole. Yields of 25–52% of the desired **247**, as the sole products, were obtained when the higher boiling solvent mesitylene was used. Proposed mechanisms include either a standard 7-*endo-trig* addition of the amidomethyl radical, followed by oxidation, or a 6-*exo-trig* addition to the indole C-2 position followed by rearrangement and oxidation. The presence of some spirocyclization product, obtained when toluene was used as the solvent, does give some credence to the latter mechanism proposal.



246

247a: R = H (52%)
247b: R = OMe (25%)
247c: R = F (45%)

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[2+2], [3+2] and [2+2+2] Cycloaddition Reactions of Indole Derivatives

Fariborz Firooznia, Robert F. Kester and Steven J. Berthel

Abstract A review with 102 references on [2+2], [3+2] and [2+2+2] cycloaddition reactions involving the indole nucleus.

Keywords [2+2] Cycloaddition · [2+2+2] Cycloaddition · [3+2] Cycloaddition · Indole

Contents

1 Introduction

The indole nucleus is ubiquitous in nature and can be found in a wide variety of natural products isolated from plant, marine, bacterial and fungal sources [1–10]. Many carbocyclic and heterocyclic compounds with varying degrees of structural

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complexity contain an indole at their core. Thus, it is not surprising that cycloaddition reactions have been employed extensively in assembling these complex natural product substructures.

In this chapter, [2+2], [3+2], and [2+2+2] cycloaddition reactions involving the indole nucleus will be reviewed. [4+2] Cycloadditions of indoles are discussed in the following chapter. The scope for this review will be limited to those reactions that involve at least two indole ring atoms as reactive centers in the cycloaddition, while reactions occurring on side chains or on peripherally attached rings will not be included. In most cases, the discussion will be limited to the cycloaddition reaction itself, and the reader is encouraged to consult the cited references for further details regarding both preceding (preparation of starting materials for the cycloaddition) and subsequent reaction steps (further manipulations of the cycloadducts, etc.). In cases where the cycloaddition plays a pivotal part in a complex natural product synthesis, some discussion on how the cycloadduct was further elaborated will be included. For the most part, we intend to cover work published after 1990, although in some cases older precedents may be discussed or cited. Wherever a major review on a particular subtopic had been published after 1990, this review was limited to newer material and/or material not covered in the earlier review. The format for this chapter is outlined above. Each reaction type has been treated separately, and within each reaction type subsections have been devised around the reaction partner and/or the reaction site on the indole moiety.

2 [2+2] Cycloadditions

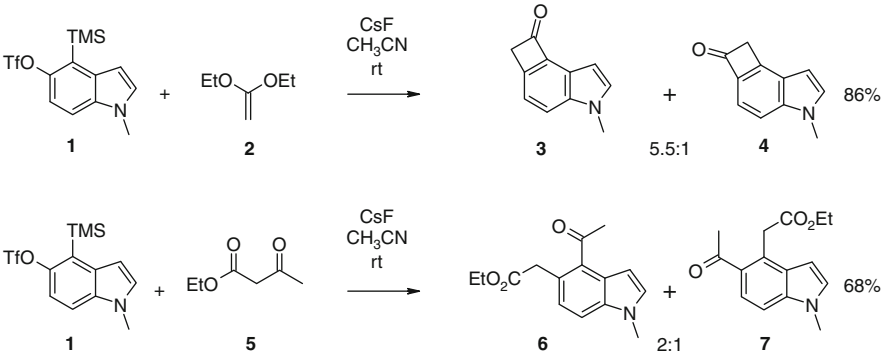
The [2+2] cycloaddition reactions of indoles are the least studied among the various cycloaddition reactions. Nevertheless, several interesting publications have appeared which highlight the utility of these reactions in the synthesis of highly substituted indole derivatives, as well as complex polycyclic structures which could serve as potential precursors to natural products such as vindorosine and members of the *Strychnos* alkaloids.

Among the variety of reactions discussed in this section, only the photochemical cycloadditions of indoles have been recently reviewed by Weedon [11]. In the interest of completeness, we will also discuss (albeit briefly) some of the papers already covered by the Weedon review.

2.1 [2+2] Cycloadditions Between Indole Aryne Molecules and Olefins

Garg and coworkers [12] developed a mild method for accessing "electrophilic indole surrogates" utilizing aryne indole derivatives (Scheme 1). These "indolynes" were in turn prepared via a similar strategy to the one developed by Kobayashi [13].

Thus, treatment of indolylsilyltriflates **1** with CsF in the presence of an appropriate trapping agent (e.g., **2**) led to the formal [2+2] cycloaddition products. An interesting variant which employed a ketoester (**5**) as the trapping agent, produced 4,5-functionalized indoles **6** and **7** through a cycloaddition reaction, followed by fragmentation of the resulting cycloadduct.



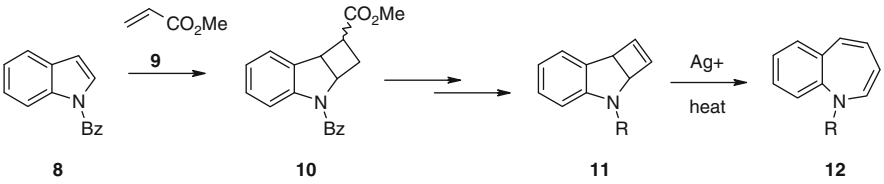
Scheme 1

Interestingly, attempts to produce and utilize 2,3-indolynes have not yet been successful.

2.2 [2+2] Photocycloaddition of Indoles and Olefins

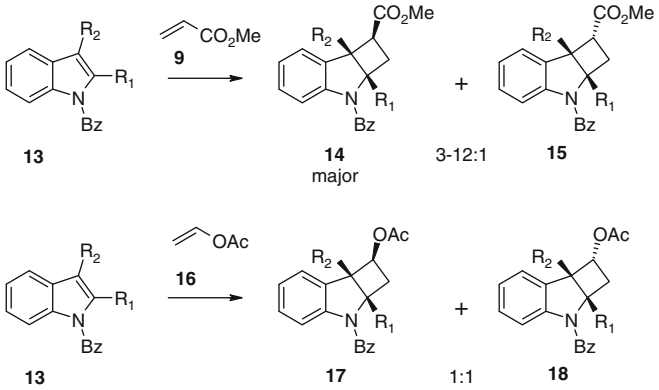
2.2.1 Intermolecular Reactions

The regiochemical and stereochemical courses of the photocycloaddition of *N*-acylindoles with monosubstituted olefins such as methyl acrylate and vinyl acetate, as well as the possible mechanistic pathways for these reactions, have been the subject of several reports. In one of the earliest examples, the photocycloaddition of 1-benzoylindole (**8**) and methyl acrylate (**9**) produced the compound **10**, which was then converted via a short synthetic sequence to a variety of 2a,7b-dihydrocyclobut[*b*]indole derivatives **11** (Scheme 2). These compounds were in turn converted to the corresponding 1*H*-1-benzazepines **12**, through silver ion-catalyzed thermolysis reactions at 100–160°C [14, 15].



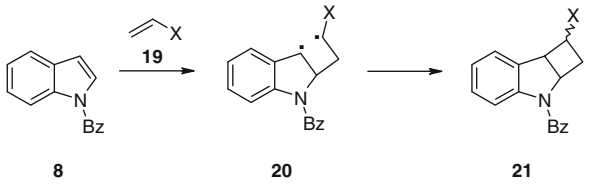
Scheme 2

The regio- and stereochemical course of the [2+2] cycloadditions between 1-benzoylindoles and different monosubstituted olefins were briefly investigated. Interestingly, both methyl acrylate and vinyl acetate produced 1-substituted cyclobut[*b*]indoles regioselectively (Scheme 3). In contrast, a distinct difference was observed between the two olefins when the stereochemical outcome of the cycloadditions was considered: While there was a significant preference for the 1-*exo*-isomer **14** in the case of methyl acrylate, there was no stereoselectivity (ca. 1:1 mixtures of the *endo*- and *exo*-isomers **17** and **18**) when vinyl acetate was used as the cycloaddition partner [16]. For further investigation of the stereochemical course of this reaction with 1,2-disubstituted ethylenes as well as cyclic olefins, see [17].



Scheme 3

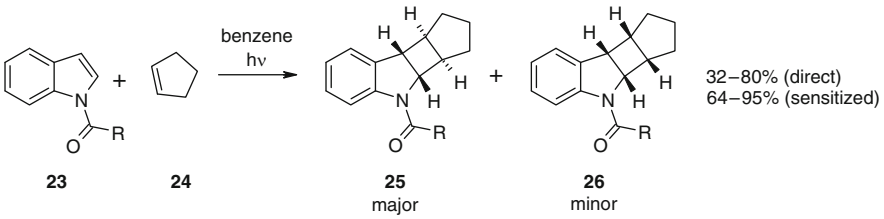
While further investigating the origin of the regiochemical course of the photocycloaddition reactions between *N*-benzoylindoles and monosubstituted alkenes, Weedon and Hastings demonstrated that the reactions involve the triplet excited state of the indole derivatives (Scheme 4). The reactions then proceed through the formation of a 1,4-biradical intermediate **20**, resulting from the bonding of the 2-position of the indole to the unsubstituted terminus of the alkene, which is least able to support a radical center [18–20].



Scheme 4

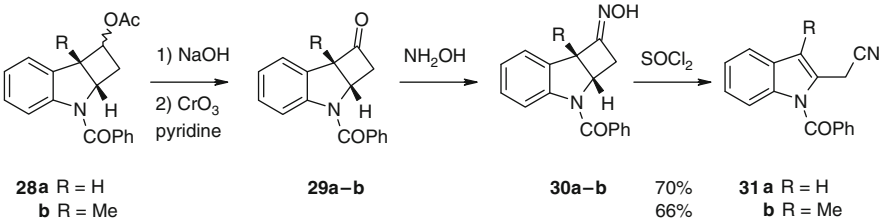
The main competing side reaction available to the triplet state radicals is the photo-Fries rearrangement [21], resulting in the formation of 3-acylindoles, instead of the

desired cyclobutane derivatives (Scheme 5). This unwanted side reaction can be suppressed in favor of the cycloaddition reaction by sensitization with acetophenone, which improved the yields of the cyclobutane adducts, **25** and **26**, dramatically [22].



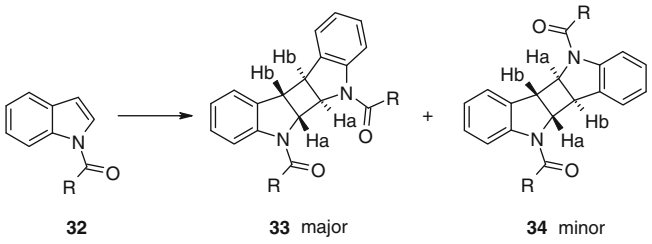
Scheme 5

The fused cyclobutane derivatives produced via the above cycloaddition reactions have been utilized as synthetic precursors for the preparation of indole-2-acetonitriles (Scheme 6) [23]. First, the acetyl-substituted cyclobutanes **28** were converted to the cyclobutanone derivatives **29**, which were in turn treated with hydroxylamine to provide the corresponding oximes. Beckmann fission of oximes **30** in the presence of thionyl chloride then produced the 1-benzoylindole-2-acetonitrile derivatives **31** in good yield.



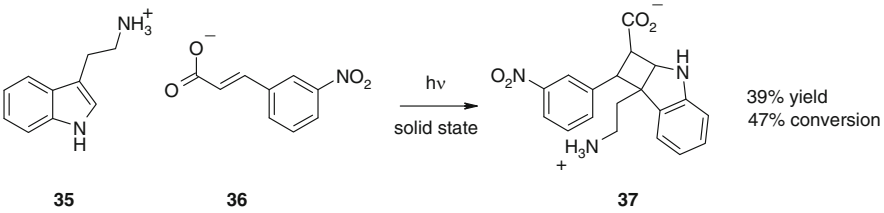
Scheme 6

Interestingly, in the absence of "external olefins" as cycloaddition partners, indoles appear to undergo photodimerization upon being subjected to ultraviolet light irradiation. Both "head-to-head" (**33**, major) and "head-to-tail" (**34**, minor) dimerization products have been observed [24] (Scheme 7).



Scheme 7

Finally, an unusual variation of the [2+2] cycloaddition was reported by Ito and Fujita [25], where direct irradiation of the crystalline salt of tryptamine (**35**) and *trans*-3-cinnamic acid (**36**) resulted in the formation of a cyclobutane adduct **37** (Scheme 8). This example was the first reported [2+2] cycloaddition between an N-unsubstituted indole and an alkene derivative.

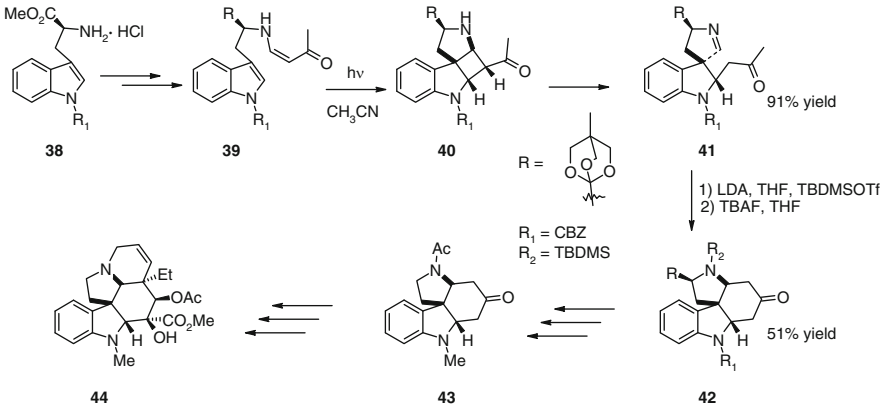


35 **36** **37**

Scheme 8

2.2.2 Intramolecular Reactions

The intramolecular variant of the [2+2] photocycloaddition of indoles has also been reported. In an elegant formal synthesis of vindorosine (**44**, Scheme 9), Winkler and coworkers employed the intramolecular photocycloaddition reaction of a vinylogous amide carbon–carbon double bond to the $\Delta^{2,3}$ alkene of an indole in a substrate (**39**) prepared from L-tryptophan methyl ester hydrochloride (**38**) [26].

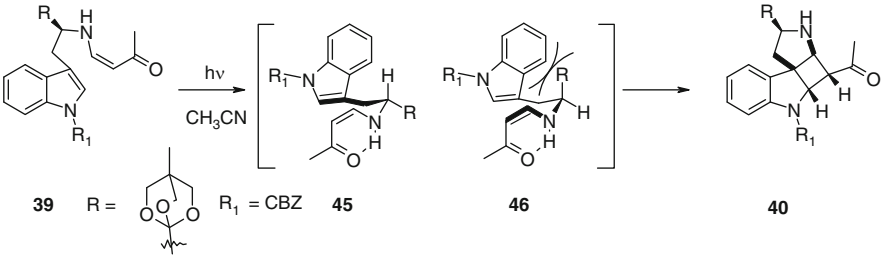


38 **39** **40** **41** **42** **43** **44**

Scheme 9

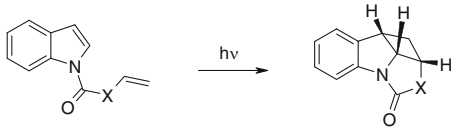
Retro-Mannich fragmentation of the cycloaddition product **40** (not isolated) resulted in the formation of the imine **41**, which upon a new Mannich closure reaction produced the cyclohexanone derivative **42**. Further manipulation of **42** resulted in the formation of **43**, which had previously been reported as a precursor for vindorosine (**44**) [27, 28].

The excellent stereoselectivity of the above photocycloaddition reaction is explained by the preferred approach of the vinylogous amide from the α-face of the indole **45**. The approach of the amide from the β-face **46**, (Scheme 10) is disfavored because of the steric interaction of the indole aromatic ring and the R substituent alpha to the vinylogous amide.



Scheme 10

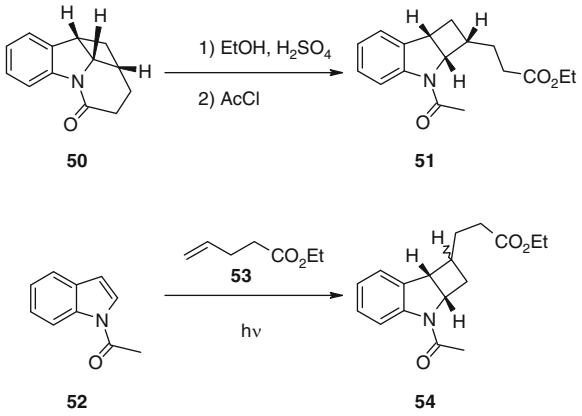
In another example of intramolecular [2+2] cycloadditions, a series of *N*-alkenoylindoles **47a–c** were irradiated to produce the corresponding cycloaddition products **49a–c** [29]. The cycloaddition reaction which produced a six-membered lactam ring **49b** proved the most efficient. Interestingly, the *N*-(alkenoxycarbonyl)indoles **48a–d** failed to undergo the intramolecular cycloaddition reaction, regardless of the length of the tether to the alkene, presumably because the preferred conformation of the alkenoxy group forces the side-chain double bonds away from the 2,3-position of the indole ring (Scheme 11).



entry	X	yield **49**
47a	$-CH_2-$	29%
47b	$-CH_2CH_2-$	92%
47c	$-CH_2CH_2CH_2-$	25%
48a	-O-	NR
48b	$-OCH_2-$	NR
48c	$-OCH_2CH_2-$	NR
48d	$-OCH_2CH_2CH_2-$	NR

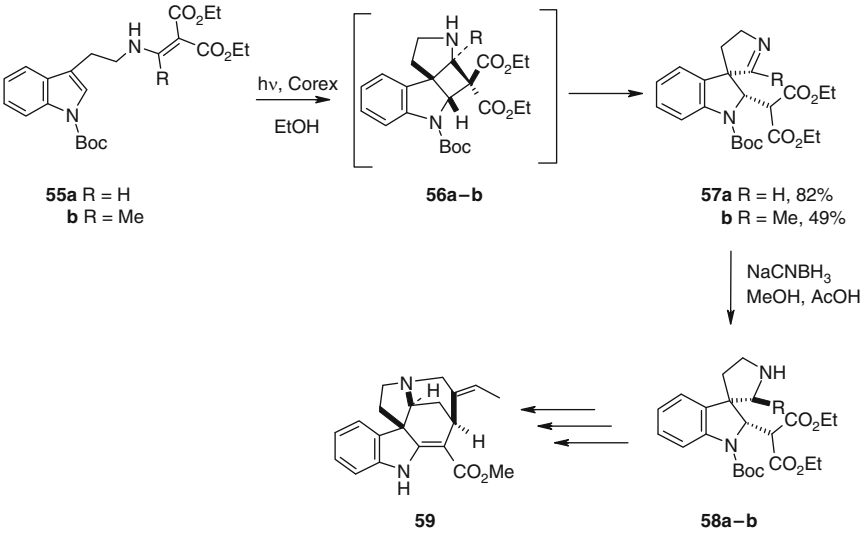
Scheme 11

The intramolecular cycloaddition reaction can serve as a complementary method to the intermolecular variant, by producing products with the "opposite" regiochemical preference. For example, product **50** was converted to **51** by sequential treatment with ethanol–sulfuric acid and acetyl chloride, thus producing a product with the opposite regiochemical outcome than compound **54**, prepared via the direct irradiation of *N*-acetylindole (**52**) with ethyl pent-4-enoate (**53**, Scheme 12).



Scheme 12

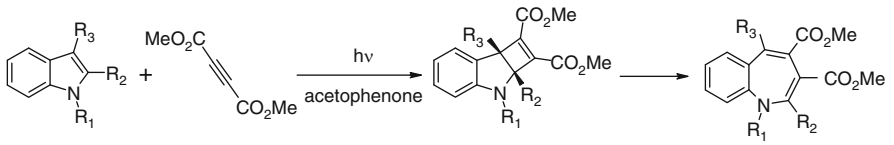
Finally, in another elegant example, White and coworkers [30] have employed an intramolecular [2+2] cycloaddition of an indole derivative as a key step in the synthesis of an intermediate useful in the synthesis of *Strychnos* alkaloids such as akuammicine (**59**) (Scheme 13). Photocycloaddition of α-amino-substituted alkylidene malonates **55a**, **b** by irradiation through Corex glass with a 450 W Hanovia mercury lamp over 7 h gave, after retro-Mannich fragmentation of the cycloadduct **56a**, **b**, spiropyrroline **57a**, **b** in good yield. The imine **57a**, **b** was isolated as a single stereoisomer, an observation which eliminates a stepwise radical mechanism for this reaction according to the authors. Reduction of **57a**, **b** with sodium cyanoborohydride gave **58a**, **b** as a single epimer resulting from delivery of hydride to the less hindered face of the imine.



Scheme 13

2.3 [2+2] Cycloadditions of Indoles and Alkynes

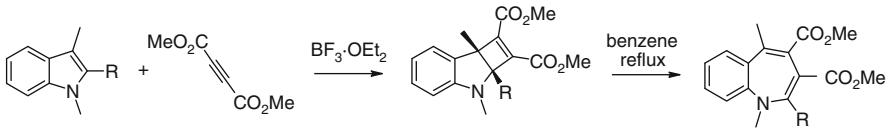
[2+2] Cycloaddition reactions of the indole 2,3-double bond are not limited to alkenes as partners. Acetylenic compounds have also been used in photochemical cycloaddition reactions with indoles to produce cyclobutenone derivatives. There have been extensive studies on the reaction of indoles with dimethyl acetylenedicarboxylate (**61**, DMAD), which produce a number of structurally distinct products [31]. By devising a photosensitized cycloaddition reaction of DMAD to activated indoles **60** in the presence of acetophenone, Neckers and Davis were able to produce the cyclobutene derivatives **62** in good yields (Scheme 14) [32]. The resulting cyclobutenes can then be converted to the corresponding benzazepines **63** via thermal ring-opening reactions.



60 **61** **62** **63**

Scheme 14

Rodrigues and Verardo [33] were able to effect the formation of similar cyclobutenone derivatives **65** from indoles **64** and DMAD at 20°C, using a catalytic amount of $BF_3{\cdot}OEt_2$. The resulting cyclobutenones **65** were then converted to the ring-opened benzazepines **66**, upon heating at reflux in benzene (Scheme 15).



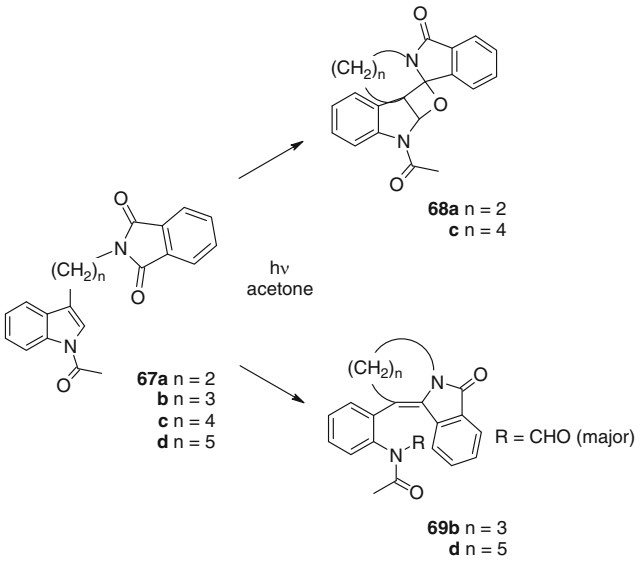
64 R = H, Me **61** **65** **66**

Scheme 15

2.4 [2+2] Cycloadditions of Indoles and Carbonyl Groups

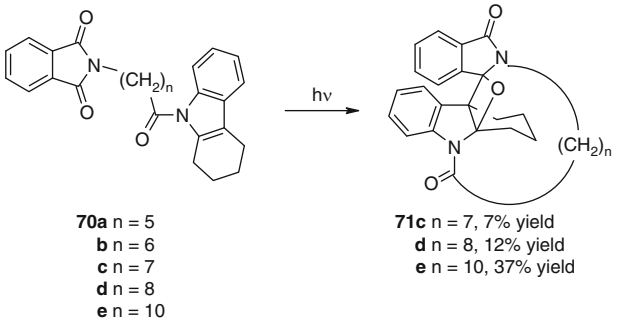
In addition to alkenes and acetylenes, carbonyl-containing compounds also participate in [2+2] cycloaddition reactions with indoles. The first example of oxetane formation via the photoreaction of indoles with a carbonyl group (a type of Paterno–Büchi reaction) was reported by Machida and coworkers [34, 35] (Scheme 16), who carried out the intramolecular cyclization of *N*-acetylindole with phthalimide tethered with appropriate linkers **67a**–**d**. Interestingly, only the

oxetane products with the two and four carbon linkers **68a**, **c** were stable enough to be isolated.



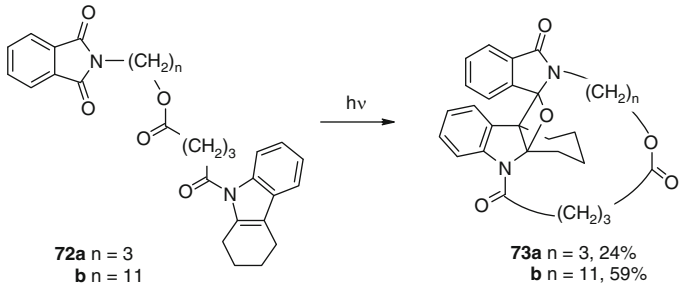
Scheme 16

In a similar fashion, the intramolecular remote Paterno–Büchi reaction of phthalimide with indole derivatives was utilized for the synthesis of a number of macrocycles in low to modest yields **71c–e** [36] (Scheme 17). Interestingly, the [2+2] adducts **71a**, **b** were not formed in cases where the linker group contained only five or six carbons.



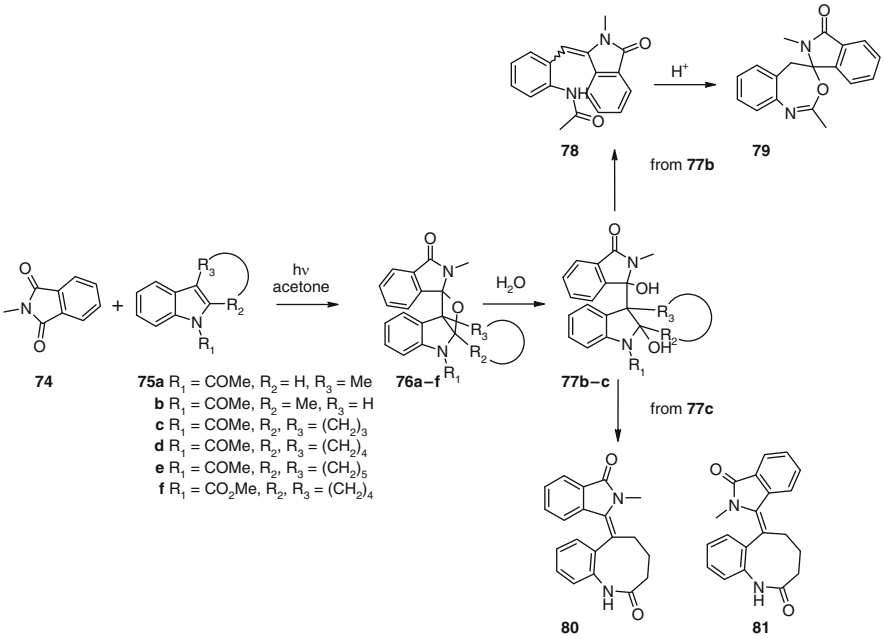
Scheme 17

Esters in the linker group between the phthalimide and the indole moieties **72a**, **b** were also tolerated, resulting in the formation of large macrocycles **73a**, **b**, including a 22-membered ring **73b** (Scheme 18).



Scheme 18

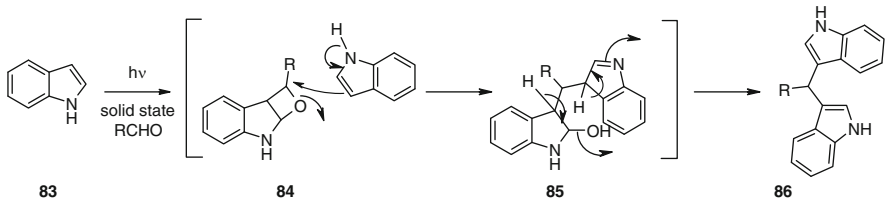
The intermolecular variant of the above reaction between *N*-methylphthalimide (**74**) and a series of *N*-acylindole derivatives **75a–f** was next examined [37, 38]. Compounds **75a** and **75d–f** produced the corresponding more sterically hindered oxetanes **76a** and **76d–f** in which the aromatic rings of the isoindolone and indoline moieties overlap (Scheme 19). Interestingly, in the cases of **75b**, **c**, the initially formed oxetanes **76b–d** were converted to a variety of products, presumably via the hydrolysis of the oxetanes, followed by ring opening of the indoline ring and subsequent reactions to produce **78–81**.



Scheme 19

Finally, it has been reported that the intermolecular photoreaction of aromatic aldehydes with indole **83** in the solid state leads to the formation of bis-indole

derivatives **86**, presumably via the formation of the [2+2] oxetane adducts **84**, and subsequent ring opening upon nucleophilic attack by a second indole moiety (Scheme 20) [39].



Scheme 20

3 Indole 2,3-Dipolar Cycloadditions

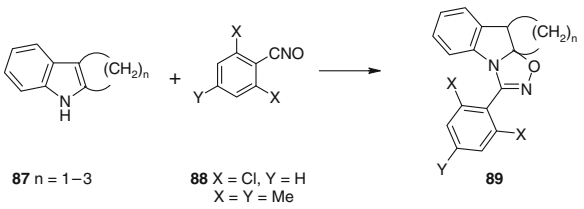
The established utility of dipolar cycloadditions to create heterocyclic ring systems [40–45] renders these reactions ideal for the rapid preparation of complex polyheterocyclic indole-containing natural products. Although several examples have been reported in which dipolar cycloadditions take place on or between indole side chains [46–52], only cycloaddition reactions involving two or more atoms of the indole ring system will be discussed in this review.

The vast majority of dipolar cycloaddition reactions with indoles as the dipolarophile occur at the 2,3-bond of the indole ring. However, dipolar cycloaddition reactions have been shown to proceed at other sites on the indole nucleus (i.e., the 4,5-bonds) as well, albeit rarely. Furthermore, although the majority of these [3+2] reactions utilize the indole system as the dipolarophile, examples of indoles serving as dipoles have also been reported.

3.1 Indole Pyrrole Ring as Dipolarophile

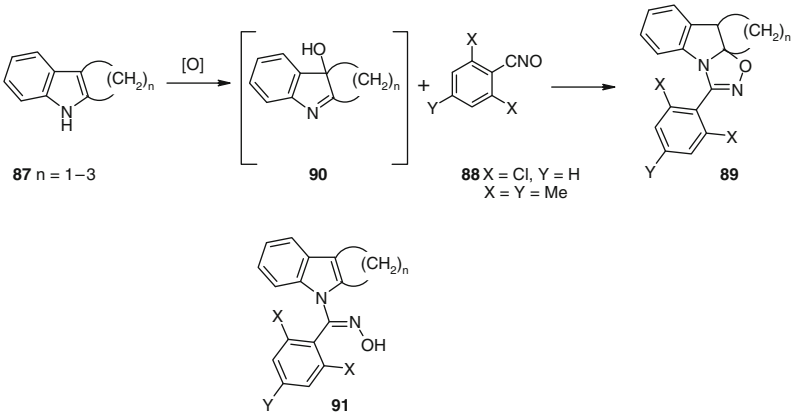
3.1.1 Indole Pyrrole Ring 1,2-Bond as the Dipolarophile

In cases where the 2,3-bond is sterically encumbered (for example, when the 2 and 3 positions are connected as part of a cycloalkane ring), dipolar cycloaddition products, consistent with addition across the 1,2-bond of the pyrrole, can be obtained [53] (Scheme 21).



Scheme 21

Two possible mechanisms for the formation of product **89** have been proposed. One postulated mechanism involves the oxidation of the indole ring of compound **87**, thereby producing the corresponding 3-hydroxy intermediate **90**, which then reacts with the dipole **88** to produce the observed product **89** (Scheme 22). Alternatively, nucleophilic addition of the indole nitrogen to the nitrile oxide **89**, followed by oxidative ring closure of the resulting intermediate **91** would also account for the formation of the cyclized product **90**. The authors favor the dipolar cycloaddition route in which the oxidized indole species **90** is the dipolarophile. The authors claim this mechanism is supported by the observation that when **90** (n = 4) is independently synthesized and isolated, its cycloaddition with dipoles yields identical products.

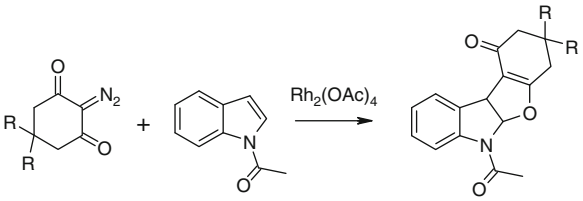


Scheme 22

3.1.2 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile with COC Dipoles, Isomunchnones

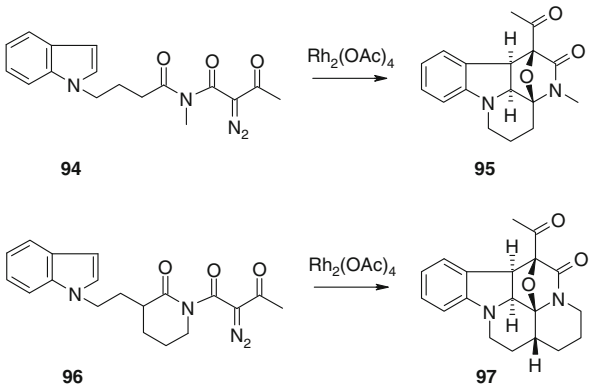
Carbonyl ylides, most often in the form of isomunchnones (formed by decomposition of diketo diazo compounds in the presence of rhodium (II) acetate, and subsequent cyclization of the intermediate rhodium carbenoid species) are by far the most studied 1,3-dipolar cycloaddition partners for indole derivatives. These cycloadditions have been employed in elegant examples of complex ring construction en route to a number of polycyclic indole-containing natural products. Preliminary work by Pirrung [54, 55] (Scheme 23) on simple intermolecular cycloadditions was followed shortly by the utilization of intramolecular examples by Padwa, Boger and others.

Early work by the Padwa group demonstrated the utility of the intramolecular dipolar cycloaddition reactions of indoles for the rapid preparation of complex ring systems. Diazoimides **94** and **96**, when treated with rhodium (II) acetate gave



Scheme 23

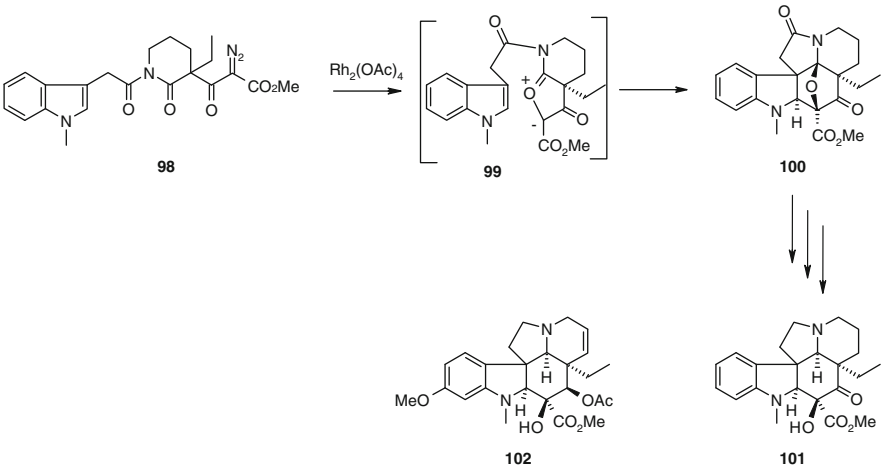
cycloadducts **95** and **97** in high yield, and with complete diastereoselectivity arising from *endo* cycloaddition of the dipole moiety (Scheme 24) [56, 57].



Scheme 24

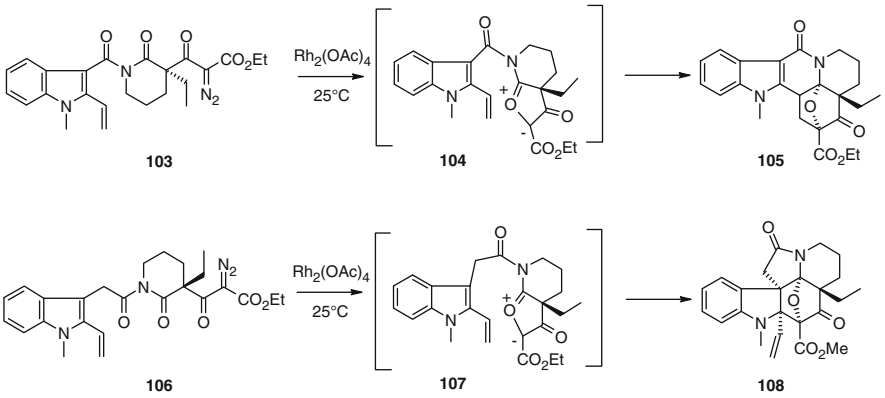
The Padwa group then applied this methodology to expeditiously assemble the pentacyclic skeleton of the *Aspidosperma* family of alkaloids [58, 59]. When diazoimide **98** was treated with a catalytic quantity of rhodium (II) acetate in benzene at 50°C, the cycloadduct **100** was isolated in 95% yield as a single diastereomer (Scheme 25). Compound **100** was further elaborated in subsequent steps to desacetoxy-4-oxo-6,7-dihydrovindorosin (**101**), a close analog of vindoline (**102**).

For the cases of indoles bearing a vinyl group at the 2-position, thus offering a second possible dipolarophile for [3+2] cycloadditions, interesting regioselectivity as a function of dipolarophile have been observed [60, 61]. Vinyl-indolyl-substituted diazo imide **103**, when treated under rhodium-catalyzed conditions, gives **105** (the product arising from cycloaddition with the vinyl group) exclusively in 92% yield. Interestingly, the homolog **106**, when subjected to the same set of conditions, gives only the cycloadduct **108** (arising from cycloaddition with the indole 2,3-double bond) in 95% yield. The authors suggest that dipole **107** derived from **106**



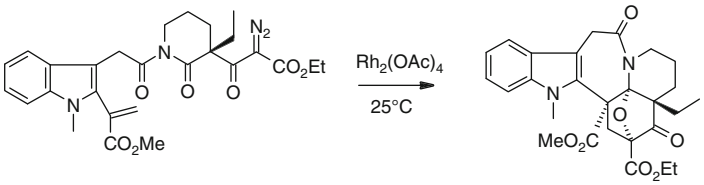
Scheme 25

(Scheme 26) resides in a conformation which allows better overlap of the dipole with the indole π-system rather than the vinyl π-system.



Scheme 26

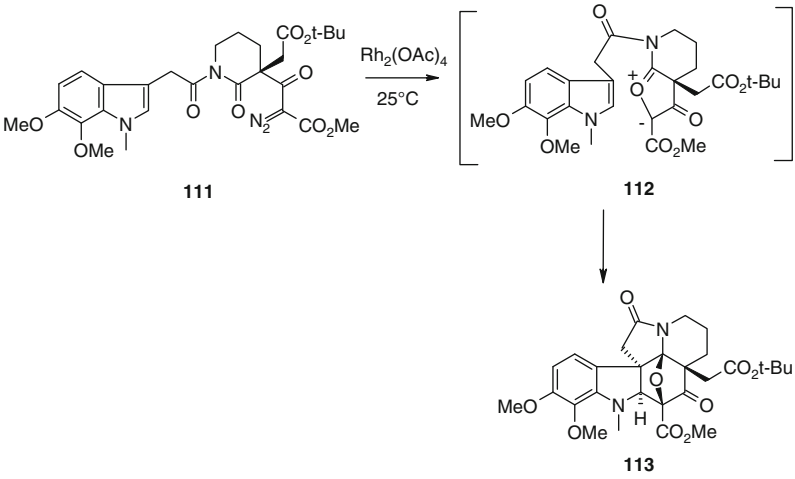
Complete reversal of the above regioselectivity for the indole 2,3-double bond is observed when the 2-vinyl moiety is substituted with a carbomethoxy group. Thus, diazo imide **109** gives **110** in 91% yield as the only product formed when treated with rhodium (II) acetate. The authors attribute this result to the higher reactivity of the activated acrylate bond towards dipolar cycloadditions (Scheme 27).



109 110

Scheme 27

The Padwa group has further demonstrated the utility of the intramolecular dipolar cycloaddition reaction in the course of their total synthesis of aspidophytine [62, 63]. Treatment of the diazo imide **111** with rhodium(II) acetate gives the key polycyclic intermediate **113** in 97% yield (Scheme 28).



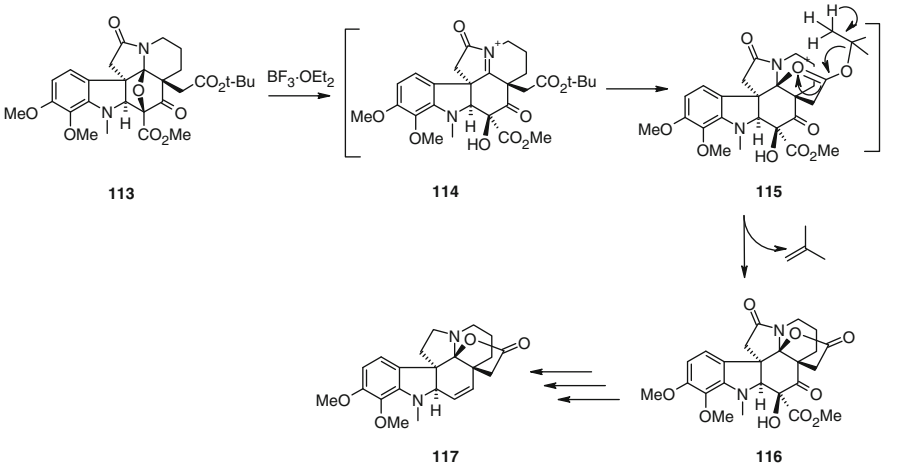
111 112

113

Scheme 28

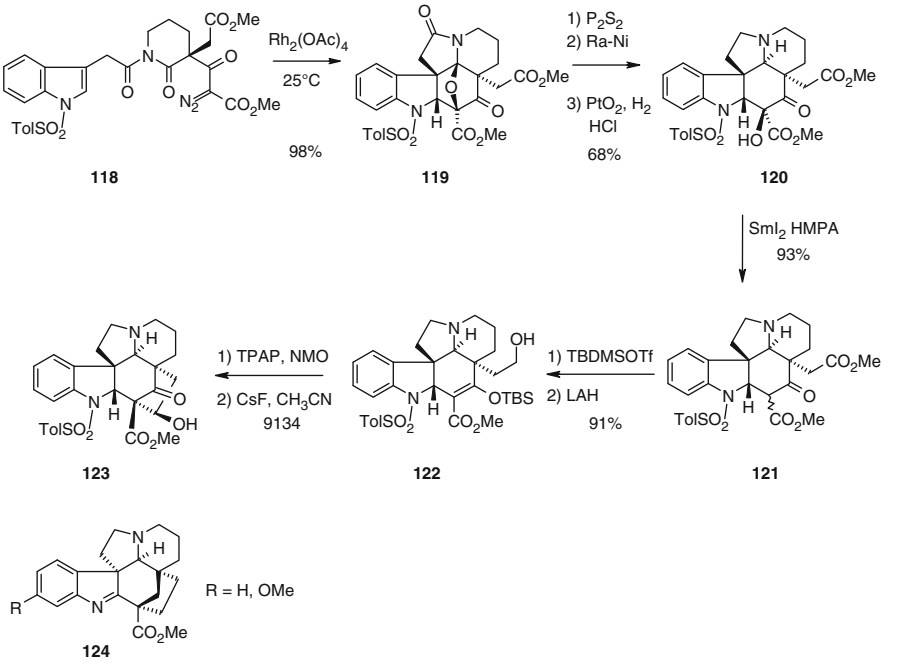
Treatment of this intermediate with $BF_3{\cdot}OEt_2$ then induced a domino fragmentation and cyclization cascade: The cleavage of the oxabicyclic ring produced the intermediate *N*-acyl iminium ion **114,** which was trapped by the pendant *t*-butyl ester carbonyl, followed by the loss of isobutene, to give the advanced intermediate **116** in 94% yield (Scheme 29). This compound, which contains the complete polycyclic framework of aspidophytine (**117**), was then further elaborated to produce the natural product in subsequent steps.

The Padwa group has also extended this methodology to provide a route to the hexacyclic framework of the kopsifoline alkaloids [64–66]. Compound **119**, prepared by treating the precursor diazo imide **118** with rhodium (II) acetate, was isolated as a single diastereomer in 98% yield (Scheme 30). This intermediate was then converted to the hydroxy ester **120** via a reductive ring-opening/cyclization sequence in 68% yield. Treatment of **120** with SmI_2 in HMPA furnished the ketoester **121** in 93%



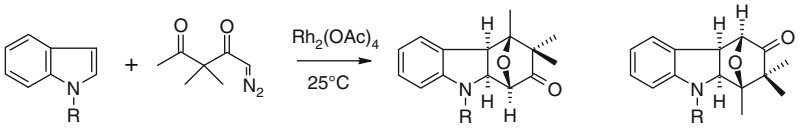
Scheme 29

yield. Conversion of **121** to the corresponding TBS silyl enol ether, followed by selective $LiAlH_4$ reduction of the nonconjugated ester, gave the primary alcohol **122** in 91% yield. Oxidation of **122** using TPAP (NMO) at 0°C, followed by treatment of the crude reaction mixture with CsF in refluxing CH_3CN then produced **123** in 34% yield for the two-step sequence. The advanced intermediate **123** contains the entire hexacyclic framework of the kopsifoline alkaloid family (**124**).



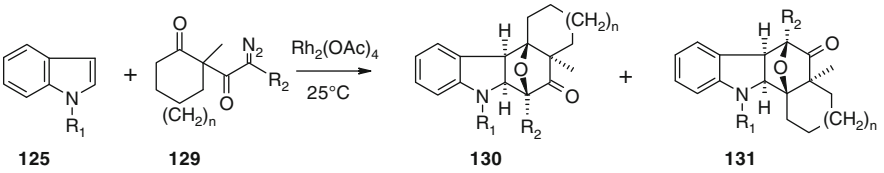
Scheme 30

Muthusamy and coworkers [67, 68] have examined the regioselectivity (with respect to dipole orientation) of intermolecular cycloadditions of carbonyl ylides with a variety of N-substituted indoles. 1-Diazo-3,3-dimethylpentane-2,4-dione (**126**), upon treatment with rhodium (II) acetate and simple indole derivatives (**125**), might be expected to give a mixture of regioisomers **127** and **128**; however, only hexahydro-2*H*-carbazol-2-ones **127** were observed in 86–97% (Scheme 31).



Scheme 31

Furthermore, the ylides formed by treating the cyclic diazo compounds **129** with rhodium (II) acetate gave, in most cases, carbazole derivatives **130** exclusively (Scheme 32). In cases where the indole nitrogen is substituted with electron-withdrawing groups, such as benzoyl or sulfonyl, reactivity is reduced and a mixture of regioisomers **130** and **131** is obtained.



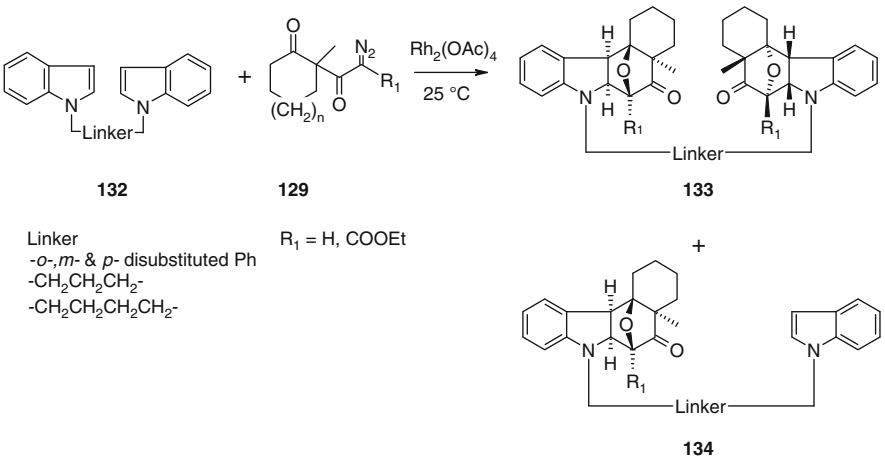
entry	R_1	R_2	n	conditions	yield 130
1	H	H	1	a	71%
2	Me	H	1	a	84%
3	Bn	H	1	a	85%
4	H	CO_2Et	1	b	69%
5	Me	CO_2Et	1	b	82%
6	Bn	CO_2Et	1	b	86%
7	H	H	0	a	34%
8	Me	H	0	a	44%
9	Bz	H	1	a	36% (**130**+**131**)
10	SO_2Ph	H	1	a	32% (**130**+**131**)

a) CH_2Cl_2, RT. b) benzene, reflux

Scheme 32

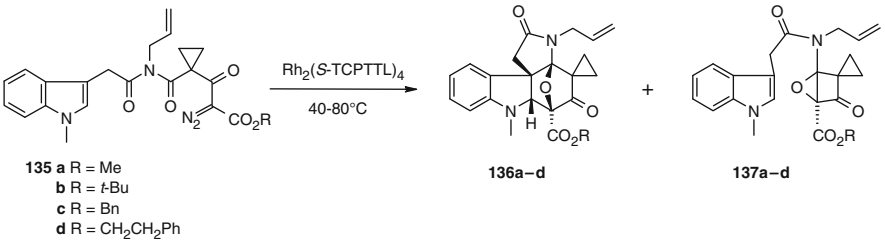
These authors also demonstrated that bis-indoles linked with alkyl or aryl spacers of different lengths (**132**) give the corresponding double 1,3-dipolar

cycloaddition products **133** along with the mono adducts **134** with similar regioselectivity and moderate yield (Scheme 33).



Scheme 33

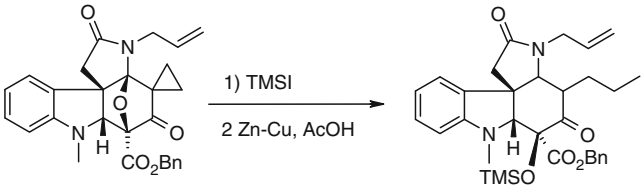
Hashimoto and coworkers [69] have recently begun to explore the use of chiral rhodium catalysts in the intramolecular dipolar cycloaddition reactions of indoles, and have applied their methodology to the synthesis of the *Aspidosperma* ring system. Thus, the cycloaddition of the cyclopropyl carbonyl ylides derived from cyclopropyl diazo-5-imido-3-ketoesters **135** upon treatment with dirhodium (II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate] gave cycloadducts **136** along with the spiro[2.3]hexanes **137** in only moderate yields (Scheme 34). Although the reaction proceeds with exclusive *endo* diastereoselectivity, only moderate enantioselectivities of up to 66% enantiomeric excess (ee) could be obtained.



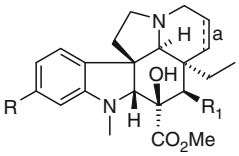
Scheme 34

Further elaboration of the above cycloadduct **136c** (R = Bn in Scheme 34) by treatment with trimethylsilyl iodide afforded the ring-opened tetracyclic compound **138** in 76% yield. The tetracyclic ketoester **138** is envisioned to serve as the

key precursor towards the total synthesis of *Aspidosperma* alkaloids such as (−)-vindorosine (**139e**) (Scheme 35).



136c **138**

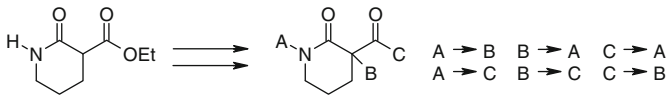


139

139a (–)-Vindoline R = OMe, R_1 = OAc, a = db
139b (+)-6,7-Dihydrovindoline R = OMe, R_1 = OAc, a = sb
139c (+)-4-Desacetoxyvindoline R = OMe, R_1 = H, a = db
139d (+)-4-Desacetoxy- 6,7-dihydrovindoline R = OMe, R_1= H, a = sb
139e (-)-Vindorosine R = H, R_1 = OAc, a = db
139f (+)-6,7-Dihydrovindoserine R = H, R_1 = OAc, a = sb
139g (+)-4-Desacetoxyvindoserine R, R_1 = H, a = db
139h (+)-4-Desacetoxy- 6,7-dihydrovindoserine R, R_1 = H, a = sb
db = double bond, sb = single bond

Scheme 35

As part of their efforts in diversity-oriented synthesis [70, 71], Schreiber and Oguri [72] devised a set of "folding strategies" that were applied to the synthesis of complex indole-containing natural products utilizing Rh(II)-catalyzed consecutive cyclization–cycloaddition sequences, similar to those developed by Padwa and coworkers (see above). On the basis of this strategy, a common scaffold **140** was envisioned as a promising starting point, allowing for various modes of intramolecular reactions. Since each of the three sites designated as A, B or C in **141** could be used for the installation of an α-diazo ketocarbonyl group or an indole moiety, there are six possible cycloaddition "folds" that may be employed to construct fused heterocyclic ring systems found in indole alkaloids starting from **141** (Scheme 36, the designations for the cyclization modes, e.g., A → B are short for: carbonyl ylide on site A reacting with dipolarophile on site B.)

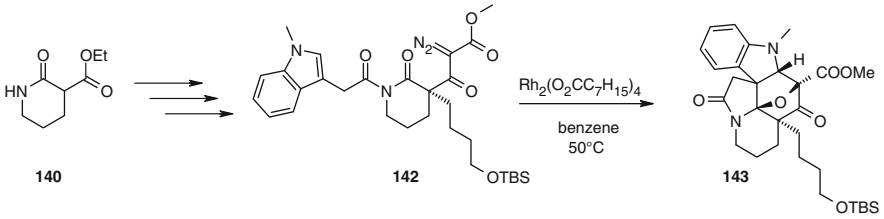


140 **141**

Scheme 36

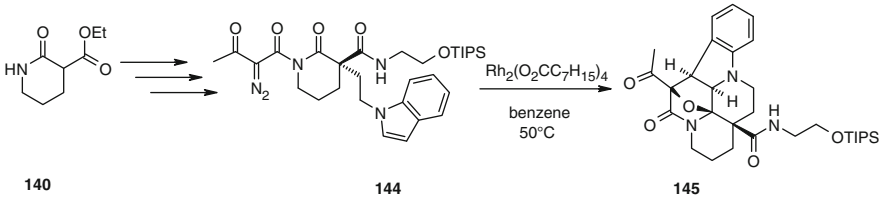
As a first attempt, the cyclization mode C → A, which was similar to Padwa's general strategy (*vide supra*) was investigated. Thus, the rhodium-catalyzed

cycloaddition of compound **142** in benzene at 50°C produced the adduct **143** in 74% yield as a single isomer (Scheme 37).



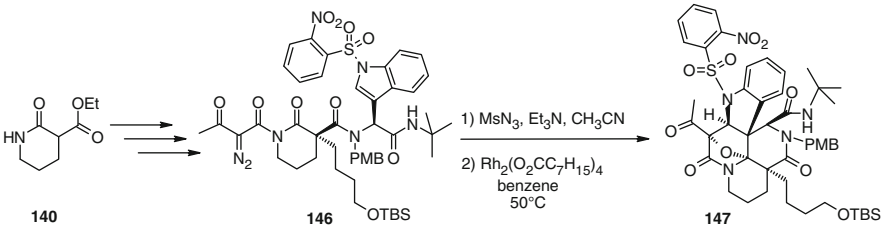
Scheme 37

The second folding mode examined was the pathway A → B, where the diazoimide **144**, after treatment with rhodium(II) catalyst in benzene at 50°C, gave the cycloadduct **145** in good yield (74%) with complete diastereoselectivity (Scheme 38).



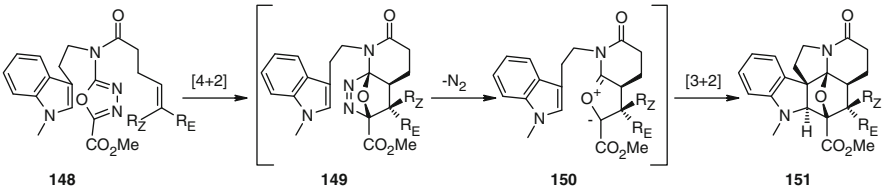
Scheme 38

From the perspective of diversity-oriented synthesis and the rapid construction of complex ring systems, the A → C pathway may offer the most promising approach. As an example, an Ugi four-component condensation reaction was used as the key step to construct **146** (Scheme 39). Conversion of **140** to the corresponding diazoimide **146** followed by rhodium(II)-catalyzed intramolecular dipolar cycloaddition then afforded the hexacyclic product **147** in 57% yield (two steps) in a highly stereocontrolled manner.



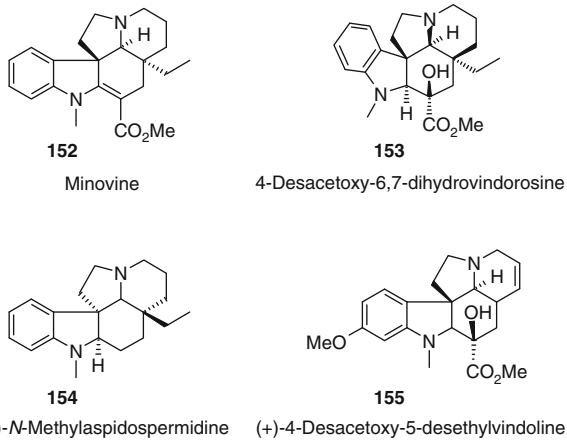
Scheme 39

An alternative method for the generation of carbonyl ylides and their use in the synthesis of complex indole-containing natural products has been developed by Boger and coworkers [73]. In this approach, the ylides are generated from precursors such as **148**, via the intramolecular Diels–Alder reactions of oxadiazoles with a suitably placed olefin, followed by the loss of nitrogen from the cycloadduct **149** to give dipoles **150** (Scheme 40). The tethered dipoles thus formed then undergo cycloaddition reactions with the nearby indole 2,3-double bond to form the hexacyclic adducts **151** in good yields.



Scheme 40

The utility of this tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition sequence was demonstrated by a number of concise total syntheses of *Aspidosperma* alkaloids [74–76], including minovine (**152**), 4-desacetoxy-6,7-dihydrovindorosine (**153**), 4-desacetoxyvindorosine (**139g**), vindorosine (**139e**), *N*-methylaspidospermidine (**154**), 6,7-dihydrovindoline (**139c**), 4-desacetoxyvindoline (**139b**), 4-desacetoxy-6,7-dihydrovindoline (**139d**), and (−)- and *ent*-(+)-4-desacetoxy-5-desethylvindoline (**155**) (Scheme 25, Scheme 41). Several of these syntheses are briefly described below.



152 Minovine

153 4-Desacetoxy-6,7-dihydrovindorosine

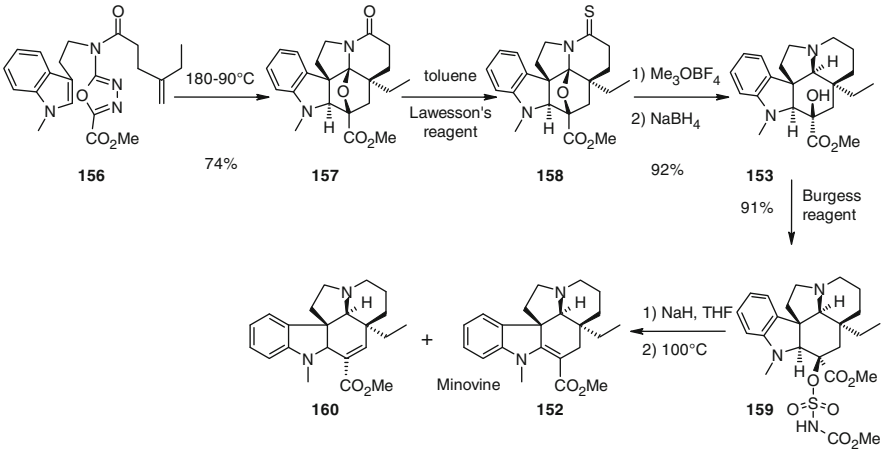
154 (+)-*N*-Methylaspidospermidine

155 (+)-4-Desacetoxy-5-desethylvindoline

Scheme 41

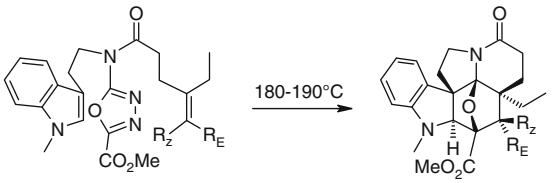
The total synthesis of *Aspidosperma* alkaloids 4-desacetoxy-6,7-dihydrovindorosine (**153**) and minovine (**152**) began by heating the 1,3,4-oxadiazole derivative **156** at 180°C in *o*-dichlorobenzene for 24 h to give the cycloadduct **157** as a

single detectable diastereomer in 74% yield (Scheme 42). Treatment of **157** with Lawesson's reagent, followed by S-methylation of the thiolactam **158** with Me_3OBF_4 and subsequent $NaBH_4$ reduction in MeOH provided 4-desacetoxy-6, 7- dihydrovindorosine (**153**) in 92% yield. Treatment of **153** with the Burgess reagent in CH_3CN gave the sulfamate **159** (91% yield), which upon heating in toluene with sodium hydride at 100°C produced minovine (**152**) and its isomer **160**.



Scheme 42

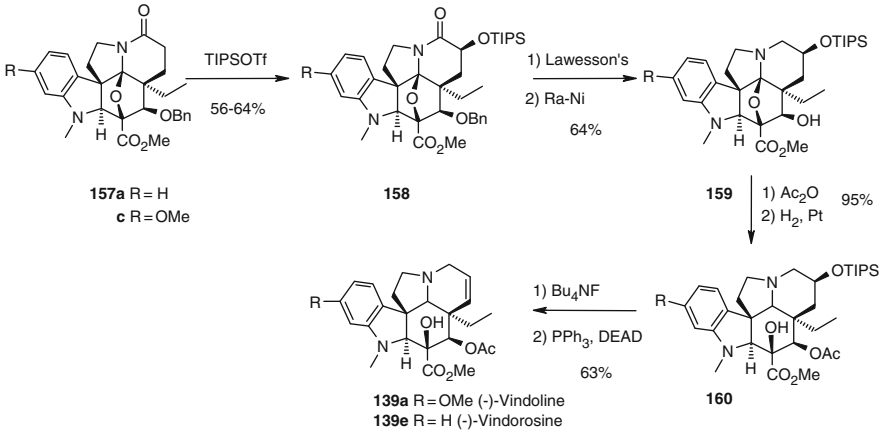
Boger and coworkers also applied the above methodology to the total synthesis of *ent*-(+) and (−)-vindoline (**139a**) [77]. Heating oxadiazoles **156a**, **b** in triisopropyl benzene gave pentacyclic products **157a**, **b**, respectively, each as single diastereomers. The reaction rate and yield were higher in the case of the *E* double bond **156b** (53% yield of **157a**, >95% yield of **157b**) (Scheme 43). Further studies indicated that the yield of the cycloaddition reaction is concentration-dependent, and a competing bimolecular 1,3-dipolar cycloaddition reaction may account for the lower yield observed for the *Z* isomer **156a**.



Scheme 43

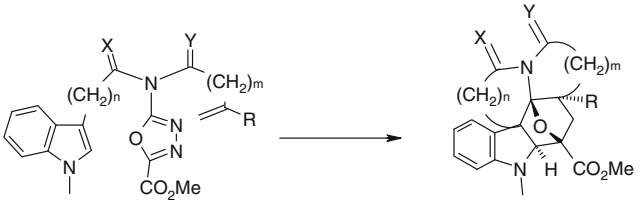
The above cycloadduct **157a** was then further elaborated to prepare *ent*-(+) and (−)-vindorosine (**139e**). Separation of the enantiomers of **157a**, followed by enolate formation and treatment with TIPSOTf, gave the protected α-hydroxylated product **158** in 56–64% yield (Scheme 44). Treatment of **158** with Lawesson's reagent,

followed by Raney Ni reduction of the thiolactam, furnished **159** in 64% yield (two steps). The remaining unprotected secondary alcohol in **159** was acetylated, and the oxido bridge was cleaved diastereoselectively by catalytic hydrogenation with PtO_2 as the catalyst, to give **160** in 95% yield (two steps). The silylated alcohol **160** was deprotected with Bu_4NF and then subjected to elimination under Mitsunobu conditions to provide (−)-vindorosine (**139e**) in 63% yield (two steps). A similar sequence was used to prepare (−)-vindoline (**139a**).



Scheme 44

Boger has shown that tether lengths that provide a 5–6 ring system after cyclization are ideal for the synthesis of vinca alkaloids such as vindoline [78]. Adjustment of the length of the tether connecting the indole to oxadiazole, or the dienophile to oxadiazole, are tolerated. As expected, varying tether lengths have effects on the reaction rates and yields of cycloaddition products **161** (Scheme 45).



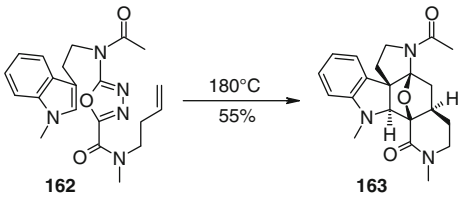
160 **161**

entry	X	Y	n	m	R	yield %	Time (h)	temp (°C)
1	H,H	O	1	2	H	87	3	180
2	H,H	O	1	2	Et	74	24	180
3	H,H	O	1	3	H	43	24	230
4	O	H,H	1	1	H	68	16	230
5	O	H,H	2	1	H	72	2	165
6	H,H	O	2	2	H	89	24	230
7	H,H	O	2	2	Et	12	20	230
8	O	H,H	3	1	H	26	24	230

Scheme 45

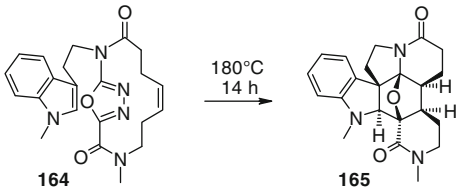
Along with varying the tether length, Boger demonstrated that alternate tethering of the dienophile through attachment at the oxadiazole C5 substituent is also tolerated. Thus, heating **162** to 180°C in dichlorobenzene gave the expected tandem cycloadduct **163** in 55% yield (Scheme 46).

Scheme 46



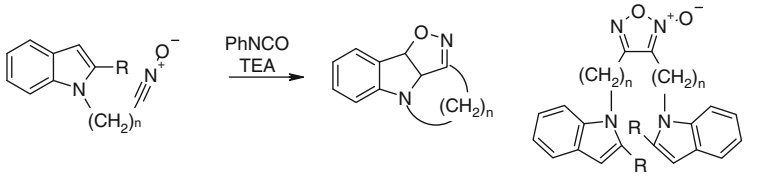
Finally, in another example to demonstrate the power of the oxadiazole tandem [4+2] cycloaddition/1,3-dipolar cycloaddition methodology, the doubly tethered unactivated cis olefin **164**, was shown to produce the heptacyclic cycloadduct **165** as a single diastereomer in 78% yield upon heating in dichlorobenzene (Scheme 47).

Scheme 47



3.1.3 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with CNO Dipoles

Hassner [79] investigated the intramolecular trapping of nitrile oxides with indoles, and demonstrated that nitrile oxides **166b**, **c** (generated in situ from the corresponding nitroalkyl derivatives upon treatment with PhNCO-Et_3N in benzene) produced [3+2] cycloadducts **167b**, **c**. Attempts at cycloaddition with shorter tethers **166a**, **d** led to nitrile oxide dimerization (furoxan) byproducts **168a**, **d** (Scheme 48).



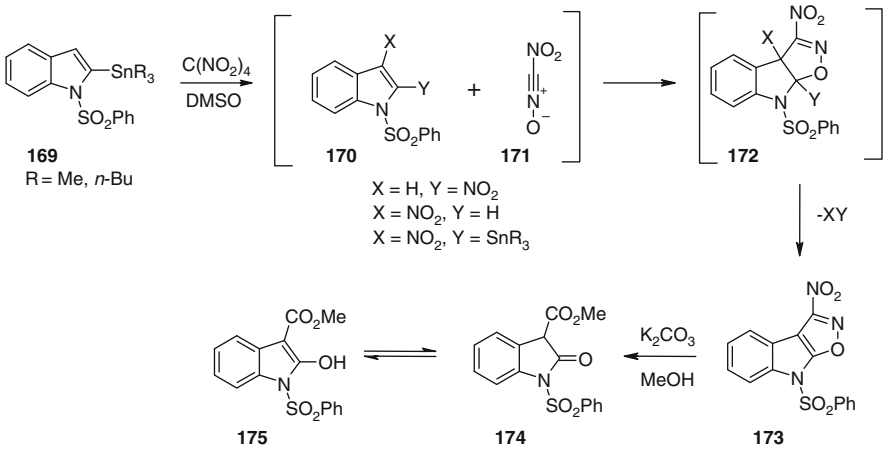
166a R = H, n = 2
b R = H, n = 3
c R = H, n = 4
d R = Me, n = 2

167b R = H, n = 3
c R = H, n = 4

168a R = H, n = 2
d R = Me, n = 2

Scheme 48

Other reports on the [3+2] cycloadditions of indoles and nitrile oxides focus on intermolecular reactions. For example, Gribble [80] has investigated the reaction of (phenylsulfonyl)-2-(tri-*n* alkylstannyl)indoles **169** with tetranitromethane to give the novel isoxazolo[5,4-b]indole derivative **173** (Scheme 49). The mechanism cascade is thought to proceed through the degradation of the dinitromethyl anion to a nitrile oxide **171**, followed by a 1,3-dipolar cycloaddition to form a nitroindole intermediate **172** and subsequent loss of nitrous acid or SnR_3NO_2. Treatment of the isoxazole **173** with base then leads to the formation of the oxindole tautomer **175** as the major product.

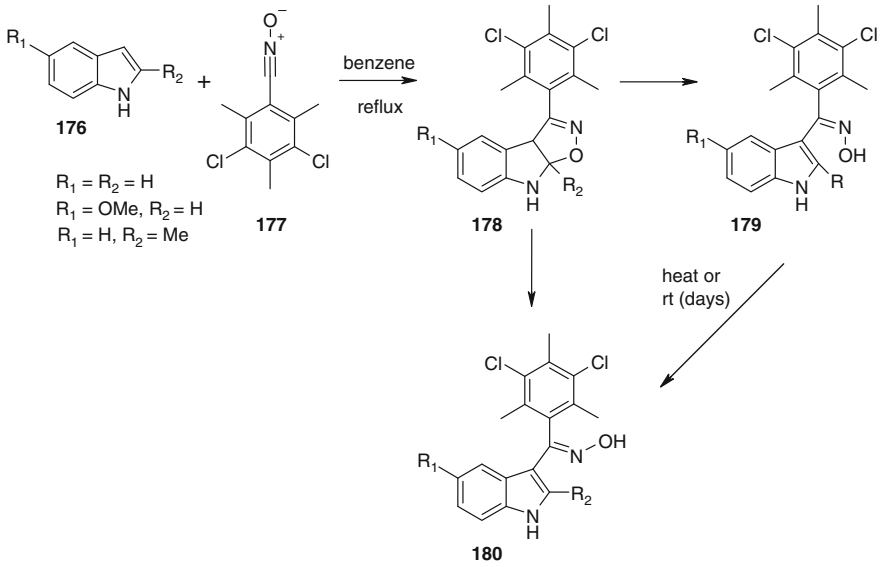


Scheme 49

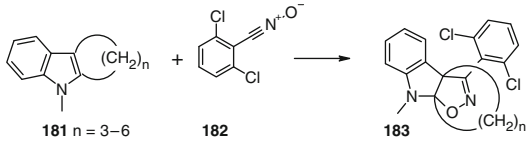
In another example of intermolecular [3+2] cycloadditions, indoles **176** (Scheme 50) react with nitrile oxides **177** in boiling benzene to give oximes **180**, after the ring opening of the isoxazole intermediates **178** [81]. Although both oximes **179** and **180** could be isolated in pure form by column chromatography, the Z isomer **179** was found to isomerize completely to the stable *E* isomer **180** upon heating for a few hours, or by standing at room temperature for several days.

In an interesting variation of the above cycloaddition reactions, it has been reported that *N*-methylcycloalkano[b]indoles **181** undergo a regioselective 1,3-dipolar cycloaddition with 2,6-dichlorobenzonitrile oxide (**182**) to give the corresponding propellanes **183** in moderate to good yields [82] (Scheme 51).

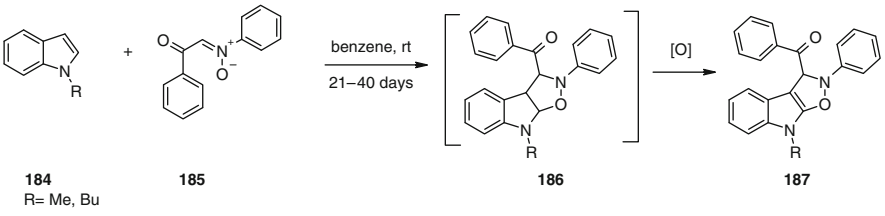
Finally, the reaction of *C*-benzoyl-*N*-phenylnitrone (**185**) with indole derivatives in benzene at room temperature for several days gives, among other products, small amounts of the isoxazolines **187**. These isoxazolines were presumably produced from the oxidation of the intermediate cycloadduct indolines **186** [83] (Scheme 52).



Scheme 50



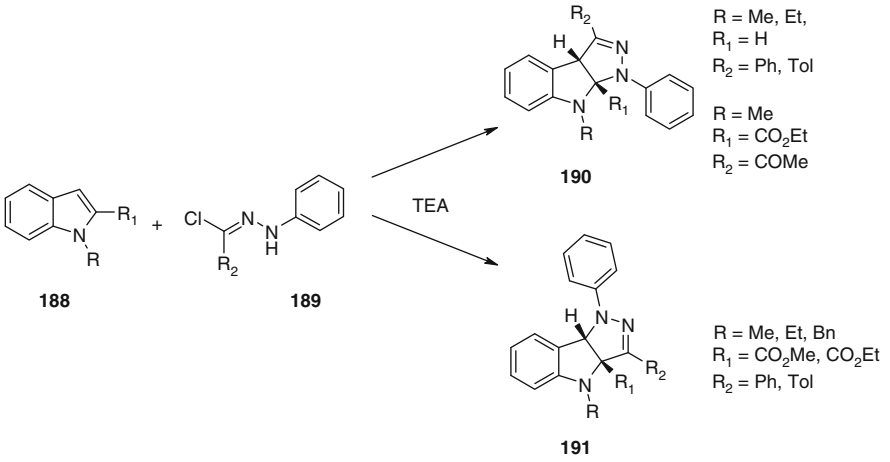
Scheme 51



Scheme 52

3.1.4 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with CNN Dipoles

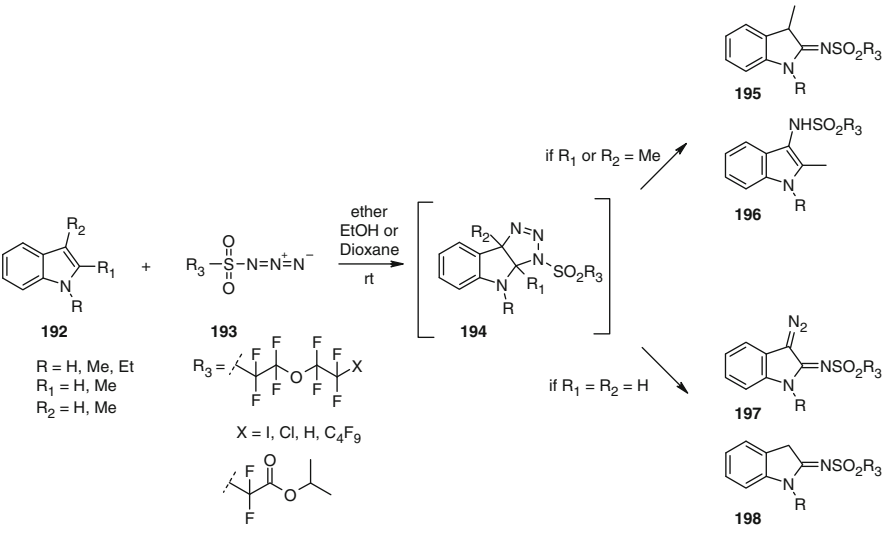
Diarylnitrilimine dipoles, formed by treating the corresponding hydrazonyl chlorides **189** with triethylamine, undergo a dipolar cycloaddition with the 2,3-bond of indoles **188** [84]. The nature of the substituents on the indole and the dipole appear to determine which of the regioisomeric pyrazolo[3,4-b]indoles (**190** or **191**) is obtained (Scheme 53).



Scheme 53

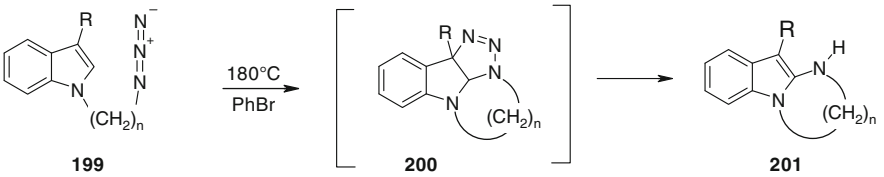
3.1.5 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with NNN Dipoles

Very few reports have been published to date on the reactions of indoles with NNN dipoles. The reaction of fluoroalkanesulfonyl azides **193** with indoles **192** results in the formation of distinct amino, imino or diazo products, **195–198** depending on the choice of solvent and the nature of substituents on the indole ring (Scheme 54). When the indole has a methyl group in the 2 or 3 position, compounds **196** or **195** are obtained, respectively. If the 2 and 3 position are unsubstituted, compounds **197** and **198** are obtained, respectively. In all cases, a dipolar cycloadduct **194** is proposed as an intermediate in the first step in the mechanism of these transformations [85, 86].



Scheme 54

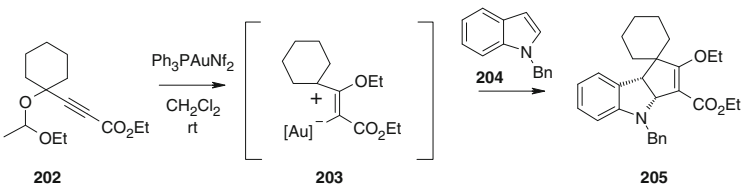
An interesting intramolecular cycloaddition reaction of indoles with azides has also been reported. Heating solutions of 1-ω-azidoalkylindoles **199**, which bear an electron-attracting substituent (e.g., CHO, COMe, CO_2Me, CN) at C-3, has led to the formation of tricyclic indoles **201** as products [87] (Scheme 55). The authors suggest that after the initial 1,3-dipolar cycloaddition, the intermediate triazoline **200** loses nitrogen (perhaps via an aziridine intermediate) to produce the tricyclic products **201**.



Scheme 55

3.1.6 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with CCC Dipoles

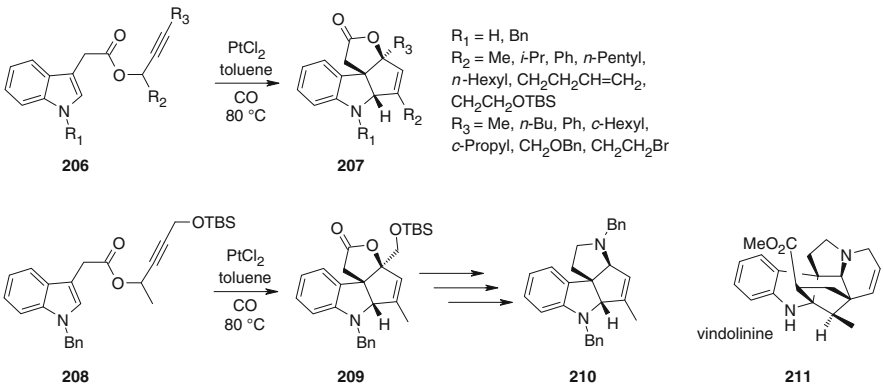
Gold-containing all-carbon 1,3-dipoles, such as **203**, are prepared in situ by the treatment of ketals and acetals with $Ph_3PAuNTf_2$ (5 mol%), and undergo [3+2] cycloadditions with *N*-benzylindole (**204**) at room temperature. In the case of **202**, the cycloaddition led to the formation of the cyclopentyl-annulated derivative **205** with good diastereoselectivity (55% yield) [88] (Scheme 56).



Scheme 56

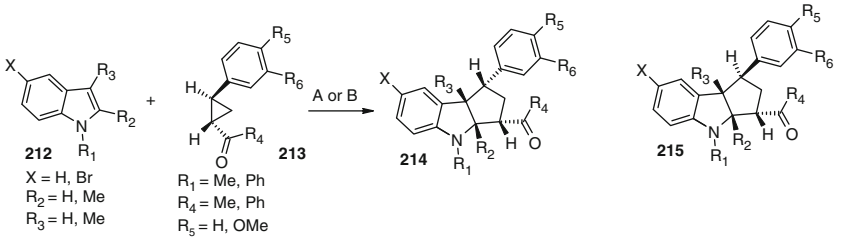
Similarly, propargylic 3-indoleacetates **206**, when treated with $PtCl_2$, undergo an intramolecular [3+2] cycloaddition across the 2,3-indole bond to form the tetracyclic lactones **207** in excellent yields. This methodology (conversion of **208** to **209**) has been successfully applied to the development of a short synthesis of the tetracyclic core of vindolinine (**211**) (Scheme 57).

All carbon dipoles, prepared in situ from 2-arylcyclopropyl ketones **213** by treatment with Lewis acids such as $BF_3{\cdot}OEt_2$ or $TiCl_4$, undergo highly diastereoselective [3+2] cycloadditions with both substituted and unsubstituted indoles **212** to produce, in most cases, the corresponding cyclopentane-annulated analogs **214** in high yields [89] (Scheme 58). In cases where the dipole had lower cation



Scheme 57

stabilization (**213**, entries 11 and 12), diastereoselectivity was degraded and a mixture of **214** and **215** was obtained.

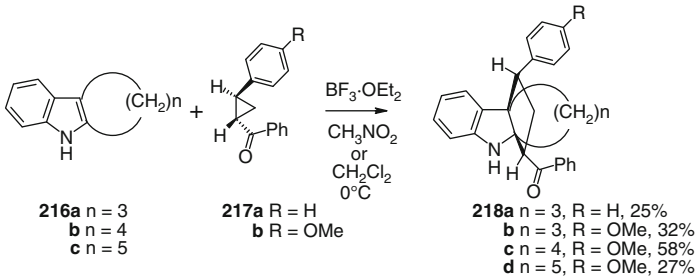


entry	X	R_1	R_2	R_3	R_4	R_5	R_6	conditions	yield	product
1	H	H	H	H	Ph	MeO	H	A	92%	**214**
2	Br	H	H	H	Ph	MeO	H	A	70%	**214**
3	H	Me	H	H	Ph	MeO	H	A	83%	**214**
4	H	H	Me	H	Ph	MeO	H	A	80%	**214**
5	H	H	H	Me	Ph	MeO	H	A	83%	**214**
6	H	H	Me	Me	Ph	MeO	H	A	93%	**214**
7	H	Me	Me	Me	Ph	MeO	H	A	-	**214**
8	H	H	H	H	Ph	MeO	MeO	B	84%	**214**
9	H	Me	H	H	Ph	MeO	MeO	B	85%	**214**
10	H	H	Me	Me	Ph	MeO	MeO	B	83%	**214**
11	H	H	H	H	Ph	H	H	A	85%	**214/215** (2:1)
12	H	H	H	H	Me	H	H	A	70%	**214/215** (3:1)

A. $BF_3{\cdot}Et_2O$, CH_3NO_2 0°C; B. $TiCl_4$, CH_2Cl_2, –78 °C

Scheme 58

For indoles, such as cyclopent[b]indole (**216a**), tetrahydrocarbazole (**216b**) and cyclohepta[b]indole (**216c**), which already possess a ring annulated in the 2,3-position, the above reactions lead to the formation of propellanes **218a**–**d** in modest yields (Scheme 59).



216a n = 3
b n = 4
c n = 5

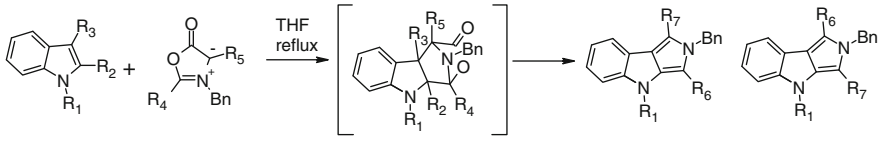
217a R = H
b R = OMe

218a n = 3, R = H, 25%
b n = 3, R = OMe, 32%
c n = 4, R = OMe, 58%
d n = 5, R = OMe, 27%

Scheme 59

3.1.7 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with CNC Dipoles Munchnones/Sydnones

Gribble and coworkers [90, 91] have shown that munchnones **220** undergo dipolar cycloadditions with 2- or 3-nitro-substituted *N*-protected indoles **219** to give, after loss of carbon dioxide from the initial cycloadduct **221**, the corresponding pyrroloindoles **222**. These products are synthetic equivalents of indole 2,3-quinodimethanes and in turn have been used as dienes in subsequent Diels–Alder reactions (see the following chapter). For munchnones that provide unsymmetrically substituted pyrroles (i.e., R_6 and R_7 are not same), good regioselectivity is observed in the cycloaddition reactions (Scheme 60).



219
R_1 = CO_2Et, SO_2Ph
R_2 = H, R_3 = NO_2
R_2 = NO_2, R_3 = H

220a R_4, R_5= Ph
b R_4, R_5= Me
c R_4= Me, R_5= Ph
d R_4= Ph, R_5= Me

221 **222** **223**

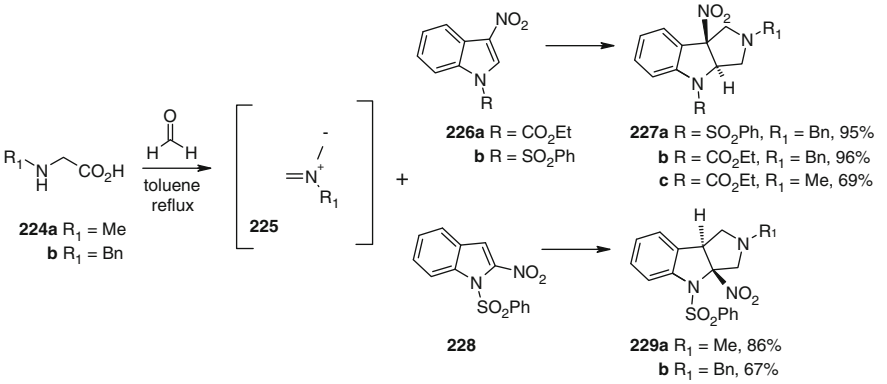
entry	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield 222
1	CO_2Et	NO_2	H	Ph	Ph	Ph	Ph	94%
2	CO_2Et	NO_2	H	Me	Me	Me	Me	53%
3	SO_2Ph	H	NO_2	Ph	Ph	Ph	Ph	65%
4	SO_2Ph	H	NO_2	Me	Me	Me	Me	67%
5	CO_2Et	NO_2	H	Me	Ph	Ph	Me	85% (9:1)*
6	CO_2Et	NO_2	H	Ph	Me	Me	Ph	88%(9:1)*
7	CO_2Et	H	NO_2	Me	Ph	Me	Ph	65%(19:1)*
8	CO_2Et	H	NO_2	Ph	Me	Ph	Me	89% (1:1)*
9	SO_2Ph	H	NO_2	Me	Ph	Me	Ph	74%(>19:1)*
10	SO_2Ph	H	NO_2	Ph	Me	Me	Ph	76%(~4:1)*

* ratio of **222** to **223** observed

Scheme 60

3.1.8 Indole Pyrrole Ring 2,3-Bond as the Dipolarophile, with Other CNC Dipoles

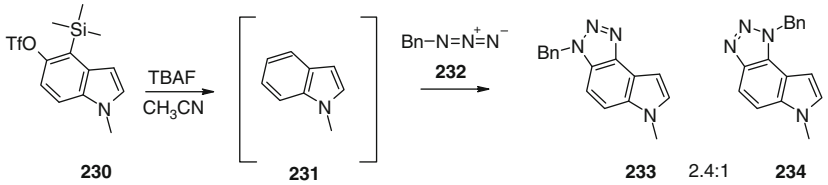
Gribble and coworkers [92] have shown that the treatment of azomethine ylides **225** generated in situ from sarcosine or *N*-benzyl glycine (**224a**, **b**) and paraformaldehyde in refluxing toluene, with 3-nitro-1-carboethoxyindole (**226a**) and 2-nitro or 3-nitro-substituted 1-(phenylsulfonyl) (**226b** and **228**), affords the hexahydropyrroloindole cycloadducts **227** and **229**, respectively, in good yields (Scheme 61). These compounds could be further elaborated to the corresponding pyrroloindoles, which serve as quinodimethane equivalents in Diels–Alder reactions (see the following chapter).



Scheme 61

3.2 Indole Phenyl Ring as Dipolarophile

Considering the lack of electrophilic reactivity, normally observed in the indole phenyl ring, it is not surprising that dipolar cycloadditions to this portion of the molecule are almost unknown. A lone example has been reported by the Garg group, which involves the reactive 4,5-indolyne species **231**[12]. Following Kobayashi's methodology for aryne generation [13, 93], the silyltriflate **230** was treated with TBAF in acetonitrile, thus generating the indolyne species **231** (Scheme 62). The dipolar cycloaddition of this aryne with benzylazide **232** then produced a mixture of indolyltriazoles **233** and **234** in 86% yield.

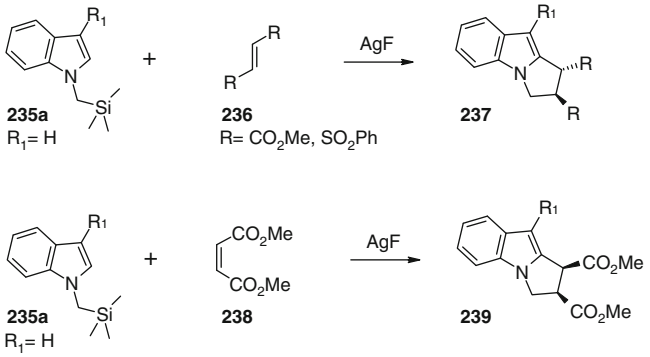


Scheme 62

3.3 *Indole Pyrrole Ring as Dipole*

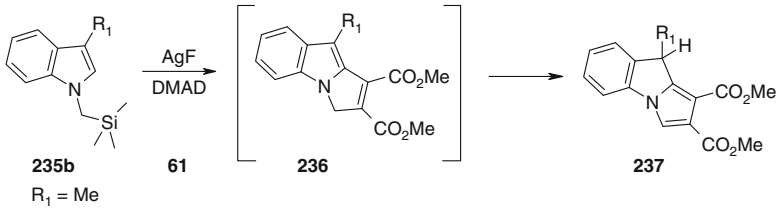
3.3.1 Indole Pyrrole Ring as the Dipole, Azomethine Ylides

While most [3+2] cycloaddition reactions with indoles employ the indole moiety as the dipolarophile component, several reports have also highlighted the utility of indoles as the source of dipoles in 1,3-dipolar cycloaddition reactions. Padwa and coworkers produced early examples in which the indole pyrrole ring acted as an azomethine ylide dipole [94, 95]. Treatment of a silylated indole **235a** with silver fluoride in the presence of a variety of dipolarophiles **236** and **238** afforded the corresponding cycloadducts **237** and **239** in 53% and 83% yield, respectively (Scheme 63).



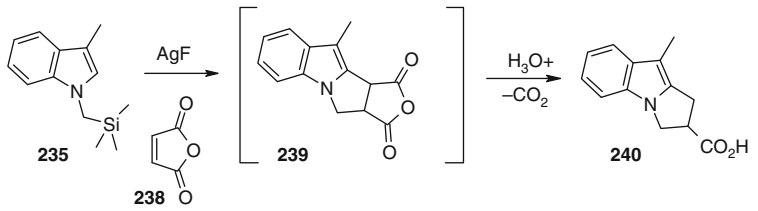
Scheme 63

Interestingly, heating a solution of **235b** with DMAD (**61**) and silver fluoride at 80°C produced pyrrole **237** in 75% yield (Scheme 64). The conversion of **235** to **237** probably proceeds via the intermediacy of the [3+2] cycloadduct **236**, which undergoes a subsequent 1,5-hydrogen shift under the reaction conditions to give **237**.



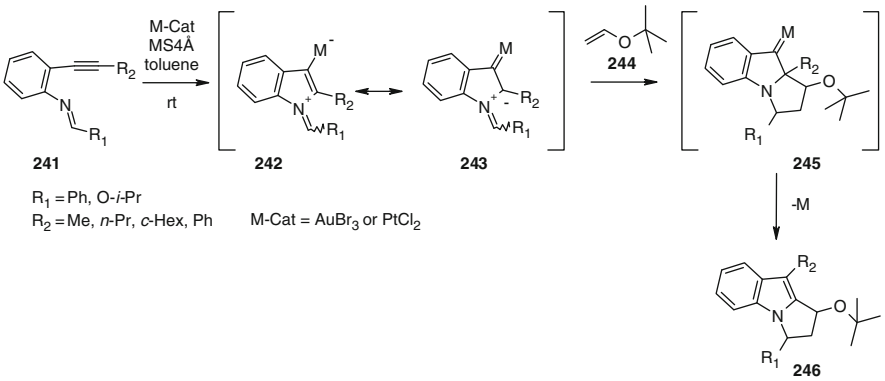
Scheme 64

When a similar cycloaddition was carried out between **235** and maleic anhydride (**238**), the major product isolated corresponded to a carboxylic acid, whose structure was assigned as **240** (Scheme 65). The formation of **240** can be rationalized by the hydrolysis and decarboxylation of the initially produced [3+2] cycloadduct **239**.



Scheme 65

Iwasawa and coworkers [96] have shown that metal-containing azomethine ylides **243**, generated by the treatment of *N*-(*o*-ethynylphenyl)imine derivatives **241** with a catalytic amount of gold or platinum halides under photoirradiation conditions, undergo [3+2] cycloaddition reactions with electron-rich alkenes **244** (Scheme 66). The resulting metal carbene complex intermediates **245** undergo facile 1,2-hydrogen migration to afford the corresponding polycyclic indole derivatives **246** in good yields.

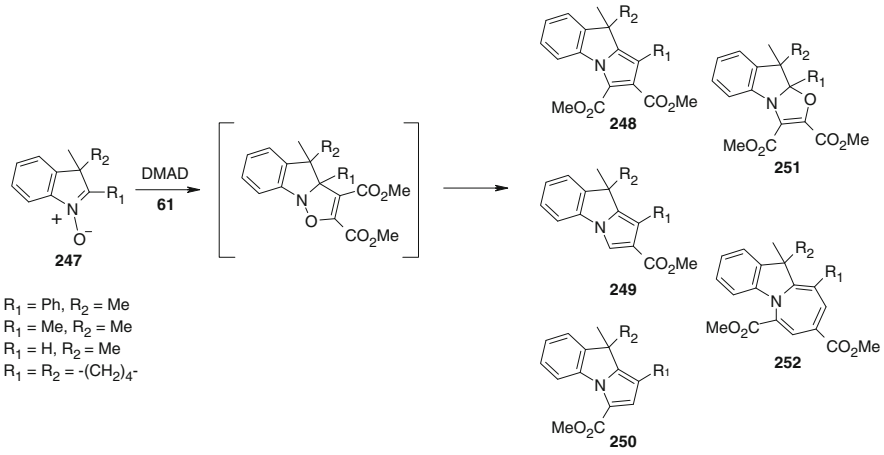


entry	R_1	R_2	catalyst	yield
1	Ph	*n*-Pr	$AuBr_3$	80%
2	Ph	*n*-Pr	$AuBr_3$	81%
3	Ph	Me	$AuBr_3$	81%
4	Ph	*c*-Hex	$AuBr_3$	89%
5	Ph	Ph	$AuBr_3$	62%
6	O-*i*-Pr	*n*-Pr	$AuBr_3$	60%
7	Ph	*n*-Pr	$PtCl_2$	81%
8	Ph	*n*-Pr	$PtCl_2$	89%
9	Ph	*n*-Pr	$PtCl_2$	74%
10	Ph	Me	$PtCl_2$	88%
11	Ph	*c*-Hex	$PtCl_2$	84%
12	Ph	Ph	$PtCl_2$	84%
13	O-*i*-Pr	*n*-Pr	$PtCl_2$	95%

Scheme 66

3.3.2 Indole Pyrrole Ring as the Dipole: *N*-Oxide

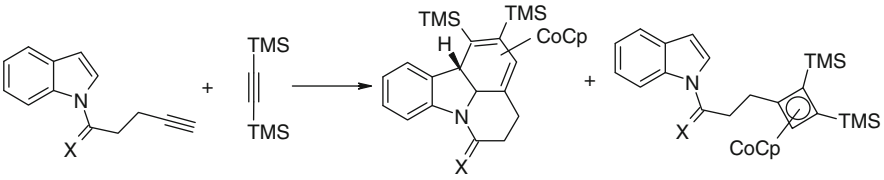
In another example involving the use of indole as a dipole, Letcher and coworkers [97] have shown that indole *N*-oxides **247**, formed by hydride reduction followed by *m*-chloroperbenzoic acid oxidation of the corresponding 3*H* indole derivatives, react with DMAD (**61**) to initially give the [3+2] cycloadducts (Scheme 67). Further rearrangements of these cycloaddition products, depending on the nature of the substituents at the 2 and 3 positions, lead to the formation of either pyrroles **248**–**250**, oxazole **251** or azepine **252** derivatives.



Scheme 67

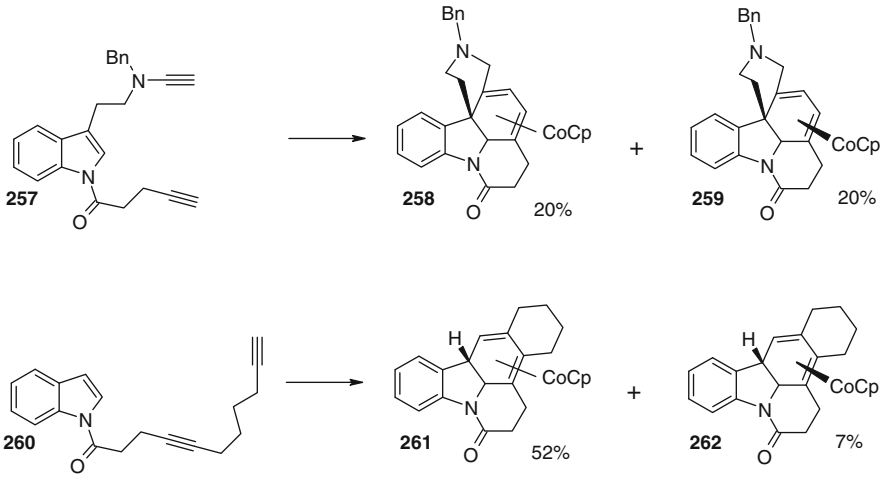
4 [2+2+2] Cycloadditions

Another reaction that has been found particularly useful in the construction of polycyclic indole-containing products involves using the indole 2,3-bond in a cobalt-mediated [2+2+2] cycloaddition reaction. The first report of this type of strategy was made by Vollhardt and coworkers in 1986 [98], in which the substrates for the [2+2+2] cycloadditions contained at least one alkyne tethered to the indole nucleus through the nitrogen atom (both amide linkages **253a** and alkyl spacers **253b** to the indole nitrogen were examined). The second alkyne cocyclization partners were either added as a separate entity (e.g., **254**), or else attached to the substrate via an appropriate spacer group (vide infra). The desired cycloaddition products were obtained in most cases in adequate yields (reactions were unoptimized). The authors observed that nitrogen activation appears to be necessary in order to obtain the desired cycloaddition product **255a**, instead of cyclobutadiene **256a**,**b** formation (Scheme 68).



Scheme 68

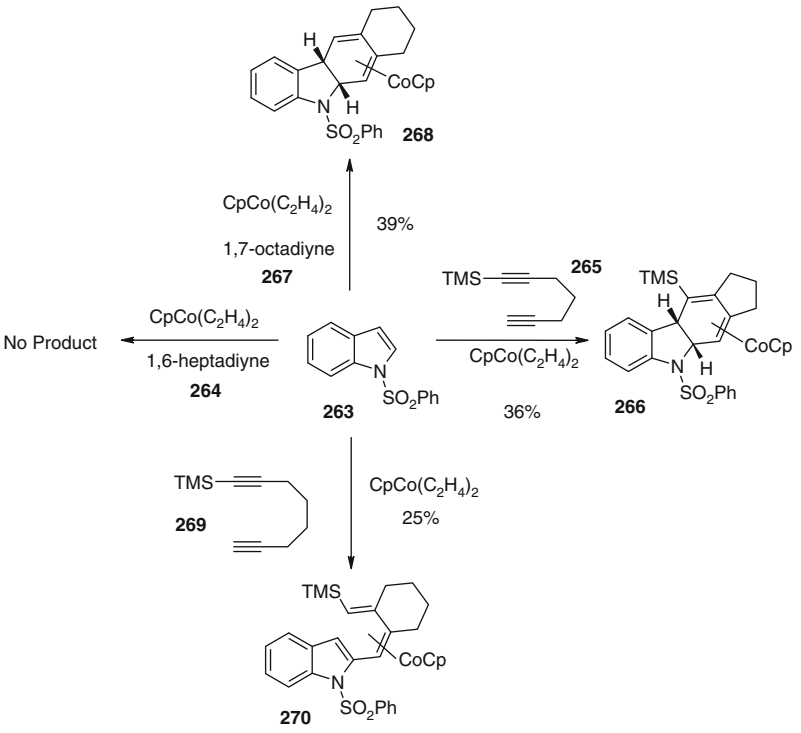
Reactions in which the third cyclization partner is tethered to the indole nucleus either at the 3-position **257** or as a dialkyne unit off the nitrogen atom **260** have also been reported (Scheme 69). It should be noted that the cobalt complexes resulting from these [2+2+2] cycloadditions can be easily demetalated by using $CuCl_2$ or $Fe(NO_3)_3$ to obtain the cobalt-free products in excellent yields. Alternatively, Ce^{4+} may be used to produce the demetalated aromatized carbazole analogs.



Scheme 69

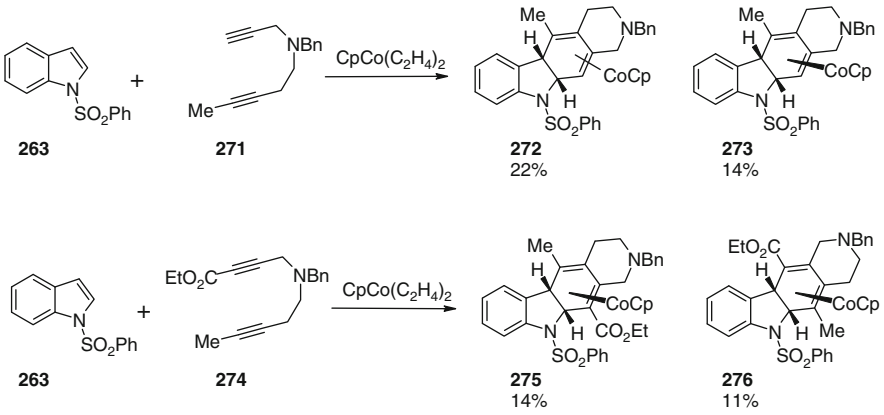
Vollhardt and coworkers further investigated the scope of these [2+2+2] reactions [99]. They explored the intermolecular reactions between simple *N*-substituted indoles and diynes. With these substrates **263**, the $CpCo(CO)_2$ catalyst used above led only to diyne trimers and oligomers, but no desired cycloaddition products. However, the use of $CpCo(C_2H_4)_2$ led to the formation of the desired cycloaddition cobalt complexes in moderate yields. It is interesting to note the difference in reactivity observed for **263** when treated with unsubstituted and trimethylsilyl-substituted diynes (Scheme 70). While the use of unsubstituted 1,6-heptadiyne (**264**) failed to produce the desired cycloaddition product, the cycloaddition with 1-trimethylsilyl-1,6-heptadiyne (**265**) resulted in the formation of a single regioisomeric product **266** in 36% yield. In contrast, the reaction of 1,7-octadiyne (**267**) with **263** produced

the cobalt cycloaddition complex **268**, whereas the reaction of **263** with 1-trimethylsilyl-1,7-octadiyne (**269**) resulted in the noncyclized cobalt complex **270**. The authors noted that they were at a loss to explain this divergent behavior.



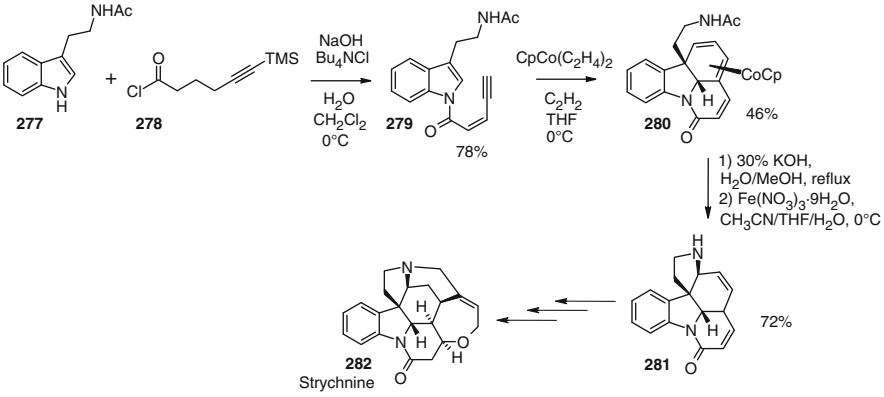
Scheme 70

From the above results, it appears that the favored regioselectivity for the cyclizations places the larger group on the diyne terminus (i.e., the trimethyl silly (TMS) group in **265** and **269**) at the site further from the *N*-phenylsulfonyl moiety (i.e., **266** and **270**). Additional investigation of the regiochemical preferences for the [2+2+2] cycloadditions was carried out using bisalkynylamines, with an eye towards the future application of this chemistry to make ellipticine (Scheme 71). Thus, **263** was found to react with diyne **271** to form the *anti* (**272**) and *syn* (**273**) cobalt complexes in roughly a 2:1 ratio. Both complexes exhibit the same regiochemical preference, with the methyl group positioned away from the *N*-phenylsulfonyl moiety. In a case where both termini of the diyne were substituted **274**, the *syn* cobalt complexes formed (**275** and **276**) offer no evidence for an electronic control of the regiochemical outcome, as **275** and **276** were isolated in a 1:1 ratio. Unfortunately, attempted cycloadditions with other differentially substituted diynes, where the ester group in **274** was replaced with TMS, $CH(OEt)_2$ or hydroxymethyl moieties, either did not yield any cycloaddition products, or in the case of the latter led to a complex mixture of at least eight cobalt complexes.



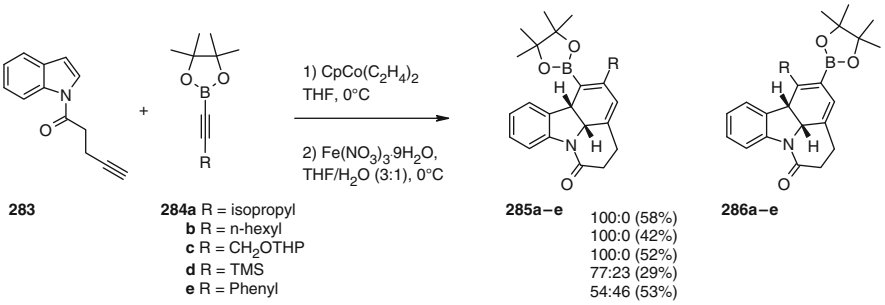
Scheme 71

Vollhardt and coworkers were able to successfully apply the [2+2+2] cycloaddition chemistry to their elegant synthesis of (±)-strychnine (**282**) [100]. In a later paper, Vollhardt describes in detail the different routes that were envisioned for the application of [2+2+2] cycloaddition chemistry to the synthesis of (±)-strychnine, and the obstacles encountered, as well as some of the limitations to the cycloaddition chemistry [101]. The successful strategy provided a short, convergent synthesis of (±)-strychnine in 14 steps (longest linear sequence). The key transformation involved the construction of the tetracyclic core structure of (±)-strychnine via the cobalt-mediated [2+2+2] cycloaddition of a functionalized tryptamine derivative **279** and acetylene gas (Scheme 72). The resulting cobalt complex **280** was carried through the deacetylation step, using the cobalt cyclopentadienyl moiety as a protecting group. Subsequent demetalation using iron (III) then resulted in the closure of the pyrrolidine ring, via a [1, 8]-conjugate addition of the amine into the conjugated lactam system, to produce the pentacyclic intermediate **281**. This intermediate was then further elaborated to complete the synthesis of (±)-strychnine (**282**).



Scheme 72

In more recent studies, Vollhardt and coworkers have begun to examine the use of boron-substituted alkynes **284a–e** in [2+2+2] cycloaddition reactions in order to produce fused cyclic borylated cyclohexadienes **285a–e**, **286a–e**. These products would in turn be useful as building blocks for the rapid construction of complex ring systems [102]. A one-pot procedure was established in which the cobalt-mediated cycloadditions were immediately followed by oxidative work up, in order to provide the stable borylated products **285a–e**, **286a–e** (Scheme 73). The reaction yields were so far unoptimized. However, the authors believe that with appropriate "fine tuning" of reaction conditions the yields can be improved. It is interesting to note the regiochemical preference in these reactions, which placed the boryl group at the terminus of the diene unit of the cyclization products (**284a–c** leading exclusively to **285a–c**), unless there were competing bulky substituents present at the other terminus of the acetylene (such as in **284d** and **284e**).



Scheme 73

5 Conclusion

This review has demonstrated that indole derivatives can participate in [2+2], [3+2], and [2+2+2] cycloaddition reactions with a wide variety of reaction partners to give an astonishing array of polycyclic frameworks. While in many cases these novel ring structures are curiosities with no current utility, several research groups have employed these reactions as key steps in complex natural product syntheses. Not surprisingly, the 2,3-bond of the indole nucleus is the primary site in the majority of these reactions; however, notable exceptions exist which provide unique structures that would be difficult to obtain using other methodologies.

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[4+2] Cycloaddition Reactions of Indole Derivatives

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Abstract A review with 141 references on [4+2] cycloaddition reactions involving the indole nucleus.

Keywords [4+2] Cycloaddition · Diels–Alder reaction · Indole

Contents

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1 Introduction

[4+2] Cycloadditions, in particular Diels–Alder reactions, have proven to be extremely powerful methods for the efficient construction of complex polycyclic derivatives [1–8]. The indole moiety, with its ability to serve as both a diene and a dienophile, thus provides an ideal starting point for the assembly of a variety of alkaloid natural products. With the electron-rich nature of the indole 2,3-bond, indoles are particularly suited as dienophiles for inverse electron demand Diels–Alder reactions. Various vinylindole derivatives, on the other hand, have been proven to be excellent dienes for [4+2] cycloadditions.

In this chapter, we have attempted to comprehensively review [4+2] cycloadditions of indoles, in which the indole nucleus serves as either the diene or the dienophile component. In most cases, the discussion will be limited to the cycloaddition reaction itself, and the reader is encouraged to consult the cited references for further details regarding the preparation of starting materials, as well as further manipulations of the cycloadducts. Wherever the cycloaddition was highlighted as a key strategic step in a complex natural product synthesis, some discussion on how the cycloadduct was further elaborated has been included. While we have chosen to focus on reports published after 1990, occasional older precedents may be discussed or cited. In cases of subtopics for which a major review had been

published after 1990, the coverage in this chapter was limited to newer material and/or material not covered in the earlier review.

2 Indoles as Dienophiles in [4+2] Cycloaddition Reactions

Indoles have been used in a variety of capacities in Diels–Alder type [4+2] cycloaddition reactions. Most often, the indole ring or a derivative thereof has been incorporated as part of the diene moiety. However, there are also several examples reported in which the indole ring, in particular the 2,3-bond, served as the dienophile component in the cycloaddition reactions. Due to the electron-rich nature of the indole 2,3-bond, its most widely reported synthetic applications as a dienophile are in inverse electron demand Diels–Alder (IDA) reactions. Nevertheless, a few reports on "normal electron demand" Diels–Alder cycloadditions of the indole 2,3-bond have also appeared in the more recent literature.

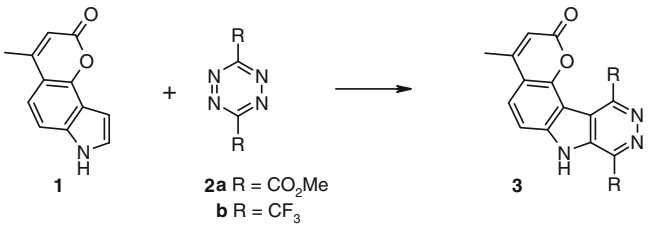
Snyder and Lee [9] were the last to comprehensively review the role of indoles as dienophiles in IDA and related reactions. In this chapter, we will mainly focus on the reports that have appeared in the literature since the above article appeared in press.

2.1 Inverse Electron Demand Diels–Alder Reactions with Azadienes

A variety of azadienes have been shown to participate in inverse electron demand Diels–Alder cycloadditions [10, 11]. A few examples of such reactions with indoles as the dienophiles have been recently reported.

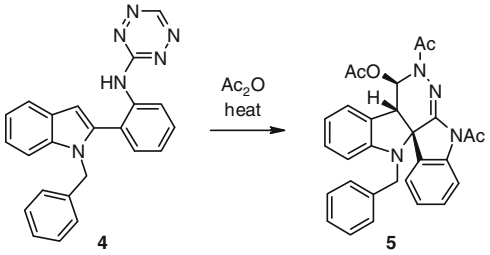
Tetrazines have been frequently used as electron-deficient dienes in IDA reactions with electron-rich dienophiles [12]. Uriarte and coworkers [13] reported the reaction of the pyrrolocoumarin **1** with 2 equivalent of either dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**2a**) or 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**2b**), followed by the release of nitrogen and aromatization, to produce the corresponding pyridazinepyrrolocoumarins **3** (Scheme 1).

An intramolecular variant of the above reaction was reported by Joule and coworkers [14] who synthesized a pentaheterocyclic structure **5** containing a



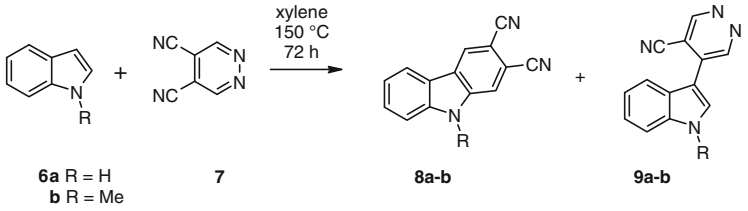
Scheme 1

synthetically challenging quaternary C-2 center in the 2,3-dihydroindole portion of the structure (Scheme 2).



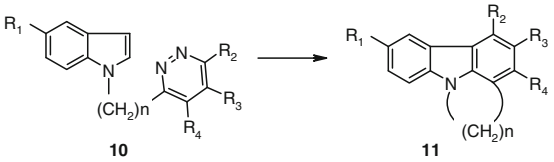
Scheme 2

4,5-Dicyanopyridazine (DCP, **7**) has also been shown to be an effective electron-deficient diene for IDA reactions. Giomi and Cecchi [15] prepared the bis-cyano-carbazole derivatives **8a–b** upon heating DCP with 2 equivalent of indole (**6a**) or 1-methyl-1*H*-indole (**6b**) in xylene. Minor products resulting from the S_NAr2 reactions on the C4-carbon of DCP were also isolated (**9a–b**). Switching the solvent system from xylene to chloroform or other efforts to improve the yields of the desired carbazoles were unsuccessful (Scheme 3).



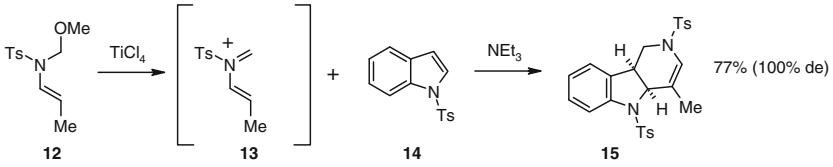
Scheme 3

In another example of intramolecular IDA reactions, a series of indolylalkylpyridazines **10** were synthesized and subjected to high temperatures in 1,3,5-triisopropylbenzene (b.p. = 232°C) for long periods (15 h to 14 days) to produce the desired carbazole derivatives **11** [16] (Scheme 4). In general, the electron-poor pyridazines (**10**, e.g., $R_3 = R_4 = CO_2Et$) provided the best yields, while unactivated pyridazines performed poorly. Trisubstituted pyridazines (**10** $R_2 = H$) reacted faster and provided the carbazole products in higher yields than the corresponding tetrasubstituted pyridazine derivatives (**10** R_2 other than H).



Scheme 4

Cationic 2-azadienes have also proven to be good diene partners in IDA cycloaddition reactions [17]. As an example, the reaction of *N*-tosyl indole (**14**) with the *N*-alkenyl iminium species **13** (generated *in situ* from the corresponding *N*-alkoxymethyl enamine derivative **12**), followed by deprotonation, produced the tricyclic indole product **15** with excellent stereochemical control (Scheme 5). The choice of tosyl group for indole protection proved crucial, as *N*-tosyl indole (**14**) is electron-rich enough to effect the [4+2] cycloaddition reaction but lacks the nucleophilicity to add to the resulting cycloadduct intermediate [18].

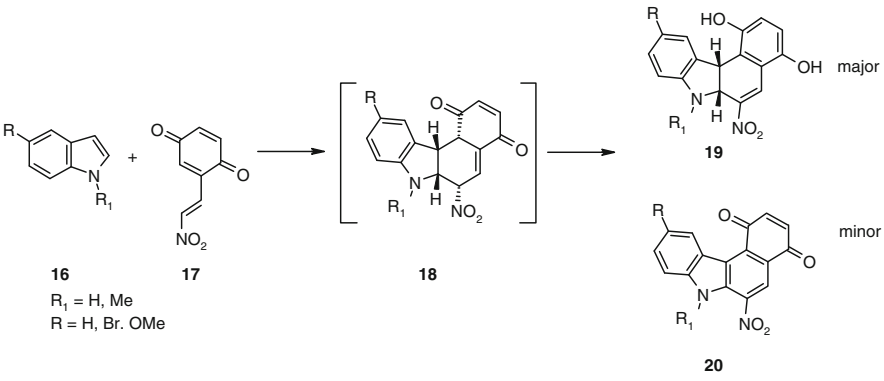


Scheme 5

2.2 *Inverse Electron Demand Diels–Alder Reactions with Other Dienes*

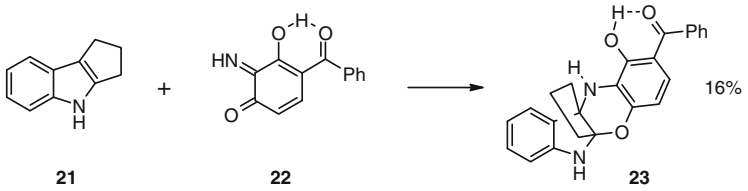
Quinones are widely used dienes in IDA reactions. It is therefore no surprise that a few reports have appeared in the literature which use the IDA cycloadditions of indoles with quinones to form novel heterocycles.

2-Nitrovinyl-substituted quinone derivatives **17** react regioselectively with indoles **16** to form the bis-phenol products **19** upon tautomerization of the cycloadducts **18**, where the most electron-deficient part of the diene (C-3) forms a bond with the most electron-rich (C-3) carbon atom of the indole (Scheme 6). In some cases, the oxidation products of the bis-phenols (i.e., quinones **20**) were also isolated as minor products [19].



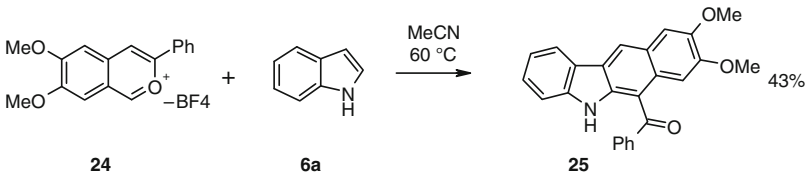
Scheme 6

Azaquinones have also been used as partners in IDA cycloadditions with indoles. In an interesting example, the reaction of commercially available 2,3-dihydro-1*H*-cyclopent[b]indole (**21**) with an electrogenerated *o*-azaquinone **22** produced the indolobenzoxazine product **23** in low yield (Scheme 7) [20].



Scheme 7

Air- and moisture-stable isochromenylium salts, such as the tetrafluoroborate salt **24** shown below, have also been reported as IDA cycloaddition partners for indoles. Thus, the [4+2] cycloaddition of **24** with indole (**6a**), followed by the ring opening of the resulting oxonium intermediate, produced the multiring naphthalene derivative **25** (Scheme 8) [21].



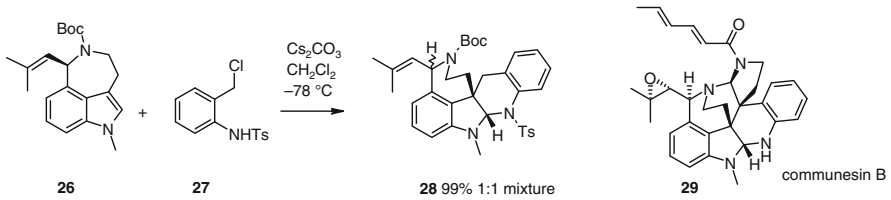
Scheme 8

2.3 *Inverse Electron Demand Diels–Alder Reactions in the Synthesis of Natural Products*

Indole and dihydroindole moieties are prevalent structural features in a variety of biologically interesting and synthetically challenging natural product molecules. A number of approaches to the preparation of indole-containing natural products have relied on the IDA cycloadditions of indoles as a key synthetic step. In particular, the IDA reaction has been especially fruitful in providing access to the key structural skeleton of the communesin family, a series of structurally interesting and biologically active *Penicillium* metabolites.

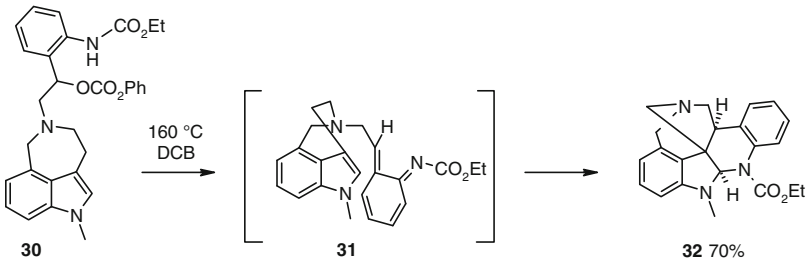
In a biomimetic approach toward the synthesis of communesin B (**29**), Stoltz and coworkers [22] described the IDA reaction of a polycyclic indole derivative **26** and a quinone methide imine formed *in situ* utilizing conditions previously reported by Corey (Scheme 9) [23].

An elegant application of the *intramolecular* IDA cycloaddition of an indole derivative with an *in situ* generated *ortho* quinone methide imine (conversion of **30**



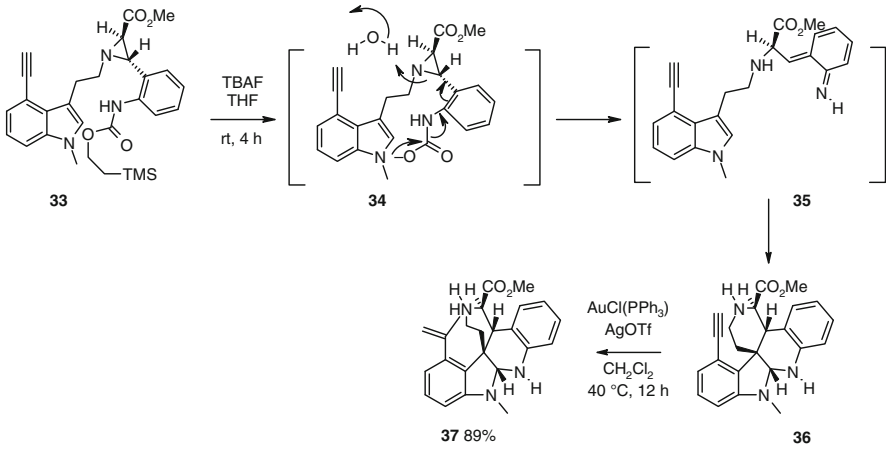
Scheme 9

to **31**) has been used by Funk and Crawley for the synthesis of a key structure bearing the hexacyclic core ring system of communesin B (i.e., compound **32,** Scheme 10) [24]. Further elaboration of this hexacyclic structure to complete the total synthesis proved difficult, however.



Scheme 10

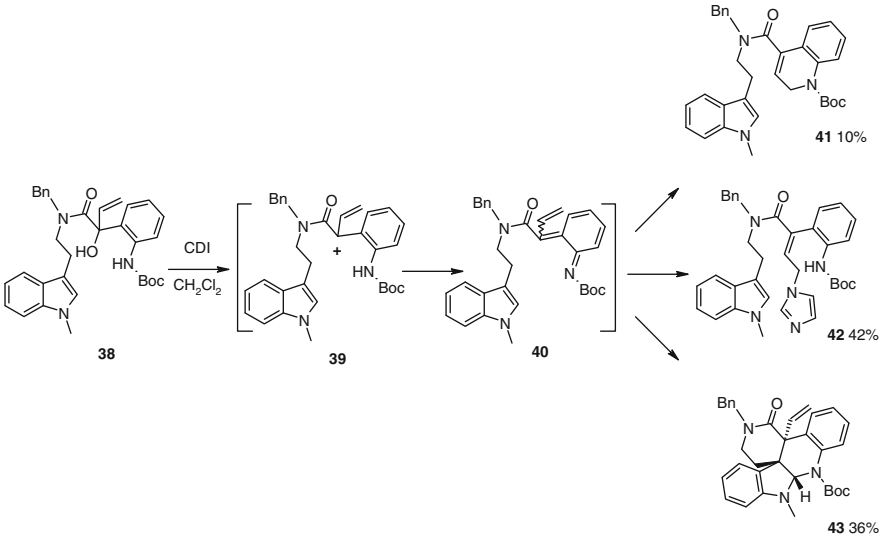
In a revised strategy toward the synthesis of the communesin family of natural products, Funk and Crawley [25] next investigated the in situ generation of a different aza-*ortho*-xylylene intermediate (**35**) from the fluoride-promoted decarboxylative ring opening of an appropriately substituted *ortho*-amino-phenylaziridine **33** (Scheme 11). The intramolecular IDA cycloaddition reaction of the above generated



Scheme 11

aza-*ortho*-xylylene in **35** with the *N*-methyl-indole moiety provided the acetylene-substituted pentacyclic intermediate **36**, which was immediately converted to the key enamine precursor **37** via a gold-catalyzed 7-*exo*-dig ring closure.

In another approach to the preparation of communesins, Adlington and George [26] also utilized what is believed to be an intramolecular IDA cycloaddition reaction of an aza-*ortho*-xylylene with an *N*-methyl-indole (compound **40**) as a key synthetic step, this time producing a pentacyclic structure **43** which contains both of the vicinal quaternary centers present in the communesin scaffold, albeit in modest yield (Scheme 12). Two additional side products **41** and **42** (possibly resulting from an electrocyclic reaction involving the vinyl group, or attack by imidazole on the terminal alkene) were also isolated. It should be noted that an alternative mechanism for the formation of the three products, which involves an allylic carbocation species (**39**), can also be postulated.



Scheme 12

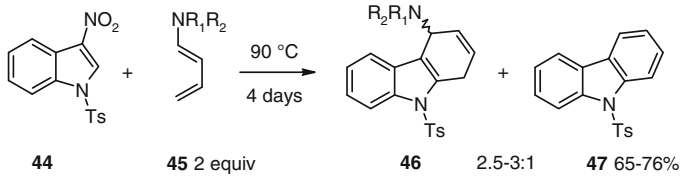
In their synthesis of (±)-perophoramidine, Funk and Fuchs [27] use the base-mediated reaction of a 3-siloxyalkyl-substituted indole with a 3-bromoindolin-2-one to produce an indolenine derivative as a key step. The formation and subsequent IDA cycloaddition of an indole-2-one derivative followed by ring opening of the cycloadduct is proposed as one possible mechanism for the above reaction. A similar approach was also used by Dalko and coworkers in the total synthesis of the bis-pyrroloindoline alkaloid (±)-N_b-desmethyl-*meso*-chimonanthine [28].

2.4 *Indoles as Dienophiles in "Normal" Electron Demand Diels–Alder Reactions*

An interesting feature of indoles is the ability to fine-tune the electronics of the ring systems, especially the 2,3 carbon–carbon double bond. While the 2,3-bond is ideally suited for IDA reactions due to its electron-rich nature, it can also be used as a dienophile in normal electron demand Diels–Alder reactions by simply placing one or more electron-withdrawing groups at appropriate position(s).

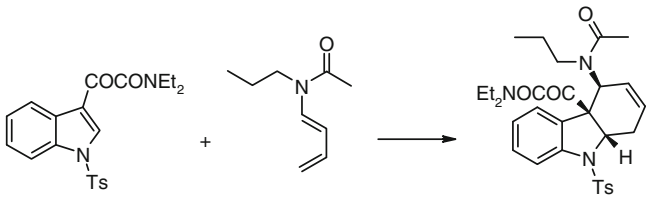
2.4.1 Recent Studies on the Scope and Limitations of the Use of Indole 2,3-Double Bond in Normal Electron Demand Diels–Alder Reactions

N-sulfonylindoles bearing a nitro group at the C-3 position have been used as dienophiles in normal electron demand Diels–Alder reactions. For example, Mancini and coworkers examined the cycloaddition reactions of *N*-tosyl-3-nitroindole (**44**) with *N*-acyl-*N*-alkylamino-1,3-butadienes **45** [29]. The Diels–Alder reactions, followed by extrusion of nitrous acid, produced the *N*-tosyldihydrocarbazoles **46**, which then partially underwent thermal aromatization with the loss of the amine substitution to the carbazole derivatives **47** (Scheme 13).



Scheme 13

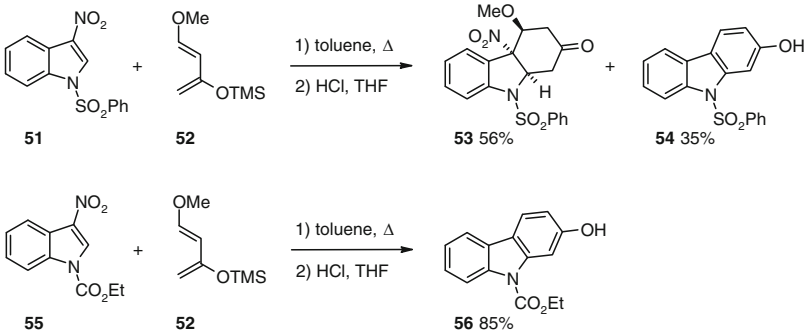
The above authors further reported the advantages of using high pressure conditions for the Diels–Alder reaction of an indoleglyoxamide derivative **48** and a dieanamide **49** [30]. While thermal conditions (120°C, 96 h) led to the formation of two diastereomeric adducts in <10% yield, the use of hyperbaric conditions (11.5 kbar, 40°C, 48 h) resulted in a 50% yield of the single *exo* adduct **50** (Scheme 14). It was noted that the high temperatures required for the thermal



Scheme 14

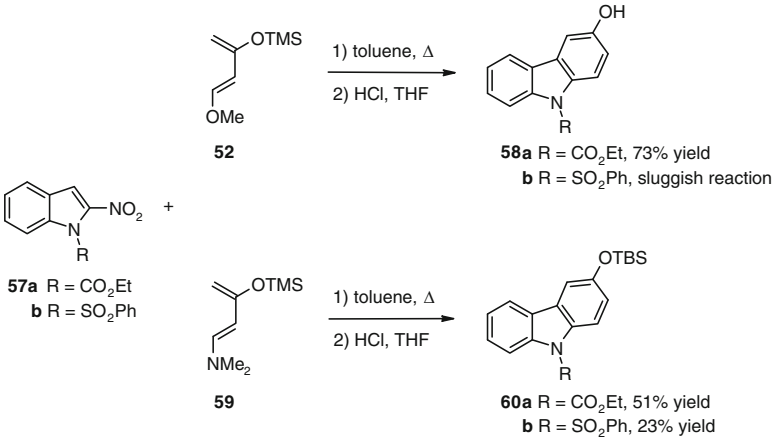
Diels–Alder conditions may result in the decomposition of the diene, and thus account for the low yield under thermal conditions.

Gribble and Kishbaugh [31] also reported the Diels–Alder reactions of phenylsulfonyl- (i.e., **51**) or ethoxycarbonyl-protected 3-nitroindole derivatives (i.e., **55**) with Danishefsky's diene (**52**) (Scheme 15). While the cycloaddition reaction with the sulfonyl-protected indole resulted in a mixture of the *exo* Diels–Alder adduct **53** and the carbazole product **54** (resulting from a subsequent acid hydrolysis of **53**), the corresponding reaction with the ethoxycarbonyl-protected indole produced solely the 2-hydroxycarbazole derivative **56** in high yield.



Scheme 15

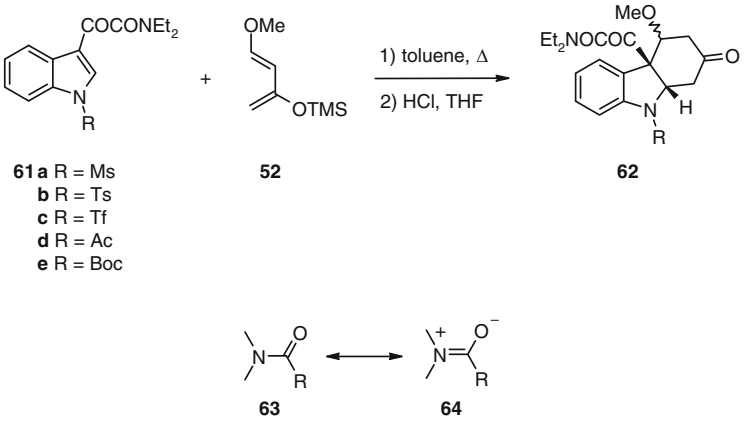
Similarly, the ethoxycarbonyl-protected 2-nitroindole derivative **57a** also participated in Diels–Alder reactions with Danishefsky's diene (**52**), as well as Rawal's diene (**59**), to produce the 3-hydroxycarbazole products **58a** and **60a** in synthetically useful yields (Scheme 16). However, the sulfonyl-protected analog **57b** did



Scheme 16

not perform as well in comparable reactions. Only in the case of Rawal's diene, a low yield of the 3-hydroxycarbazole derivative **60b** was isolated.

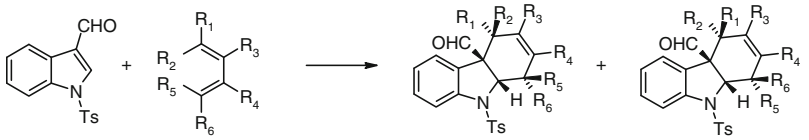
Piettre and coworkers have examined the effects of various electron-withdrawing groups (containing a sulfonyl or carbonyl moiety) as substituents on the indole nitrogen on Diels–Alder reactions with Danishefsky's diene (**52**) [32] (Scheme 17). Interestingly, they found that while the conversion rates for the sulfonyl-containing compounds **61a–c** to the Diels–Alder adducts corresponded well with the electronegativities of the sulfonyl groups (Tf > Ts > Ms), none of these derivatives were as efficient in [4+2] cycloaddition reactions as the corresponding carbonyl-containing acetyl- (**6d**) or *tert*-butoxycarbonyl (Boc)-protected (**6e**) indoles. This interesting observation could be explained by the greater ability of *N*-acetyl or *N*-Boc derivatives to delocalize electrons (and thus impart partial double bond character to the N–C bond) when compared with the *N*-sulfonyl analogs (**63**↔**64**).



Scheme 17

As previously noted, the typical high temperatures and long reaction times required for the normal electron demand Diels–Alder reactions with electron-poor indoles have rendered such approaches less attractive for the synthesis of more sensitive and highly functionalized substrates in total synthesis. Recently, there have been a few reports on attempts to accelerate these cycloaddition processes. For example, Piettre and coworkers investigated the activation of the dienophilic indoles under high pressure [33]. Thermal Diels–Alder reactions of *N*-tosyl-indole-3-carboxaldehyde (**65**) with dienes **66a** and **66b** (195°C, sealed tube, 72 h) resulted in conversions of 67% and 25%, respectively (Scheme 18). By increasing the pressure for the above reactions to 16 kbar (48 h, 50°C), the corresponding cycloadditions with dienes **66a** and **66b** resulted in conversions of 93% and 86%, respectively.

Furthermore, the addition of 0.1 equivalent of $ZnCl_2$ proved highly beneficial for the above reactions. In the case of the dienophile **66a**, carrying out the



65 **66a** $R_1 = R_2 = R_5 = R_6 = H$, $R_3 = R_4 = CH_3$ **67** **68**

b $R_1 = R_3 = R_4 = R_6 = H$, $R_2, R_5 = (CH_2)_2$-

c $R_2 = R_3 = R_5 = R_6 = H$, $R_1 = OMe$, $R_4 = OTMS$

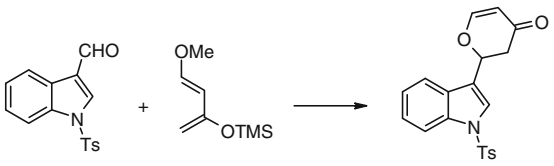
entry	66	temp °C	time (h)	pressure (kbar)	Lewis Acid	conversion (%)	yield 67 + 68	ratio 67/68
1	a	200	72			67	60	
2	a	200	216			85	71	
3	a	60	96	12		65	nd	
4	a	50	48	16		93	46	
5	a	25	24	16	$ZnCl_2$	96	46	
6	b	195	72			25	25	80:20
7	b	45	144	12		30	nd	93:7
8	b	50	48	16		86	50	96:4
9	b	70	120		$ZnCl_2$	61	48	96:4
10	b	25	48	16	$ZnCl_2$	100	62	>98:2
11	c	195	72			100	57*	75:25
12	c	45	96	12		100	92*	80:20
13	c	25	24	16	$ZnCl_2$	100	dec	

*Isolated in the form of the ketone resulting from hydrolysis of the silyl enol ether group

Scheme 18

cycloaddition with **65** in the presence of 0.1 equivalent of $ZnCl_2$ at 16 kbar for only 24 h, and at the reduced temperature of 25°C, resulted in 96% conversion. When **65** was treated with cyclohexadiene (**66b**) in the presence of 0.1 equivalent of $ZnCl_2$ (48 h at 25°C, 16 kbar), quantitative conversion was observed. The above report also briefly examined the impact of high pressure and Lewis acid catalysis on the stereochemical outcome of the Diels–Alder reactions. In the case of cyclohexadiene (**66b**), the thermal reaction resulted in a 4:1 mixture of *endo* (**67b**) and *exo* (**68b**) cycloadducts. This ratio was increased to 93:7 at a pressure of 12 kbar and to 96:4 at 16 kbar. Addition of $ZnCl_2$ at high pressure provided virtually clean *endo* isomer **67b** (>98:2), and the *exo* isomer **68b** was not detectable by ^1H NMR.

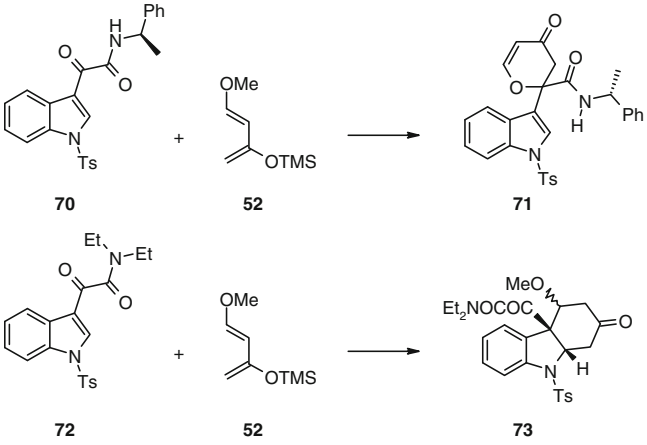
Interestingly, when the same indole-3-carboxaldehyde derivative **65** is subjected to Diels–Alder reactions with Danishefsky's diene (**52**), either under thermal or hyperbaric activation, it is the aldehyde and *not* the indole carbon–carbon double bond that serves as the dienophilic component (Scheme 19) [34]. The hetero-Diels–Alder reaction with the carboxaldehyde proceeded at quantitative conversion (82% yield) under thermal conditions (12 equiv Danishefsky's diene, 170°C, 24 h) and provided the cycloadduct **69** in quantitative yield under hyperbaric conditions (12 equiv Danishefsky's diene, 45°C, 96 h, 12 kbar).



65 52 69

Scheme 19

Indole-3-ketoamides **70** are especially interesting when involved in Diels–Alder reactions with Danishefsky's diene (**52**). The site of dienophilicity for these compounds appears to be dependent on the number of the substituents as well as the nature of the substituents on the acyclic nitrogen atom. While mono *N*-substituted ketoamides almost exclusively undergo hetero-Diels–Alder reactions with the keto moiety serving as the dienophile, a reversal of site selectivity (i.e., the indole 2,3-bond serving as the dienophile) is observed when *N*, *N*-disubstituted analogs are chosen as cycloaddition partners [34]. For example, with the mono-substituted ketoamide **70**, the Diels–Alder reaction with Danishefsky's diene (**52**) (12 kbar, 25°C, 36 h) provided the heterocycloadduct products **71** in 92% yield (Scheme 20) as a 2:1 mixture of *endo*/*exo* cycloadducts. In contrast, the reaction of the *N*, *N*-diethyl derivative **72** and Danishefsky's diene (catalytic EuFOD, 12 kbar, 25°C, 38 h) proceeded exclusively with the indole 2,3-double bond acting as the dienophile to afford a 4:1 mixture of *endo*/*exo* cycloadducts **73** in 99% yield.



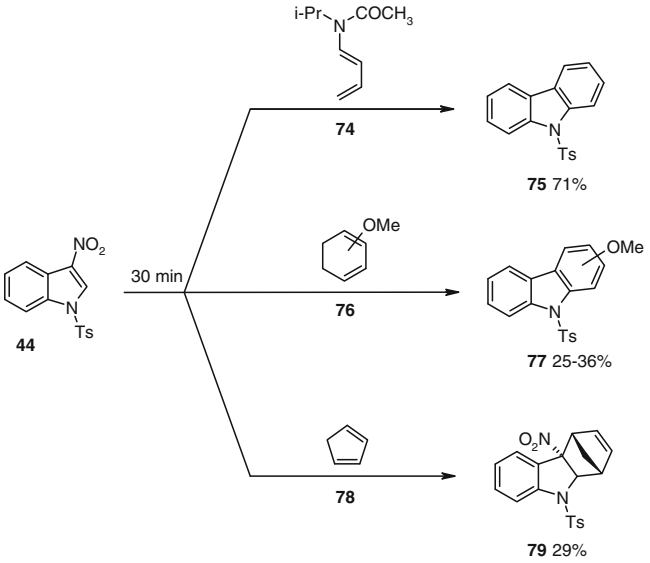
70 52 71

72 52 73

Scheme 20

Based on the above reports, hyperbaric conditions and Lewis acid catalysis are both helpful in reducing reaction times for difficult normal electron demand Diels–Alder reactions with indoles as dienophiles. Microwave-assisted Diels–Alder reactions have also been reported, where reaction times have been cut down to less than 1 h [35].

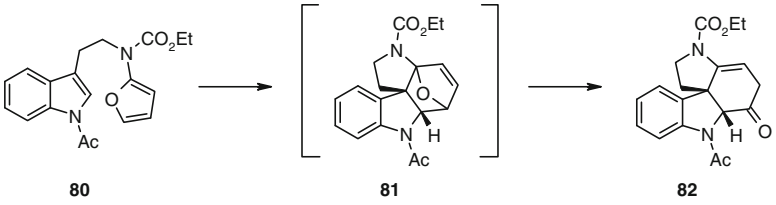
Using a 12:1 diene: indole ratio and a 50 W microwave at 100°C, a variety of reactions between *N*-tosyl-3-nitroindole (**44**) and several dienes were performed at much shorter times (Scheme 21) (30–45 min). It is noteworthy that the reaction with cyclopentadiene (**78**) did not occur at all under conventional heating conditions.



Scheme 21

2.4.2 Applications of the Normal Electron Demand Diels–Alder Reactions of the Indole 2,3-Double Bond in Total Synthesis

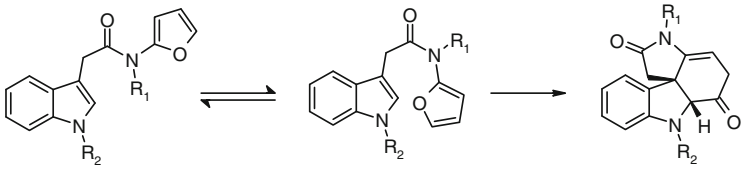
The use of intramolecular Diels–Alder reactions which use the 2,3-double bond of the indole system as a dienophile appears ideally suited for the synthesis of *Aspidosperma* and *Strychnos* alkaloid core structures. In an early example of this approach, Padwa and coworkers [36] first explored the intramolecular cyclization/rearrangement cascade reaction of the amidofuran derivative **80** as an entry to the tetracyclic core of the *Strychnos* alkaloids (Scheme 22). After heating **80** at 240°C



Scheme 22

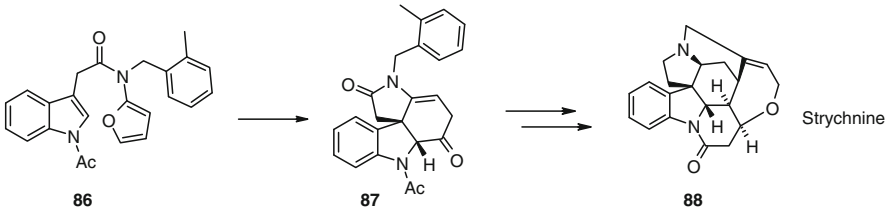
for 18 h, the desired Diels–Alder product **82** was isolated in 30% yield (62% based on recovered starting material).

To improve the cyclization yield in the above reaction, the aminoethyl linker between the furan and indole moieties was modified to contain a secondary amide, which would allow a higher population of the reactive *s*-trans conformation, placing the furan ring in closer proximity to the indole π-bond. Thus, treatment of **83a** and **83b** at 200°C for only 2 h resulted in the formation of the corresponding tetracyclic adducts **85a** and **85b** in 77% and 91% yields, respectively (Scheme 23). More importantly, the iodine-containing derivative **83c**, which possesses a "handle" to allow further elaboration of the final ring, produced the corresponding tetracyclic product **85c** in 74% yield, after only 1.5 h at 200°C.



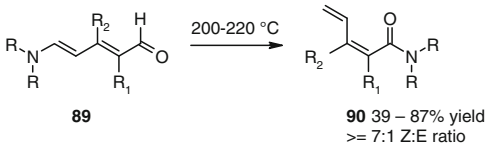
Scheme 23

A similar strategy was used in Padwa's synthesis of (±)-Strychnine (**88**) [37], along with other members of the *Strychnos* alkaloid family [38]. Thus, heating the amidofuran derivative **86** in the presence of catalytic MgI_2 in a microwave reactor (toluene, 150°C, 30 min) afforded the key tetracyclic intermediate **87** in 95% yield (Scheme 24). This intermediate was then used as the main precursor for (±)-Strychnine, (±)-Strychnopivotine, (±)-Tubifolidine, and (±)-Valparicine [38].



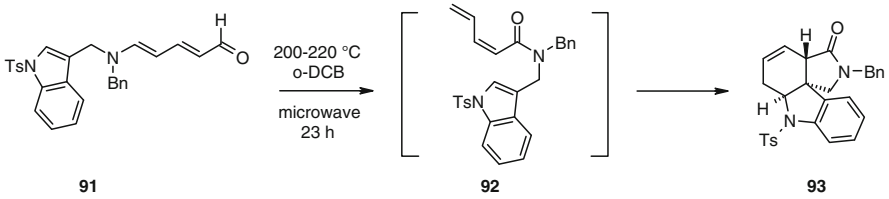
Scheme 24

Vanderwal and coworkers [39] have recently reported an interesting method for the synthesis of polycyclic lactams from the pericyclic cascade reactions of Zincke aldehyde derivatives (5-amino-2,4-pentadienals). Under thermal conditions, Zincke aldehydes **89** are converted to Z-α,β,γ,δ-unsaturated amides **90** via a cascade of pericyclic rearrangements [40] (Scheme 25).



Scheme 25

Starting with an indole-containing Zincke aldehyde substrate **91**, the above authors [39] were able to effect a similar pericyclic rearrangement, followed by an intramolecular cycloaddition reaction of the resulting diene-amide **92**, thus accessing a tetracyclic product **93** which could possibly serve as a key precursor in the synthesis of indole alkaloid analogs (Scheme 26).

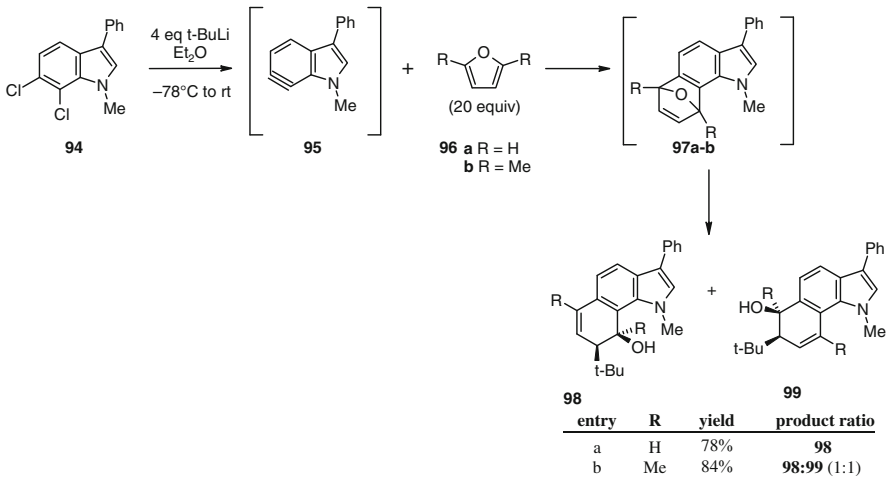


Scheme 26

2.5 Cycloadditions Involving Indole Aryne Derivatives or Double Bonds in the Benzoid Portion of the Indole

The majority of cycloaddition reactions which involve indoles as dienophiles occur using the 2,3-bond in some manner (IDA or normal electron demand Diels–Alder reactions). However, cycloaddition reactions on the benzoid portion of the indole nucleus have also been explored. These reactions, which mainly involve the use of an aryne species as the dienophile component, will be reviewed below. On the other hand, the use of 4,7-indoloquinone species in which the 5,6-bond may act as a dienophile [41–50], or reactions involving other similarly oxidized systems as dienophiles [51, 52], will not be further discussed.

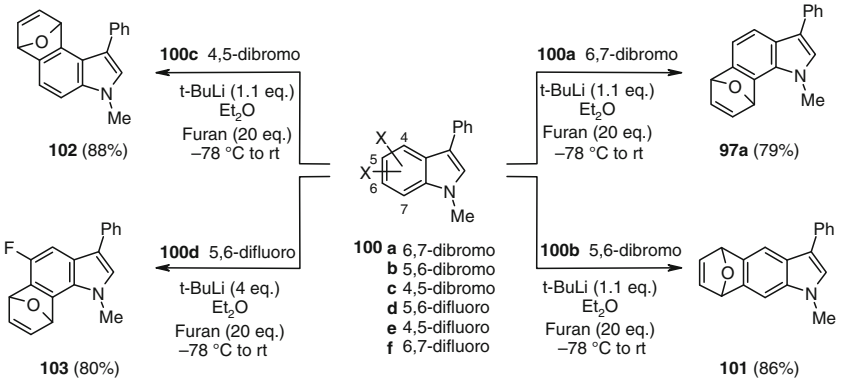
While aryne systems have been known for many years, the use of indole arynes had not been reported until Buszek's recent publications in which the indole aryne Diels–Alder reactions were explored as an attractive route into such natural product targets as teleocidins, trikentrins and herbindoles. Buszek's original work [53] investigated the formation of the indole arynes from 4,5-, 5,6-, and 6,7-dihaloindoles and their subsequent trapping with furan derivatives. The initial reaction (Scheme 27), in which the dichloro indole **94** was treated with excess *t*-butyllithium in the presence of furan (**96a**), produced a single regioisomeric product, namely the alcohol **98**. It is believed that this product arises from trapping the aryne species



Scheme 27

(**95**) generated *in situ* with furan, followed by a subsequent S_N2' nucleophilic attack from the excess *t*-butyllithium on the cycloadduct **97a**.

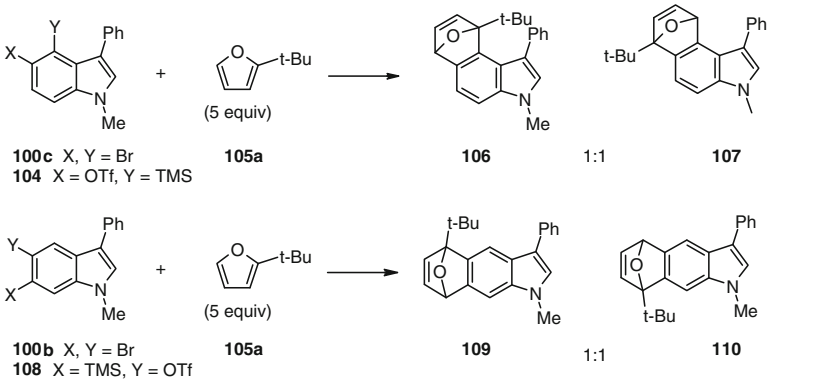
Interestingly, when the number of equivalents of *t*-butyllithium was reduced from 4.0 to 1.1, all three benzyne-furan cycloadducts (i.e., **97a**, **102**, and **103**) resulting from the three possible dibromoindole starting materials (**100a–c**) were isolated in excellent yields (Scheme 28). It is noteworthy that while the *ortho* dichloro- and dibromo-substituted indoles (**94**, **100a–c**) resulted in clean formation of the aryne species, the *ortho* difluoro derivatives **100d–f** did not behave in the same way. The attempted Diels–Alder reactions with 4,5 and 6,7-difluoroindoles **100e** and **100f** resulted only in the recovery of starting material. However, in the case of 5,6-difluoroindole **100d**, the cycloaddition resulted in the formation of **103**,



Scheme 28

the product obtained from deprotonation at C-7 and elimination of the 6-fluoro substituent to generate the 6,7-aryne, which then underwent the Diels–Alder reaction.

Buszek and coworkers next conducted additional studies to further understand the regioselectivity of these indole-aryne cycloaddition reactions [54]. They chose to generate the indole-aryne systems either from the 4,5- or 5,6-*ortho*-dibromo species **100c** and **100b** by treatment with *n*-BuLi (2.2 equiv) in toluene, or from the corresponding *o*-trimethylsilyl triflates **104** and **108** by treatment with tetrabutylammonium triphenyldifluorosilicate (TBAT, 2.5 equiv) in THF or CsF (3 equiv) in acetonitrile. It was observed that for either the 4,5- or 5,6- indolyne systems thus prepared, there are no regiochemical preferences in the cycloaddition reactions with *t*-butylfuran (**105a**) (Scheme 29).

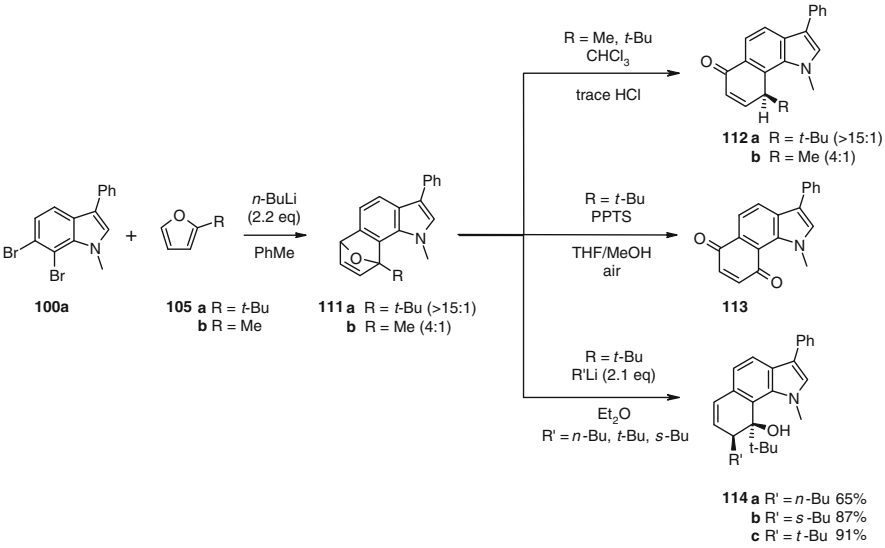


entry	indole	conditions	Products	yield
1	**100c**	*n*-BuLi, PhMe	**106:107**	88%
2	**104**	TBAT, THF	**106:107**	88%
3	**104**	CsF, MeCN	**106:107**	88%
4	**100b**	*n*-BuLi, PhMe	**109:110**	86%
5	**108**	TBAT, THF	**109:110**	89%
6	**108**	CsF, MeCN	**109:110**	89%

Scheme 29

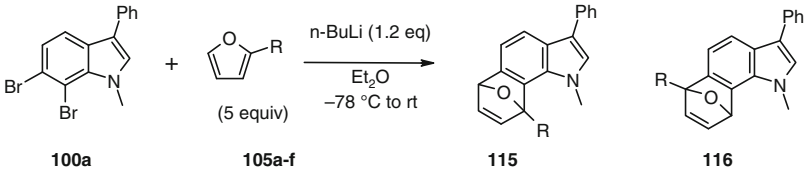
In contrast, the cycloaddition reactions of the 6,7 indolyne system (prepared from **100a**) with furans **105a–b** proceeded with a dramatic preference for the more sterically hindered cycloaddition products **111a–b** (Scheme 30). The above cycloadducts **111a–b** were then treated with trace amounts of acid to yield the enones **112a–b,** which did not further aromatize, as that would put the bulky *t*-butyl or methyl groups (Scheme 30, R in **111a–b**) in the same plane as the *N*-methyl group on the indole ring. The enone bearing the bulky *t*-butyl group (**111a**) was also subjected to hydrolysis in air to furnish **113**. Finally, treatment of **111a** with carbon-based nucleophiles provided the S_N2' products **114a–c**, resulting from the attack of the nucleophiles from the side opposite to the bulky *t*-butyl group (Scheme 30).

Further investigation of the regiochemical course of the cycloaddition reactions involving the 6,7-indolyne systems (prepared from the dibromo derivative **100a**) was conducted using a series of 2-substituted furans **105a–f** containing electron-donating



Scheme 30

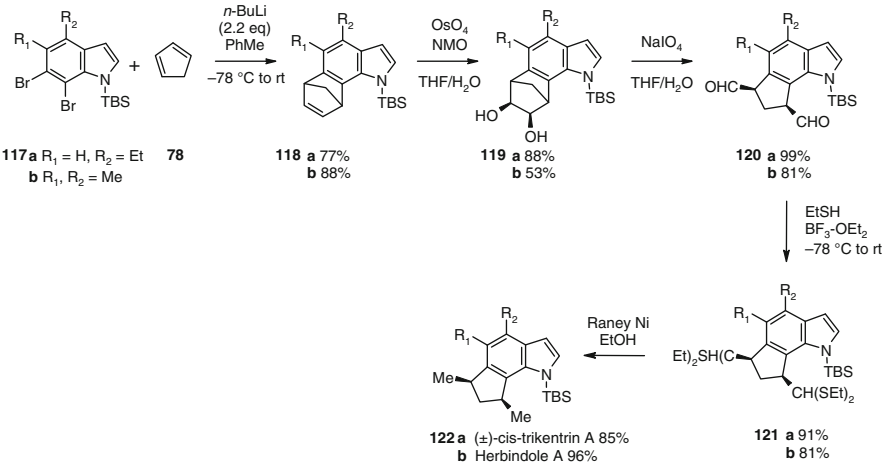
n-alkyl, branched alkyl, and aryl groups, as well as electron-withdrawing substituents. It was observed that with electron-donating groups, the regioselectivity favored the more hindered products **115**, whereas with the electron-withdrawing sulfone moiety the less sterically hindered product **116** was favored (Scheme 31).



entry	R	115:116 ratio	Yield
1	Me	80:20	89%
2	Et	84:16	90%
3	i-Pr	94:6	88%
4	*t*-Bu	98:2	91%
5	Ph	>99:1	92%
6	SO_2Ph	>1:99	83%

Scheme 31

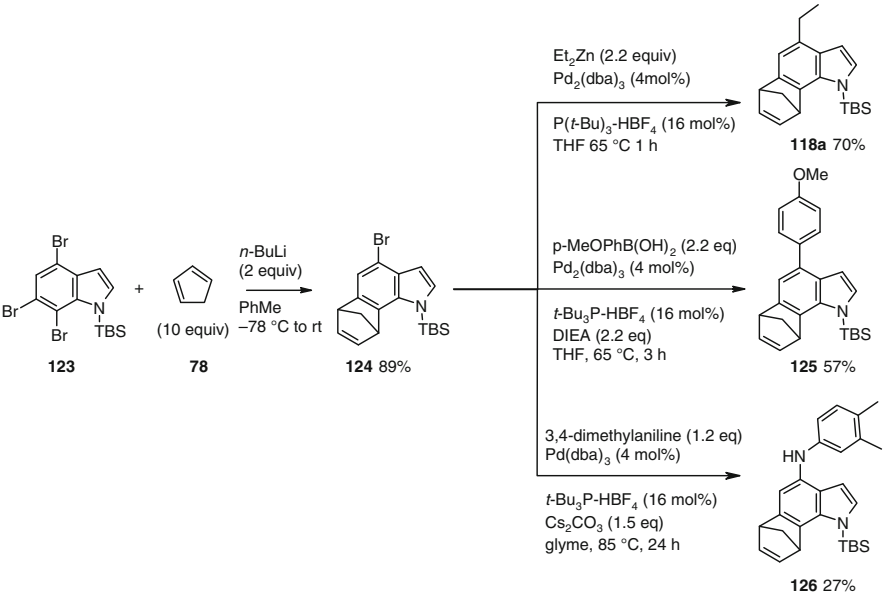
In an interesting application, Buszek and coworkers used the above indolyne cycloaddition methodology as the key step in their syntheses of (±)-*cis*-trikentrin A (**122a**) and (±)-herbindole A (**122b**) [55] (Scheme 32), thus forming the tetracyclic intermediates **118a–b**. The choice of toluene (instead of ether or THF) as the solvent for the halogen-metal exchange proved crucial to obtain the desired



Scheme 32

cycloadducts **118a–b** in high yields. Once these intermediates were at hand, they were further modified through a sequence of four additional steps to obtain either (±)-*cis*-trikentrin A (**122a**) or (±)-herbindole A (**122b**).

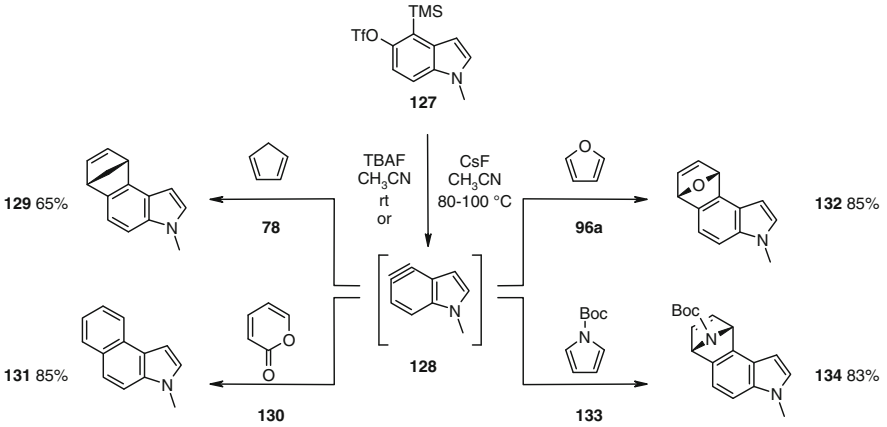
Finally, Buszek and coworkers demonstrated that an appropriately substituted tri-bromo indole derivative such as **123** could undergo aryne formation and subsequent cycloaddition, followed by a metal-catalyzed cross-coupling reaction, to provide access to more complex structures (Scheme 33). As an example, a formal



Scheme 33

synthesis of (±)-*cis*-trikentrin A utilized the bromo-substituted cycloadduct **124**, which underwent a Negishi cross-coupling reaction to yield compound **118a**, described above in Scheme 32. The bromoindole **124** was also shown to be a substrate for both Suzuki–Miyaura and Buchwald–Hartwig couplings, albeit at modest to low yields, to provide **125** and **126**, respectively [56].

Additional work examining the electrophilic nature of the indolyne systems was carried out by Garg and coworkers [57], who explored a variety of cycloaddition reactions ([4+2], [2+2], and [3+2]), as well as attack by various nucleophiles, on simple non-functionalized indolyne derivatives. Starting with the *ortho*-trimethylsilyl-triflate derivative **127** as the indolyne precursor, a number of [4+2] cycloaddition products were obtained with various diene partners in high yields (Scheme 34).



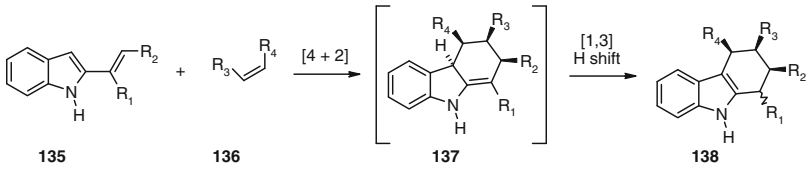
Scheme 34

3 Indole as Diene: 2-Vinylindoles

The 2,3-bond in the indole nucleus can participate in cycloaddition reactions in a variety of capacities. In a previous section, we have reviewed the role of the 2,3-bond as the *dienophile* in Diels–Alder chemistry. In addition, the 2,3-bond may also be combined with a vinyl group in either the second or third position of the indole nucleus and thus take part as the *diene* in Diels–Alder cycloadditions. These vinylindole species are very useful synthetically and provide access to complex polycyclic structures in a very efficient manner. This section will mostly cover research published over the past 15 years. Readers interested in earlier work on this chemistry are referred to the excellent reviews by Pindur [58, 59].

3.1 General Considerations: Regio and Stereochemistry

Pindur [60] examined the intermolecular Diels–Alder reaction between *N*,3-unsubstituted 2-vinylindoles **135** with substituted dienophiles **136** and found the reactions to be highly regio- and diastereoselective processes, leading to the formation of tetrahydrocarbazoles **138** (Scheme 35) via a [4+2] cycloaddition reaction followed by a [1,3] hydrogen shift.

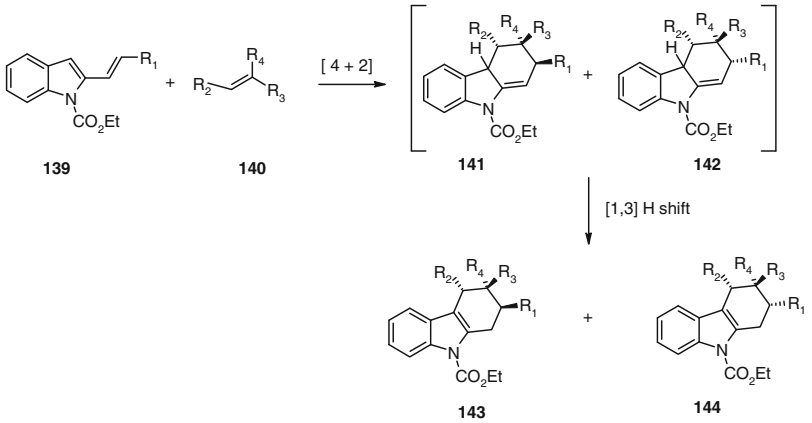


entry	R_1	R_2	R_3	R_4	Yield	Condition
1	Me	H	COPh	CO_2Me	68%	toluene 110 °C
2	H	Me	COEt	H	46%	silica gel 20 °C
3	H	Ph	CO_2Me	H	47%	toluene 110 °C

Scheme 35

In a later study, Rossi and coworkers explored the reactions of *N*-protected indole derivatives, namely [(E)-2-vinyl]-indole-1-carboxylic acid ethyl esters **139**, with dienophiles **140** [61]. Under Pindur's conditions (molecular sieves in refluxing toluene or silica gel at room temperature), only very low yields of products were obtained after long reaction times. Thus, the conditions were modified to include an excess of the dienophile and 15% magnesium perchlorate in refluxing toluene to obtain good yields of the desired cycloadducts. The reactions between dienes **139** and olefins **140** are presumed to proceed via a Diels–Alder cycloaddition reaction to form intermediates **141** and **142,** followed by [1,3] hydrogen shifts to produce the more stable 1,2,3,4-tetrahydrocarbazoles **143** and **144** (Scheme 36). An alternative mechanism featuring a stepwise process involving Michael addition-type intermediates which then would undergo a 6π electrocyclization to form the carbazoles was ruled out, since in all the reactions performed there were no intermediates detected that would have arisen from the nucleophilic attack of the indole C3 on the alkene.

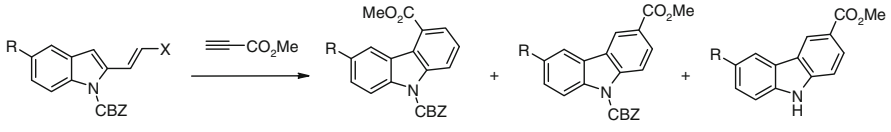
The regiochemical course of the above reactions was similar to what was observed in Pindur's work. However, the diastereoselectivity for the Diels–Alder reactions involving *N*-acylated indoles **139** was quite different than that previously reported. When the unprotected indole derivatives **135** were subjected to Diels–Alder cycloadditions, the *endo* products were formed almost exclusively. In contrast, the cycloadditions with *N*-protected indoles in the presence of magnesium perchlorate as the Lewis acid provided a wide range of *endo*/*exo* product ratios (**143**:**144**, Scheme 36).



entry	R_1	R_2	R_3	R_4	Yield	ratio 143:144
1	p-tolyl	H	CO_2Me	H	60%	3.3:1
2	p-tolyl	H	CO_2Et	Me	66%	54:1
3	Me	H	CO_2Me	H	67%	1.4:1
4	Me	CO_2Me	CO_2Me	H	46%	1:2.2

Scheme 36

Back and coworkers studied the cycloaddition reactions of sulfur-substituted vinylindole derivatives **145a–f** and examined the effects of the various oxidation states of the sulfur atom in controlling the regioselectivity (Scheme 37). The Diels–Alder reactions between the vinylogous 2-sulfonylindoles **145a–c** and methyl propiolate (**146**) followed by DBU-induced elimination of *p*-toluenesulfinic acid zproduced the 4-substituted carbazole derivates **147a–c** exclusively [62]. In contrast, when electron-donating sulfide analogs **145d–f** were used, the corresponding cycloaddition reactions in refluxing toluene proceeded slowly and resulted in the formation of mixtures of regioisomers. Addition of a Lewis acid catalyst (either $AlCl_3$ in CH_2Cl_2 or $MeAlCl_2$ in toluene) afforded in good yields the 3-substituted



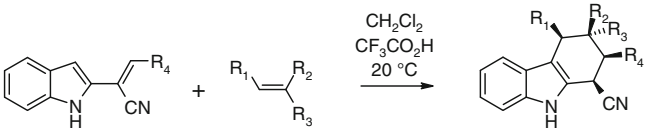
diene	R	X	conditions	Yield 147	Yield 148	Yield 149
145a	H	Ts	A	76%	0%	0%
145b	Me	Ts	A	73%	0%	0%
145c	CO_2Me	Ts	A	65%	0%	0%
145d	H	SPh	B or C	0%	45%	17%
145e	Me	SPh	B or C	0%	57%	0%
145f	CO_2Me	SPh	B or C	0%	6%	69%

conditions: A) toluene/reflux, DBU; B) $MeAlCl_2$, toluene C) $AlCl_3$, CH_2Cl_2

Scheme 37

carbazoles **148d–f**. When $MeAlCl_2$ in toluene was used, deprotected carbazoles **149d,f** were observed as well as the CBZ-protected products [63].

Blechert and coworkers have developed a very efficient one-pot synthesis of 2-vinylindole derivatives, starting from an aldehyde, phenylhydroxylamine, and cyanoallene [64]. These 2-vinyl indole species have demonstrated good synthetic utility in constructing linear carbazole skeletons that could be useful as key intermediates in the assembly of indole alkaloids [65]. Early on, it was discovered that the Diels–Alder reactions of the 2-vinylindole species **150** did not proceed under thermal conditions, and the use of Lewis acids did not offer any advantages. However, cycloadditions with electron-deficient dienophiles **151** (at room temperature in chloroform/dichloromethane and in the presence of trifluoroacetic acid), followed by aromatization, led to the formation of the tetrahydrocarbazole structures **152** (Scheme 38). These reactions were found to proceed with high selectivity for the *endo* products. The tetrahydrocarbazoles **152** could then be oxidized with DDQ to form the corresponding carbazoles in good yields.



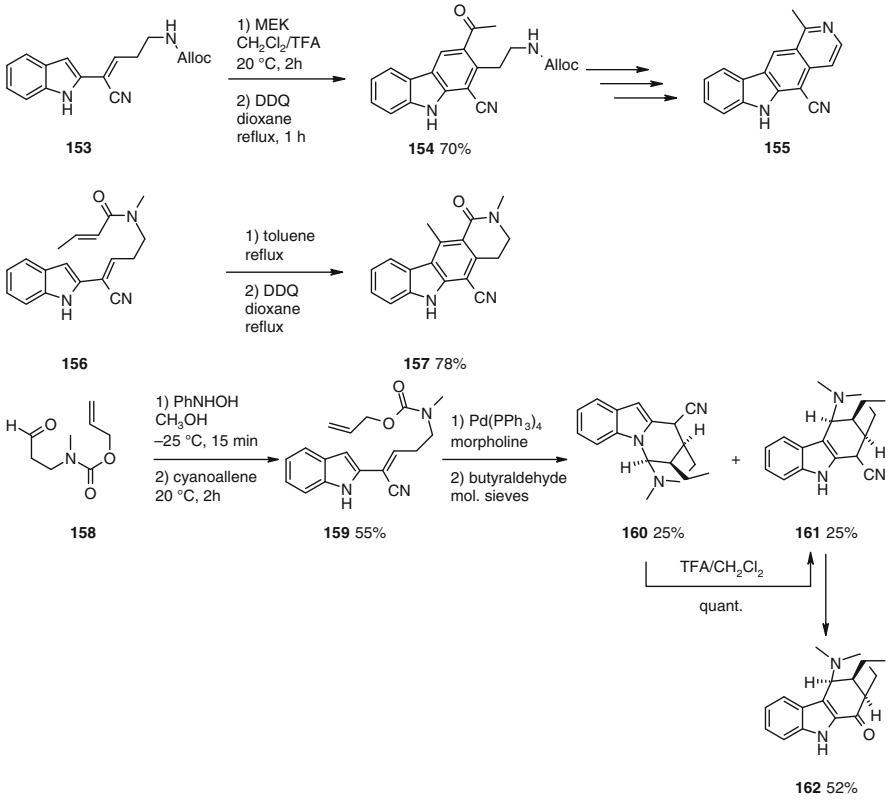
150 **151** **152**

entry	R_1	R_2	R_3	R_4	Yield
1	H	$C(O)CH_3$	H	Me	90%
2	H	$C(O)CH_3$	H		60%
3	H	$C(O)CH_3$	H		81%
4	$-CH_2(CH_2)_2CO-$		H	Me	50%
5	H	CHO	Et	Me	60%

Scheme 38

3.2 Application of [4+2] Reactions with 2-Vinylindoles to the Synthesis of "Linear" Indole Alkaloids

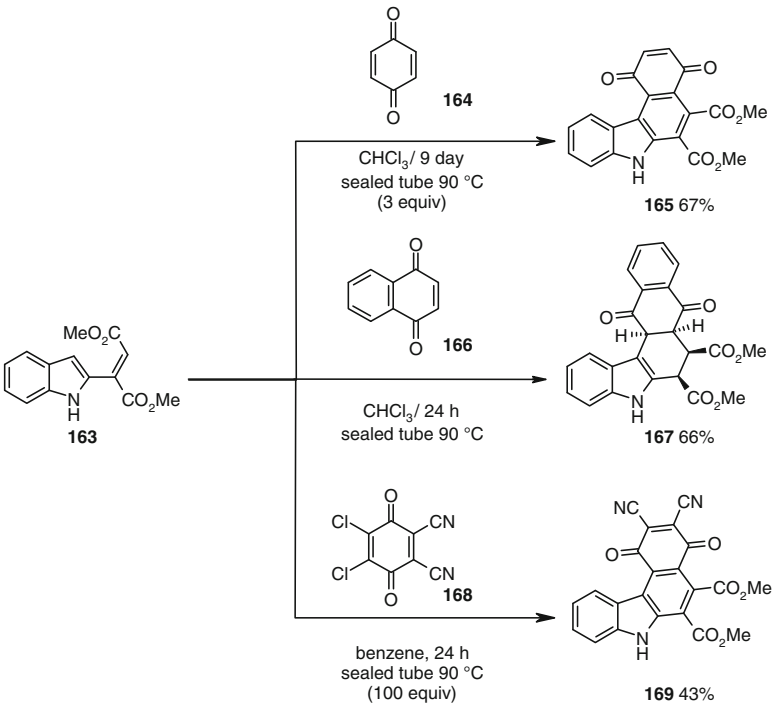
Diels–Alder reactions using 2-vinylindoles as the diene were used as the key step in syntheses of olivacine derivatives (**155**), ellipticine derivatives (**157**), and (±)-3-epi-dasycarpidone (**162**) [65] (Scheme 39). In the synthesis of (±)-3-epi-dasycarpidone, the appropriate 2-vinylindole **159** was prepared via a one-pot procedure, and then subjected to deprotection of the allyl carbamate, and subsequent enamine formation, followed by an intramolecular Diels–Alder reaction to produce **161**, thereby producing the indole alkaloid framework in three steps from a rather simple starting material, **158**. The attempted cycloaddition reaction



Scheme 39

sequence also led to the formation of **160**, via enamine formation, followed by Michael addition and a subsequent Mannich reaction. This material could, however, be converted back to **161** in quantitative yield upon treatment with TFA. Reduction of **161** with DIBAL-H and work up in the presence of air provided (±)-3-epi-dasycarpidone (**162**).

Saracoglu and Cavdar investigated the Diels–Alder cycloadditions of 2-vinylindoles with various substituted quinone compounds [66] (Scheme 40). Thus, the cycloaddition reaction between 2-vinylindole **163** and naphthoquinone (**166**), followed by a [1,3]-hydrogen shift, provided compound **167**. Similar to what was seen previously, the secondary orbital interactions between the diene and the dienophile lead to the formation of the *endo* product. Other quinone dienophiles, such as *p*-benzoquinone (**164**) and DDQ (**168**), also participated in similar cycloaddition reactions to produce quinolinocarbazole derivatives. In the case of DDQ, overoxidation by elimination of 2 moles of HCl from the cycloaddition product led to the formation of compound **169**.

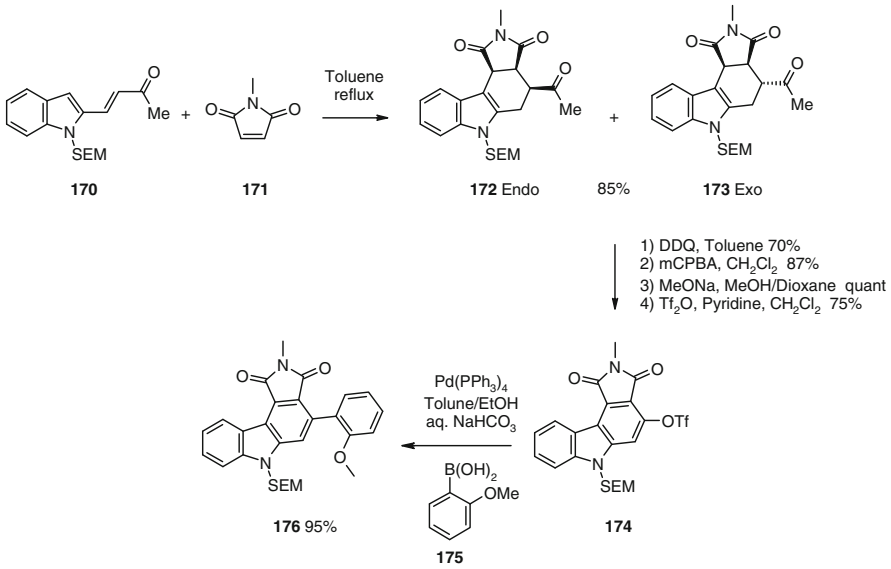


Scheme 40

3.3 Application of [4+2] Reactions with 2-Vinylindoles to the Synthesis of Pyrrolo and Indolocarbazoles

In the late 1990s, McCort and coworkers developed a general method to synthesize aryl- and heteroaryl-pyrrolocarbazole derivatives, which are useful as protein kinase C inhibitors. [67]. The reaction sequence started with the methyl ketone derivative of 2-vinylindole **170**, which underwent a cycloaddition reaction with *N*-methylmaleimide (**171**) to afford a mixture of the *endo* and *exo* products **172** and **173** (15:85 ratio) in excellent yield. The mixture was then oxidized with DDQ to afford the corresponding aromatized derivative. Baeyer–Villiger rearrangement followed by removal of the resulting acetyl ester and subsequent reaction with triflic anhydride produced the triflate **174**. This triflate could serve as a key starting material for various palladium-catalyzed cross-coupling reactions to further elaborate the newly formed carbazole nucleus. As an example, a Suzuki coupling reaction with **174** was used to produce **176** (Scheme 41).

There have also been reports on the construction of structurally similar indolocarbazoles via using a [4+2] cycloaddition strategy with 2,2′-biindoles and



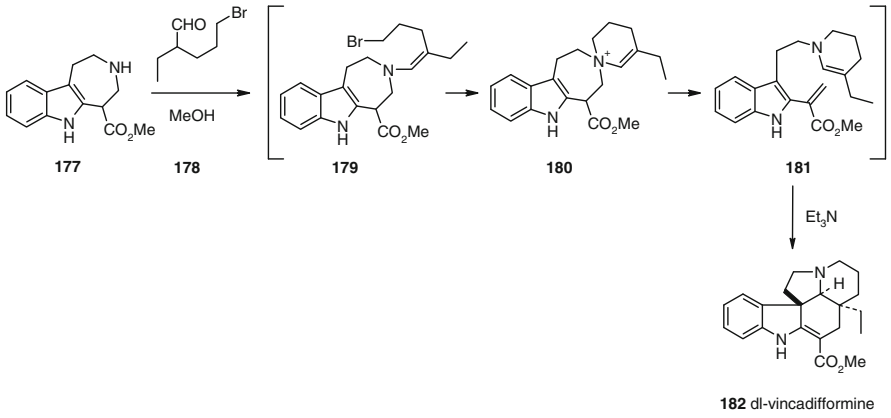
Scheme 41

maleimides. In these cases, it appears that the reaction mechanisms did not involve a concerted [4+2] cycloaddition, but instead proceeded via a stepwise mechanism involving Michael additions [68–70].

3.4 Application of [4+2] Reactions with 2-Vinylindoles to the Synthesis of Vinca Alkaloids

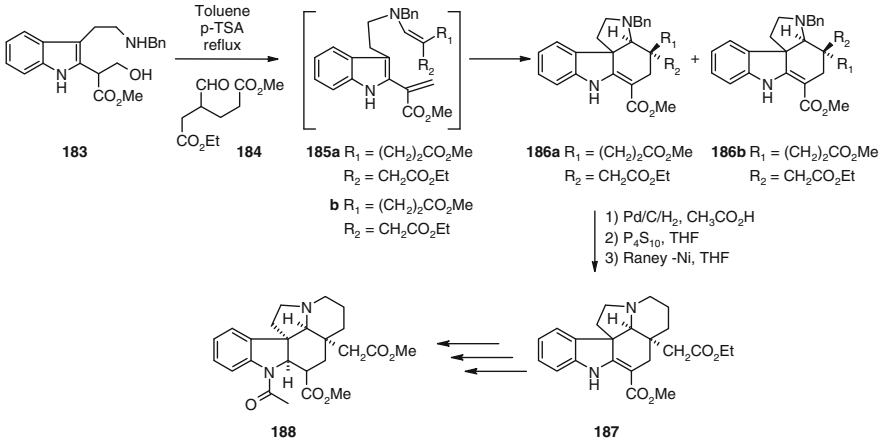
The use of 2-vinylindole species has played a large role in the total synthesis of the pentacyclic *Aspidosperma* alkaloids. In 1978, Kuehne reported an elegant synthesis of DL-vincadifformine (**182**) that featured as a key step the reaction of an indoloazepine **177** with the bromoaldehyde **178**, thus leading to the *in situ* formation of 2-vinylindole species **181**, which in turn underwent an intramolecular Diels–Alder reaction to provide **182** [71] (Scheme 42). Kuehne and others have used this same methodology, using the *in situ* generation of a 2-vinyl indole, followed by an intramolecular Diels–Alder reaction, to synthesize a number of *Aspidosperma* alkaloids and their analogs [72].

More recently, Kalaus and Szantay have made use of a similar approach to synthesize a variety of pentacyclic indole alkaloids containing the aspidospermane, ibophyllidine, and iboxyphylline core structures. In one approach, featured in the formal total synthesis of (±)-12-demethoxy-N(1)-acetylcylindrocarine (**188**) [73], a benzyl-protected tryptamine derivative **183** was treated with an appropriately substituted aldehyde (**184**) to form the enamine species **185a–b**, which then underwent



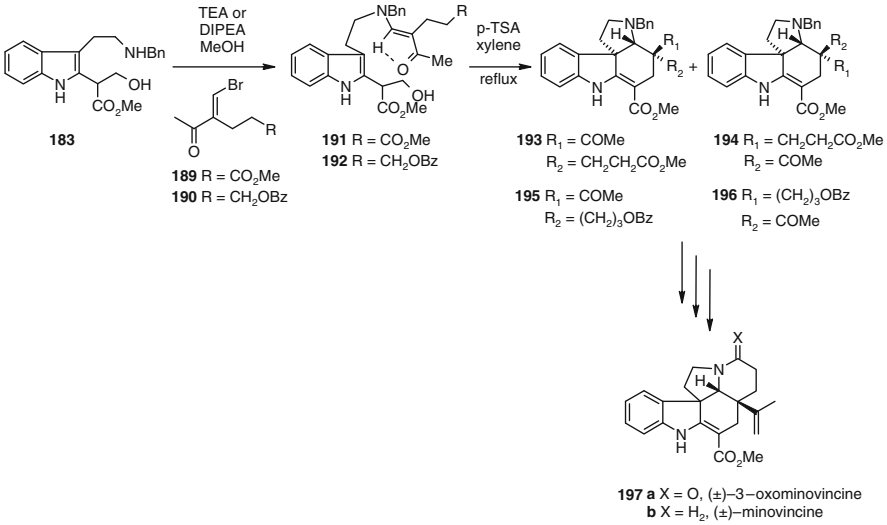
Scheme 42

intramolecular Diels–Alder reactions to form **186a** and **186b** in a 3:1 ratio. The synthesis was completed by debenzylation of **186a**, thus resulting in a spontaneous intramolecular acylation to form the final D-ring. The resulting amide carbonyl group was converted to the thioamide analog and then reduced with Raney Nickel, to provide 19-2-ethoxycarbonyl-19-demethylvincadifformine (**187**), which represents a formal total synthesis of (±)-12-demethoxy-*N*(1)-acetylcylindrocarine (Scheme 43) [74].



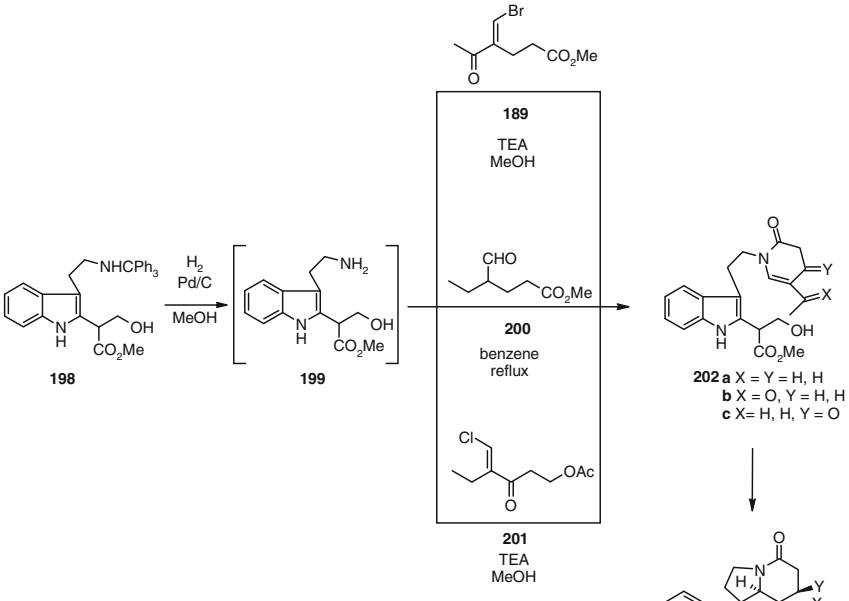
Scheme 43

Similarly, the synthesis of (±)-3-oxominovincine (**197a**) [75] and (±)-minovincine (**197b**) [76] (Scheme 44) used the above strategy, this time forming the key enamines **191** and **192** by the treatment of the tryptamine derivative **183** with the vinyl bromide derivatives **189** and **190**, respectively. Treatment of the above enamines with *p*-toluenesulfonic acid in xylene at reflux gave the cycloaddition products **193–196** as a 1:1 mixture of epimers for each pair (**193**:**194**, **195**:**196**). The above cycloadducts are then converted via a series of simple synthetic steps to (±)-3-oxominovincine (**197a**) and (±)-minovincine (**197b**).



Scheme 44

In an alternative approach to the synthesis of similar alkaloids, Kalaus and Szantay chose to construct the D-rings first, before the pivotal Diels–Alder reactions (Scheme 45). Thus, deprotection of the trityl-protected tryptamine derivative

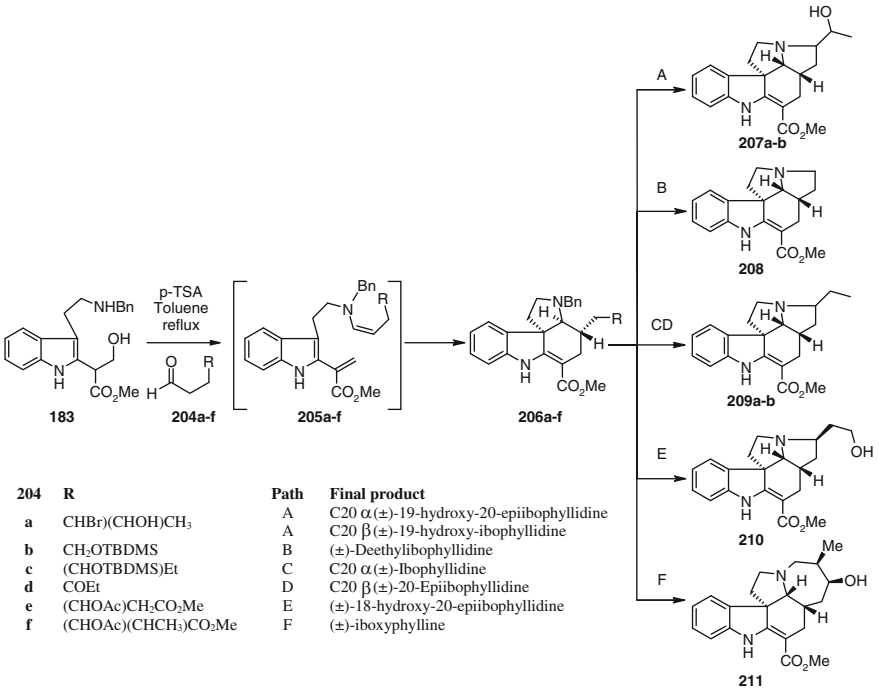


entry	name	compound	X	Y	Conditions
1	3-oxovincadifformine	**203a**	H,H	H	Ac_2O, toluene, Δ
2	3-oxominovincine	**197b**	O	H	p-TSA, xylene, Δ
3	15b-hydroxyvincadifformine	**203b**	H, H	OH	1) *p*- TSA, xylene, Δ 2) L-Selectride

Scheme 45

198 to form **199**, followed by immediate treatment with the aldehyde or vinyl halide species **189**, **200** and **201** (due to the unstable nature of **199**), resulted in the formation of D-ring cyclized structures **202a–c**. These intermediates were then dehydrated to form the corresponding 2-vinylindole species which underwent the key intramolecular Diels–Alder reactions to form the full pentacyclic ring systems in 3-oxovincadifformine (**203a**) or 3-oxominovincine (**197a**) [77]. Alternatively, treatment of the cycloaddition product **202c** with L-selectride® produces 15β-hydroxyvincadifformine (**203c**) [78].

Kalaus and Szantay were also able to use the same 2-vinylindole Diels–Alder strategy to synthesize representative structures from the ibophyllidine and iboxyphylline families, in which the D-ring is either a five- or seven-membered ring, respectively (Scheme 46). These syntheses relied on intermediates **205a–f** as the key precursors for the pivotal Diels–Alder reactions [79]. Using this powerful methodology, (±)-19-hydroxy-20-epiibophyllidine (**207a**), (±)-19-hydroxyibophyllidine (**207b**) [80], (±)-deethylibophyllidine (**208**) [81], (±)-ibophyllidine (**209a**), (±)-20-epiibophyllidine (**209b**) [82], (±)-18-hydroxyl-20-epiibophyllidine (**210**) [83], and (±)-iboxyphylline (**211**) [84] were prepared.

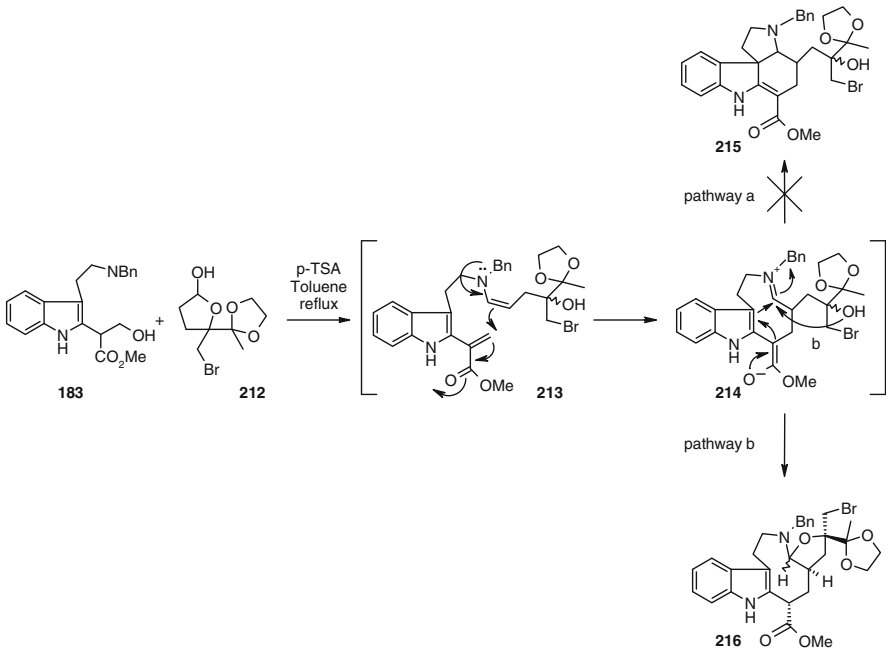


204	R
a	CHBr)(CHOH)CH_3
b	CH_2OTBDMS
c	(CHOTBDMS)Et
d	COEt
e	(CHOAc)CH_2CO_2Me
f	(CHOAc)($CHCH_3$)CO_2Me

Path	Final product
A	C20 α(±)-19-hydroxy-20-epiibophyllidine
A	C20 β(±)-19-hydroxy-ibophyllidine
B	(±)-Deethylibophyllidine
C	C20 α(±)-Ibophyllidine
D	C20 β(±)-20-Epiibophyllidine
E	(±)-18-hydroxy-20-epiibophyllidine
F	(±)-iboxyphylline

Scheme 46

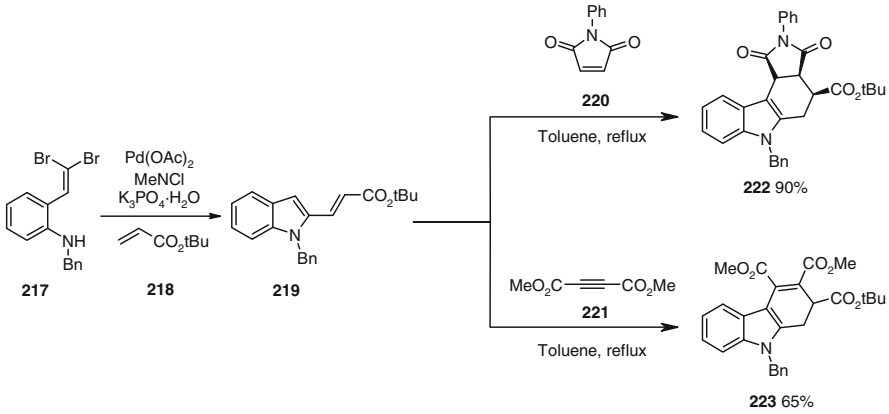
Most recently, Kalaus and Szantay have re-examined the mechanism of the intramolecular reactions involving the previously described *in situ* generated 2-vinylindole derivatives, casting some doubt on whether the reactions indeed proceeded via a concerted [4+2] cycloaddition pathway. While attempting to synthesize compounds from the pandoline structural class, treatment of the tryptamine derivative **183** with the aldehyde precursor **212** resulted in the formation of a unique cyclic cabinolamine ether **216**, instead of the expected product from the Diels–Alder reaction (**215**) (Scheme 47) [85]. It is now believed that a stepwise mechanism involving a zwitterionic intermediate **214** could be involved. Cyclization of this intermediate via pathway "a" would lead to the formation of the desired "Diels–Alder product" **215**, whereas participation of the hydroxyl group via pathway "b" would lead to the formation of the isolated product **216**. Quantum mechanical calculations undertaken to investigate the mechanism of the "cycloaddition reaction" also seem to support the involvement of a stepwise process. Interestingly, attempts to perform the "Diels–Alder reaction" without the ester group failed [86], thus providing further support for a stepwise mechanism.



Scheme 47

Finally, Lautens and coworkers developed a very efficient route to synthesize the 2-vinylindole derivative **219** through a palladium-catalyzed tandem Buchwald–Hartwig/Heck sequence. The diene thus prepared were then used in

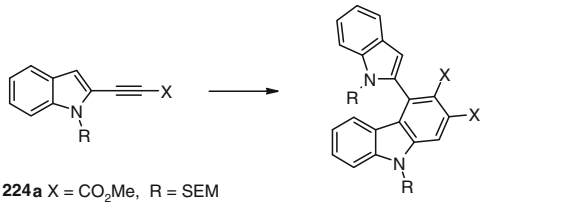
Diels–Alder reactions with *N*-phenylmaleimide (**220**) and dimethyl acetylenedicarboxylate (**221**) to yield carbazole derivatives **222** and **223**, respectively [87] (Scheme 48).



Scheme 48

3.5 2-Alkynyl Indoles and 2-Allenylindoles as Dienes in Cycloaddition Reactions

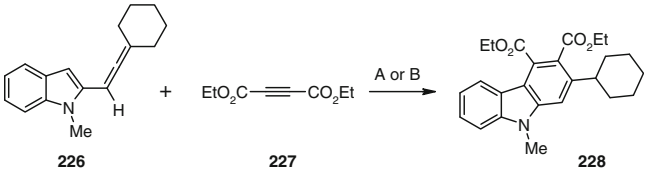
Both 2-alkynylindoles and 2-allenylindoles have been shown to participate as dienes in Diels–Alder reactions. While attempting to promote the cyclization reactions of indol-2-ylacetylenes **224a–b** with dienophiles, Passarella and coworkers observed the formation of dimerization products **225a–b** (Scheme 49) [88]. These products were formed via an enyne-alkyne [4+2] cycloaddition reaction between two molecules of the indol-2-ylacetylene species. Interestingly, such



Scheme 49

reactions were found to occur only when electron-withdrawing groups were present at the alkyne terminus.

Ishikura and coworkers demonstrated the use of 2-allenylindoles **226** as the diene component in [4+2] reactions with diethyl acetylenedicarboxylate (**227**) in the synthesis of substituted carbazole systems **228** [89]. The above cycloadditions could be carried out under both thermal and high pressure conditions, albeit in low yields (Scheme 50).



226 **227** **228**

Entry	conditions	yield
A	150 °C, sealed tube, 20 h	28%
B	RT, 980 MPa, 20 h	35%

Scheme 50

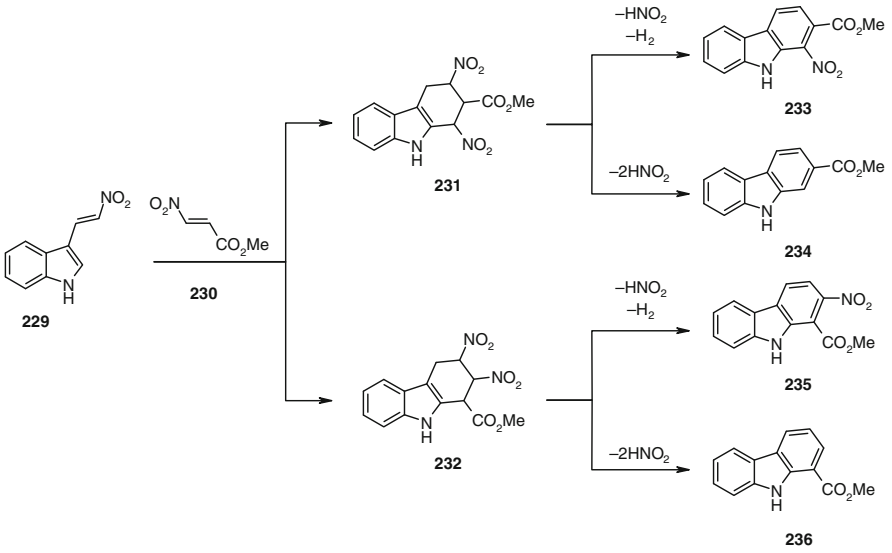
4 Indole as Diene: 3-Vinylindoles

Similar to the 2-vinylindole species, the 3-vinylindole derivatives have also been extensively used in synthesis, due to their ability to take part as the 4π component in Diels–Alder reactions with various dienophiles. While some of the work in this field has involved structurally "simple" 3-vinylindole species, bicyclic structures such as biindoles, indole-quinones, and indole-maleimides have also been used as the 4π components.

4.1 Simple 3-Vinylindole Systems

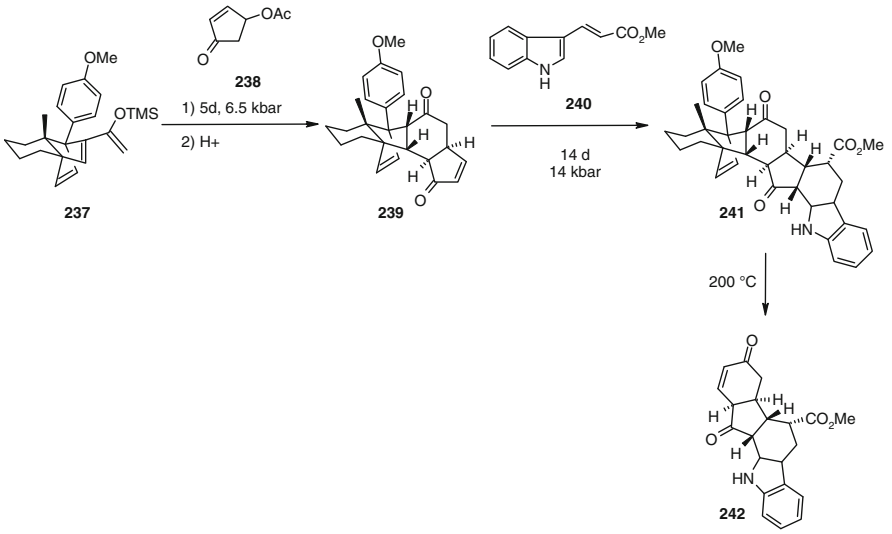
The Diels–Alder reaction between 3-(2-nitroethenyl)indole (**229**) and methyl 3-nitroacrylate (**230**) in the presence of aluminum chloride in boiling toluene was shown to lead to the formation of both the nitro carbazole species **233** and **235**, in very low yield (8%, 1:10), and the corresponding compounds without the nitro group, **234** and **236** (25%, 10:1) [90]. The reaction was presumed to proceed via the cycloaddition adducts **231** and **232** (34%, 3:2), followed by dehydrogenation and denitration (Scheme 51).

Wolter and coworkers have examined a strategy involving sequential cycloadditions, followed by retro-Diels–Alder reactions, to construct polycyclic ring systems



Scheme 51

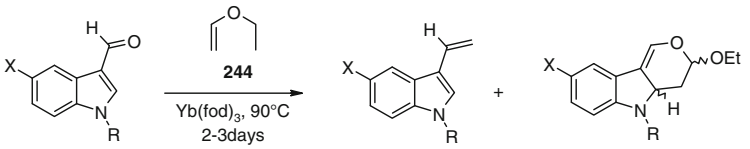
(Scheme 52) [91]. The β-indolylacrylate **240** was thus subjected to a Diels–Alder reaction with enone **239** (prepared via a Diels–Alder cycloaddition of the diene **237** and cyclopentenone **238**), thereby providing the *endo* product **241** in 72% yield and



Scheme 52

with high selectivity. A subsequent retro-Diels–Alder process was then used to "unmask" the desired cyclohexanone **242** albeit in low (20%) yield.

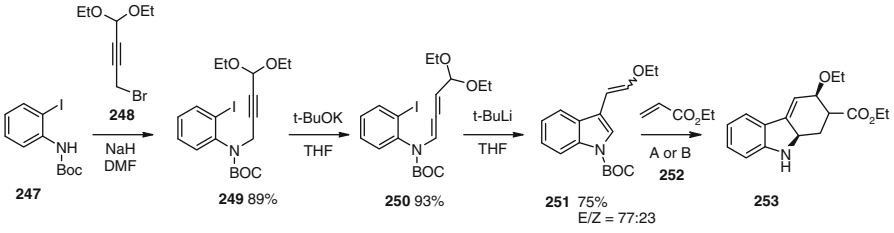
Merour and coworkers demonstrated the use of 3-formylindoles **243a–c,** bearing an electron-withdrawing group at the indole nitrogen, as the 4π components in Diels–Alder reactions with 1-ethoxyethene (**244**), to produce the tricyclic derivatives **246** (Scheme 53) [92]. It is noteworthy that the reactions with **243a–c** do not proceed exclusively in [4+2] fashion, thereby leading to the formation of side products arising from the [2+2] reactions involving only the aldehyde moieties (i.e., the 3-vinylindole products **245**) in significant quantities (5–56%). Interestingly, a phenylsulfonyl group on the indole nitrogen seemed to be necessary to obtain at least some of the [4+2] cycloaddition products, whereas an acetyl substituent on the indole nitrogen only led to the formation of the [2+2] side product **245b**.



243	R	X	245	246	*endo/exo*	recovered 243
a	SO_2Ph	H	56%	15%	68/32	10%
b	$COCH_3$	H	32%	--	--	40%
c	SO_2Ph	Br	5%	30%	50/50	60%

Scheme 53

Maddaluno and Le Strat devised a new method to construct the 3-vinylindole system **251** starting with the acetylene precursor **249**, which was isomerized to the allene moiety **250** and then subjected to halogen-metal exchange and ring closure upon treatment with *t*-BuLi, resulting in the formation of **251** as a 77:23 mixture of E and Z isomers (Scheme 54) [93, 94]. Only the E-isomer was found to participate in the Diels–Alder reaction with ethyl acrylate (**252**), regioselectively



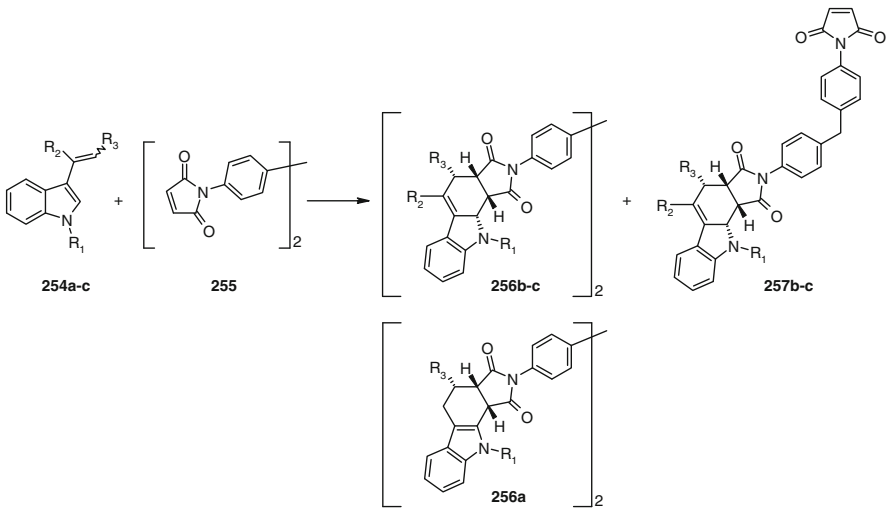
entry	conditions	yield of 253 (based on E-isomer)	Endo/exo
A	toluene, 110 °C, 1 atm	61%	27:73
B	THF, RT, 12 KBar	70%	70:30

Scheme 54

producing the cycloadduct **253**. Interestingly, the thermal reaction conditions led to a preference for the *exo* product, while the *endo* product was preferred under high pressure.

4.2 Application of Diels–Alder Reactions with 3-Vinylindoles in the Synthesis of Biscarbazoles

Pindur and coworkers examined the [4+2] cycloaddition of 3-vinylindole species **254** to bismaleimide (**255**) in an effort to form biscarbazole derivatives which might be able to adopt a helical shape, thus gaining the potential for DNA minor groove binding and/or DNA intercalation (Scheme 55) [95]. With *N*-phenylsulfonyl-protected indoles, the Diels–Alder reactions occurred at room temperature to provide a mixture of the *endo*, *endo*-bis (**256b–c**) and *endo*-mono cycloaddition (**257b–c**) products. The *E*-isomers of the dienes appear to be the more reactive species, as the *E* stereochemistry is reflected in the cycloaddition products **256c** and **257c**. The [4+2] cycloaddition with the less reactive *N*-methyl indole derivative **254a** required elevated temperatures (refluxing in chloroform) and thus provided the dimeric structure **256a** that had undergone a [1,3]-hydrogen shift to reform the indole nucleus as the sole product.

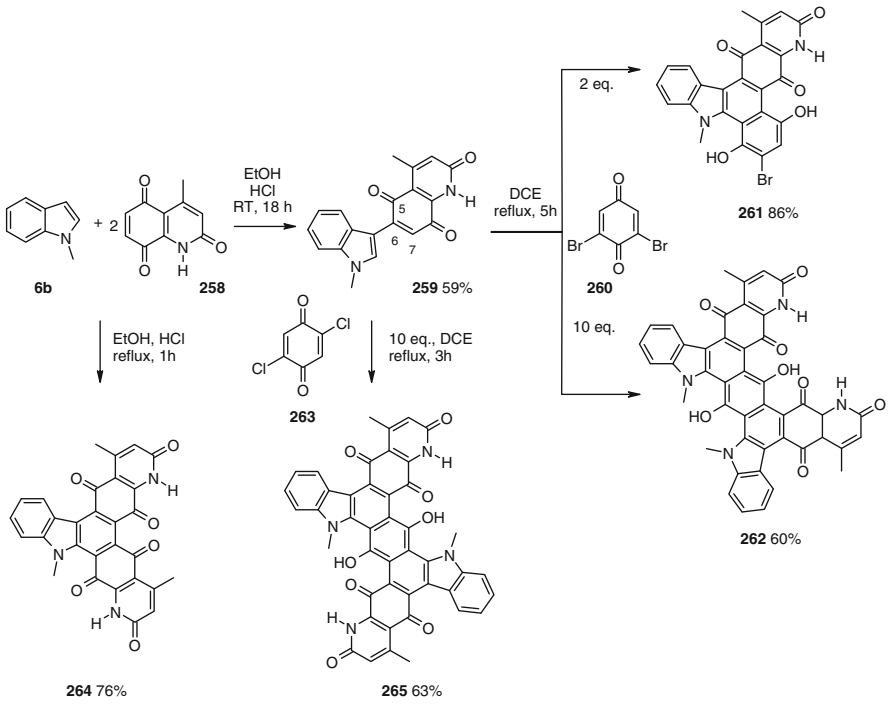


entry	R_1	R_2	R_3	conditions	product
a	Me	H	CO_2Me (E)	4 d, $CHCl_3$, reflux	**256**
b	SO_2Ph	Me	H	6 d, $CHCl_3$, RT	**256 + 257**
c	SO_2Ph	H	OMe (E/Z 2;1)	6 d, $CHCl_3$, RT	**256 + 257**

Scheme 55

4.3 3-Quinone-Indole Systems as Dienes

Menendez and coworkers have reported the formation of large heterocyclic quinone species containing 6, 7, or 11 rings in their core structure, using multicomponent reactions involving indole and various quinone systems (Scheme 56) [96]. First, thermal reaction of indole **6b** with 2 equivalent of the quinone **258** resulted in the formation of the heptacyclic product **264** as a single regioisomer. It is proposed that **264** arises from a cascade reaction sequence involving the Michael addition of the indole onto the quinone to yield a hydroquinone intermediate, that is then oxidized *in situ* to provide the quinone derivative **259**. Diels–Alder reaction of **259** with a second molecule of quinone **258**, followed by subsequent oxidation, then leads to the formation of product **264**. The regiochemical outcomes for both the Michael addition step and the cycloaddition step are rationalized based on the electron donation of the nitrogen atom in the quinone species to the C5 carbonyl, thus rendering the conjugated C7 position less electrophilic than the C6 position. When the above reaction sequence between **6b** and **258** was run at room temperature, it was possible to isolate the proposed intermediate quinone species **259**. This intermediate was then treated with 2 equivalent of 2,6-dibromobenzoquinone

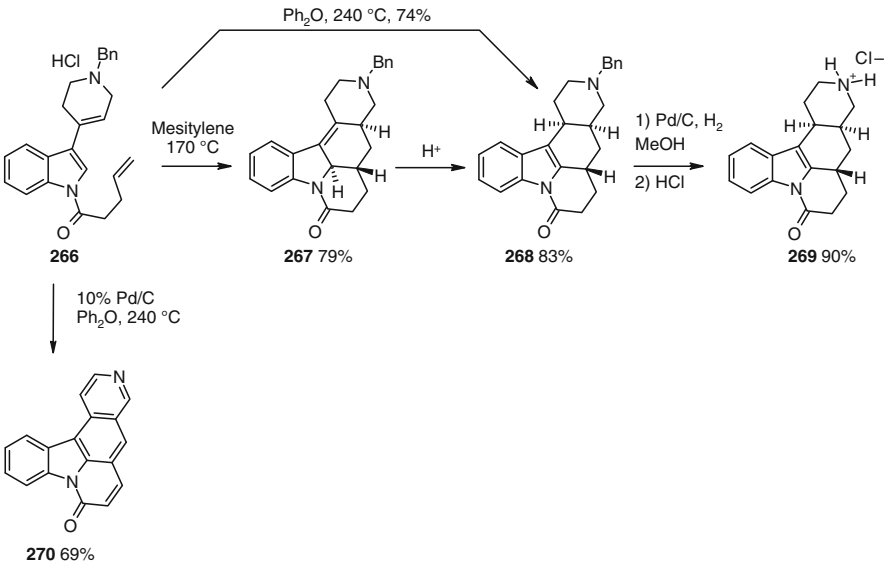


Scheme 56

(**260**) to produce the hexacyclic structure **261**. When a large excess (10 equiv) of the benzoquinone **260** was used, the double cycloaddition product **262** was isolated instead. A similar reaction with 10 equivalent of 2,5-dichlorobenzoquinone (**263**) provided the regioisomeric compound **265**.

4.4 Application of Diels–Alder Reactions with 3-Vinylindoles in the Synthesis of Novel Pentacyclic Systems

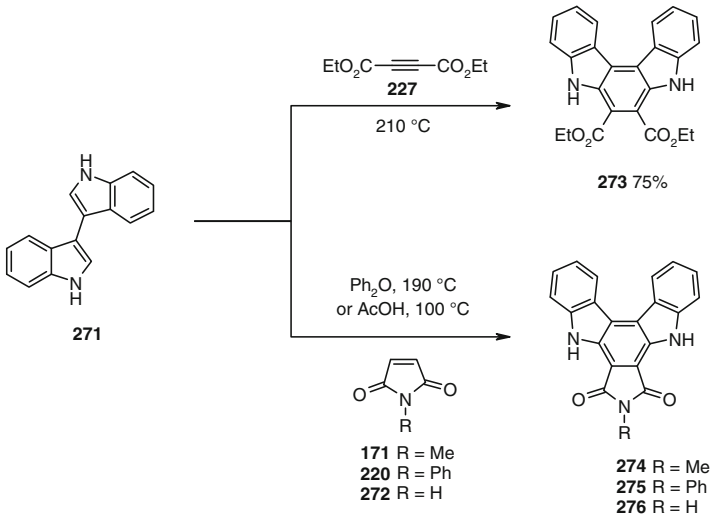
In an elegant application of 3-vinylindoles to Diels–Alder chemistry, Gharagozloo and coworkers examined the *intramolecular* cycloaddition reaction of 3-(tetrahydropyridinyl)indole with an appropriately tethered olefin, to produce novel pentacyclic ring systems [97]. Thus, heating the acylated indole derivative **266** in mesitylene at 170°C produced the cycloaddition product **267** in good yield. Subsequent treatment with acid then induced a [1,3]-H shift to produce the indole species **268**. Alternatively, heating **266** at higher temperatures (diphenylether, 240°C) led directly to the formation of indole **268** in excellent yield. Removal of the benzyl group in **268** via catalytic hydrogenation in turn furnished **269**. The fully aromatic product **270** was prepared from compound **266**, via cyclization and catalytic dehydrogenation at 240°C (Scheme 57).



Scheme 57

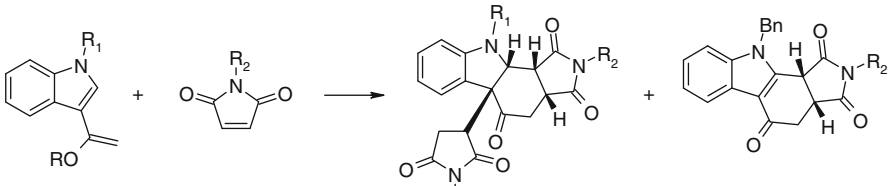
4.5 *Application of Diels–Alder Reactions with 3-Vinylindoles in the Synthesis of Indolocarbazoles and Pyrrolocarbazoles*

Bergman and Desarbre studied the reactions of 3,3′-biindolyl species with dienophiles. Similar reactions with 2,2′-biindolyl species are usually plagued with difficulties in obtaining the cycloaddition products [98]. The reaction of diethyl acetylenedicarboxylate (**227**) with 3,3′-biindolyl species **271** (210°C) resulted in the formation of the 1:1 cycloaddition product **273** in very good yield (Scheme 58). This result is in stark contrast to the same reaction using 2,2′-biindolyl [99] in which an undesired 2:2 adduct was formed. Next, the cycloadditions of **271** with the maleimide derivatives **171**, **220**, and **272** were attempted, thus producing the [4+2] cycloaddition products **274–276**, respectively. It was noted that in one case when diethyl azodicarboxylate (DEAD) was used, a product that resulted from the Michael addition to the second position of the 3,3′-indolyl system was also isolated, thus casting a doubt on whether these reactions are proceeding through a [4+2] cycloaddition mechanism. However, in cases involving reactions with acetylene and maleimides, no such Michael addition products were isolated.



Scheme 58

Otto and coworkers examined the cycloaddition reactions between *N*-protected 3-{1-[(trimethylsilyl)oxy]ethenyl}-1*H*-indoles **277a–b** and maleimides **220** and **278**, and were able to identify some interesting reaction pathways that occur as a result of the choice of protecting group on the nitrogen atom (Scheme 59) [100]. When the tosyl-protected indole **277a** was used in cycloaddition reactions with



277 a R = TMS, R_1 = Tos
b R = TMS, R_1 = Bn
c R = TMS, R_1 = Piv
d R = TMS, R_1 = Boc

220 R_2 = Ph
278 R_2 = Et

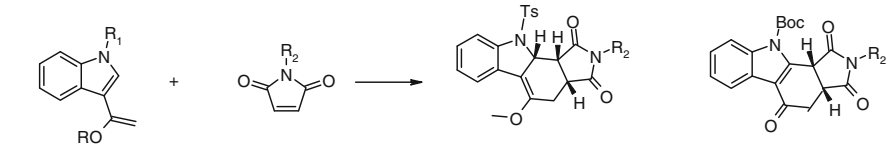
279 R_1 = Tos, R_2 = Ph
280 R_1 = Tos, R_2 = Et

281 R_2 = Ph
282 R_2 = Et

Scheme 59

maleimides **220** and **278** (toluene, room temperature), the only products obtained were the 1:2 adducts **279** and **280**, respectively (~30% yield), which arose from [4+2] cycloadditions, followed by a Michael addition. Similar results were obtained when the tosyl-protecting group was switched to pivaloyl (**277c**) or BOC (**277d**). However, when the non-electron-withdrawing benzyl-protecting group was used (**277b**), no reaction took place at room temperature or refluxing conditions, even after several days. Only when the reaction of **277b** and the maleimides **220** and **278** was conducted in the presence of $EtAlCl_2$ in CH_2Cl_2 at −78°C, followed by acidic workup, the 1:1 cycloaddition products **281** and **282** were obtained, albeit in very low yields (2%).

Next, Otto and Bleile explored the reactions of 3-(1-methoxyvinyl)indoles and maleimides, which produced only the [4+2] cycloaddition products with no 2:1 adducts being formed (Scheme 60) [101]. Similar to previous results, the nature of the products obtained once again depended on the choice of the indole nitrogen protecting group. When the tosyl-protected derivative **277e** was treated with maleimides **220** and **278** (toluene, room temperature), cycloadducts which retained the methoxy functionality (**283** and **284**) were isolated in ~25% yield. However, use of the BOC-protected indole **277f** led to the isolation of the α,β-unsaturated ketone derivatives **285** and **286**. These products then served as precursors for the synthesis of interesting carbazole and pyrrolocarbazole structures.



277 e R = Me, R_1 = Tos
f R = Me, R_1 = Boc

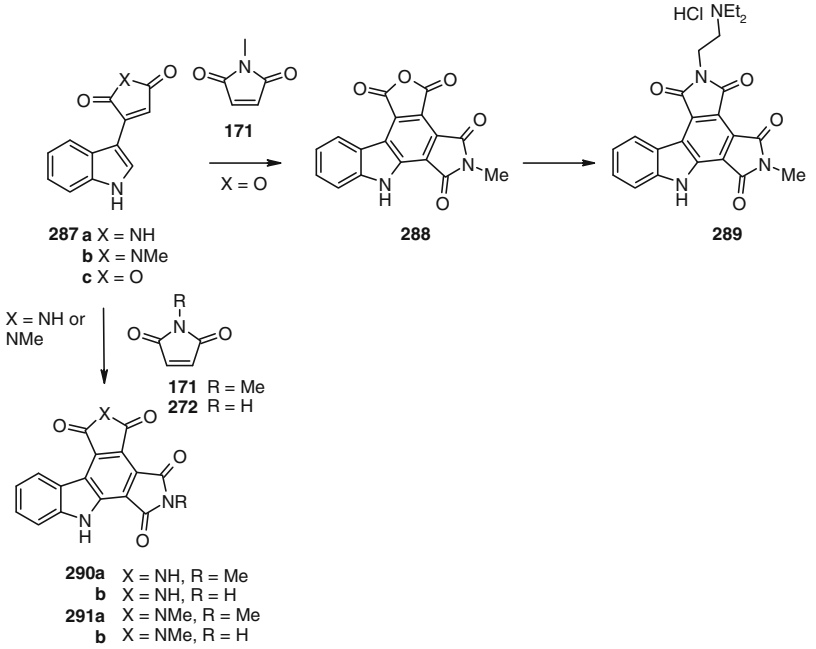
220 R_2 = Ph
278 R_2 = Et

283 R_2 = Ph
284 R_2 = Et

285 R_2 = Ph
286 R_2 = Et

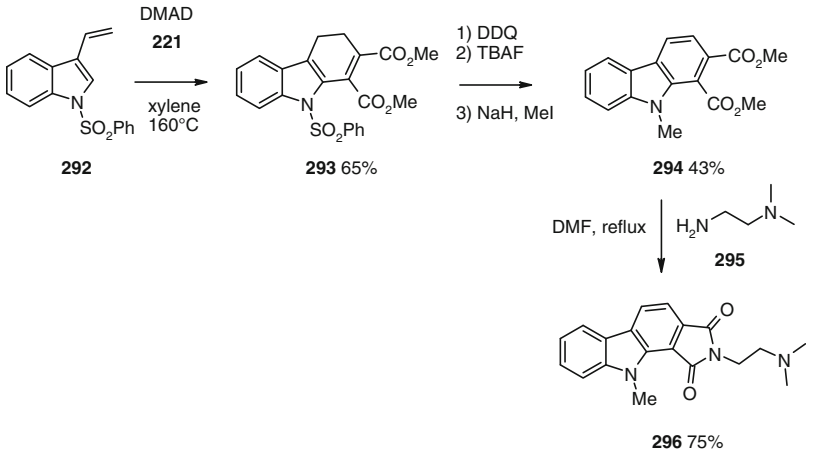
Scheme 60

In a work aimed at synthesizing granulatimide analogs in which the imidazole ring is replaced with a maleimide, Prudhomme and coworkers used the cycloaddition between a 3-maleimide-substituted indole derivative (i.e., **287a–b**) and another maleimide unit as the key step (Scheme 61) [102]. Thus, the reactions between indoles **287a** or **287b** with maleimides **171** and **272**, after aromatization of the initial [4+2] cycloadducts, led to the formation of the pentacyclic granulatimide analogs **290a–b** and **291a–b**. In an effort to prepare analogs corresponding to the more potent and biologically active rebeccamycins, **287b** was converted to the corresponding anhydride **287c** and then treated with *N*-methylmaleimide (**171**) to furnish the cycloadduct **288.** The reaction of diethylaminoethylamine with **288** then produced **289** [103].



Scheme 61

Bailly and coworkers were interested in synthesizing structures containing a carbazole nucleus with a fused imide ring and examining their effects on DNA, human topoisomerases, and P388 leukemia cells [104]. Thus, the Diels–Alder reaction between the 3-vinylindole species **292** and DMAD (**221**) was used as the key synthetic step to provide the cycloaddition product **293**. This cycloadduct was in turn oxidized to the carbazole moiety **294**, bearing a diester functionality that could then be cyclized with an appropriate amine **295** to produce the *N*-substituted imide ring in the final product **296** (Scheme 62).

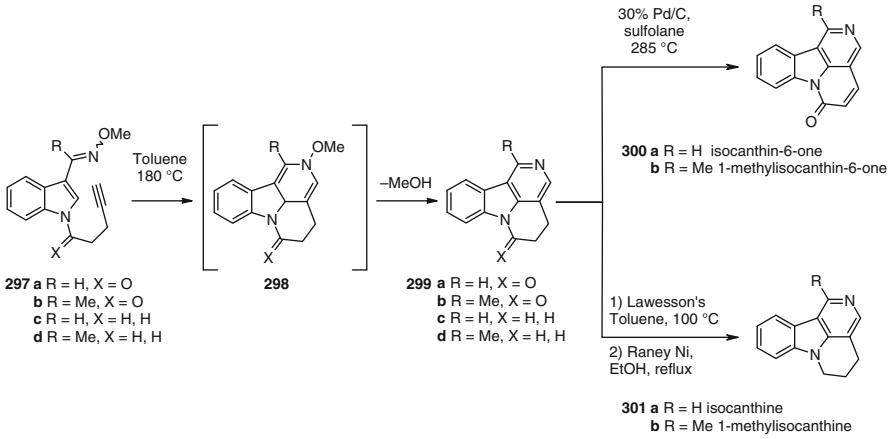


292 **293** 65% **294** 43% **296** 75%

Scheme 62

4.6 *Application of Diels–Alder Reactions with 3-Vinylindoles in the Synthesis of β- and γ-Carboline Alkaloids*

In an elegant example, Markgraf and coworkers were able to make use of the *intramolecular* Diels–Alder reactions of 1*H*-indole-3-carbaldehyde *O*-methyl-oximes **297a–b** with an alkyne tethered to the indole nitrogen as the key step to construct the tetracyclic core structures for isocanthin-6-one (**300a**) [105] and 1-methylisocanthine (**300b**) in a very efficient manner (Scheme 63) [106]. Thus, the intramolecular [4+2] cycloadditions with **297a–b**, and subsequent elimination of methanol, followed by oxidation of the resulting carbolines **299a–b** led to the



297 a R = H, X = O
b R = Me, X = O
c R = H, X = H, H
d R = Me, X = H, H

298

299 a R = H, X = O
b R = Me, X = O
c R = H, X = H, H
d R = Me, X = H, H

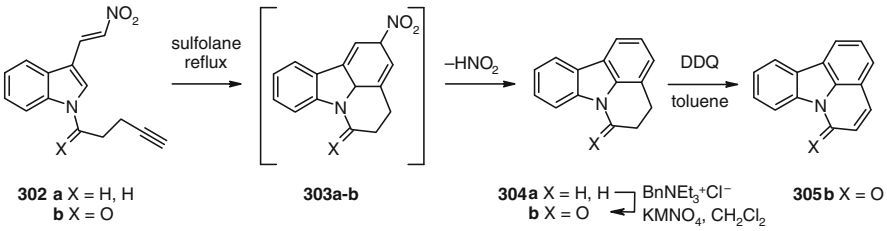
300 a R = H isocanthin-6-one
b R = Me 1-methylisocanthin-6-one

301 a R = H isocanthine
b R = Me 1-methylisocanthine

Scheme 63

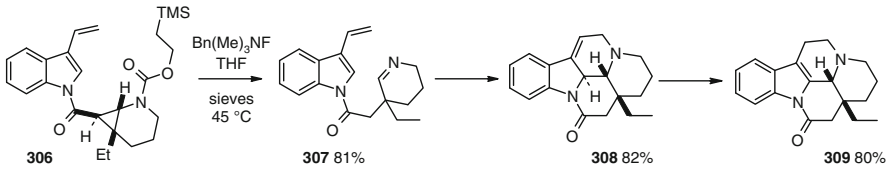
formation of **300a–b** in a short synthetic sequence. Interestingly, when starting materials in which the alkyne was tethered to the indole nucleus through an alkyl linkage (**297c–d**) instead of an amide (as in **297a–b**) were used, the intramolecular cycloadditions produced either a very low yield (**299c**) or no desired product at all (**299d**). It was proposed that the amide linkage restricts the orientation of the tethered alkyne into a more favorable position for the cycloaddition reaction, whereas with the alkyl tether the alkyne-bearing side chain is much less restricted to rotate, thus making the intramolecular reactions more difficult. Since **297c–d** proved unsuitable substrates for the intramolecular reaction, the amide cycloaddition products **299a–b** were used instead to complete the syntheses of isocanthine (**301a**) and 1-methylisocanthine (**301b**) via conversion to the corresponding thioamide derivatives and subsequent reduction with Raney nickel [106].

Markgraf and coworkers were also able to construct the carbocyclic analogs of canthine and canthin-6-one using a similar strategy [107], this time using the intramolecular cyclizations of tethered alkynes to nitro-substituted 3-vinylindole derivatives **302a–b** (Scheme 64). The intermediates from the cycloaddition then formed the aromatized compounds **304a–b** upon loss of HNO_2. Once again, the cycloaddition reaction with the starting material bearing the amide tether (**302b**) proceeded better (95% yield) than the corresponding reaction with the starting material bearing the alkyl tether (**302a**, 40% yield). The carbocyclic canthine analog **304a** was oxidized with *in situ* generated benzyltriethylammonium permangnate (BTAP) to give a mixture of **304b** and the carbocyclic analog of canthin-6-one **305b**. Alternatively, **305b** could also be prepared via the oxidation of **304b** with DDQ.



Scheme 64

Greico and Kaufman used a similar strategy, this time involving the Diels–Alder reaction of 3-vinylindole with an appropriately tethered imine, to construct the pentacyclic eburnamonine structure in a very efficient manner [108] (Scheme 65). At first attempt, the thermal Diels–Alder reaction of imine **307** in 1,2-dichlorobenzene at 180°C afforded the cycloadduct **308** in only 32% yield, and without the formation of eburnamonine (**309**). Next, cycloadditions under acidic conditions were examined. The optimal conditions were found to involve conducting the reaction at 5 M lithium perchlorate–diethyl ether with 0.1 equivalent of camphorsulfonic acid, thus affording the Diels–Alder product **308** in 96% yield.

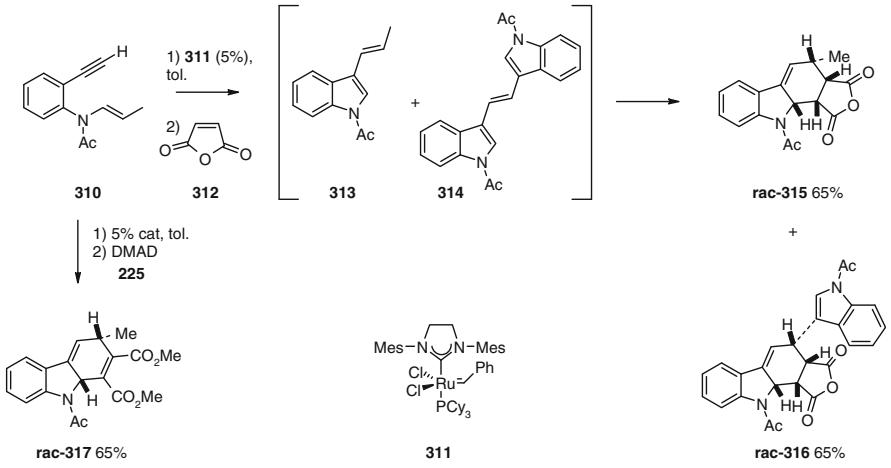


Scheme 65

Interestingly, the cycloaddition reaction proceeded cleanly even without any acid, as long as lithium perchlorate or other lithium salts were added. Alternatively, stirring the imine **307** in ethyl acetate with Florisil at 50°C also led to the formation of the cycloadduct **308** in 82% yield. The final conversion of **308** to (±)-eburnamonine (**309**) required the isomerization of the double bond using deoxygenated 6.0 M sulfuric acid in refluxing ethanol.

4.7 Tandem Reactions and Multicomponent Syntheses

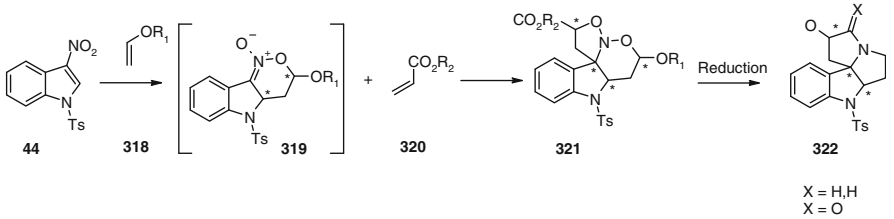
Perez-Castells and coworkers devised a tandem enyne methathesis Diels–Alder reaction strategy for the assembly of polycyclic indole structures [109]. The enyne metathesis reaction using Grubbs's catalyst (**311**) with the 2-alkynylaniline **310** in the absence of a dienophile proceeded to form the mono- and bis-indole derivatives **313** and **314** (Scheme 66). Testing the hypothesis that a Diels–Alder cycloaddition with an activated diene might be faster than the undesired cross-metathesis reaction which led to the formation of **314**, a one-pot reaction with maleic anhydride (**312**) as the dienophile was conducted. Disappointingly, the above reaction resulted in a



Scheme 66

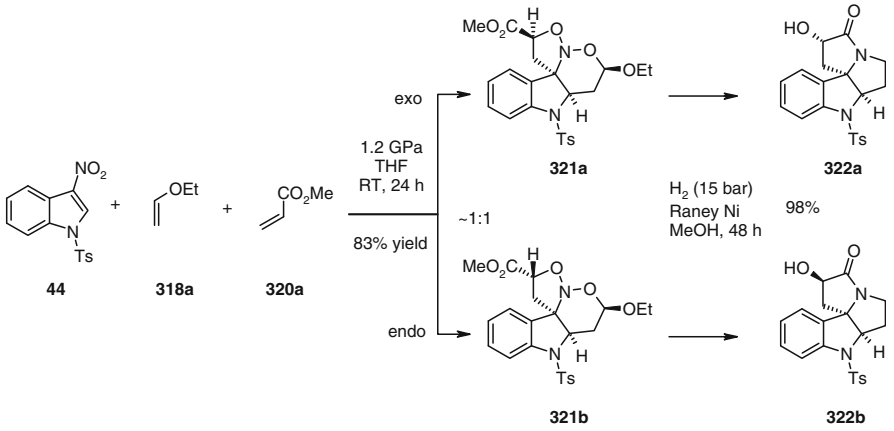
1:1.5 mixture of cycloadducts **315** and **316**. However, with DMAD (**221**) as the dienophile, only a single product (**317**) resulting from the enyne metathesis followed by cycloaddition was obtained in good yield.

Chataigner and Piettre examined using a 3-nitroindole species in a domino process that would make use of an inverse electron demand Diels–Alder reaction, followed by a [3+2] cycloaddition with an electron-deficient olefin [110] (Scheme 67). They chose an alkyl vinyl ether (**318**) as the electron-rich dienophile for the Diels–Alder step, and an acrylic acid ester (**320**) as the electron-poor olefin for the [3+2] reaction, hoping that the product from the multicomponent reaction (**321**) could then be reduced to form the tetracyclic structure **322**.



Scheme 67

At first attempt, simply mixing the starting materials **44**, **318a**, and **320a** at room temperature in dichloromethane resulted in a low yield (20%) of products **321a** and **321b**. A number of alternative reaction conditions were tried to optimize the above tandem process, including Lewis Acid catalysis, higher temperature, and microwave conditions. Of all the variations investigated, hyperbaric conditions were found to produce the best result (Scheme 68). Remarkably, although this multicomponent reaction could theoretically lead to the formation of eight diastereomers, only two were formed in the product mixture and were readily separable. Based on



Scheme 68

these results, it was concluded that the Diels–Alder reaction apparently proceeded with complete *endo* selectivity, while the subsequent [3+2] cycloaddition occurred with a preference for attack from the bottom face of the Diels–Alder product, resulting in only a mixture of isomers at the carbon atom bearing the ester functionality. The nitrosoacetals **321a** and **321b** were then converted by catalytic hydrogenation to the α–hydroxylactams **322a** and **322b**, respectively, with no observed loss of stereochemistry. Other acrylic acid esters, such as *t*-butyl, phenyl, and 1-naphthyl esters, also underwent the multicomponent reaction to produce the corresponding products in good yields (83–99%) and with good *endo* selectivity.

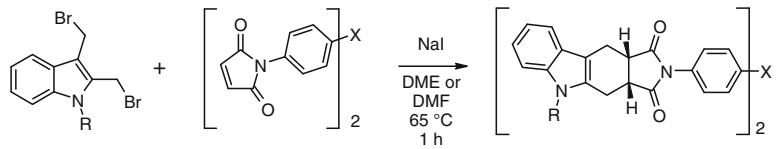
5 Indoles as Dienes: Noncyclic Indolo-2,3-quinodimethanes

Ortho-quinodimethanes have been used in numerous synthetic applications for the construction of various polycyclic ring systems found in structurally complex target molecules, via [4+2] Diels–Alder type cycloadditions. In this context, indolo-2,3-quinodimethanes have become increasingly useful as synthetic precursors to a variety of interesting [*b*]annelated indoles, carbazoles, and alkaloids [111].

There have already been a few excellent reviews published on the synthesis and utility of indolo-2,3-quinodimethanes [112, 113]. In this chapter, we will mainly focus on the more recent papers that have appeared in the literature since the above reviews appeared in press.

5.1 Indolo-2,3-quinodimethanes from Bis(bromomethyl)indoles

Pindur and coworkers have reported the *in situ* generation and subsequent Diels–Alder reactions of *N*-substituted 2,3-quinodimethanes with a variety of maleimides [95]. Thus, treatment of bis(bromomethyl)indoles **323a–c** with maleimides **324a–c** in a 2:1 molar ratio, in the presence of sodium iodide (DME or DMF, 65°C, 1 h), produced the corresponding double Diels–Alder adducts **325** in 60–79% yield (Scheme 69). In all cases, the products formed were the *meso* isomers, as would be expected from the preference for the *endo* approach, as well as *cis*-selectivity (with respect to the dienophiles).



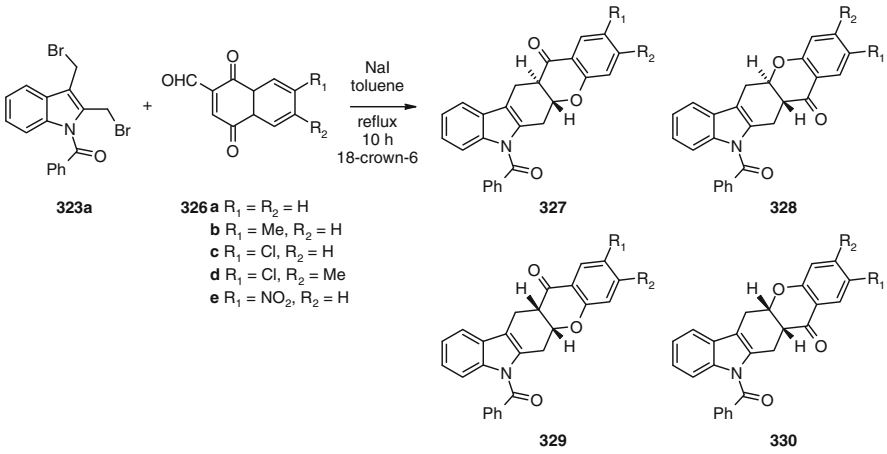
323a R = Bz
b R = SO_2Ph
c R = Ac

324a X = CH_2
b X = SO_2
c X = CO

325

Scheme 69

Similarly generated indolo-2,3-quinodimethanes also participated in Diels–Alder reactions with 3-formylchromones **326a–e**, resulting in the formation of a variety of cycloaddition products, due to non-regioselective reactions (Scheme 70) [114, 115]. The formation of the *trans* diastereomers **327** and **328** was attributed to the enolization of the expected *cis* cycloadducts **329** and **330** during purification on silica gel and subsequent conversion to the more stable *trans* isomers. The authors noted that the choice of toluene as solvent and 18-crown-6 as the phase transfer catalyst were crucial for obtaining synthetically useful yields of the various reaction products (in a related paper, an interesting side product was reported, which was formed from the reaction of a similarly generated indolo-2,3-quinodimethane species with the exo-methylene double bond of another indole moiety [116]).

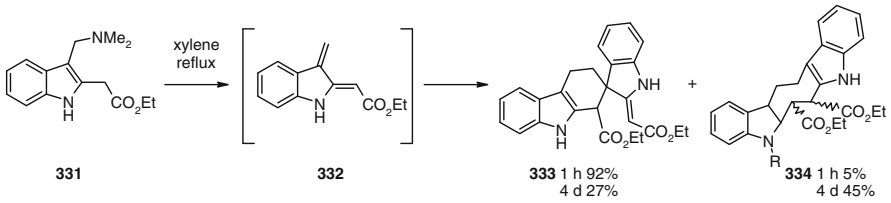


Scheme 70

5.2 *Indolo-2,3-quinodimethanes from Gramine Derivatives*

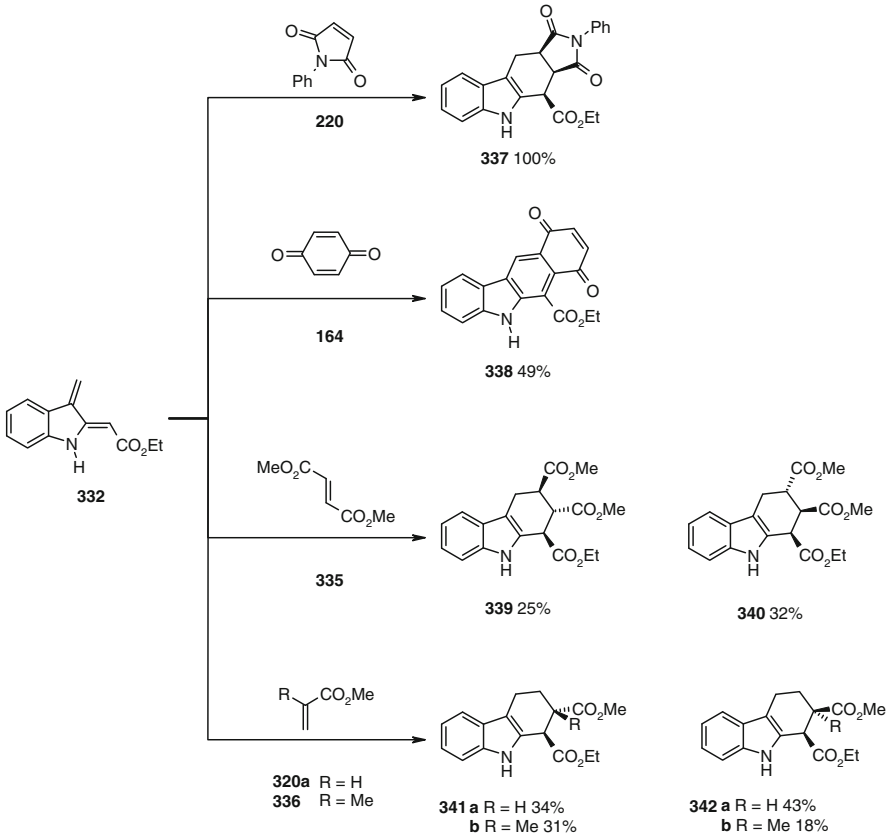
Lévy and coworkers reported the *in situ* generation of an indolo-2,3-quinodimethane species **332** from the thermolysis of ethyl 3-dimethylaminomethyl-2-indolylacetate (**331**) in refluxing xylene (1 h) and its subsequent dimerization to form the spirocyclic derivative **333** in 92% yield (Scheme 71) [117]. The formation of an eight-membered ring side product (**334**) was also observed (5% yield). Prolonged heating (4 days) of gramine **331** resulted in a higher yield of **334** (45%), at the expense of the spirocyclic derivative **333** (27% yield), thus suggesting that **333** is a precursor for **334** via a thermal rearrangement process.

In an accompanying paper [118], Lévy and coworkers further investigated the Diels–Alder reactivity of the indolo-2,3-quinodimethane species **332** above (generated *in situ* from gramine **331**, under refluxing conditions in toluene for 2 h) with a



Scheme 71

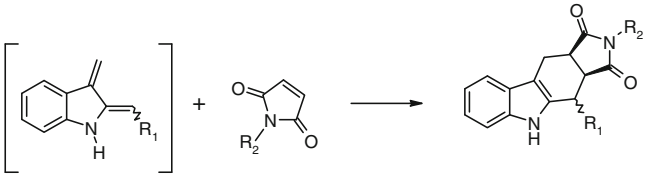
variety of dienophiles (Scheme 72). In the presence of *N*-phenylmaleimide (**220**), the *endo* [4+2] cycloaddition product, namely the tetrahydrocarbazole **337**, was formed in quantitative yield. A similar reaction with dimethyl maleate (**335**) resulted in the formation of the two cycloadducts **339** (25%) and **340** (32%). When methyl acrylate (**320a**) or methyl methacrylate (**336**) were used as dienophiles, the corresponding [4+2] adducts **341a** and **342a** (for methyl acrylate), and **341b** and **342b** (for methyl methacrylate), were isolated. Thus, the regiospecific cycloadditions appear to proceed with lack of stereospecificity. Finally, the *in situ* formation of **332** in the presence of



Scheme 72

p-benzoquinone (**164**) led to the formation of the naphthoquinone derivative **338** (due to overoxidation of the cycloaddition product by quinone).

Interestingly, activation of the 2-methylene unit with the ester moiety was not required for the successful outcome of the above Diels–Alder reactions. Thus, the indole analogs **343a–e** participated in [4+2] cycloaddition reactions with maleimides **171**, **220**, and **344** to produce the cycloadducts **345a–e** in 40–75% yields (Scheme 73).



343a R_1 = Ph
b R_1 = TMP
c R_1 = H
d R_1 = Et
e R_1 = $CH_2NMe(CH_2)_2NMe_2$

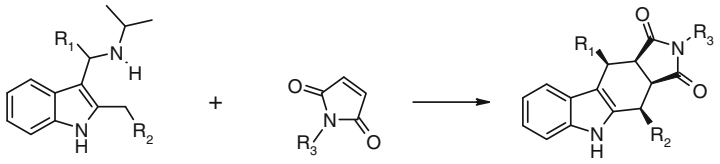
171 R_2 = Me
220 R_2 = Ph
344 R_2 = Bn

345 a R_1 = Ph, R_2 = Bn
b R_1 = TMP, R_2 = Bn
c R_1 = H, R_2 = Ph
d R_1 = Et, R_2 = Me
e R_1 = $CH_2NMe(CH_2)_2NMe_2$, R_2 = Bn

Entry	Diene	Dienophile	Product	Yield
1	**343a**	**344**	**345a**	43%
2	**343b**	**344**	**345b**	75%
3	**343c**	**220**	**345c**	56%
4	**343d**	**171**	**345d**	70%
5	**343e**	**220**	**345e**	40%

Scheme 73

Next, similar reactions were carried out between maleimides **171** and **344**, and gramines **346a–c**, which bear a substituent at the 2-methylene position (Scheme 74).



346 a R_1 = Me, R_2 = CO_2Et
e R_1 = Ph, CO_2Et
c R_1 = R_2 = Ph

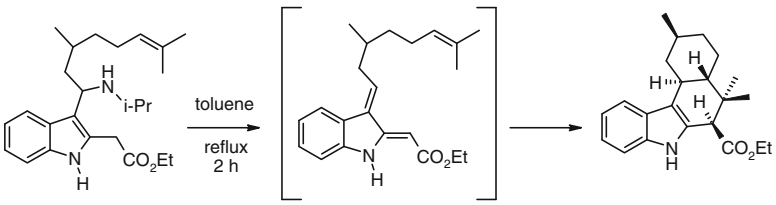
171 R = Me
344 R = Bn

347a-c

347	R_1	R_2	R_3	Yield
a	Me	CO_2Et	Me	100%
b	Ph	CO_2Et	Me	96%
c	Ph	Ph	Bn	55%

Scheme 74

Finally, an intramolecular Diels–Alder reaction with an indolo-2,3-quinodimethane derivative prepared from a gramine precursor was investigated. In this manner, gramine **348** was heated at reflux in toluene (2 h) to produce the tetracyclic product **350** (34% yield) (Scheme 75), thus demonstrating the excellent stereocontrol inherent



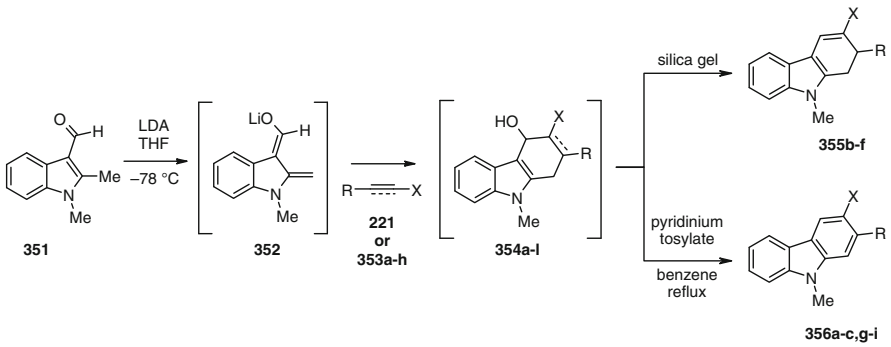
348 349 350

Scheme 75

in these [4+2] cycloaddition reactions. Remarkably, the three newly constructed chiral centers were formed with complete control of relative stereochemistry.

5.3 In Situ *Generated Indole-2,3-dienolates as Indolo-2,3-quinodimethanes*

Junjappa and coworkers briefly investigated the generation of indole-2,3-dienolates via a LDA-induced deprotonation of 1,2-dimethylindole-3-carboxaldehyde (**351**) at −78°C. The dienolate species **352** thus generated then participated in highly regioselective [4+2]-cycloadditions with a number of electron-poor dienophiles (**221**, **353a–h**) (Scheme 76) to produce a variety of substituted dihydrocarbazole



351 352 221 or 353a-h 354a-l

#	dienophile	product	R	X	yield
221	$MeO_2CC{\equiv}CCO_2Me$	**356a**	CO_2Me	CO_2Me	76%
353a	CH_2=CH-CN	**355b**	H	CN	78%
353a	CH_2=CH-CN	**356b***	H	CN	76%
353b	CH_2=CH-CO_2Et	**355c**	H	CO_2Et	84%
353b	CH_2=CH-CO_2Et	**356c***	H	CO_2Et	72%
353c	CH_2=CHCOMe	**355d**	H	COMe	80%
353c	CH_2=CHCOMe	**356d***	H	COMe	76%
353d	EtO_2CCH=$CHCO_2Et$	**355e**	CO_2Et	CO_2Et	73%
353e	C_6H_5CH=$CHCO_2Me$	**355f**	C_6H_5	CO_2Me	79%
353f	C_6H_5CH=$CHNO_2$	**356g**	C_6H_5	NO_2	72%
353g	O_2NCH=$C(SMe)_2$	**356h**	SMe	NO_2	68%
353h	$MeO_2C(CN)CH$=$C(SMe)_2$	**356i**	SMe	CN	69%

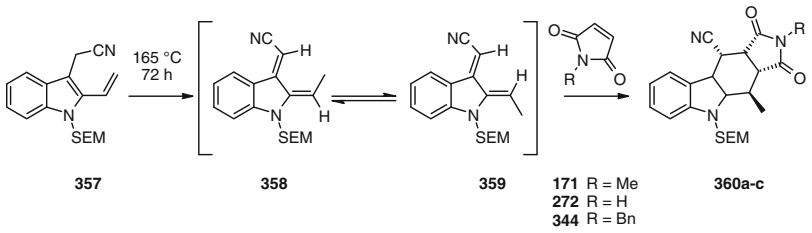
* Obtained after refluxing with TsOH

Scheme 76

derivatives **355**, which could be converted to the corresponding carbazoles **356** upon treatment of the crude reaction mixtures with pyridinium tosylate in refluxing benzene for 24 h [119]. With unsymmetrical dienophiles, the regioselectively could be explained with the nucleophilic end of the indole dienolate forming a bond with the electrophilic terminus of the dienophile.

5.4 *Indolo-2,3-quinodimethanes from 3-Cyanomethyl-2-vinylindoles*

Laronze and Sapi investigated the thermal conversion of 3-cyanomethyl-2-vinylindoles to indole-2,3-quinodimethanes via a [1,5]-H shift [120]. The choice of the protecting group on the indole nitrogen proved crucial to the success of the [1,5]-H shift, as well as the stereochemical outcome of the subsequent Diels–Alder reaction. The SEM group was demonstrated to be the protecting group of choice. Thus, the cycloaddition reactions of the 3-cyanomethyl-2-vinylindole **357** with maleimides **171**, **272**, and **344** led to the formation of tetracyclic derivatives **360a–c** (bearing a 1,4-*trans* relationship between the cyano and methyl substituents) as the major products (Scheme 77). Presumably, the diene **359** is the thermodynamically favored diene formed as a result of the [1,5]-H shift, thus accounting for the predominant formation of the *trans* cycloadducts.



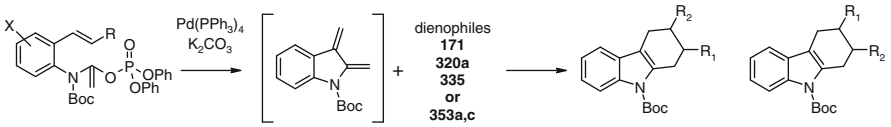
368	R	Yield	total 1,4-cis CN and Me
a	H	35%	12%
b	Me	68%	11%
c	Bn	59%	9%

Scheme 77

5.5 *Indolo-2,3-quinodimethanes from Intramolecular Heck Reactions of α-Phosphono Enecarbamates*

Fuwa and Sasaki have recently reported an interesting approach to the synthesis of nitrogen heterocycles via a tandem intramolecular Heck/Diels–Alder cycloaddition

cascade [121]. Thus, the intramolecular Heck reaction of α-phosphono enecarbamate **361a** resulted in the generation of the corresponding indole-2,3-quinodimethane **362**, which in turn underwent Diels–Alder cycloadditions with a number of dienophiles to produce the resulting tetrahydrocarbazoles **363a–e** and **364a–e** in good yields (Scheme 78). The reaction cascade proceeded in better yields in polar solvents (DMF, dioxane, CH_3CN) and with lower yields in THF and toluene. The reactions were not highly regioselective, regardless of the choice of solvent or reaction temperature.



361a
R = H, X = H

362

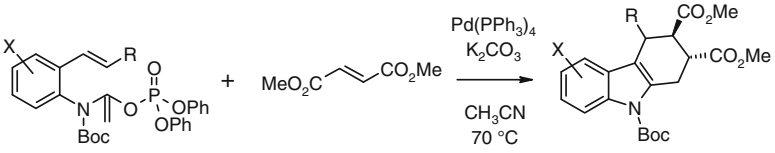
363a-e

364a-e

entry	dienophile	conditions	R_1	R_2	yield	Product(s)
1	**320a**	DMF, 80 °C	CO_2Me	H	75%	2:1 **363a:364a**
2	**320a**	Dioxane, 80 °C	CO_2Me	H	75%	2:1 **363a:364a**
3	**320a**	THF, reflux	CO_2Me	H	59%	2:1 **363a:364a**
4	**320a**	Toluene, 100 °C	CO_2Me	H	32%	2:1 **363a:364a**
5	**353a**	DMF, 80 °C	CN	H	61%	2:1 **363b:364b**
6	**353c**	DMF, 80 °C	COMe	H	85%	2:1 **363c:364c**
7	**335**	CH_3CN, 70 °C	CO_2Me	CO_2Me	83%	trans **364d**
8	**171**	CH_3CN, 70 °C			64%	cis **364e**

Scheme 78

To investigate the effects of various substituents on the α-phosphono enecarbamate core structure, a variety of chloro- or methoxy-substituted substrates **361b–h** were prepared and treated with $Pd(PPh_3)_4$, K_2CO_3, and dimethyl fumarate (**335**) in CH_3CN at 70°C. In all cases, the desired tetrahydrocarbazoles **364** were formed in good to excellent yields (Scheme 79).



361b-h

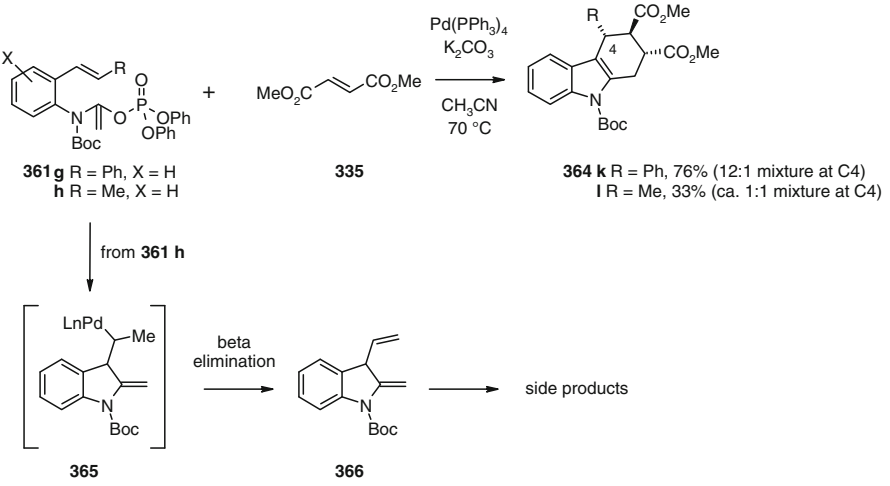
335

364f-l

#	R	X	yield	product
361b	H	3-MeO	75%	**364f**
361c	H	4-MeO	76%	**364g**
361d	H	5-MeO	85%	**364h**
361e	H	4-Cl	93%	**364i**
361f	H	5-Cl	91%	**364j**
361g	Ph	H	76%	12:1 diastereomers **364k**
361h	Me	H	33%	1:1 diastereomers **364l**

Scheme 79

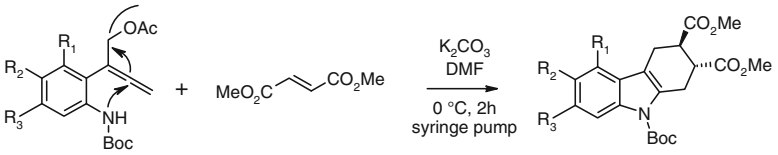
Upon closer examination, one possible limitation of this chemistry was illustrated when the effects of substitutions on the vinyl group were investigated. In the case of the cycloaddition reaction between dimethyl fumarate (**335**) and the phenyl-substituted α-phosphono enecarbamate **361g**, the desired carbazole **364k** was formed as a 12:1 mixture of diastereomers at C4 (favoring the all *trans* product shown) in 76% yield (Scheme 80). When the methyl-substituted analog **361h** was used, however, the desired carbazole **364l** was formed in poor yield (33%) and with complete lack of stereocontrol (ca. 1:1 mixture of diastereomers at C4). The low yield for the attempted cycloaddition with **361h** was explained by an undesired β-elimination reaction of the cyclopalladation intermediate **365** and subsequent side reactions resulting from the newly formed diene **366**.



Scheme 80

5.6 *Indolo-2,3-quinodimethanes from Intramolecular Heck Reactions of α-Phosphono Enecarbamates*

Mukai and coworkers have developed a novel method for the generation of indolo-2,3-quinodimethanes, using *ortho*-allenylanilines as precursors [122]. After some initial screening, the acetates **367a–f** were chosen as the optimal substrates for the base-promoted generation of the corresponding quinodimethane species, and subsequent cycloadditions with dimethyl fumarate (**335**), to produce the tetrahydrocarbazoles **368a–f** (Scheme 81). It was found that the reactions worked best if



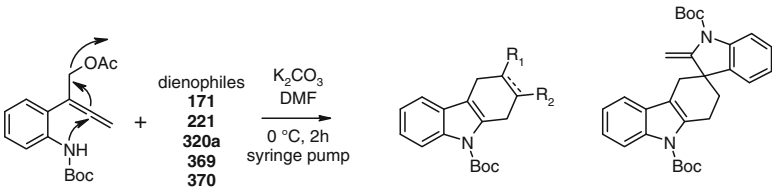
367a-f **335** **368 a-f**

368	R_1	R_2	R_3	
a	H	H	H	93%
b	OMe	H	H	81%
c	H	OMe	H	79%
d	H	$-OCH_2O-$		54%
e	H	CO_2Et	H	69%
f	H	Cl	H	56%

Scheme 81

the acetate substrates **367** were added via a syringe pump (2 h) to a suspension of the dienophile **335** and 3 equivalent of K_2CO_3 in DMF at 0°C.

To further investigate the scope of this methodology, the reactions of allenylaniline **367a** with a variety of dienophiles were next examined. In sharp contrast to the reaction with dimethyl fumarate (**335**) above, the attempted cycloaddition of **367a** with the *cis* isomer dimethyl maleate (**369**) resulted in only a 7% yield of the desired cycloadduct **371a** (Scheme 82). The major product isolated was instead the dimer **372** (85%). A similar outcome was also observed for methyl propiolate (**370**). However, the remaining dienophiles produced mainly the desired cycloadducts **371b–d**, with varying amounts of dimer **372** as the by-products.



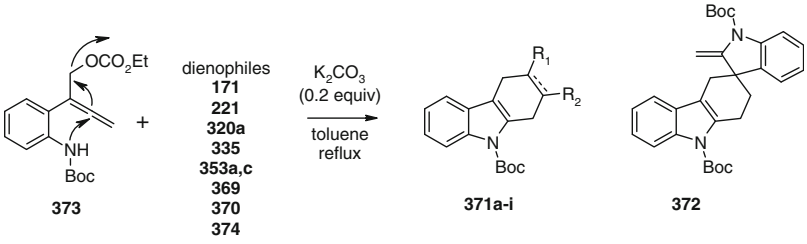
367a **371a-e** **372**

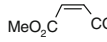
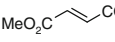
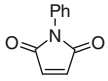
#	dienophile	R_1	R_2	Product(s)
369	MeO_2C CO_2Me	CO_2Me	CO_2Me	cis **371a** (7%), **372** (85%)
171	Ph N O O	Ph N O O		cis **371b** (87%)
320a	CH_2=CH-CO_2Me	CO_2Me, H		**371c*** (52%), **372** (30%)
221	$MeO_2CC{\equiv}CCO_2Me$	CO_2Me	CO_2Me	olefin **371d** (48%), **372** (17%)
370	H-C≡CCO_2Me	CO_2Me, H		olefin **371e** (8%), **372** (76%)

* mixture of regioisomers

Scheme 82

The above findings, particularly the unacceptably low yield for the attempted cycloaddition reaction with dimethyl maleate (**369**), prompted Mukai and coworkers to further investigate the choice of leaving group (i.e., acetate) in the allenylaniline starting materials. These efforts led to the discovery that the ethyl carbonate derivative **373**, when treated with a *sub-stoichiometric* amount of K_2CO_3 (0.2 equiv), provided the optimal conditions for the generation and cycloaddition reactions of indolo-2,3-quinodimethane species [123]. Thus, heating a toluene solution of **373** and dimethyl maleate (**369**) at reflux in the presence of 0.2 equiv of K_2CO_3 for 1 h provided the desired cycloaddition product **371a** in 82% yield (+4% of the trans diastereomer), with only a minor amount (13%) of the undesired dimer **372** as the by-product (Scheme 83). A variety of other olefinic or acetylenic dienophiles also provided the desired carbazole derivatives in good yields under similar reaction conditions. Impressively, the reaction of **373** with methyl propiolate (**370**) produced the corresponding carbazole derivative **371e** in 70% yield, a dramatic improvement over the corresponding reaction with **367a** as starting material. Even a non-electron-deficient dienophile such as styrene (**374**) participated in the cycloaddition reaction under these improved conditions.



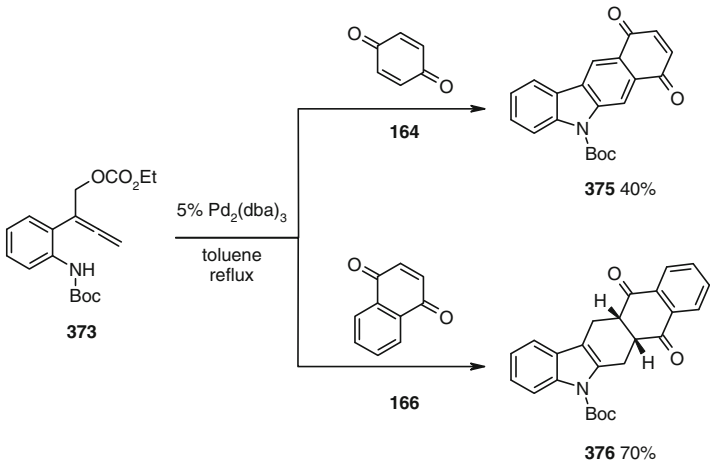
#	dienophile	time	R_1	R_2	product
369		1	CO_2Me	CO_2Me	cis **371a** (82%), **372** (13%)
335		2.5	CO_2Me	CO_2Me	trans **371f** (93%)
320a	CH_2=CH-CO_2Me	3	CO_2Me, H		61:30* **371c** (91%)
353a	CH_2=CH-CN	1	CN, H		**371g** (82%)
353c	CH_2=CHCOMe	1	COMe, H		62:20* **371h**, **372** (14%)
221	$MeO_2CC{\equiv}CCO_2Me$	1.5	CO_2Me	CO_2Me	olefin **371d** (93%)
370	H-C≡CCO_2Me	2	CO_2Me, H		47:23* olefin **371e** (70%)
171		9			cis **371b** (34%), **372** (23%)
374	CH_2=CH-Ph	9	Ph, H		36:4* **371i** (40%), **372** (11%)

* ratio of 2 regioisomer to 3 regioisomer

Scheme 83

Despite significantly expanding the reaction scope, the improved conditions described above were not suitable to effect the desired cyclization of **373** with *p*-quinone (**164**) or naphthoquinone (**166**), presumably due to the instability of

the quinones under the basic reaction conditions. To circumvent this limitation, the indolo-2,3-quinodimethane species was instead prepared by treatment of the "allylic" carbonate **373** with Pd(0). Thus, when a toluene solution containing **373** and *p*-quinone (**164**) was heated at reflux in the presence of 5 mol% $Pd_2(dba)_3$ for 10 min, the desired [4+2] product **375** was formed in 40% yield. Similarly, treatment of **373** with 1,4-naphthoquinone (**166**) under Pd-catalyzed conditions resulted in the formation of the cycloadduct **376** in 70% yield (Scheme 84).



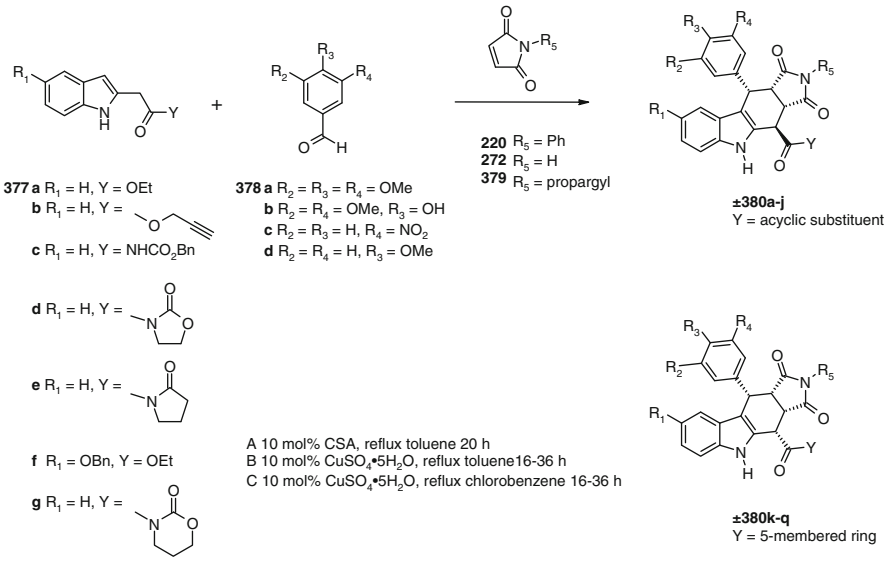
Scheme 84

It should be noted that while particularly advantageous for the above reactions with quinone derivatives, the Pd-mediated generation of indolo-2,3-quinodimethanes is not suitable when acetylenic dienophiles are used, as both DMAD (**221**) and methyl propiolate (**370**) tend to undergo Pd-catalyzed trimerization reactions. Nevertheless, the approaches developed by Mukai and coworkers offer an elegant and useful access route to a variety of indolo-2,3-quinodimethanes and their subsequent Diels–Alder reaction products.

5.7 Multicomponent Synthesis with Indole-2,3-quinodimethanes

Wong and coworkers recently reported an interesting application of multicomponent synthesis to the preparation of aryl-pyrrolo-tetrahydrocarbazoles, via the *in situ* formation of indolo-2,3-quinodimethanes and subsequent [4+2] cycloadditions with maleimides [124]. A variety of indoles **377a–g** were treated with aldehydes **378a–d** and maleimides **220**, **272,** and **379** in the presence of $CuSO_4.5H_2O$

(10 mol%), to produce the cycloadducts **380a–q** in yields ranging from 44% to 90% (Scheme 85). Remarkably, in most cases, only one product featuring a set relative stereochemistry was isolated in racemic form. Interestingly, for indoles bearing acyclic Y-substituents, the cycloadducts **380a–j** were the only ones isolated, while the "all-*cis*" products **380k–q** were formed when the indoles contained a five-membered ring as the Y-substituent were used.



entry	377	378	maleimide	Catalyst	Product	yield
1	**a**	**a**	**220**	B	**±380a**	74%
2	**a**	**b**	**220**	B	**±380b**	65%
3	**a**	**a**	**272**	B	**±380c**	52%
4	**a**	**b**	**272**	C	**±380d**	44%
5	**f**	**a**	**220**	B	**±380e**	47%
6	**c**	**a**	**220**	B	**±380f**	56%
7	**a**	**c**	**220**	B	**±380g**	90%
8	**a**	**d**	**379**	B	**±380h**	76%
9	**b**	**b**	**220**	B	**±380i**	69%
10	**d**	**a**	**220**	B	**±380k**	73%
11	**e**	**a**	**220**	B	**±380l**	68%
12	**d**	**b**	**220**	B	**±380m**	63%
13	**d**	**a**	**272**	B	**±380n**	66%
14	**d**	**b**	**272**	C	**±380o**	54%
15	**d**	**c**	**220**	B	**±380p**	77%
16	**g**	**a**	**220**	B	**±380j,q** (9:1)	59%

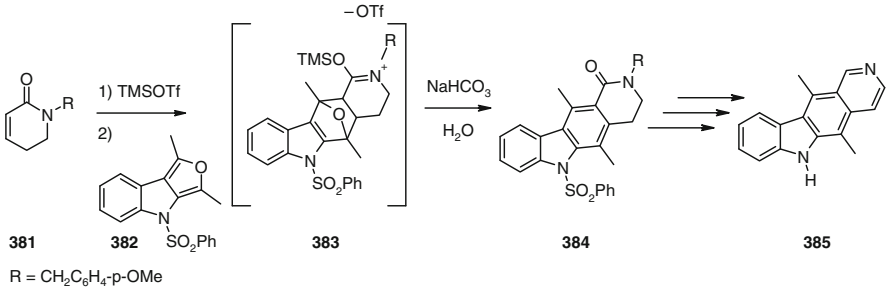
Scheme 85

Using a somewhat similar strategy, Sapi and coworkers [125] have also reported an interesting multicomponent synthesis of carbazoles. While a cycloaddition reaction with a quinodimethane could be postulated as a possible mechanistic pathway for this remarkable reaction, most evidence points in favor of the involvement of a stepwise ionic process.

6 Indoles as Dienes: Fused Cyclic Indolo-2,3-quinodimethanes

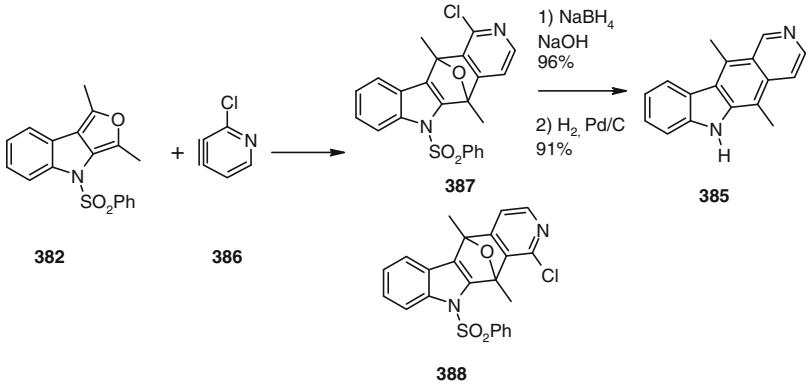
6.1 *Furo[3,4-b]indoles as Indolo-2,3-quinodimethanes Analogs*

The furo[3,4-*b*]indole analogs serve as "fused" indolo-2,3-quinodimethanes and have been widely used in Diels–Alder cycloaddition reactions. Recent publications have reviewed the various methods developed for the synthesis of furo[3,4-*b*]indoles [126], as well as the pioneering work on the utility of these precursors in cycloaddition reactions to produce various heterocyclic derivatives [127]. The early application of [4+2] cycloaddition reactions with furo[3,4-*b*]indoles to the synthesis of natural products was highlighted by the first regioselective Diels–Alder synthesis of ellipticine (**385**), which involved a cycloaddition reaction of the furoindole **382** with a dihydropyridone derivative **381** as the key step (Scheme 86) [128].



Scheme 86

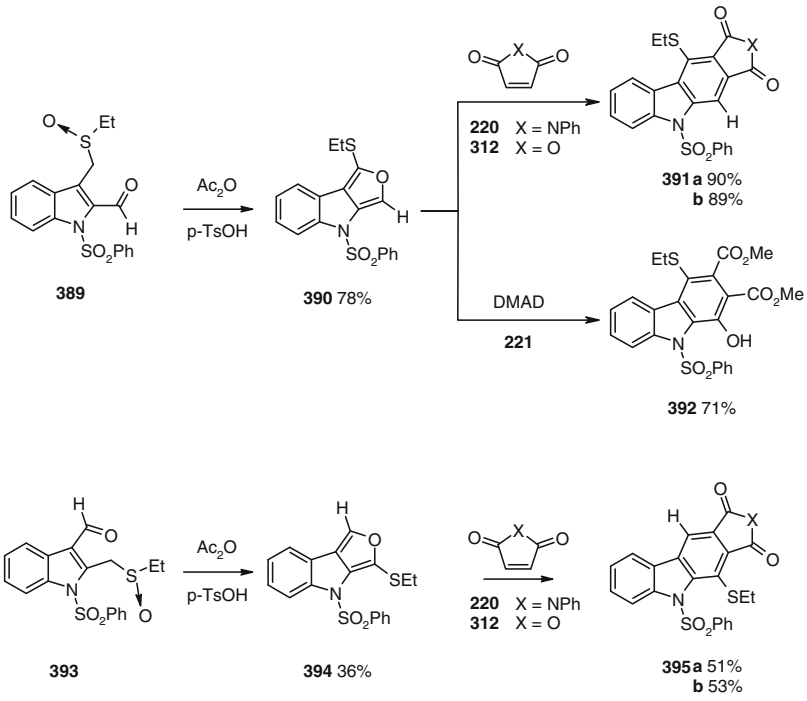
In a conceptually similar approach to ellipticine, Guitián and coworkers [129] used the Diels–Alder reaction of the same indolofuran derivative **382** with the 3,4-didehydropyridine derivative **386**, to produce a mixture of two cycloadducts **387** and **388** (2.4:1) in 89% yield (Scheme 87). The intermediate **387** was then



Scheme 87

converted into ellipticine (**385**) via reductive cleavage of the ether bridge, followed by hydrogenolysis (87% overall yield).

Padwa and Kappe [130] have reported an elegant preparation of furo[3,4-*b*]indoles via a Pummerer rearrangement strategy. Thus, treatment of sulfoxides **389** and **393** with Ac_2O and *p*-TsOH afforded the corresponding ethylthio-substituted furo[3,4-*b*] indole derivatives **390** and **394**, which were then subjected to Diels–Alder cycloaddition reactions with typical dienophiles (e.g., DMAD, maleic anhydride) to produce a variety of substituted carbazoles **391a–b**, **392**, and **395a–b** (Scheme 88). The lone pair of electrons on the SEt substituent is believed to assist the *in situ* ring opening of the oxobridge of the Diels–Alder cycloadducts and thus lead to the formation of the carbazole derivatives.

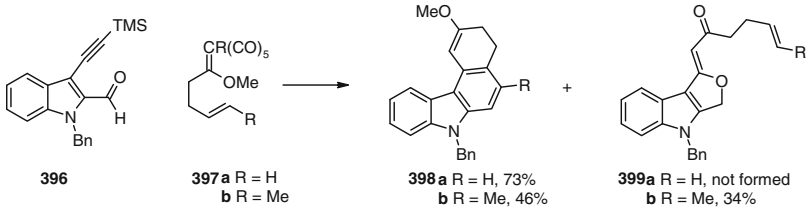


Scheme 88

In addition to the above intermolecular reactions, the *intramolecular* Diels–Alder cycloadditions of furo[3,4-*b*]indoles have also been reported.[1] Herndon and coworkers [131] used the coupling reaction of the *N*-benzylindolynal derivative **396** with Fischer carbenes **397a–b** to obtain the carbazoles **398a–b**, presumably via the

[1]For additional examples, see [127].

in situ formation of furo[3,4-*b*]indole intermediates. In the case of **397b**, an apparently more sluggish Diels–Alder reaction led to the isolation of alkylidenefuranone **399b** as a side product (Scheme 89).



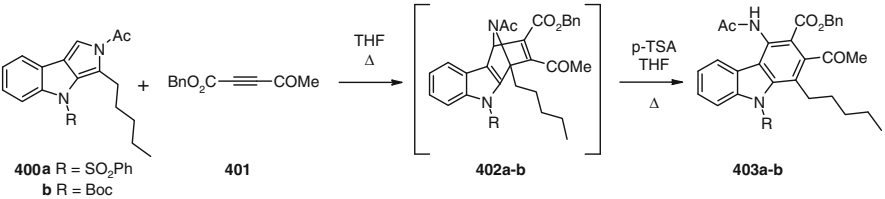
396 **397a** R = H, **b** R = Me → **398a** R = H, 73%; **b** R = Me, 46% + **399a** R = H, not formed; **b** R = Me, 34%

Scheme 89

6.2 *Pyrrolo[3,4-*b*]indoles as Indolo-2,3-quinodimethanes Analogs*

The pyrrolo[3,4-*b*]indoles offer an alternative approach to access indolo-2,3-quinodimethane analogs and have also been used in Diels–Alder cycloaddition reactions with acetylenes to produce a variety of substituted carbazoles. The most widely used methods developed for the synthesis of pyrrolo[3,4-*b*]indoles have already been reviewed [126, 127] and thus will not be discussed here.

The pyrrolo[3,4-*b*]indole derivatives **400a–b** undergo synthetically useful Diels–Alder reactions with acetylenic dienophile **401**, and the resulting cycloadducts **402a–b** are readily transformed *in situ* to the corresponding amino-substituted carbazoles **403a–b** following treatment with acid (Scheme 90) [127].

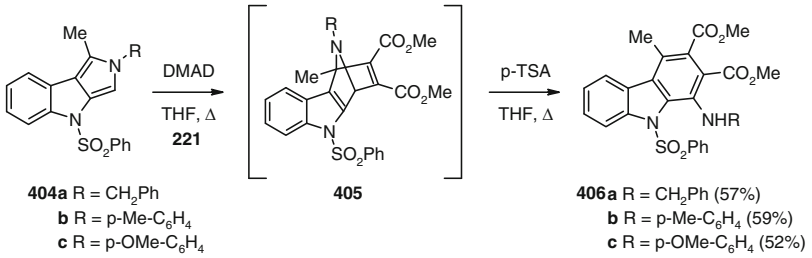


400a R = SO_2Ph, **b** R = Boc; **401**; **402a-b**; **403a-b**

403	R	Yield	regioisomers
a	SO_2Ph	80%	2.8:1
b	Boc	80%	ca. 3:1

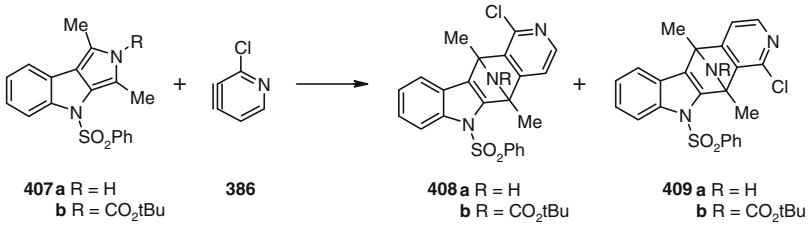
Scheme 90

Similarly, the pyrrolo[3,4-*b*]indole derivatives **404a–c** undergo [4+2] cycloadditions with DMAD (**221**), and the resulting cycloadducts **405a–c** are readily transformed *in situ* to the corresponding amino-substituted carbazoles **406a–c** following treatment with acid (Scheme 91) [132].



Scheme 91

Pyrrolo[3,4-b]indoles also undergo Diels–Alder reactions with aryne derivatives. Thus, the reaction of indolopyrrole **407a** with 2-chloro-3,4-didehydropyridine (**386**) leads to the formation of the corresponding cycloadducts **408a** and **409a** in 44% total yield, with modest regioselectivity (1.7:1 ratio) toward **408a** (Scheme 92). Interestingly, when the more sterically hindered diene **407b** was subjected to similar conditions, a complete loss of regioselectivity was observed, as **408b** and **409b** were formed in a 1:1 ratio (52% total yield) [133].



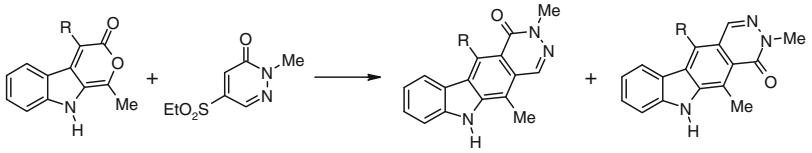
Scheme 92

6.3 *Pyrano[3,4-b]indolones as Indolo-2,3-quinodimethanes Analogs*

Pyrano[3,4-*b*]indole-3-ones serve as another alternative precursor to indolo-2,3-quinodimethane analogs and have been shown to readily participate in Diels–Alder cycloaddition reactions with a variety of electron-deficient dienophiles [112]. For reactions with electron-rich alkenes, however, heating in a sealed tube and very long reaction times (80–120°C, several days) were reported to be necessary [134, 135], thus reducing the usefulness of these reactions as a general synthetic approach.

It is not surprising then that since the publication of the Pindur review [112], there have been a few additional reports highlighting the utility of pyrano[3,4-*b*] indole-3-ones as building blocks in Diels–Alder reactions, all using electron-deficient dienes. Haider et al. [136] investigated the cycloadditions of pyranoindolones

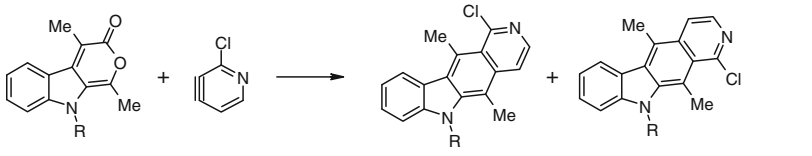
410a–b with the *N*-methyl-pyridazinone derivative **411**. While no reaction occurred at 156°C (in bromobenzene), the cycloaddition with **410a** was effected at a temperature of 190°C in a higher boiling solvent (1,2,4-trichlorobenzene) (Scheme 93). The use of excess pyranoindolone was required, and exclusion of oxygen was crucial to ensure the success of the reaction. Under the optimized conditions, the Diels–Alder reaction, followed by spontaneous elimination of carbon dioxide and ethanesulfinic acid, provided the two regioisomeric products **412a** and **413a** in a 1:3 ratio (43% total yield).



Scheme 93

In the case of the less sterically hindered pyranoindolone **410b**, the cycloaddition with **411** proceeded at a lower temperature of 180°C. More interestingly, the two regioisomeric products **412b** and **413b** were formed in a 3:1 ratio, this time around 48% total yield, with an apparent opposite sense of regiochemical preference. The authors attribute this observed reversal in regioselectivity to steric factors.

More recently, the cycloaddition of pyranoindolones with arynes has been briefly investigated. When **410a** was treated with 2-chloro-3,4-didehydropyridine (**386**), the expected two regioisomeric cycloadducts **415a** and **416a** were formed in a 1:1 ratio (21% total yield) (Scheme 94). Interestingly, when the phenylsulfonyl-protected diene **414** was subjected to similar reaction conditions, cycloadduct **415b** was the only product formed (20% yield). The authors have found no explanation for the different results observed above [133].

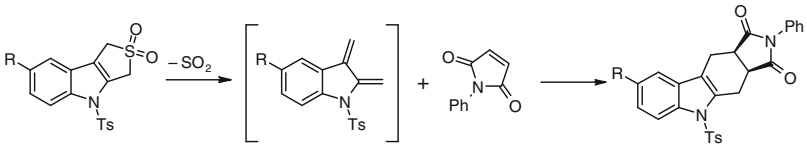


entry	R	yield 415	yield 416
a	H	10%	10%
b	SO_2Ph	20%	not obs.

Scheme 94

6.4 Indolo-3-sulfolenes as Indolo-2,3-quinodimethanes Analogs

The extrusion of SO_2 from heteroaromatic-fused 3-sulfolenes has been successfully used as a general strategy for the synthesis of a variety of *o*-quinodimethane derivatives [137]. This synthetic approach is quite attractive due to the relative ease with which the sulfolenes are prepared, as well as the stability of these versatile precursors. Under thermal conditions (150°C), indolo-3-sulfolenes **417a–b** readily produce the quinodimethane intermediates **418a–b**, which then undergo Diels–Alder cycloaddition reactions with *N*-phenylmaleimide (**220**) to produce the [4+2]-cycloadducts **419a–b** in good yields (Scheme 95) [138].



417a R = H
b R = Br

418a-b

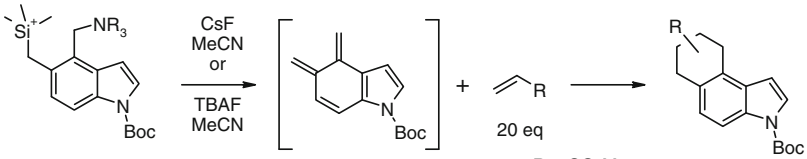
220

419a R = H, 80%
b R = Br, 76%

Scheme 95

6.5 Indolo-4,5-quinodimethane Analogs

An alternative way in which *the benzoid portion* of the indole ring system can be used in Diels–Alder chemistry is by using it as part of an *ortho*-quinodimethane species, which upon cycloaddition with a dienophile would then lead to the formation of interesting tricyclic-fused ring systems. Snieckus and Kinsman [139] used the silylated derivative **420** and the Saegusa-Ito procedure to generate the indolo-4,5-quinodimethane species **421**, which was then trapped with a large excess of olefinic dienophiles (Scheme 96). Using methyl acrylate or acrylonitrile as the dienophile, this procedure resulted in excellent yields of the cycloadducts **422**, albeit as a 3:2 ratio of inseparable regioisomers. Other dienophiles, such as dimethyl fumarate, dimethyl maleate, dimethyl acetylenedicarboxylate, *N*-phenylmaleimide, and diisopropyl azodicarboxylate, were also shown to participate in the cycloaddition reaction.



420

421

320a R = CO_2Me
353a R = CN

422 >95 %

Scheme 96

7 Conclusion

This review has demonstrated that indole derivatives can participate in [4+2] cycloaddition reactions with a wide variety of reaction partners to give an astonishing array of polycyclic frameworks. While in many cases these novel ring structures are curiosities with no current utility, several research groups have used these reactions as key steps in complex natural product syntheses. Not surprisingly, the pyrrole ring of the indole nucleus typically acts as the dienophile or part of the diene; however, notable exceptions exist, which provide entry into unique scaffolds that would be difficult to obtain using other methodology.

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Oxindoles and Spirocyclic Variations: Strategies for C3 Functionalization

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Abstract This chapter provides an overview of emerging strategies for the selective introduction of functionality at oxindole C3. Specific emphasis has been devoted toward asymmetric methods for the introduction of C3 quaternary centers and spirocyclic ring systems. The chapter has been divided into two sections on general methodology for the stereoselective synthesis of oxindoles and spirooxindoles, respectively. A third section is devoted toward efforts in natural product total synthesis involving oxindole or spirocyclic variants as targets or key intermediates.

Keywords Chiral quaternary center · Diastereoselective · Enantioselective · Oxindole · Spirooxindole

Contents

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1 Introduction

In light of their diverse portfolio of regulatory function within systems of biological and medicinal importance, it is no surprise that the bridging and spiraling heterocyclic scaffolds that adorn the natural world have continued to materialize within the creative hands of the synthetic chemist (for a few lead references on oxindole natural product synthesis see [1–5]). And while much has been learned through accelerating efforts to achieve the total synthesis of natural products, controlled access to local chemical environments defined by the asymmetry of quaternary centers remains a significant challenge.

This chapter is a survey of recent works in the general area of oxindole and spirooxindole synthesis with specific attention on strategies for the installation of the C3 quaternary centers that characterize members of this unique family of indole alkaloids. As investigations that have resulted in modest observed selectivities represent important opportunities for further synthetic advancement, those studies will be described alongside illustrations of chemical technologies that represent the state of the art of the discipline.

Within the following sections on general methodology, examples of oxindoles with relatively simple substitution patterns have been selected for making reasonable comparisons between different strategies for bond construction. Applications of methods toward the synthesis of densely functionalized oxindoles within sensitive chemical environments appear within the section on natural product total synthesis.

2 Methods for Quaternization at Oxindole C3

Numerous creative solutions for asymmetric bond installation have been unveiled as a result of experimental efforts directed toward quaternization of oxindole C3. Examples in this section have been broadly categorized on the basis of the nature of the functionality that has been installed at C3 (i.e., C3-carbon, C3-oxygen, or C3-nitrogen bond construction).

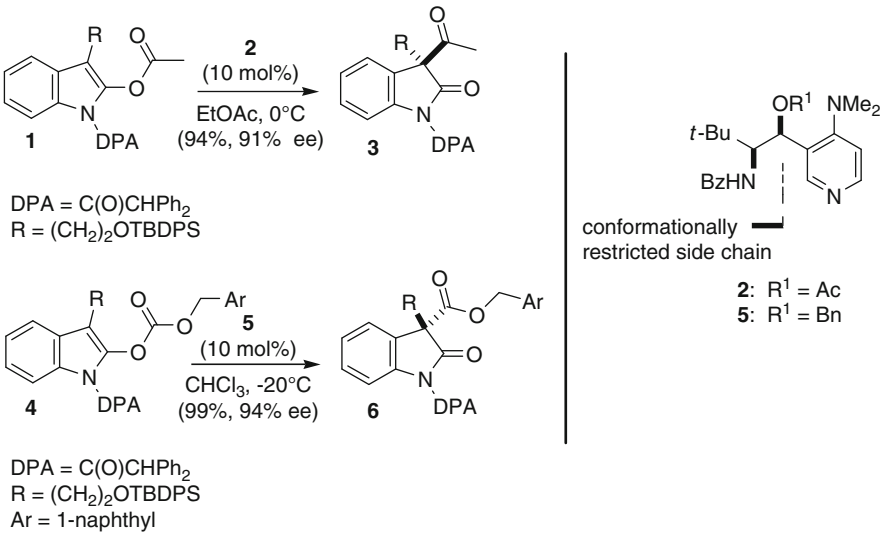
2.1 Construction of All-Carbon Quaternary Centers

The selective construction of all-carbon quaternary centers is a unique challenge within the realm of organic synthesis that has received significant attention in recent years. Many of the synthetic strategies for chiral oxindole synthesis described within this chapter rely on racemic 3-alkyl or 3-aryl oxindole precursors that are available through a manifold of well established synthetic protocols. Although the synthesis of C3 monosubstituted oxindoles will not be treated in detail within this

review, methods for accessing those materials can be found within the references of the works cited herein. A few recent approaches to mono-alkylation or arylation at oxindole C3 have been reported by the Buchwald group [6], Durbin and Wills [7], Jensen and Madsen [8], the Trost group [9], Zhu and coworkers [10], the Felpin group [11], the Yu group [12], Dauban and coworkers [13], and the Grigg group [14].

2.1.1 Functional Group Transfer from C2 to C3

A variety of methods have been developed for the selective installation of chirality at oxindole C3 that involve transfer of functionality from indole C2. The Vedejs group has prepared a small collection of chiral DMAP (4-(*N*,*N*-dimethylamino) pyridine) derivatives bearing conformationally restricted side chains that have been employed as nucleophilic catalysts to direct the transfer of indolyl C2 acetate or carboxylate groups to oxindole C3 with excellent enantiofacial selectivity [15]. As illustrated in Scheme 1, indolyl acetate **1** was converted to the chiral oxindole **3** (94%, 91% ee) using DMAP catalyst **2**, while the opposite sense of enantioselectivity was observed when indolyl carboxylate **4** was treated with DMAP catalyst **5** to afford **6** as the major oxindole adduct (99%, 94% ee). In addition to probing modifications of the DMAP side chains, it was demonstrated that the overall rate of the reaction catalyzed by DMAP **2** was decreased when the indolyl acetate **1** contained a branched isopropyl substituent at C3; however, good enantioselectivity was observed with the branching substituent (82%, 94% ee). It was also



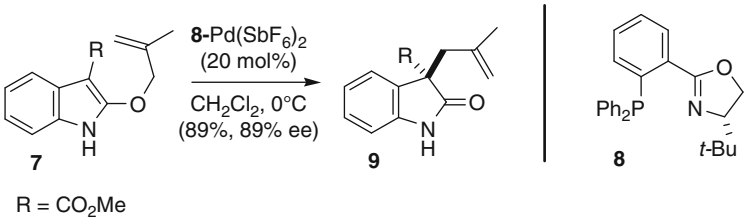
Scheme 1 Conformationally restricted nucleophilic catalysts

demonstrated that the rate of C2 to C3 ester migration was accelerated by the presence of the *N*-acyl protecting group.

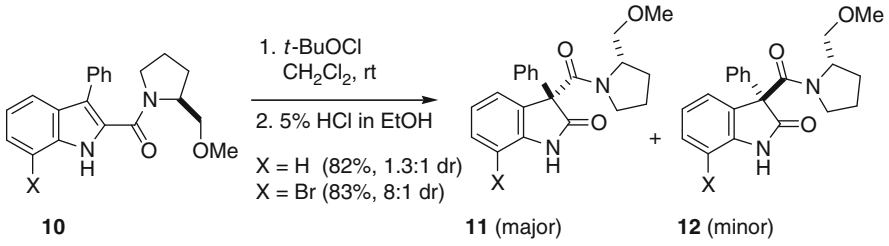
Linton and Kozlowski have installed quaternary centers at oxindole C3 in enantioselective fashion via the Pd-catalyzed rearrangement of 2-allyloxy indoles (Scheme 2) [16]. For example, indole **7** underwent an enantioselective Meerwein–Eschenmoser–Claisen rearrangement in the presence of $Pd(SbF_6)_2$ and the chiral phosphinooxazoline ligand **8** to afford oxindole **9** in 89% yield and 89% ee. A two-point coordination of the chiral palladium catalyst to the C3 carbonyl and C2 oxygen (6-membered coordination system) has been proposed to rationalize the enantioselectivity of the transformation. Modest to good enantioselectivities were also observed for a series of bisphosphine chiral ligands.

Moody and coworkers have observed an intriguing enhancement of diastereoselectivity for the C2 to C3 oxidative rearrangement of indole-2-carboxamides in cases where a bulky substituent was present at indole C7 [17]. Accordingly, oxidative migration of the chiral pyrrolidinamide substituent of **10** (X = H) afforded a 1.3:1 mixture of diastereomeric oxindoles **11** and **12** while similar conversions of the 7-bromo or 7-phenyl analogs of **10** afforded the corresponding oxindoles **11** and **12** in diastereomeric ratios of 8:1 and 11:1, respectively (Scheme 3).

The Movassaghi group has investigated the stereoselective C2 to C3 migration of a 2-phenyl substituent on diastereomerically pure hydroxyindolenines **13** [18]. The requisite hydroxyindolenines were prepared via oxidation of 2-phenyl L-tryptophan with Davis' oxaziridine (3-*n*-butyl-1,2-benzisothiazole-1,1-dioxide oxide). The oxidation step proceeded with modest diastereoselectivity, providing a 2:1 mixture of the (3*R*) and (3*S*)-hydroxyindolenines **13** that were separated. As illustrated for



Scheme 2 Catalytic Meerwein–Eschenmoser–Claisen rearrangement

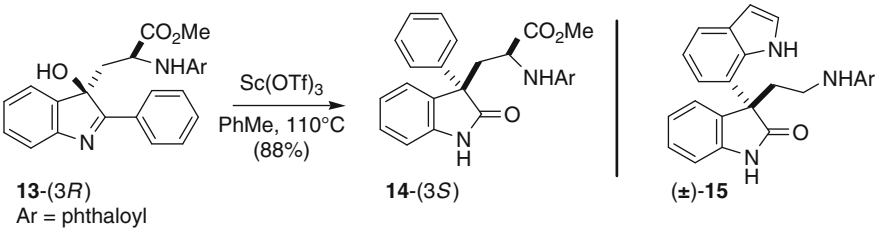


Scheme 3 Diastereoselective oxidative rearrangement

the (3*R*)-diastereomer in Scheme 4, treatment of either hydroxyindolenine diastereomer **13** with scandium trifluoromethanesulfonate afforded the corresponding C3-phenyl oxindoles **14** with complete diastereofacial selectivity. The C2 to C3 migration of a 7-indolyl substituent on an achiral 3-hydroxyindolenine platform was also observed to afford 3-(7-indolyl)oxindole **15** that houses an oxindole C3 to indole C7 quaternary junction, a common structural feature found in natural product scaffolds.

2.1.2 Direct C–C Coupling at C3

An alternate approach to construction of chiral oxindoles bearing a 3-aryl substituent or a 3-vinyl group has been developed by Buchwald and coworkers who employed a Pd-catalyzed direct coupling strategy (Scheme 5) [19]. In one example, 3-methyl oxindole **16** was quaternized at C3 in 96% ee upon treatment with 4-bromoanisole **17** in the presence of catalytic palladium and the chiral amino phosphine ligand **18**. The unique bidentate ligand employed in this work possesses both axial chirality and asymmetry at phosphorus. Two additional ligands with only axial chirality, KenPhos and $(i\text{-Pr})_2$MOP, were evaluated and proved to be less effective (74–78% ee) for exerting enantioselective control over the direct C–C coupling.

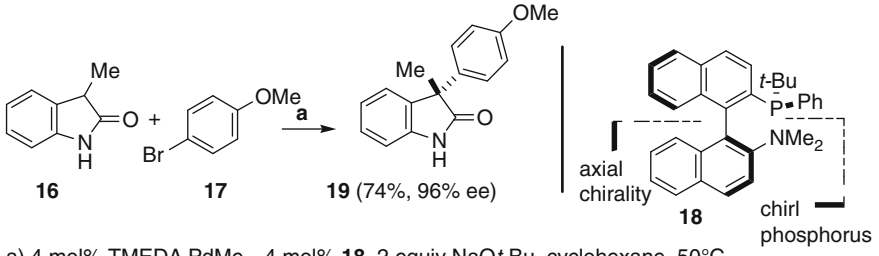


13-(3*R*)
Ar = phthaloyl

14-(3*S*)

(±)-**15**

Scheme 4 Oxidative rearrangement of 2-aryl tryptamine derivatives



16 **17** **19** (74%, 96% ee)

18

a) 4 mol% TMEDA·$PdMe_2$, 4 mol% **18**, 2 equiv NaO*t*-Bu, cyclohexane, 50°C

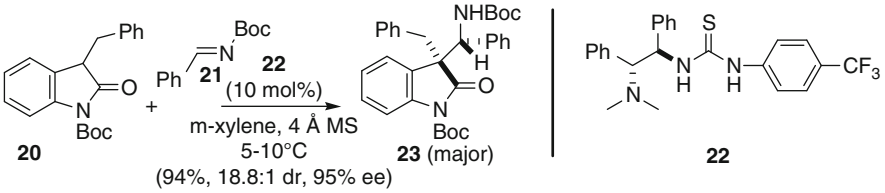
Scheme 5 Carbon–carbon coupling using axially chiral P-stereogenic ligand

2.1.3 Electrophilic Trapping of Oxindole Enolates

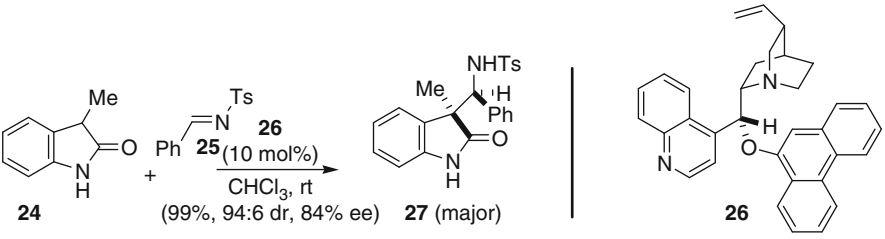
Asymmetry at oxindole C3 has been established using variations of electrophilic trapping of oxindole enolates directed by chiral catalysts. In one account, a chiral thiourea-tertiary amine catalyst **22** (Scheme 6) has been used to direct a stereoselective organocatalytic Mannich reaction involving addition of oxindole **20** to the Boc-protected imine **21** to afford the *syn*-diastereomer **23** as the major addition product with good enantioselectivity (95% ee, 18.8:1 dr) [20]. The transfer of chirality from the organic catalyst **22** to the oxindole was suggested to occur via a hydrogen bonding interaction between the N-Boc carbonyl of the imine **21** and the thiourea catalyst **22**. A bi-functional chiral primary amine thiourea catalyst has been employed by Melchiorre and coworkers for directing the conjugate addition of oxindoles to α,β-unsaturated aldehydes via iminium ion activation; good enantioselective and diastereoselective control was observed [21].

Chen and coworkers employed the cinchona alkaloid-derived catalyst **26** to direct Mannich additions of 3-methyloxindole **24** to the *N*-tosylimine **25** to afford the all-carbon quaternary center of oxindole **27** with good enantioselectivity (84% ee) [22]. The outcome of this Mannich reaction is notable in that it provided very good selectivity for the *anti* diastereomer (*anti*/*syn* 94:6). The mechanism of asymmetric induction has been suggested to involve a hydrogen bonding network between the cinchona alkaloid **26**, the oxindole enolate of **24**, and the imine electrophile **25** (Scheme 7). Asymmetric allylic alkylation of oxindoles with Morita–Baylis–Hillman carbonates has been reported by the same group [23].

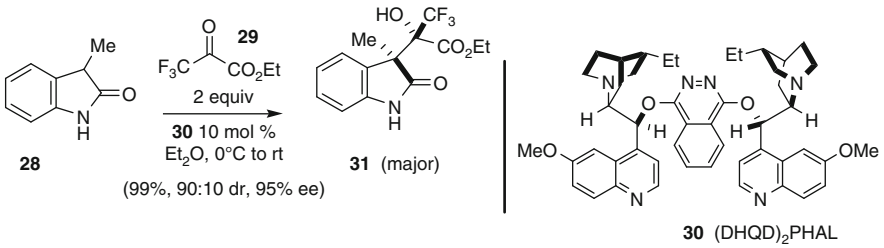
Cinchona based catalysts, e.g., **30** (Scheme 8), also have been used by Shibata, Toru, and coworkers to direct enantioselective Aldol-type reactions of 3-substituted



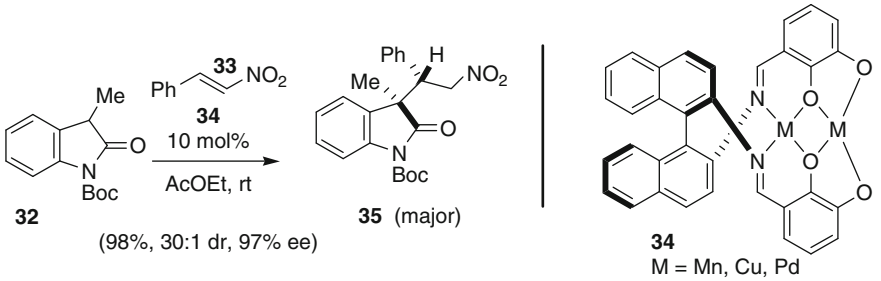
Scheme 6 Organocatalytic *syn*-Mannich reaction



Scheme 7 Organocatalytic *anti*-Mannich reaction



Scheme 8 Organocatalytic Aldol-type reaction



Scheme 9 Catalytic 1,4-addition to nitroalkenes

oxindoles with ethyl trifluoropyruvate [24]. In one example, electrophilic trapping of the enolate of oxindole **28** afforded the chiral oxindole **31** with good enantioselectivity (95%) and a preference for the (*S,S*)-diastereomer when the reaction was facilitated by commercially available biscinchona catalyst $(DHQD)_2PHAL$ **30**. A mechanism involving deprotonation of the oxindole by the quinuclidine moiety of the catalyst **30** with concomitant positioning of the oxindole in the U-shaped cleft of the catalyst through a π-stacking interaction with the quinoline ring system has been put forward to explain the stereoselectivity. The (*R,R*)-diastereomer of **31** was available through application of the pseudoenantiomeric cinchona catalyst $(DHQ)_2PHAL$. It was also demonstrated that the CF_3 subunit of the pyruvate electrophile **29** was essential for promoting the asymmetric transformation of oxindole **28** to **31**.

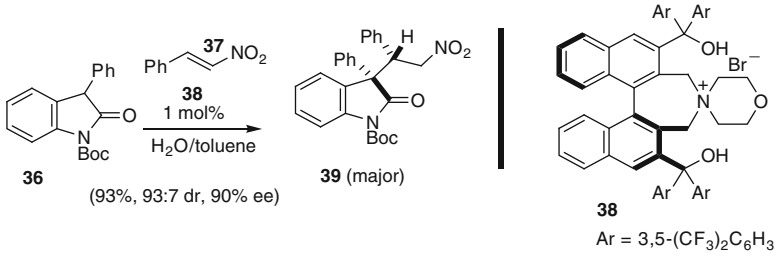
Asymmetric addition of an oxindole enolate to nitroalkenes has been observed by Matsunaga, Shibasaki, and coworkers [25]. As illustrated in Scheme 9, chiral oxindole **35** was prepared with good diastereoselective and enantioselective control (30:1 dr, 97% ee) upon treatment of oxindole **32** with nitroalkene **33** in the presence of the bimetallic (Mn_2) Schiff Base complex **34**. Control experiments with various heterobimetallic complexes (Cu/Mn or Pd/Mn with organic catalyst **34**) and a mononuclear complex of Mn with organic catalyst **34** led to decreased selectivity, highlighting the importance of the homodinuclear Mn_2-**34** complex for promoting the stereoselective transformation.

An all organic catalyst system **38** has been reported by the Maruoka group for directing asymmetric additions of oxindole enolates derived from **36** to nitroalkenes **37** under phase-transfer conditions [26] (Scheme 10). The methodology was extended to the synthesis of a tetrahydropyrroloindole scaffold bearing two chiral centers. Asymmetric Michael and Mannich reactions of 3-aryloxindoles directed by chiral phosphonium salt phase-transfer catalysts have been described by the same group [27].

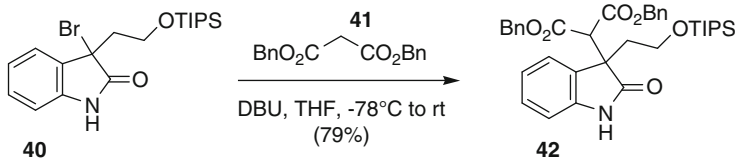
A unique inversion on the theme of trapping an electrophile with enolate nucleophile has been reported by Krishnan and Stoltz who have installed all-carbon quaternary centers at oxindoles, e.g., **42**, in racemic fashion through the treatment of electrophilic 3-halooxindoles with nucleophilic malonates, e.g., **40**–**41,** using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) for the deprotonation step (Scheme 11) [28]. An asymmetric variation of the chemistry in Scheme 11 has been reported by the same group who constructed enantioenriched oxindoles using catalytic Cu(II)-Lewis acid and a chiral bis(oxazoline) ligand [29].

2.1.4 Asymmetric Ring Closures

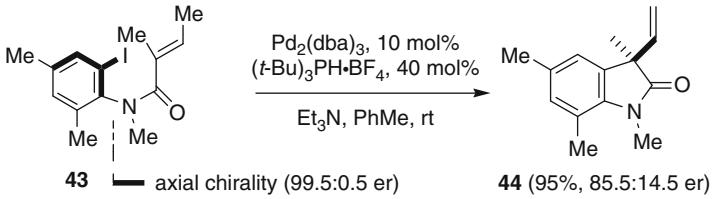
The selective installation of stereochemistry at oxindole C3 also has been achieved through the implementation of various asymmetric cyclization strategies. In an intriguing mechanistic investigation illustrated in Scheme 12, Curran and coworkers have reported the synthesis of oxindole **44** (85.5:14.4 dr, 86% chirality transfer from the chiral axis of **43** to the C3 stereocenter of **44**) from the



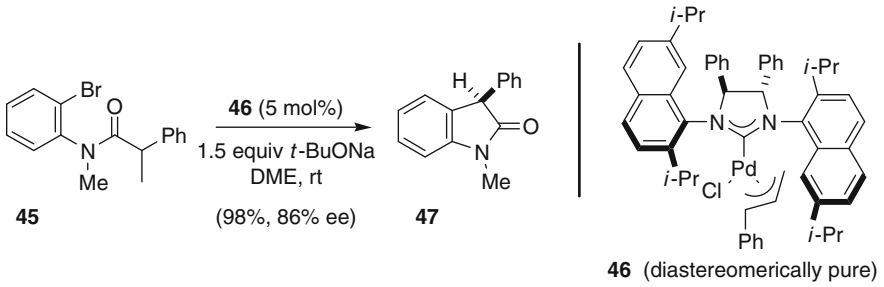
Scheme 10 Organocatalytic 1,4-addition to nitroalkenes



Scheme 11 Malonate addition to 3-halooxindoles



Scheme 12 Heck reaction of axially chiral *o*-iodoacrylanilides

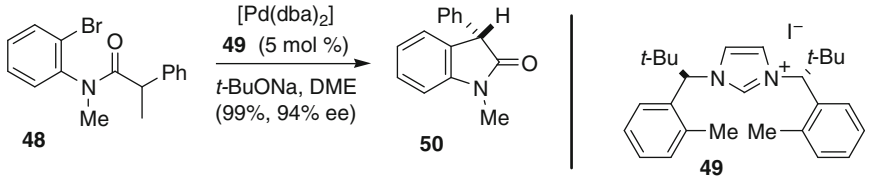


Scheme 13 Asymmetric α-arylation of amides

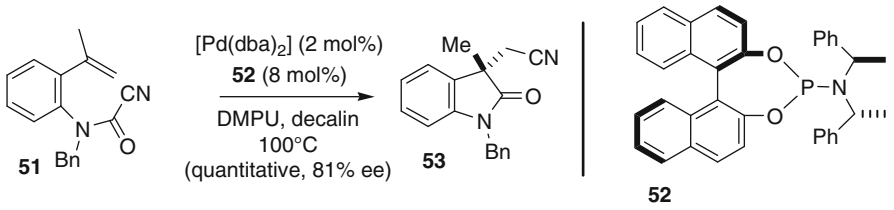
enantioenriched, axially chiral *o*-iodoanilide **43** by means of a low-temperature Heck reaction using an *achiral* palladium catalyst [30]. From the data obtained, the authors propose that the stereochemical control observed for asymmetric variants of Heck cyclizations (i.e., Heck reactions involving the action of *chiral* ligand-palladium sources on racemic *o*-iodoanilides) is dictated by a dynamic kinetic resolution that occurs at the stage of oxidative addition across the aryl iodide bond.

Building from early studies reported by the Hartwig group [31], investigation of the Pd-catalyzed intramolecular α-arylation of amides has received significant attention. Enantioselective ring closure of the *o*-bromoanilide **45** to afford chiral oxindole **47** (86% ee) was observed by the Dorta group who employed the diastereomerically pure *N*-heterocyclic carbene-palladium complex **46** to promote the transformation (Scheme 13) [32]. The chiral catalyst **46** was isolated from a crude mixture of three diastereomers via column chromatography. The two diastereomeric counterparts to **46** (differentiated by *syn* or *anti* configurations of the naphthyl side chains) both displayed decreased enantiocontrol (67% ee and 20% ee for the *syn* and *anti* diastereomeric Pd-complexes, respectively). A steric interaction between the α-aryl substituent of the anilide **45** and the naphthyl side chain of the catalyst **46** has been used to explain the stereochemical outcome of this intramolecular cyclization.

Kündig and coworkers have studied a variety of chiral *N*-heterocyclic carbene ligands, e.g., **49**, for the synthesis of all-carbon or heteroatom containing (methoxy or amino) quaternary centers at oxindole C3 [33, 34]. For example, oxindole **50** was prepared via asymmetric intramolecular cyclization of the corresponding *o*-bromoanilide **48** in 94% ee (Scheme 14).



Scheme 14 Asymmetric α-arylation of amides

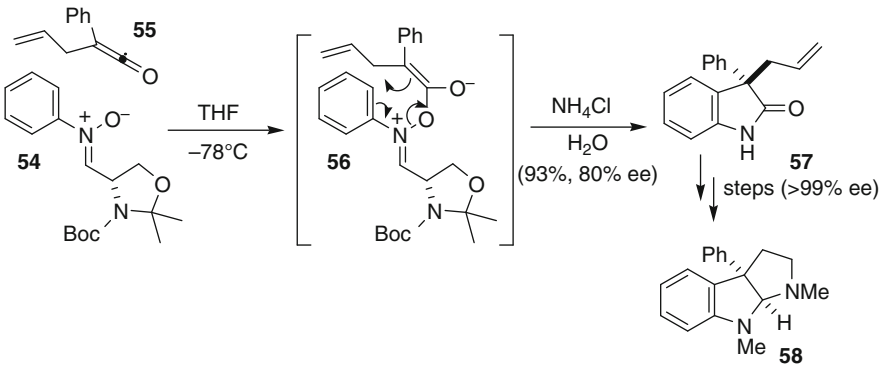


Scheme 15 Pd-catalyzed cyanoamidation

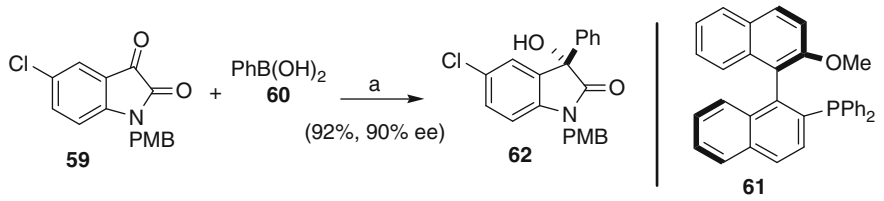
The Takemoto group has reported a methodology for oxindole ring synthesis that relies on a palladium-catalyzed cyanoamidation [35]. In one example (Scheme 15), the quaternary center of **53** was set in 81% ee upon treatment of the cyanoformamide precursor **51** with catalytic Pd and chiral phosphoramidite ligand **52** in the presence of DMPU (*N,N*-dimethylpropylene urea). The authors have proposed a mechanism involving initial oxidative addition of the chiral palladium-complex across the carbonyl-cyano bond of **51**, followed by insertion across the *ortho*-tethered π-system. A variation of this cycloamidation chemistry has been reported independently by Reddy and Douglas who observed enantioselectivities up to 99% and have applied their methodology to the synthesis of (+)-horsfiline, (−)-coerulescine, and (−)-esermethole [36].

An intermolecular cyclization approach to C3 asymmetric oxindoles has been devised by Smith and coworkers who paired chiral *N*-phenylnitrone nucleophiles with ketene electrophiles, e.g., intermolecular fusion of **54** and **55** [37]. As illustrated in Scheme 16, the oxindole skeleton **57** materialized in 87% ee following a proposed sequence of nitrone addition to the ketene, a hetero-Claisen rearrangement, imine hydrolysis and, finally, cyclization to generate the lactam linkage. As an extension of this methodology, (*S*)-3-allyl-3-phenyloxindole **57** was transformed into enantiopure 3-phenyl-hexahydropyrroloindole scaffold **58**.

Two examples of cyclization strategies leading to C3 quaternized oxindoles in the absence of asymmetric control have been disclosed by Klumpp and coworkers (aryl substitution at C3) [38] and the Ackerman group (alkyl and aryl substitution at C3 of 4-azaoxindoles) [39]. A direct carbon–carbon coupling of an anilide (i.e., no *ortho*-halogen) in racemic form has been reported by Perry and Taylor who employed Pd-catalysis with $Cu(OAc)_2$ as the oxidant [40].



Scheme 16 Asymmetric hetero-Claisen rearrangement



a) $[RhCl(C_2H_4)_2]_2$ (5 mol% Rh), **61** (10 mol%), KOH (15 mol%), THF/H_2O, 50°C

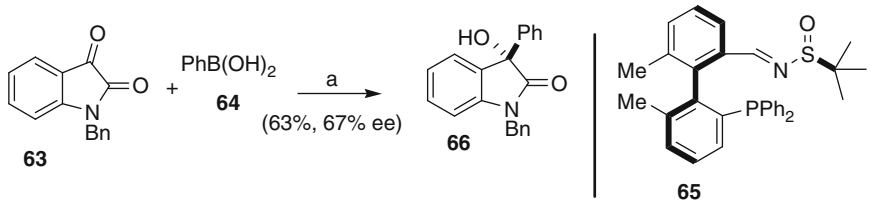
Scheme 17 Rhodium-catalyzed addition of arylboronic acid to isatin

2.2 Construction of Heteroatom Containing C3 Quaternary Centers

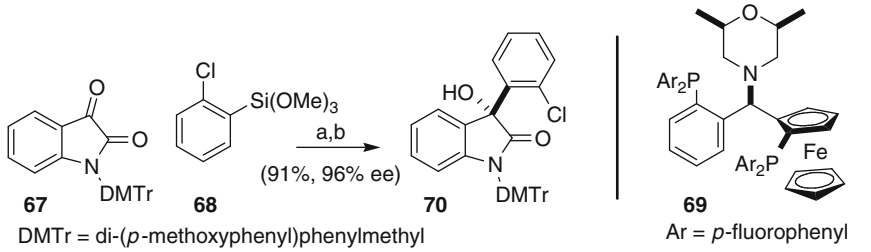
2.2.1 Synthesis of 3-Hydroxyoxindoles Via Additions to Isatins

The asymmetric addition of organometallic species to isatins represents a very direct strategy for entry into oxindoles bearing a hydroxyl functionality at tetra-substituted C3. In one report, Vries, Feringa, Minnaard, and coworkers observed rhodium/chiral phosphoramidite-catalyzed addition of phenylboronic acid to isatin with moderate enantioselectivity (55% ee) [41]. Using an alternate rhodium system, the Hayashi group observed good enantioselectivity for addition of arylboronic acids to isatins [42]. In one example, the 3-hydroxy-3-phenyloxindole **62** was prepared in 90% ee upon treatment of the isatin precursor **59** with catalytic rhodium in the presence of the axially chiral (*R*)-MeO-mop monophosphine ligand system **61** (Scheme 17).

An alternate palladium-catalyzed addition of arylboronic acid to isatins has been described by Qin and coworkers (Scheme 18) [43]. The stereochemical outcomes of



Scheme 18 Palladium-catalyzed addition of arylboronic acid to isatin

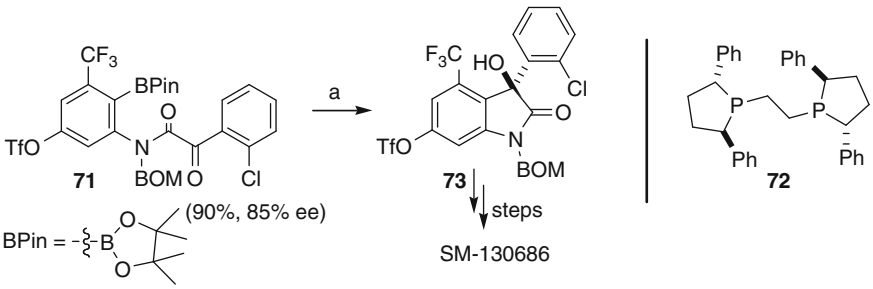


Scheme 19 Intermolecular Cu(I)F-catalyzed coupling

the transformations were influenced by enantiomerically pure biphenyl phosphinoimine ligand systems, e.g., **65**. In one experiment, oxindole **66** with the (*S*)-configuration was prepared with moderate enantioselectivity of 67% ee. The enantiomeric oxindole was available in 62% ee through application of a diastereomeric phosphinoimine ligand (i.e., the axial conformer of **65**).

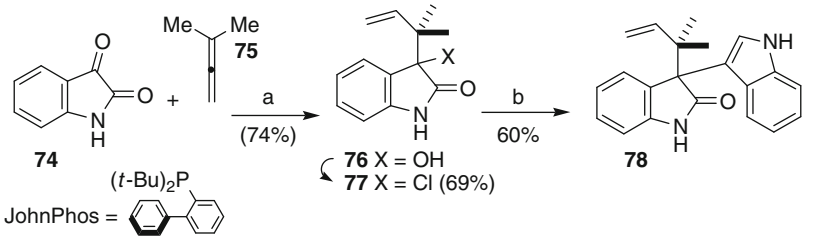
Aryl or alkenyltrimethoxysilanes, e.g., **68**, have been employed as nucleophiles in asymmetric additions to isatins under Cu(I)F catalysis. Using the Taniaphos derivative **69** (Scheme 19) as a chiral ligand, Shibasaki and coworkers observed good enantioselectivities for the conversion of isatin **67** to C3 quaternized alcohol **70** (80–96% ee for a variety of isatin and organosilane combinations) [44]. While attempts to produce enantiopure **73**, a key intermediate en route to clinically useful SM-130686, using the intermolecular arylsilane addition chemistry were unsuccessful, the chiral center of **73** was constructed in enantioselective fashion (85% ee) via a CuF catalyzed intramolecular arylation of **71** using the bis-chiralphosphine (*R*,*R*)-**72** (Ph-BPE) (Scheme 20). The presence of the CF_3 functionality at C4 of **71** has been suggested as the likely cause of the failed intermolecular approach.

Grant and Krische have described a racemic protocol for the synthesis of all-carbon C3 quaternary centers from 3-hydroxy-3-*tert*-prenyloxindole **76** that was accessed via ruthenium catalyzed addition of 1,1-dimethylallene **75** to isatin **74** [45]. As outlined in Scheme 21, **76** was converted to the electrophilic 3-chloro derivative, which was trapped with indole under basic conditions to afford **78** in 60% yield. A mechanism has been proposed for the C–C bond-forming event that involved first-order ionization of chloride ion assisted by delocalization of oxindole



a) $CuF{\cdot}3PPh_3{\cdot}_2EtOH$ (10 mol%), **72** (14 mol%), toluene, 40°C

Scheme 20 Intramolecular Cu(I)F-catalyzed coupling



a) $RuHCl(CO)(PPh_3)_3$ (2.5 mol%), JohnPhos (5 mol%), HCO_2H (100 mol%), THF, 65°C.
b) Indole, K_2CO_3, DCM, 25°C.

Scheme 21 Ruthenium-catalyzed *tert*-prenylation of isatin

N-anion through the benzenoid system. The Krische group has also reported the iridium-catalyzed enantioselective allylation, crotylation, or prenylation of isatins [46].

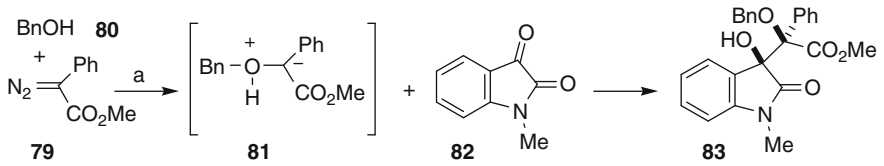
A variety of protocols for the synthesis of 3-alkyl or 3-aryl 3-hydroxyoxindoles without control of stereochemistry at C3 have been described [47–49].

In one account, Hu and coworkers prepared 3-hydroxyoxindoles **83** in diastereoselective fashion, 98:2 erthyro:threo (stereochemically undefined at C3), via addition of the oxonium ylide **81** to isatin **82** (Scheme 22) [50].

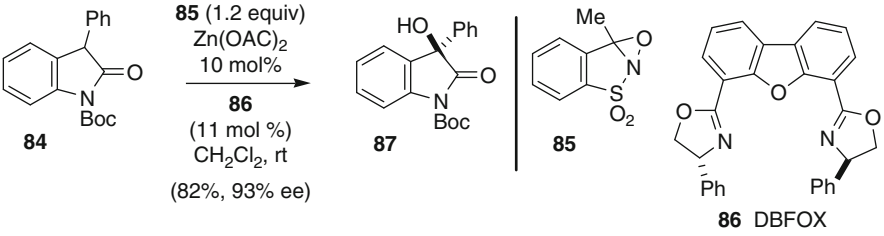
Syntheses of symmetrical 3,3-diindolyl or 3,3-dipyrrolyl oxindoles from isatins have also been reported [51, 52].

2.2.2 Direct Hydroxylation of C3-Substituted Oxindoles

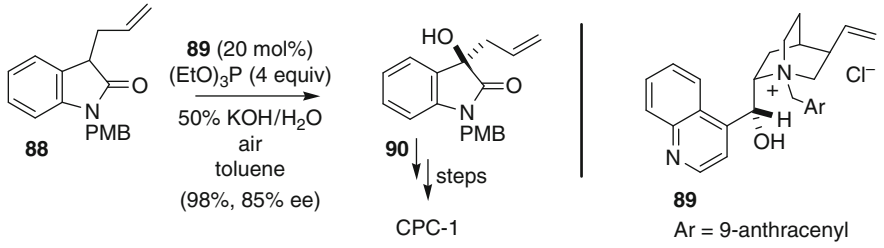
Given the variety of methods for accessing 3-alkyl or 3-aryl oxindoles in racemic form, the direct asymmetric hydroxylation of 3-substituted oxindoles represents a conceptually appealing strategy for controlled installation of hydroxyl-bound



Scheme 22 Oxonium ylide trapping with isatin



Scheme 23 Enantioselective hydroxylation of oxindoles



Scheme 24 Enantioselective hydroxylation of oxindoles with molecular oxygen

quaternary centers at oxindole C3. Accordingly, Shibata, Toru, and coworkers have developed a catalytic enantioselective protocol for the preparation of 3-hydroxy-3-aryloxindoles [53]. In one experiment, oxindole **87** was prepared in 93% ee upon treatment with oxaziridine **85** and a catalytic amount of the DBFOX-Zn(II) chiral Lewis acid system **86** (Scheme 23).

Using molecular oxygen as the oxidizing agent, the Itoh group has achieved the enantioselective preparation of 3-allyl-3-hydroxyoxindole **90** (85% ee) under phase-transfer conditions with the cinchonidine derived catalyst **89** [54]. The oxindole **90** was further manipulated to a key intermediate that has been applied in a prior synthesis of the hexahydropyrroloindole CPC-1 [55] (Scheme 24).

Racemic entry to quaternary C3 hydroxy oxindoles from C3-substituted indoles has been achieved using a variety of oxidants including dimethyldioxirane [56], $CeCl_3 \cdot 7H_2O$/IBX [57], or PCC (pyridinium chlorochromate) with polyaniline salt (PANI) as acid catalyst [58].

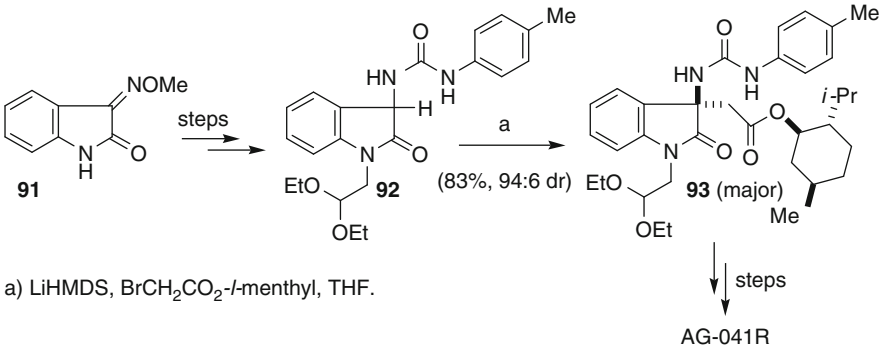
2.2.3 Synthesis of 3-Aminooxindoles from Isatins

Isatins have served as valuable precursors for the preparation of oxindoles bearing amino functionality at stereodefined C3. In a report from the Emura group, isatin derived oxime **91** (Scheme 25) was transformed to the urea derivative **92** which underwent a diastereoselective alkylation at C3 to afford the *l*-menthol adduct **93** (94:6 dr) [59]. Lithium counterions proved to be more effective than potassium ions for achieving diastereocontrol of the enolate alkylation; a mechanism has been suggested involving lithium ion chelation between the oxindole enolate of **92**, the carbonyl of the urea functionality at C3, and the carbonyl of the menthyl ester electrophile.

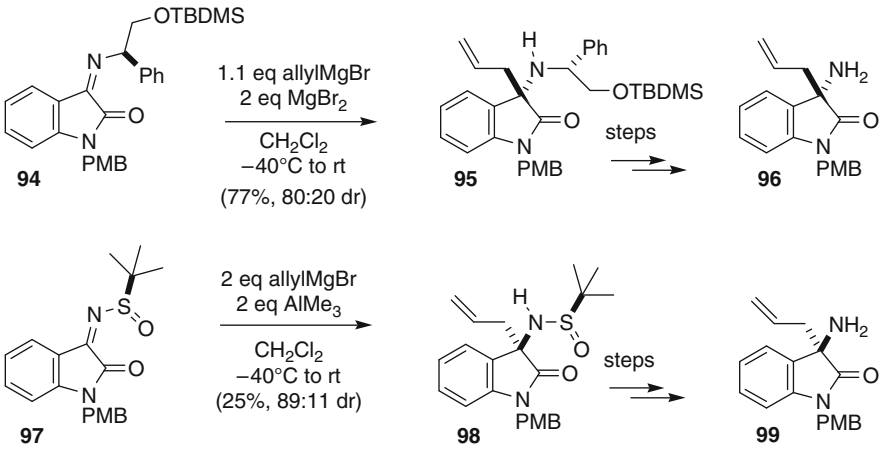
Silvani and coworkers have converted isatin to the chiral imines **94** and **97** that were employed as electrophiles for the diastereoselective addition of Grignard reagents [60]. As illustrated in Scheme 26, addition of allyl Grignard to **94** or **97** afforded the amino-substituted quaternary oxindoles **95** or **98** with good diastereoselectivity (80:20 and 89:11 dr, respectively). Grignard adducts **95** and **98** were further manipulated to afford the enantiomeric pair of 3-amino-3-allyloxindoles (*S*)-**96** and (*R*)-**99**, respectively.

2.2.4 Synthesis of 3-Aminooxindoles from Oxindole Enolates

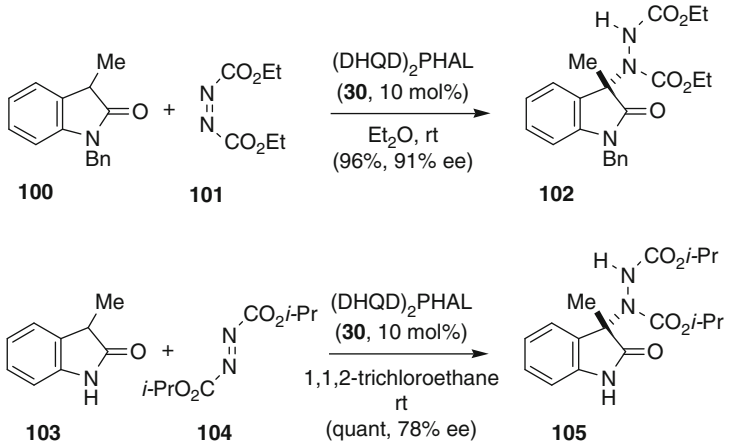
The Barbas group has employed a cinchona alkaloid to direct an enantioselective α-amination of oxindoles using diethyl azodicarboxylate as the electrophilic species (Scheme 27) [61]. In one example, *N*-benzyl protected 3-methyloxindole **100** was transformed to the amino-substituted oxindole **102** in 91% ee using $(DHQD)_2PHAL$



Scheme 25 Diastereoselective alkylation



Scheme 26 Grignard additions to imines of isatin



Scheme 27 Organocatalyitc α-amination reactions

as the chiral catalyst. The generality of this methodology was established with the successful amination of a variety of 3-substituted oxindoles without loss of enantioselectivity, e.g., 3-allyl and 3-(2-methylallyl)oxindole in 94% ee and 95% ee, respectively. In a report from a separate group, Chen and coworkers observed similar asymmetric amination in modestly reduced enantioselectivity (78% ee) by employing *N*-unprotected oxindole **103** and trapping with diisopropyl azodicarboxylate **104** using $(DHQD)_2PHAL$ as the organic catalyst [62]. In an additional variation on this theme, Shibasaki, Matsunaga, and coworkers have trapped oxindole enolates with di-*tert*-butyl azodicarboxylate [63]; excellent selectivity for the (*S*) or (*R*) enantiomer was observed using the organic catalyst **34** (illustrated in Scheme 9) as a monometallic or bimetallic complex with Ni, respectively.

2.2.5 Ring Cyclizations to 3-Amino, Alkoxy, or Hydroxyoxindoles

The Marsden group has published a collection of articles detailing the synthesis of heteroatom containing C3 quaternized oxindoles [64–66]. The transformations involved the palladium-catalyzed intramolecular arylation of anilides bearing either amino or alkoxy functionality alpha to the anilide carbonyl. Under microwave conditions, a variety of 3-alkoxy-3-aryl, 3-amino-3-aryl, or 3-amino-3-alkyloxindoles have been prepared in racemic form. In one example, 3-indolyloxindole **107** was prepared in 65% yield (Scheme 28).

An asymmetric variant of palladium-catalyzed cyclization of anilides to quaternary 3-hetero-oxindoles has been reported by the Kündig group (see Sect. 2.1.4) [33, 34].

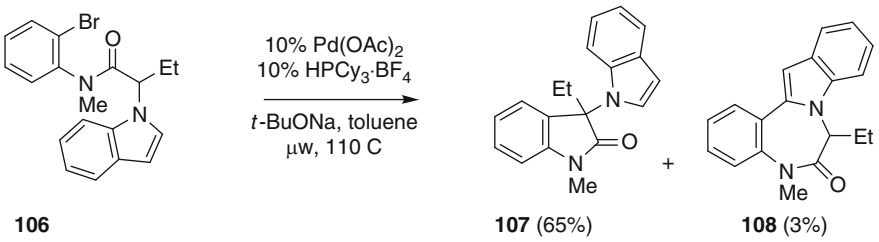
3 Methods for Spirocyclization at Oxindole C3

The intriguing architectures that characterize the spirooxindole family of indole alkaloids have stimulated a wealth of investigations directed toward precision spirocyclization. As with the preceding section, examples of spirooxindole syntheses have been organized on the basis of the specific type of bond that has been set at C3 (C3-carbon, C3-oxygen, or C3-nitrogen functionalization).

3.1 Synthesis of All-Carbon C3 Spirocenters

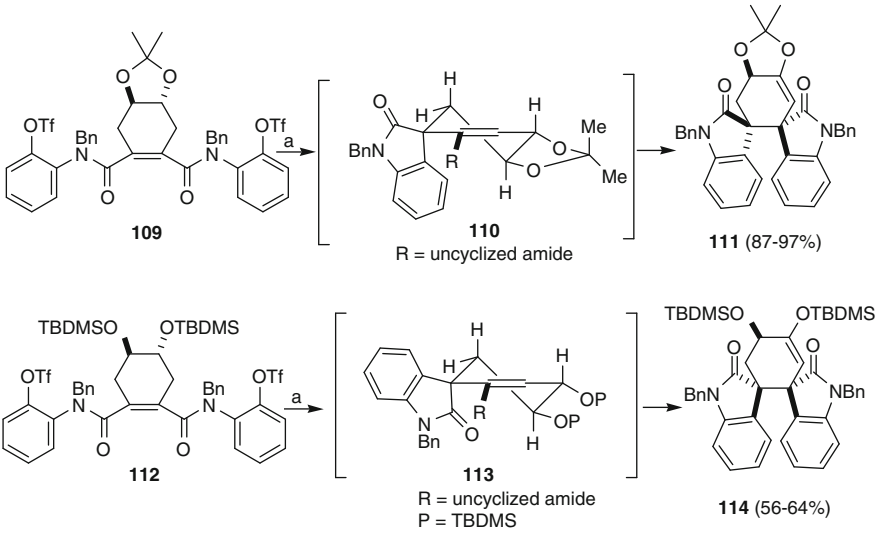
3.1.1 Intramolecular Spirocyclic Ring Closures

A variety of different tactics have been used to establish all-carbon spirocyclic moieties at oxindole C3. Overman and Watson have conducted an extensive investigation of intramolecular Heck reactions leading to the diastereoselective formation of spirocyclic dioxindoles, e.g., **111** and **114** (Scheme 29) [67–69]. Interestingly, while sequential Heck cyclizations of acetonide protected bis-anilide



106 **107** (65%) **108** (3%)

Scheme 28 Intramolecular arylation of enolates

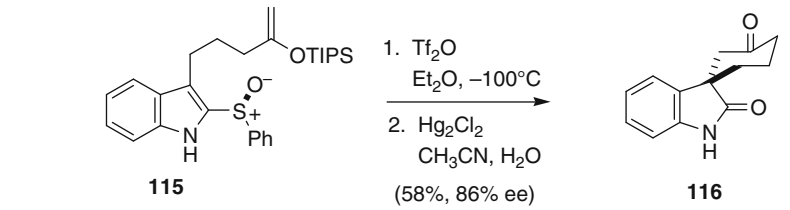


a) 20 mol% $Pd(PPh_3)_2Cl_2$, 10 equiv Et_3N, DMA, 100°C

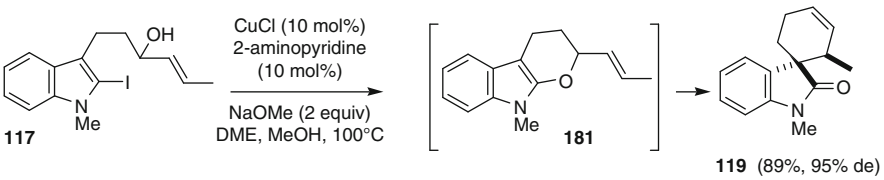
Scheme 29 Sequential intramolecular Heck reactions

109 afforded the *trans*-oriented spirooxindole **111** with excellent diastereocontrol, the disiloxy derivative **112** afforded the *cis*-fused dispirooxindole **114**. Through a series of control experiments that produced mono-cyclized spirooxindole adducts, it was demonstrated that the *cis*- or *trans*-selectivity of the second Heck cyclization step was dependent on the relative orientation of the spirooxindole from the first cyclization, e.g., conformation **110** or **113**. The stereochemical outcome of the first spirocyclization step in the acetonide series (i.e., intermediate **110**) has been rationalized through identification of unfavorable eclipsing interactions that are avoided between the newly formed oxindole spirocenter and the cyclohexene bound pseudoaxial and pseudoequatorial hydrogens on the adjacent carbon, as well as steric interactions that are avoided between the oxindole and the neighboring uncyclized amide functionality (R-group). The origin of diastereoselection for the first Heck spirocyclization in the bis-TBDMS protected system has not been fully revealed.

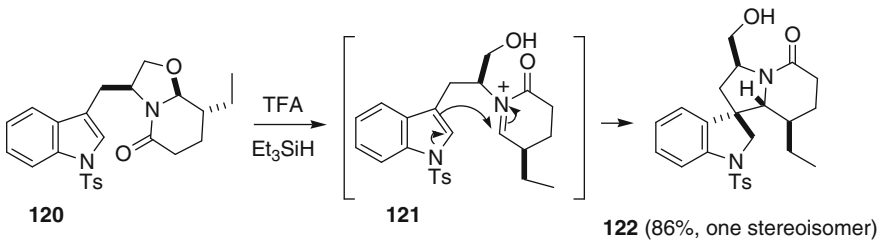
Chiral indole-2-sulfoxides have been employed by Feldman and Karatjas for asymmetric spirooxindole synthesis [70]. In one example, treatment of **115** with triflic anhydride initiated a Pummerer-type cyclization of the silyl enol ether side chain onto C3 (Scheme 30). Sequential hydrolysis of the resulting thioimidate intermediate with aqueous $HgCl_2$ afforded the spirocyclohexanone functionalized oxindole **116** in modest yield and enantioselectivity at −78°C (33, 67% ee). Improved selectivity (58, 86% ee) was observed at lower reaction temperature (−110°C).



Scheme 30 Pummerer-initiated cyclization of chiral indole-2-sulfoxide



Scheme 31 Intramolecular Ullmann coupling and Claisen rearrangement



Scheme 32 Lewis-Acid promoted enantioselective spirocyclization

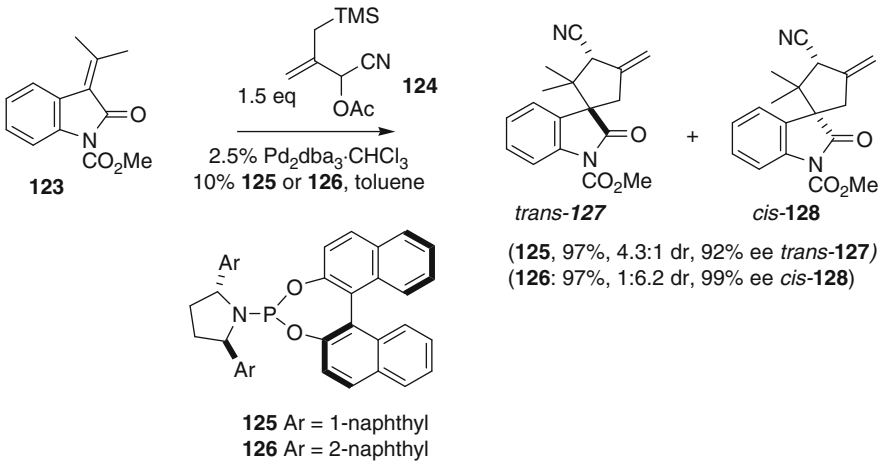
The Kobayashi group has observed the intramolecular diastereoselective spirocyclization of racemic 2-haloindoles bearing a C3-tethered allylic alcohol [71, 72]. For example, CuCl-catalyzed intramolecular Ullmann coupling of **117** followed by spontaneous Claisen rearrangement of the intermediate pyranoindole **118** afforded, in a one-pot synthesis, the all-carbon quaternary center of spirooxindole **119** in 95% de (Scheme 31). The methodology has been extended to the synthesis of hexahydropyrroloindoles, e.g., (±)-debromoflustramine B and E.

Although outside the specific realm of oxindole synthesis, an interesting intramolecular route into a spiroindoline scaffold has been reported by Amat, Bosch, and coworkers who unexpectedly observed the Lewis-acid catalyzed cyclization of tryptophan derived oxazolopiperidone lactams **120** in the presence of triethyl silane [73]. In the event, spiroindoline **122** was obtained as a single stereoisomer in 86% optimized yield (Scheme 32). It was demonstrated that the hydroxymethyl group of the ring-opened oxazolidine was important for directing the stereochemical outcome of the transformation as removal of the ethyl side chain of the lactam ring did not diminish the selectivity of the spirocyclization.

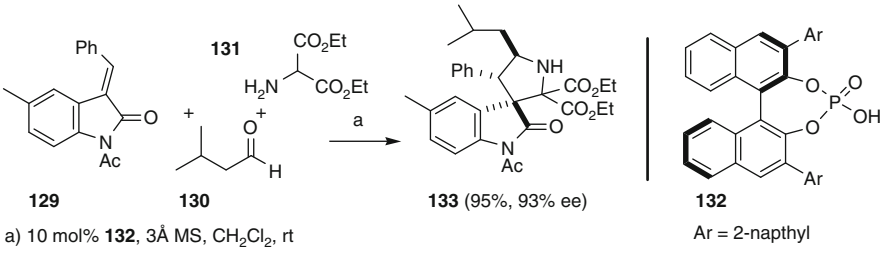
3.1.2 Intermolecular Spirocyclic Ring Closures

The Trost group has devised a strategy for stereoselective spirocyclic ring installation across 3-alkylidene oxindoles via palladium-catalyzed [3+2] cycloaddition with cyano-substituted trimethylenemethane (Scheme 33) [74, 75]. As illustrated, the opposite sense of diastereoselectivity was observed depending on the choice of chiral ligand **125** or **126**. Preferential orientation of the benzenoid portion of the oxindole as dictated by the varied steric environments of the naphthyl ring systems on the catalysts has been put forth as a rationale for the observed difference in stereochemical outcomes. Spirooxindoles **127** and **128** were obtained in 92% ee and 99% ee, respectively. A variation of this methodology has been applied in the racemic synthesis of marcfortine B [75].

Various 3-methyleneoxindoles have been converted to spirooxindoles in enantioselective fashion by Gong and coworkers who made use of a chiral organic catalyst to direct 1,3-dipolar cycloadditions across the exocyclic π-system [76]. As illustrated in Scheme 34, azomethine ylide formation arising from condensation of



Scheme 33 Palladium-catalyzed trimethylenemethane-[3+2]-cycloaddition



Scheme 34 Three-component 1,3-dipolar cycloaddition

amine **131** and aldehyde **130** in the presence of chiral phosphoric acid **132** was followed by asymmetric cycloaddition onto the benzylidene oxindole **129** to afford the spirocyclic system **133** in 93% ee. Hydrogen bond interactions between the chiral phosphoric acid catalyst, N–H of the azomethine ylide, and carbonyl of the oxindole have been invoked to explain the enantioselectivity of the cycloaddition. In addition to H-bonding, a π-stacking interaction between the conjugated esters of the azomethine ylide and the benzenoid ring of the oxindole has been suggested as a control element for directing the regiochemistry of the cyclization. An asymmetric spirocyclization via [4+2] cycloaddition of Nazarov reagents across methylene oxindoles has been reported by the same group [77].

3.2 Synthesis of Heteroatom Containing C3 Spirocycles

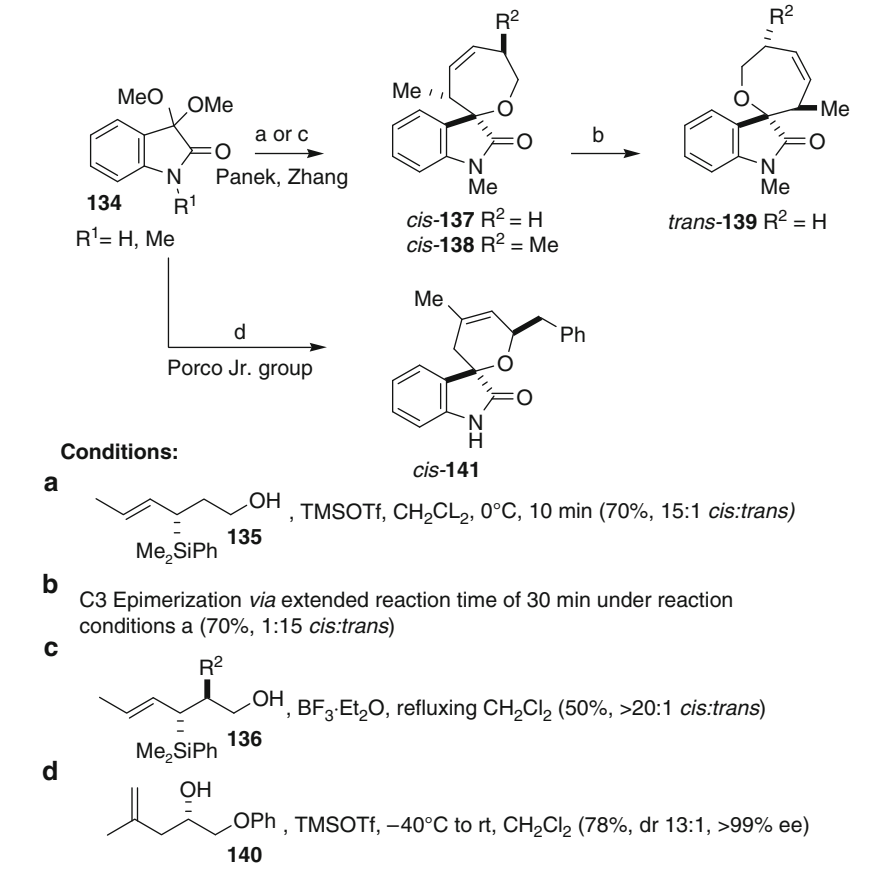
3.2.1 Synthesis of Oxaspirocycles

Two independent reports have appeared that detail methodology for the introduction of pyran or oxepene spirocyclic moieties onto oxindole scaffolds by means of a Prins cyclization (Scheme 35). In one study by Zhang and Panek, treatment of isatin dimethylketal **134** with silyl alcohol (*S*)-**135** afforded predominately *cis*-**137** or *trans*-**139** depending on reaction time and solvent polarity [78]. A mechanism involving epimerization of the *cis*-product to the *trans* adduct was put forward to explain the observed *trans*-selectivity with increased reaction time in polar solvents. A cyclic transition state involving a (*Z*)-oxonium intermediate formed via condensation of silyl alcohol **135** with isatin **134** was invoked to rationalize the preferential formation of the *cis*-spirocycle under kinetic control. Further optimization led to the formation of spirooxindoles **138**, e.g., R^1, R^2 = Me, as single diastereomeric products (>20:1 *cis*:*trans*); epimerization at oxindole C3 was not observed under these conditions.

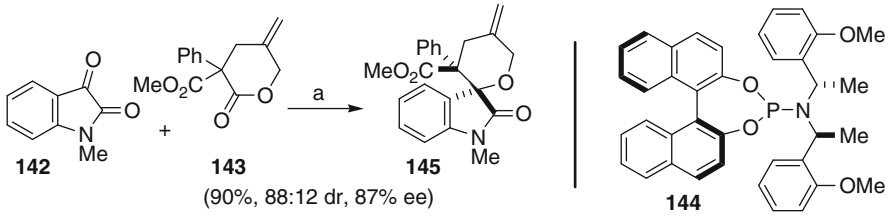
In a separate investigation by Porco, Jr. and coworkers, the isatin derivative **134** (R^1 = H) was converted to spirooxindole pyran **141** in 13:1 dr and 99% ee by means of a Prins-type cyclization involving homoallylic alcohol **140** [79]. The diastereoselectivity of the transformation has been proposed to arise from a preferred chair-like transition state with the benzenoid ring of oxindole in a pseudoequatorial orientation. Spirooxindole oxepenes also were prepared via diastereoselective spiro-annulation of isatins with bis-homoallylic alcohols.

A palladium-catalyzed spirocyclization between isatin and γ-methylidene-δ-valerolactones, e.g., **142** and **143** (Scheme 36), has been developed by Shintani, Hayashi, and coworkers for the preparation of tetrahydropyranyl fused oxindoles [80]. An enantioselective variant of the transformation was observed using phosphoramidite ligand **144** for the Pd-catalyzed decarboxylative cyclization. In the event, spirooxindole **145** was produced in 88:12 dr and 87% ee.

Nair and coworkers have installed spirocyclic γ-butyrolactone ring systems across isatin in racemic form using homoenolate nucleophiles (Scheme 37) [81].

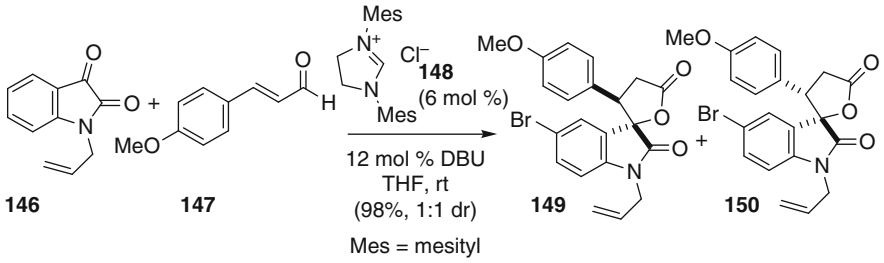


Scheme 35 Acid-promoted [5+2]-annulation of chiral silyl alcohols (a–c); Prins cyclization (d)

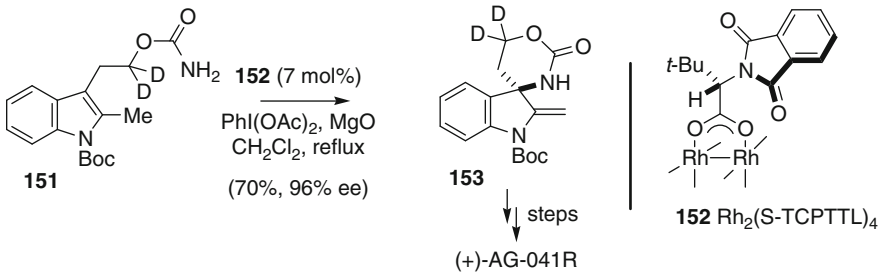


Scheme 36 Palladium-catalyzed decarboxylative cyclization

The requisite homoenolates were prepared through treatment of cinnamaldehyde derivatives, e.g., **147**, with *N*-heterocyclic carbenes derived from imidazolium ion **148** and DBU.



Scheme 37 *N*-heterocyclic carbene-catalyzed coupling of enals and isatins



Scheme 38 Intramolecular aza-spiroannulation

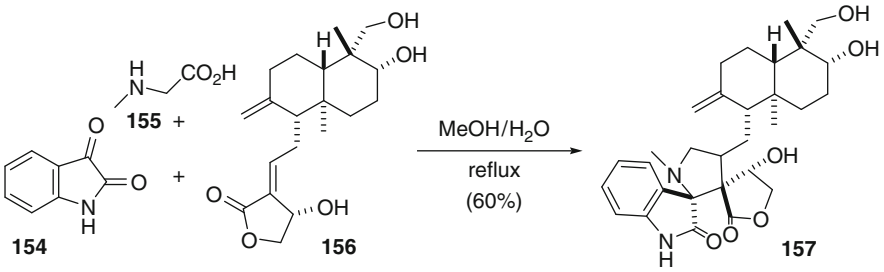
3.2.2 Synthesis of Azaspirocycles

In an approach to the gastrin receptor antagonist (+)-AG-041, the Iwabuchi group has prepared the nitrogen-substituted spirocycle **153** by means of an oxidative intermolecular aza-spiro-annulation (Scheme 38) [82]. Accordingly, indole **151** was treated with dirhodium catalyst **152** in the presence of $PHI(OAc)_2$ and MgO to afford spirocycle **153** in 70% yield and 96% ee. The deuterium labeling was necessary for successful implementation of the spirocyclization.

The densely functionalized dispiro species **157** has been stitched together by Mondal and coworkers who choreographed a three-component azomethine ylide strategy for spirocyclization [83]. In the event, isatin **154**, amino acid (sarcosine **155**), and the exocyclic α,β-unsaturated lactone (andrographolide **156**) were combined to afford the aza-spirooxindole **157** in 60% yield (Scheme 39).

4 Natural Product Total Synthesis

The rich and diverse history of investigation within the realm of oxindole natural product total synthesis has resulted in an outpouring of literature on that topic. As the confines of this chapter prevent a comprehensive review of those works, this



Scheme 39 Azomethine ylide cycloaddition to di-spiropyrrolidino-oxindoles

section is intended as a brief survey of methodology that has been developed for installation of oxindole C3 quaternary centers within the specific context of natural product total synthesis. Select examples presented below include syntheses involving oxindoles employed as key intermediates en route to various heterocyclic scaffolds as well as natural products that house the native oxindole framework.

4.1 Oxindole Intermediates in Natural Product Synthesis

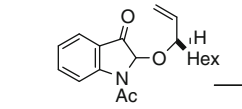
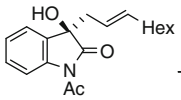
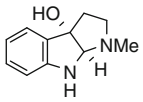
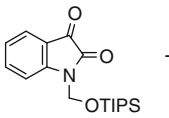
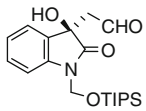
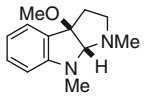
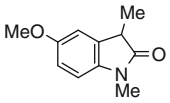
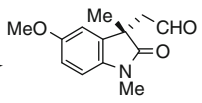
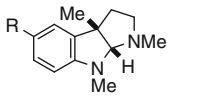
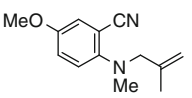
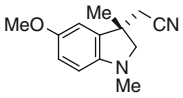
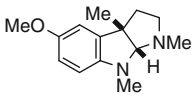
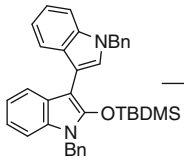
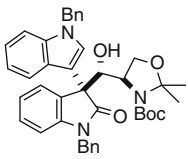
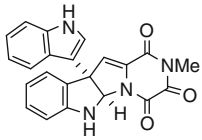
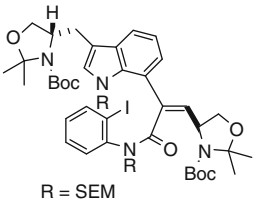
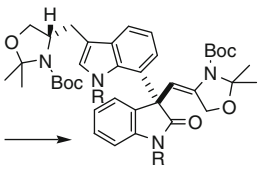
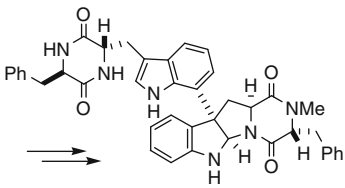
Oxindoles with defined stereochemistry at C3 have served as valuable precursors for entry into tetrahydro- or hexahydropyrroloindole natural product scaffolds. As illustrated in Table 1, a variety of approaches to asymmetric oxindole synthesis have been applied for introduction of the key C3 stereocenters embodied within (+)-alline [84, 85], CPC-1 [86], (−)-esermethole (a formal synthesis of (−)-physostigmine) [87–90], (+)-gliocladin C [91], and (+)-asperazine [92].

The Danishefsky group has reported the rearrangement of azaspiroindolenine **161** to access the polycyclic skeleton **162**, a core ring system that has been further elaborated to phalarine **163** [93, 94]. As outlined in Scheme 40, the requisite indolenine **161** was prepared via ring opening of the spirooxindole **158**, followed by intramolecular condensation of the keto-tethered aniline **160**.

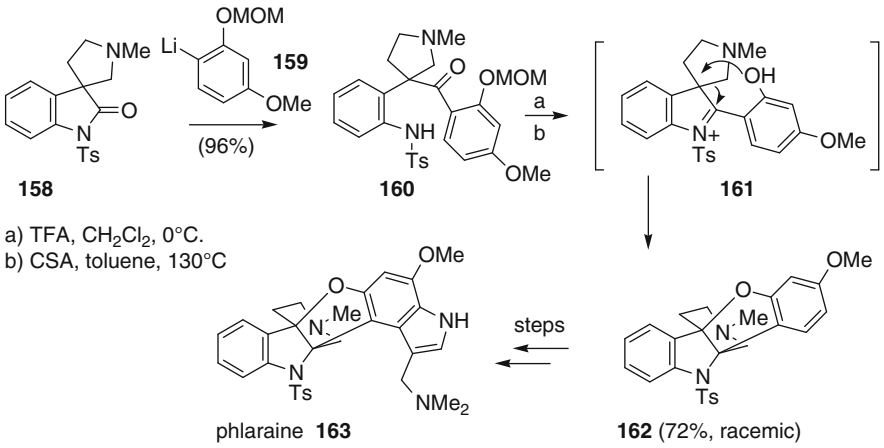
As a key intermediate in an approach to the communesins, Weinreb and coworkers have constructed the all-carbon quaternary center of oxindole **166**. The tandem Heck cyclization/carbonylation sequence illustrated in Scheme 41 provided **165** as a single stereoisomer in 79% yield [95]. Further manipulation of **165** revealed the vicinal pair of all-carbon stereocenters housed within **166**. An approach to the synthesis of (±)-communesin F has been reported by the same group [96].

With the identification of the hemiaminal moiety at the core diazonamide A in 2001 [97], numerous retrosynthetic approaches to the molecule have taken advantage of the logical disconnection at the anomeric carbon to reveal an oxindole

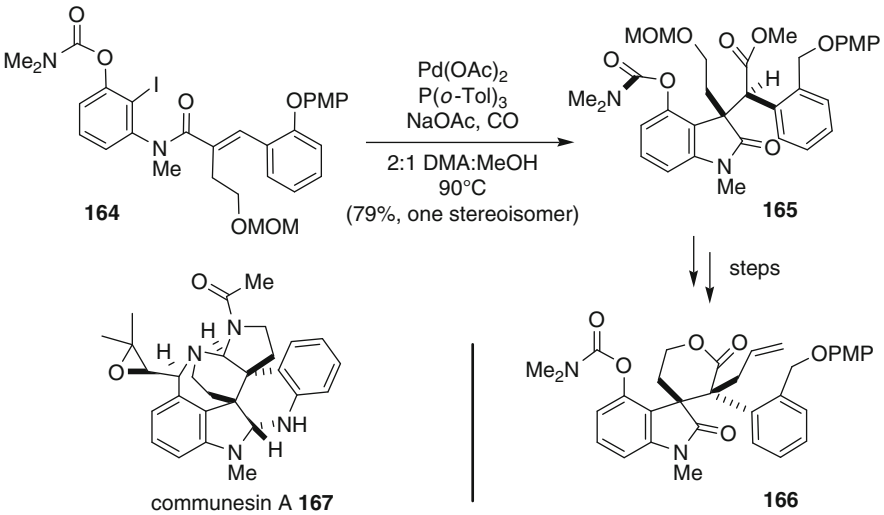
Table 1 Pyrrolidinoindoline natural products from oxindole precursors

Methodology	Oxindole	Natural product
 **1. Claisen rearrangement**	 (91%, 85% ee)	 **(+)-alline**
 **2. Asymmetric Aldol**	 (75%, 85% ee)	 **CPC-1**
 **3. Asymmetric Alkylation**	 (98%, 82% ee)	 steps R = MeO: (-)-esermethole R = $MeNHCO_2$: **(-)-physostigmine**
 **4. Intramoleculare Arylcyanation**	 (88%, 96% ee) to oxindole (40%)	 steps (-)-esermethole **(-)-physostigmine**
 **5. Mukaiyama aldol**	 (75–89% 80:1 dr)	 **(+)-gliocladin C**
 R = SEM **6. Intramolecular Heck**	 (66%, one stereoisomer)	 **asperazine**

precursor (see **175** in Scheme 42). Accordingly, a variety of tactics for the synthesis of the alkaloid have been described that involve construction of the all-carbon C10 quaternary center (diazonamide A numbering) on an oxindole scaffold. Completed



Scheme 40 Azaspiroindoline route to phalarine

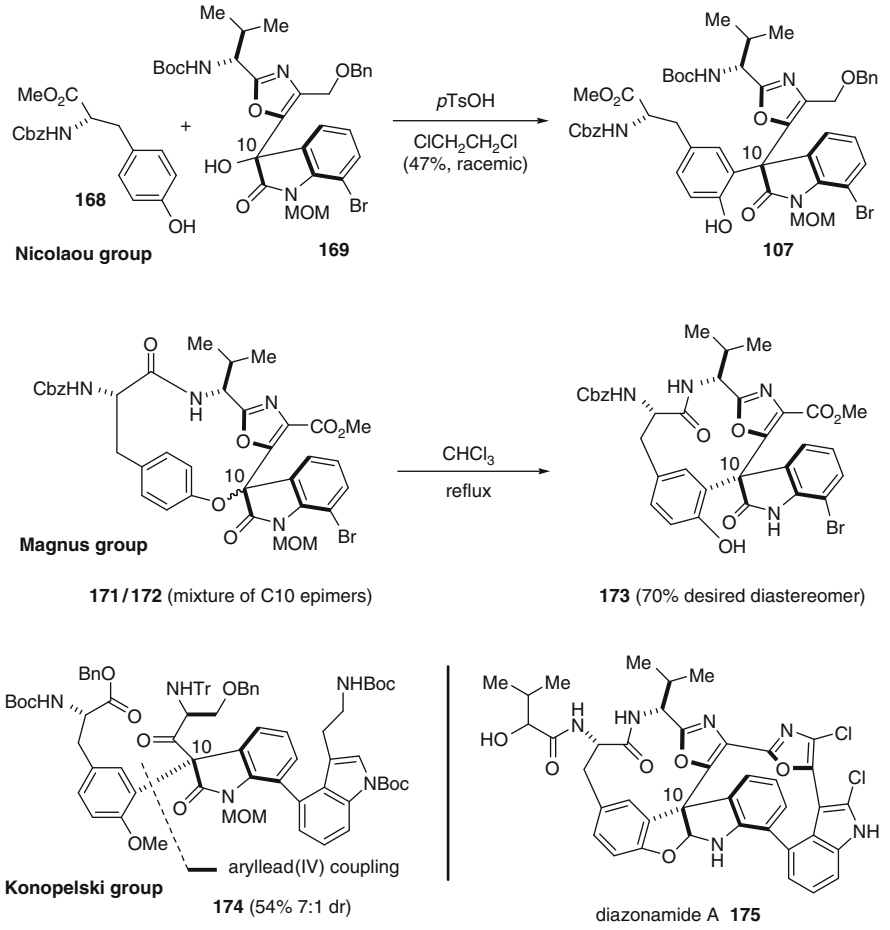


Scheme 41 Tandem intramolecular Heck cyclization/carbonylation en route to communesin core

works on the total synthesis of diazonamide A have been reported by Harran and coworkers [97, 98] and the Nicolaou group [99, 100].

In one approach reported by Nicolaou and colleagues, the C10 quaternary center was constructed via aromatic substitution using an oxindole C3 electrophile (the tosyl derivative of **169**) as illustrated in Scheme 42. The all-carbon quaternary center of **170** was set in 47% yield as a 1:1 mixture of oxindole C3 epimers.

An intriguing advancement in the realm of diazonamide A chemistry has been made by the Magnus group which has observed a unique O-aryl to C-aryl migration



Scheme 42 Synthetic approaches to diazonamide A

as part of a broad series of investigations directed toward the transformation of heteroatom-substituted quaternary centers (O- or N-substituted) to all-carbon quaternary centers [101–103]. Judicious application of the migratory sequence to a diazonamide A precursor has allowed for stereocontrolled entry to the illusive C-10 quaternary center. In one example, a racemic mixture of the C10-aryloxy oxindoles **171**/**172** was transformed to a mixture containing 70% of **173** and 30% of the C10-epimer. It is noteworthy that the Magnus protocol has provided a stereoselective route to oxindole **173**, a key intermediate prepared in racemic fashion in Nicolaou's total synthesis of diazonamide A.

Konopelski and coworkers have employed a direct coupling strategy for installing the crucial oxindole stereocenter of a diazonamide precursor [104]. Accordingly, oxindole **174** was prepared in 54% yield as a 7:1 ratio of C10-epimers.

A three-point coordination between the C3 enolate anion, sodium cation, and the C3 tethered NTr group has been suggested as the origin of the stereoselectivity of the transformation.

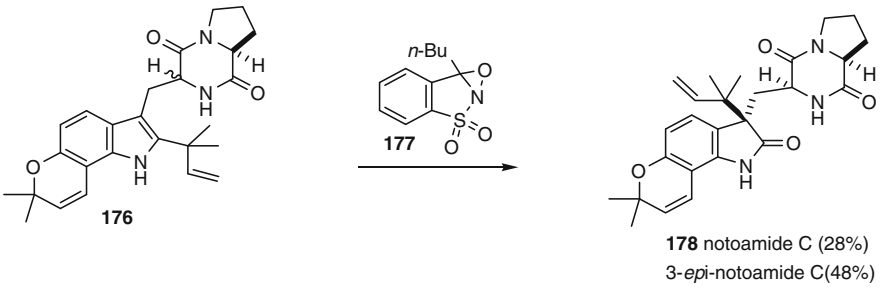
A small sampling of alternate racemic entries into the C10-quaternary center of diazonamide A includes the trapping of formaldehyde with a 3-aryloxindole enolate by the Nicolaou group [100], trapping of a 3-aryloxindole with Mander's reagent ($CNCO_2Me$) by Zajac and Vedejs [105], and an oxidative rearrangement sequence for conversion of a 3-arylindole-2-carboxylate to C3 quaternized 3-aryloxindole-3-carboxylate by Moody and coworkers [106].

4.2 Oxindole Natural Product Total Synthesis

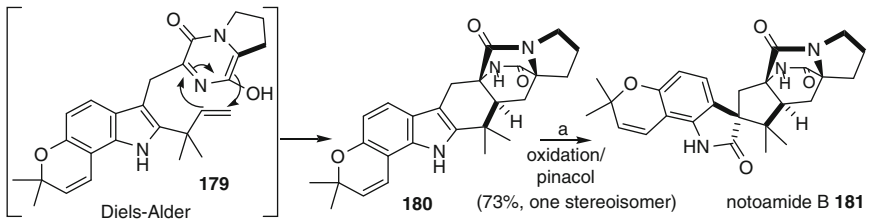
The Williams group has installed the all-carbon quaternary center of notoamide C **178** (28%) along with 3-*epi*-notoamide C (48%) via a pinacol rearrangement set forth through oxidation of the indole C2–C3 bond with the Davis oxaziridine **177** (Scheme 43) [107–109].

The spirocyclic ring system of notoamide B **181** also has been constructed by the Williams group using a pinacol rearrangement strategy [109]. In the event, stephacidin A **180** was treated with oxaziridine **177** to afford **181** in 73% yield as a single stereoisomer. The requisite precursor for the transformation, stephacidin A **180**, was prepared using a biomimetic intramolecular Diels–Alder reaction for construction of the 2,3-annulated indole ring system of **180** as illustrated in Scheme 44.

In their approach to the total synthesis of (+)-alstonisine **184**, Cook and coworkers have employed a pinacol rearrangement strategy that was set up by a stereospecific osmylation reaction (Scheme 45) [110]. The key step involved treatment of indole **182** with OsO_4, and then with $NaHSO_3$ to prepare the indole C2,C3-diol that underwent pinacol rearrangement to afford **183** as a single diastereomer (81% yield). Coordination of OsO_4 to the piperidine ring nitrogen has been suggested as the origin of the diastereoselectivity of the transformation.

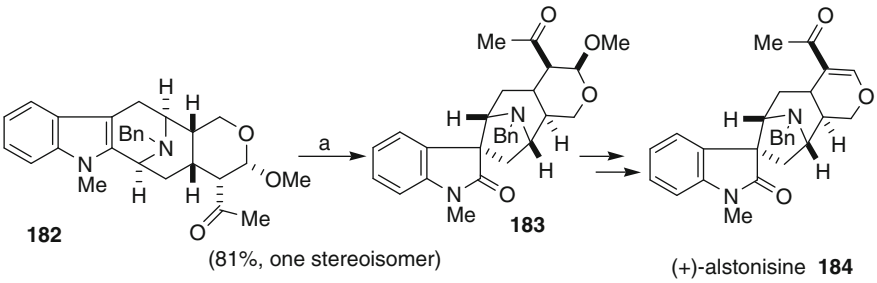


Scheme 43 Pinacol route to notoamide C



a) Davis oxaziridine **177**, CH_2Cl_2

Scheme 44 Pinacol route to notoamide B



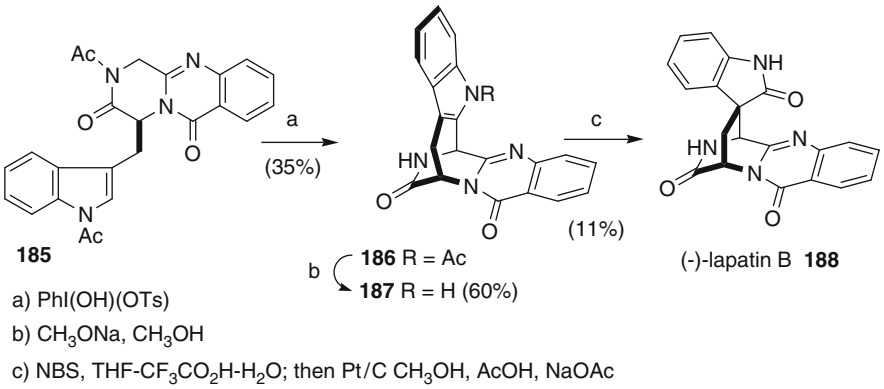
a) 1 equiv OsO_4, py, THF, rt; then, aq. $NaHSO_3$, rt

Scheme 45 Pinacol route to (+)-alstonisine

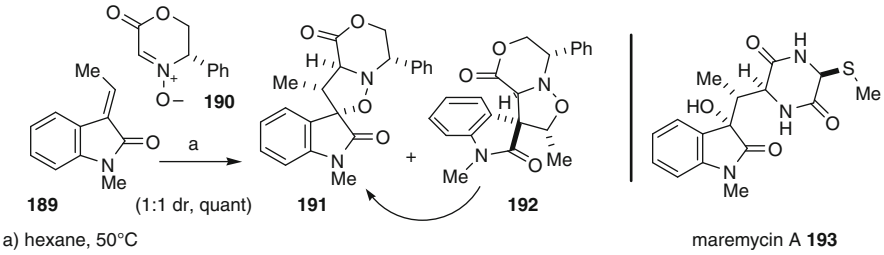
In an additional variation on the theme of spirocyclization via oxidative rearrangement chemistry, oxidation across the indole 2,3-π system has been employed by Martin and coworkers in their approach to the core spirocyclic ring structure of citrinadin A [111]. The key epoxidation/spirocyclization was carried out in diastereoselective fashion using an indole *N*-chiral auxiliary, (−)-8-phenylmethol carbamate, to direct the asymmetric event.

The Hart group has constructed the esthetically appealing spiro-bridged scaffold of the quinazolinone alkaloid (−)-lapatin B **188** (Scheme 46) [112, 113]. Entry into the spirocyclic ring system was set up by an initial oxidative cyclization of indole-tethered quinazolinone **185** to afford bridged indole **186**. After removal of the acetyl groups, spirocyclization was carried out using a sequence of electrophilic bromination of **187** with aqueous NBS (*N*-bromosuccinimide), followed by hydrogenolysis of the resulting brominated oxindoles to produce **188** (11%) along with the oxindole C3 epimer (11%). A variation on this synthetic strategy involving selenium-promoted cyclization in lieu of the oxidative cyclization (vis-à-vis **185** to **186**) also has been reported by the Hart group for the synthesis of the spirooxindole-fused quinazolinone (−)-serantrypinone [113].

Tamura and coworkers have used a cycloaddition strategy to generate the spirooxindole **191**, a key intermediate in the total synthesis of maremycin A **193**



Scheme 46 Oxidative cyclization route to (−)-lapatin B

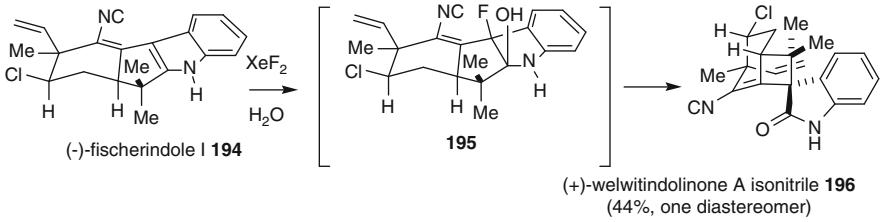


Scheme 47 Nitrone cycloaddition route to maremycin A

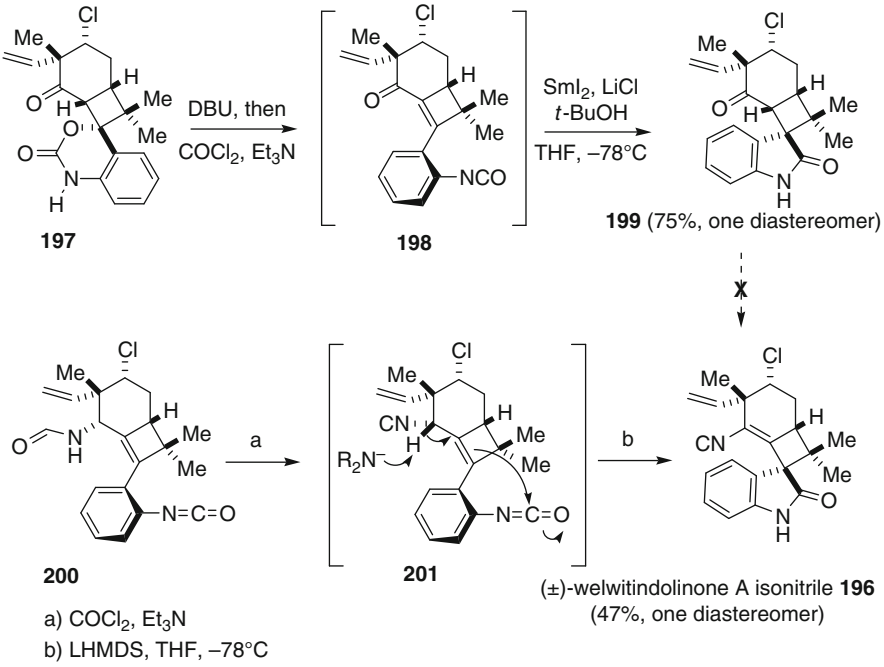
(Scheme 47) [114]. In the event, nitrone **190** and ethylidene oxindole **189** underwent 1,3-dipolar cycloaddition to afford a 1:1 mixture of desired adduct **191** and regioisomeric **192** in quantitative yield. Interestingly, it was observed that heating of the undesired oxindole **192** with ethylidene oxindole **189** led to a 10% yield of the desired regioisomer **191** via a sequence of cycloreversion of **192** followed by recycloaddition onto **189**.

The spiraled architecture of welwitindolinone A isonitrile **196** has inspired the development of a variety of strategies for its construction. A beautifully simple protecting group-free synthesis of (+)-welwitindolinone A has been achieved by Baran and coworkers [115–117]. As depicted in Scheme 48, the key step for installation of the all-carbon quaternary center at oxindole C3 involved fluorohydroxylation of (−)-fischerindole 1 **194** via treatment with aqueous XeF_2. The desired natural product, **196**, was obtained as a single diastereomer in 44% yield. The origin of the asymmetry at oxindole C3 can be traced back to enantiopure carvone oxide.

The Wood group has detailed extensive studies directed toward the total synthesis of (±)-welwitindolinone A isonitrile (Scheme 49) [118]. In one approach that did not materialize into a viable route to (±)-**196**, an intricate spirocyclization



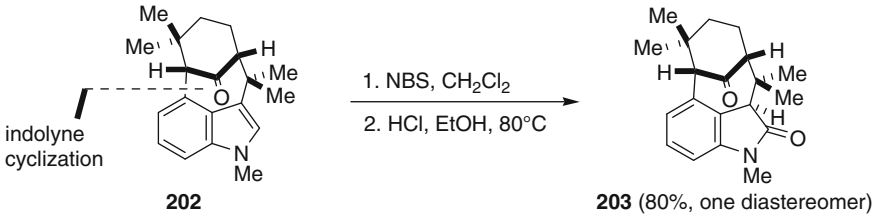
Scheme 48 Entry to (+)-welwitindolinone A via electrophilic fluorination and [1,5] sigmatropic-shift



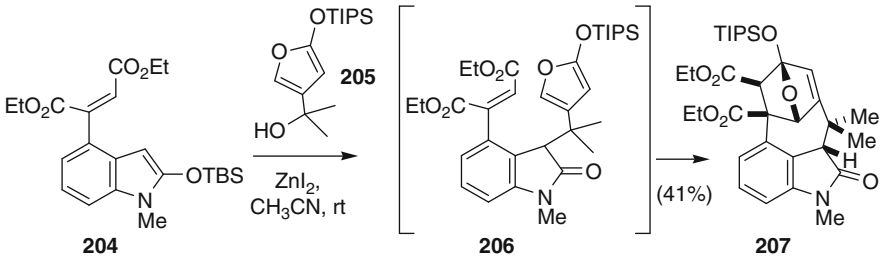
Scheme 49 Approaches to (±)-welwitindolinone A isonitrile

sequence was developed that involved conversion of spiro-carbamate **197** to oxindole **199** in 75% yield via sequential decarboxylation, isocyanate formation, and then SmI_2/LiCl-mediated cyclization of **198**. Using an alternate strategy, the spirocyclic ring juncture of the desired natural product was revealed via a well conceived anionic cyclization sequence that provided (±)-**196** from isocyanate **200** in 47% yield.

In an approach to the core of *N*-methylwelwitindolinone C isothiocyanate, the Garg group employed a diastereoselective oxidation of indole **202** using NBS, and then ethanolic HCl to access the oxindole subunit of **203** [119]. The C7 ring juncture of the bicyclic core was set using an indolyne cyclization strategy



Scheme 50 Diastereoselective oxidation to *N*-methylwelwitindolinone C core



Scheme 51 Alkylation/cyclization route to welwitindolinone bicyclic core

(Scheme 50). An alternate approach to the oxindole C3 to C7 bicyclic core found in members of welwitindolinone family has been reported by the Shea and coworkers who set the C3 linkage via a ZnI_2 promoted coupling of silyl ketene aminal **204** with functionalized furan **205** (Scheme 51) [120]. An intramolecular cycloaddition between C3 tethered furan of **206** and C7 pendant α,β-unsaturated ester closed the bridged oxindole scaffold of **207** in 41% yield.

5 Concluding Remarks

The challenge of establishing oxindole C3 quaternary centers continues to inspire inventive bond-forming solutions, and through the rigorous examination of the problem, a number of strategies for selective C3 bond installation (all-carbon or heteroatom containing) have reached an advanced stage of evolution. While much emphasis has been placed on the development of catalytic, asymmetric protocols for precision installation of oxindole C3 quaternary centers, a few successful target-specific strategies also have been devised that avoid implementation of chiral catalysts by taking advantage of the native asymmetry of advanced natural product intermediates. Although not addressed directly in the discussion above, the behind-the-scenes methodology for preparation of enantiomeric or pseudoenantiomeric catalyst systems is a topic deserving careful review. Finally, with the allure of

devising an asymmetric protocol that is general in scope and application, it would not be unexpected to see future iterations of the works described herein tailored to suit quaternary environments outside the specialized area of oxindole chemistry.

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Advances in the Total Syntheses of Complex Indole Natural Products

Liangfeng Fu

Abstract Total syntheses of several complex indole alkaloids having potent biological activities are discussed in detail.

Keywords Biological activity · Indole · Natural products · Total synthesis

Contents

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1 Introduction

Since its first isolation in 1866, indole is one of the most important building blocks in natural occurring compounds. Moreover, indole has shown wide application in medicinal chemistry and in many other areas of chemistry.

At least one thousand publications have described the isolation or synthesis of the natural products of indole in the last decade, including many complex indole alkaloids, especially those with novel skeletons, potent biological activities, or posing synthetic challenges. Manzamine A (**1**) (for recent isolations see [1–8]; for recent syntheses see [9–11]) and vinblastine (**2**) (for recent isolations see [12–17]; for recent syntheses see [18–22]) (Fig. 1) are two recent typical examples of great interest for both their syntheses and biological applications.

In this chapter, only indole alkaloids initially described since 2000 will be covered.

2 Indole Alkaloids with Potent Biological Activity

2.1 Actinophyllic Acid

Actinophyllic acid (**3**), an indole alkaloid with novel 1-azabicyclo-[4.4.2]dodecane and 1-azabicyclo[4.2.1]nonane fragments, was isolated from the tree *Alstonia actinophylla*, collected on the Cape York Peninsula, Queensland, Australia, in 2005 by Quinn, Carroll and coworkers [23]. As a carboxypeptidase U inhibitor (IC_{50} = 0.84 μM), actinophyllic acid shows potential application for the treatment of cardiovascular disorders [23]. Much effort has been devoted to this unique molecule, including recent synthetic studies by Wood and coworkers [24], but only Overman et al. has accomplished its synthesis [25].

Overman's retrosynthetic analysis is depicted in Scheme 1. Pentacyclic ketone **4**, derived from allylic alcohol **7** by an aza-Cope-Mannich rearrangement of formaldiminium ion derivative **6** furnished **3** through the C5 hemiketal disconnection. An intramolecular oxidative coupling of a dienolate generated from indole-

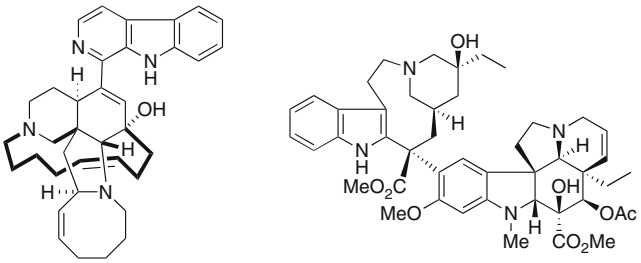
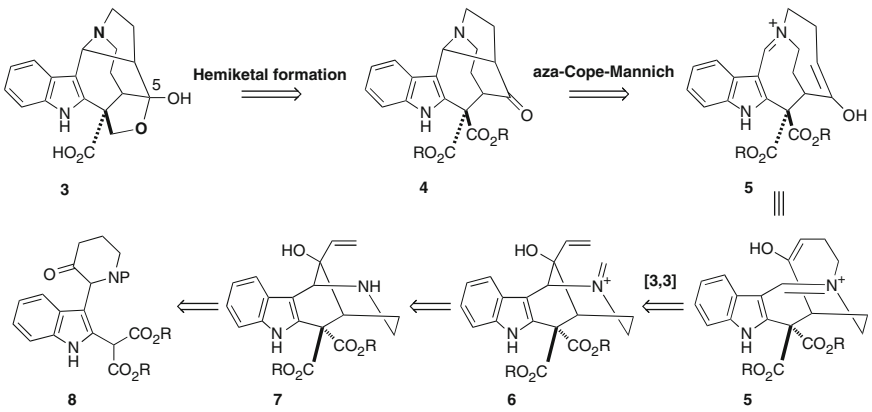


Fig. 1 Manzamine A (1) and Vinblastine (2)



Scheme 1 Retrosynthetic analysis of actinophyllic acid (3)

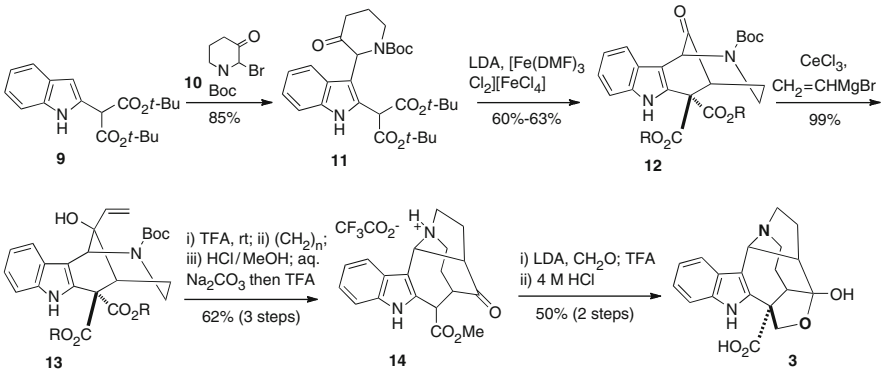
2-malonate precursor **8** formed the hexahydro-1,5-methanoazocino[4,3-*b*]indole ring system in allylic alcohol **7**.

The forward synthesis commenced with readily prepared indole di-*tert*-butyl malonate **9**. Treatment of **9** with bromopiperidone **10** afforded indole **11**, which underwent an intramolecular oxidative coupling using a Fe(III) oxidant [Fe $(DMF)_3Cl_2$][$FeCl_4$] to provide tetracyclic ketone **12** and the keto-bridged hexahydroazocino[4,3-*b*]indole ring system in one step. $CeCl_3$-mediated vinylmagnesium bromide addition to the bridged ketone afforded tertiary alcohol **13** as a single diastereomer. Exposure of **13** to TFA to cleave the Boc and *tert*-butyl esters, and a one-pot aza-Cope rearrangement promoted by formaldehyde, followed by esterification with methanol gave keto ester **14**. The final two-step installation included a stereoselective aldol reaction for the tetrahydrofuran ring formation and acid hydrolysis gave actinophyllic acid (**3**) (Scheme 2).

This racemic synthesis of actinophyllic acid (**3**) was accomplished in eight steps with an overall 15% yield from the readily available indole di-*tert*-butyl malonate **9**. The intramolecular oxidative coupling of ketone and malonate enolates and an aza-Cope-Mannich rearrangement for the construction of the unprecedented actinophyllic acid ring skeleton are the key transformations.

2.2 Communesin F and Perophoramidine

Communesin A (**15**) and B (**16**) were first isolated from a strain of *Penicillium* sp. found growing on the marine alga *Enteromorpha intestinalis* in 1993 by Numata and coworkers [26]. Subsequently, six other members (communesin C, D, E, F (**17**), G, H) were identified (Fig. 2). All communesins show potent cytotoxicity against P-388 lymphocytic leukemia cells, among which communesin B is the most biologically active [27].



Scheme 2 Total synthesis of actinophyllic acid (3) by Overman and coworkers

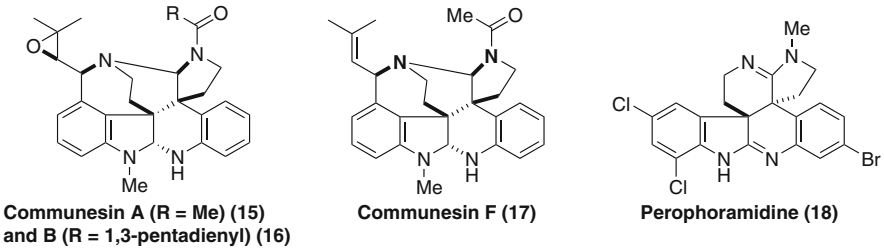
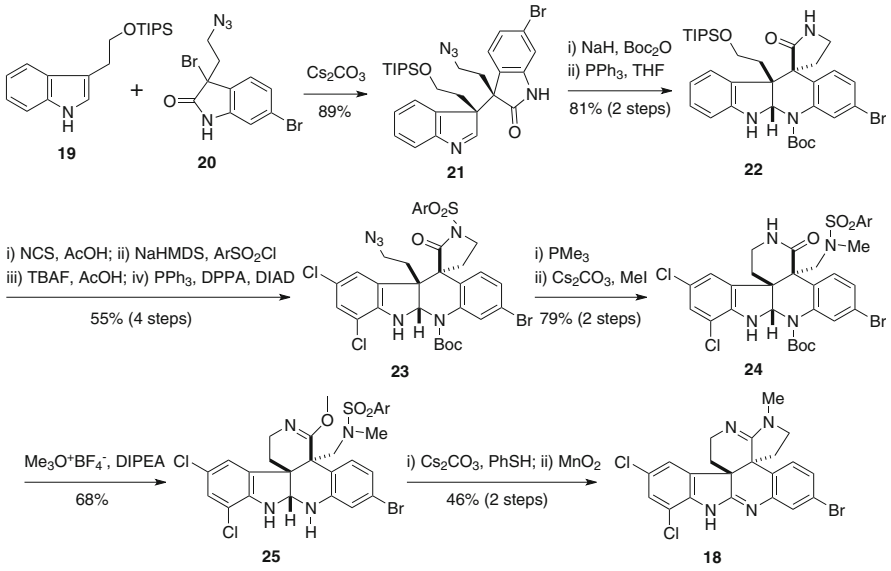


Fig. 2 Communesin A (15), B (16), F (17) and Perophoramidine (18)

Perophoramidine (**18**) shares the same connectivity as the communesins, but **18** contains a bis-amidine rather than the bis-aminal functionality present in **15–17**. The *trans*- rather than the *cis*-stereochemical relationship of the vicinal quaternary centers is another distinguishing feature. Moreover, **18** lacks the azepine ring system of communesin A, and **18** contains two chlorines on the aromatic ring [28].

Although the polycyclic framework and multiple stereocenters of communesins and perophoramidine have attracted intensive synthetic efforts in recent years, only syntheses by Funk et al. (perophoramidine) [27, 28], Qin et al. (communesin F) [27, 29], and Weinreb et al. (communesin F) [30] have been reported.

Funk's synthesis in 2004 [28] of perophoramidine (Scheme 3), commenced with a base-catalyzed coupling reaction between indole **19** and 3-bromoindolin-2-one **20**. Boc protection of the resulting lactam **21** followed by reduction of the azido functionality led to transamidation and closure of the resulting carbamate upon the indolenine to deliver the aminal **22**. Chemoselective chlorination and protection of the lactam followed by a two-step deprotection and conversion of the resulting alcohol to the azide afforded amide **23**. A second transamidation reaction followed by selective methylation gave lactam **24**. Treatment of lactam **24** with Meerwein's reagent gave imidate **25**, which underwent a Fukuyama deprotection of the sulfur

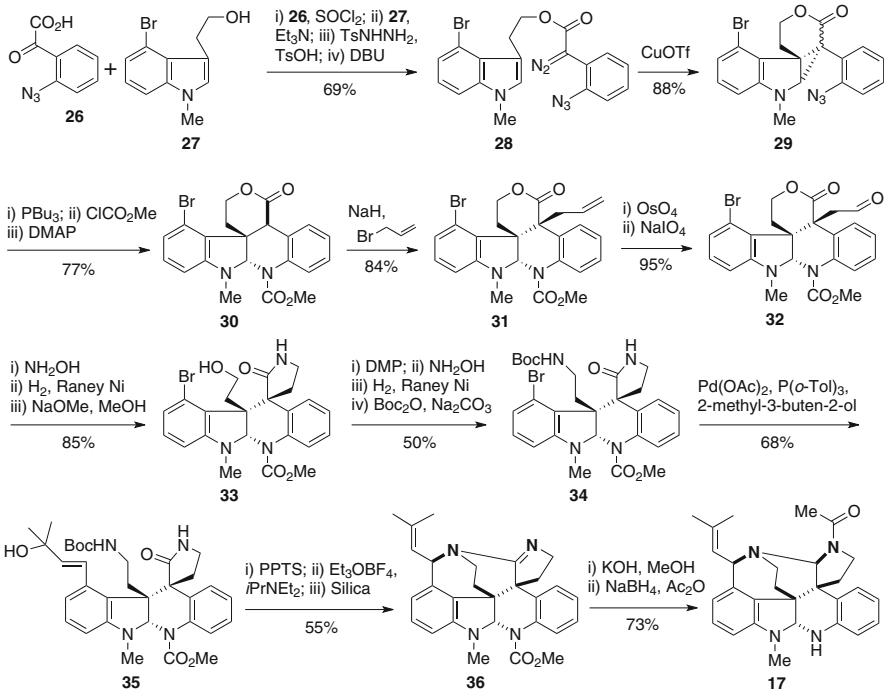


Scheme 3 Total synthesis of perophoramidine (18) by Funk and coworkers

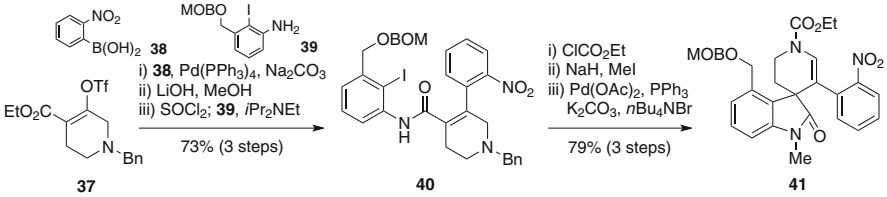
amide followed by attack of the resulting methylamine from the α-face of the imidate to introduce the more basic of the two amidine functionalities. The remaining amidine formed upon oxidation to furnish perophoramidine (**18**).

In 2007, Qin and coworkers [29] reported the first synthesis of communesin F (**17**) (Scheme 4). Capitalizing on previous model studies, they installed the crucial vicinal quaternary stereogenic centers by an intramolecular cyclopropanation, which gave rise to cyclopropane **29** as the key intermediate. Thus, their synthesis commenced with diazoester **28** formed from keto acid **26** and alcohol **27**. Copper (I)-catalyzed cyclopropanation gave spirolactone **29**, which was converted into aminal **30** through an S_N1-type ring opening of the cyclopropane. The subsequent allylation to give **31** was based on the approach of Weinreb and coworkers. The formation of aldehyde **32** was followed by cyclization to amide **33**. Transformation of the primary alcohol into the Boc-protected amine **34** and a Heck reaction to insert the aromatic prenyl side chain afforded the tertiary alcohol **35**. Cyclization in the presence of PPTS to give the aurantioclavine ring was followed by conversion to the corresponding amidine **36**, which was deprotected and reduced to furnish the racemic alkaloid **17** in 23 steps and approximately 3% overall yield.

In 2010, Weinreb and coworkers reported their synthesis of communesin F (**17**) [30]. The synthesis began with known enol triflate **37**. A Suzuki-Miyaura cross-coupling with *O*-nitrophenyl boronic acid (**38**) followed by a two-step reaction with iodoaniline **39,** afforded amide **40**. A one-pot displacement of the benzyl group with ethyl carbamate, amide nitrogen protection, and a subsequent intramolecular Heck reaction provided enamide **41** (Scheme 5).



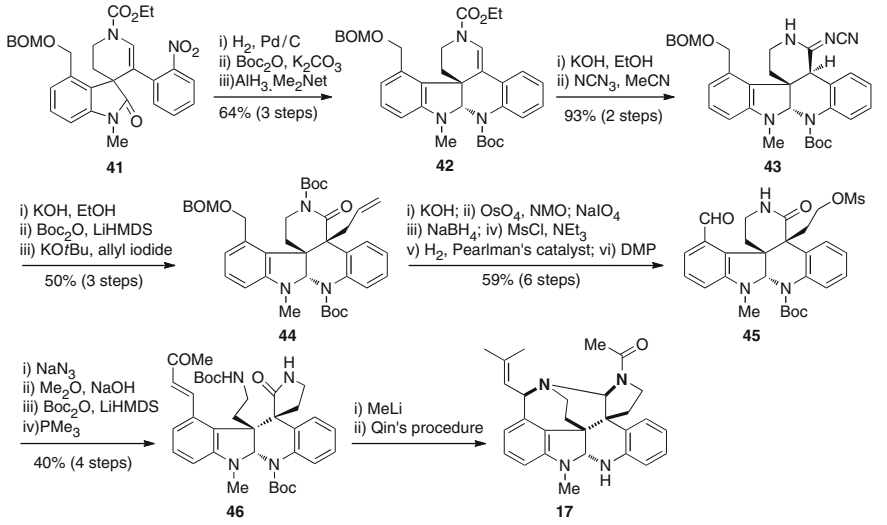
Scheme 4 Total synthesis of communesin F (17) by Qin and coworkers



Scheme 5 Synthesis of fragment 41

With **41** in hand, a two-step nitro reduction and protection, followed by partial reduction of the lactam and resulting cyclization furnished aminal **42**. Further treatment with cyanogen azide generated *N*-cyanoamidine **43**. Hydrolysis and amide protection followed by alkylation with allyl iodide yielded olefin **44** as a single diastereomer. Conversion of **44** to aldehyde **45** was the followed reaction of the mesylate with azide, a cross-aldol reaction with acetone, lactam reprotection with Boc, and trimethylphosphine-mediated reductive rearrangement to provide spiro-γ-lactam **46**. Methyllithium addition to lactam **46** and similar chemistry as reported by Qin et al. gave communesin F (**17**) (Scheme 6).

The key feature of the Funk synthesis of perophoramidine (**18**) is the base-promoted alkylation between 3-alkylindoles and 3-bromo-3-alkylindolin-2-ones



Scheme 6 Completion of the synthesis of communesin F (17)

for the installation of the main skeleton. This is a relatively short synthesis of only twelve steps and an overall 10% yield. In contrast, the synthesis of communesin F (**17**) by Qin and coworkers takes advantage of intramolecular cyclopropanation, ring opening, and ring closing reactions for the installation of the multi-ring skeleton. The very recent synthesis by Weinreb et al. focused on a novel intramolecular Heck reaction of a tetrasubstituted alkene, reductive aminal formation, and a stereoselective allylation for a quaternary carbon.

2.3 Diazonamide A

2.3.1 Introduction

The marine metabolite diazonamide A (**47**) (Fig. 3) was isolated from the colonial ascidian *Diazona angulata*, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines [31]. The original structure of diazonamide A was suggested by an X-ray crystallographic study of the *p*-bromobenzoyl derivative of diazonamide B (**48**) (Fig. 3). Harran and coworkers completed the synthesis of the proposed diazonamide A [32], which differs from the natural diazonamide A, and thus the revised structure is **47** [33].

Diazonamide A causes cells to arrest in mitosis, and after exposure to the drug, treated cells lose both interphase and spindler microtubules. It has equivalent activity to dolastatin 10 and is far more potent than dolastatin 15. This inhibition of microtubule assembly is accompanied by potent inhibition of tubulin-dependent

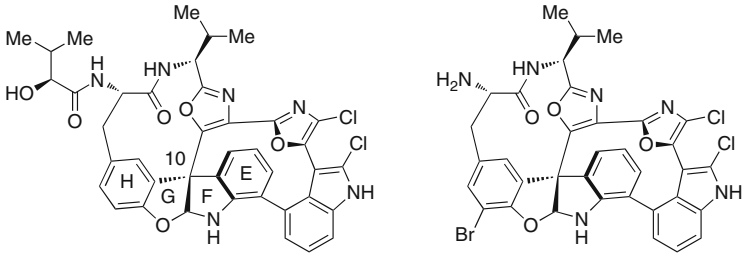


Fig. 3 Diazonamide A (47) and diazonamide B (48)

GTP hydrolysis, which is also comparable to dolastatin 10. However, the remaining biochemical properties of diazonamide A and its analog differ significantly from those of dolastatin 10. The former exhibits in vitro activity against human colorectal carcinoma and murine melanoma cancer cell lines ($IC_{50} < 15$ ng/ml against HCT-116 and B-16). A few analogs of **47**, both natural and synthetic, exhibit potent anticancer activity against HCT116 colon and PC-3 prostate cancer cells [34–37].

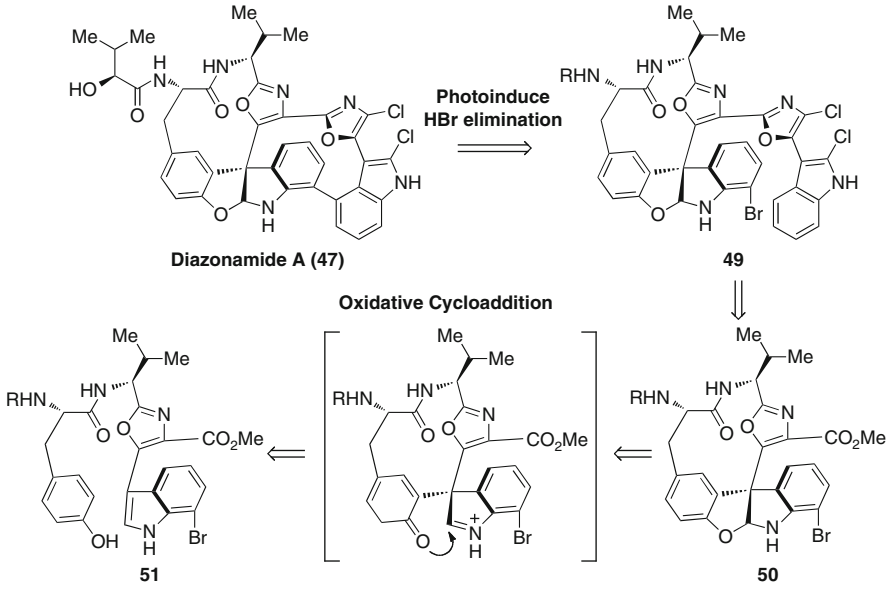
Diazonamide A possesses ten exquisitely arrayed rings and unique elements of stereochemistry, including a rigid EFGH tetracyclic system. The quaternary center at C10 presents the central cornerstone of any synthetic strategy. Finally, the two severely constrained 12-membered rings present an enormous synthetic challenge.

Several research groups have been attracted both by the potent biological activity of diazonamide A and its highly strained and unprecedented structure, and syntheses have been achieved by Harran et al. [38] and Nicolaou et al. [39, 40], and formal syntheses are described by Magnus et al. [41] and Sammakia et al. [42].

2.3.2 Synthesis by Harran and Coworkers

Following the synthesis of the originally proposed incorrect structure of diazonamide and its revision, Harran and coworkers reported a concise and flexible synthesis of diazonamide A (**47**) [38]. Retrosynthetically, **47** was realized from intermediate **49** by photoinduced electron transfer mediated HBr elimination. Intermediate **49** was derived from methyl ester **50** through oxazole formation, which in turn was accessed through an oxidative cycloaddition from phenol derivative **51** (Scheme 7).

Synthesis of **51** commenced with racemic 7-bromotryptophan methyl ester (**52**), a three-step process involving treatment with acyl chloride **53**, Yonemitsu oxidation and degradation with HBr/AcOH afforded oxazole **54**. Condensation of **54** with sulfonamide **55** gave phenol derivative **56**, which underwent the key oxidative cycloaddition reaction mediated by $PhI(OAc)_2$ to deliver the desired **57**. A three-step functional group manipulation followed by acylation with 7-hydroxy tryptamine **58** afforded diamide **59**. A subsequent two-step benzylic oxidation and cyclodehydration sequence gave bis(oxazoyl)indole **60** (Scheme 8).



Scheme 7 Retrosynthetic analysis of diazonamide A (47) by Harran and coworkers

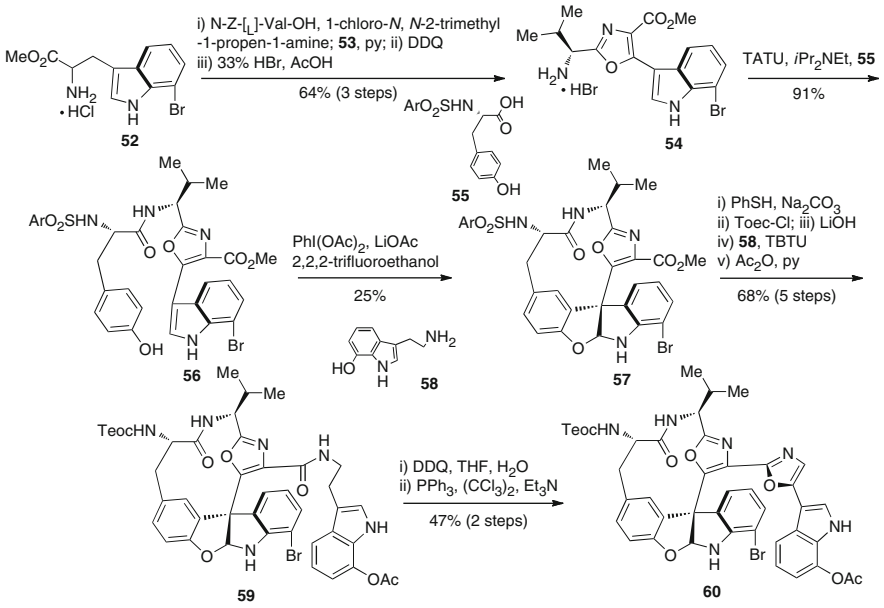
With intermediate **60** in hand, a key photoinduced HBr elimination furnished the second 12-membered ring and provided intermediate **61**. After reductive removal of the spectator phenol through its triflate, selective acylation, indole C-2 chlorination, and treatment with tris(dimethylamino)sulfur trimethyldifluorosilicate, afforded the desbromo diazonamide B (**62**). Finally, phosphoryl cyanide-mediated condensation with commercial (*S*)-α-hydroxyisovaleric acid delivered (-)-diazonamide A (**47**) (Scheme 9).

This synthesis features an efficient nine-step protocol (longest linear sequence) and the key steps are oxidative cycloaddition and photoinduced electron transfer mediated elimination of HBr for the installation of the left and the right 12-membered rings, respectively.

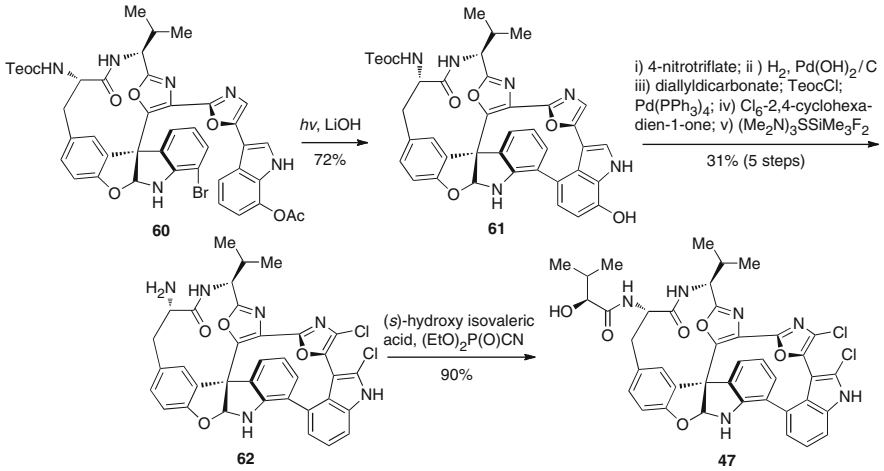
2.3.3 Synthesis by Nicolaou and Coworkers

Shortly after Harran's structure revision of diazonamide A (**47**), Nicolaou and coworkers reported the first total synthesis [39]. Retrosynthetically, assembly of fragments **63**–**67** could lead to diazonamide A through side-chain excision, chlorination, macrolactamization, aminal and oxazole formation, and bis-aryl ring realization (Scheme 10).

Commencing with oxazole **66** generated in two steps from oxazole ester derivative **68**, deprotonation of **66** followed by quenching with isatin derivative **67** provided tertiary alcohol **69** in 73% yield. Refluxing **69** with phenol **65** in the

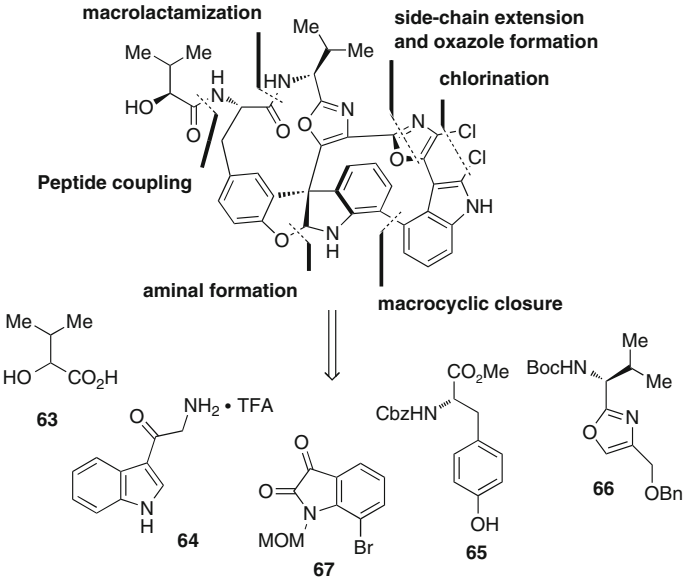


Scheme 8 Synthesis of Intermediate 60



Scheme 9 Total synthesis of diazonamide A (37) by Harran and coworkers

presence of *p*TsOH furnished compound **70**, establishing the crucial quaternary center of diazonamide A. Boc protection of the primary amine and separation of the two C-10 isomers followed by MOM protection gave lactamization precursor **71**. Three-step macrolactamization followed by MOM and benzoxy deprotection afforded lactam **72** (Scheme 11).



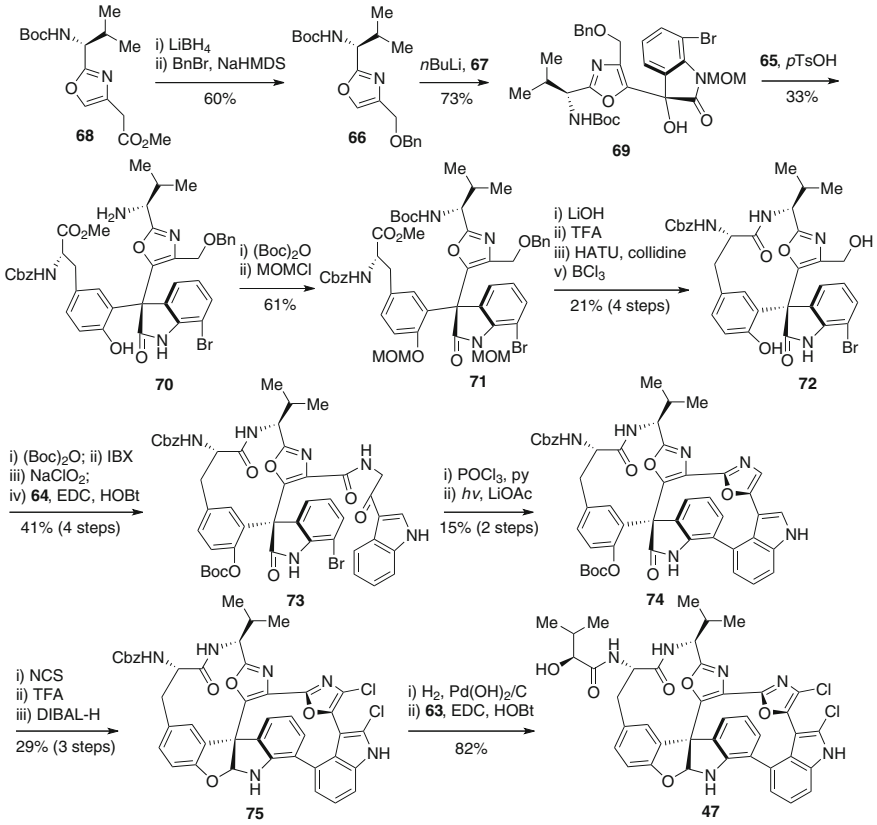
Scheme 10 Retrosynthetic analysis of diazonamide A (47) by Nicolaou and coworkers

With intermediate **72** in hand, reprotection of the phenolic hydroxy group, and a two-step oxidation with IBX and $NaClO_2$ followed by coupling with indole ammonium salt **64** afforded keto amide **73**. Gabriel-Robinson cyclodehydration of **73** for a second oxazole formation followed by a critical photoinduced radical cyclization using a Witkop-type reaction furnished the second 12-membered ring, albeit in low yield. Selective aromatic bis-chlorination and removal of Boc was followed by a key DIBAL-mediated reductive cyclization to provide cyclic aminal **75** in 55% overall yield. Hydrogenolysis of the Cbz group followed by coupling with hydroxy carboxylic acid **63** afforded diazonamide A (**47**) (Scheme 11).

In contrast to his first synthesis (*vide supra*), Nicolaou's second synthesis formed the left-side 12-membered in a late stage, through a macrolactamization process [40]. Retrosynthetic excision of the side chain and the chlorine atoms, and disconnection of the macrolactam, aminal, oxazole and bis-aryl ring system leads to fragments **76** and **77** (Scheme 12).

The preparation of **76** began with phenol **65**. A key $TiCl_4$-mediated coupling with isatin **67** afforded a tertiary alcohol, which was reduced to form **78** via the chloride. Ester reduction followed by *p*-TsOH-catalyzed reaction with 2,2-dimethoxypropane afforded acetonide **79**. Oxindole silylation and an aldol reaction with HCHO provided an equimolar mixture of both C10 stereoisomers **80**. A two-step protection followed by 9-BBN reduction of the lactam gave fragment **76** in good yield (Scheme 13).

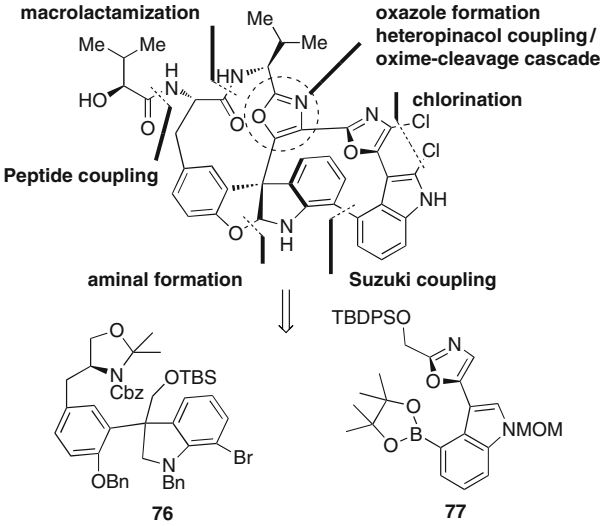
Suzuki coupling of **76** with **77** afforded intermediate **81** in 78% yield. A tandem deprotection/oxidation sequence using TBAF and SO_3·py, and selective capture of the more reactive aldehyde with $MeONH_2$·HCl gave aldehyde-oxime **82**.



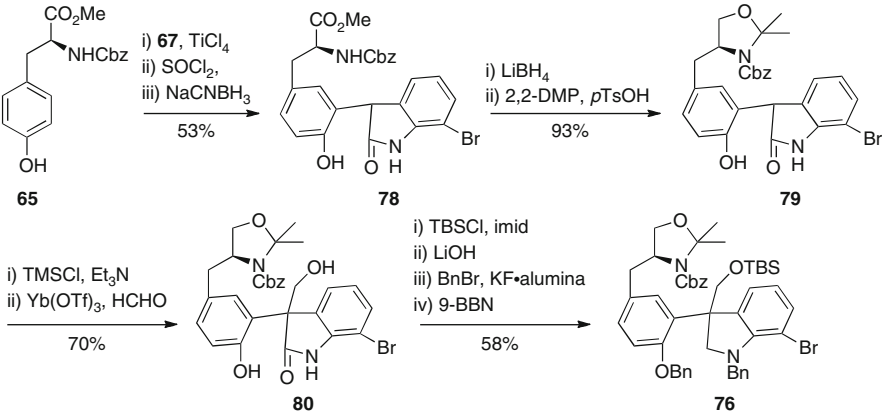
Scheme 11 Total synthesis of diazonamide A (47) by Nicolaou and coworkers

SmI_2-mediated radical cyclization followed by peptide coupling reaction with FmocValOH provided intermediate **83**. TPAP mediated oxidation of **83** and subsequent Robinson-Gabriel cyclodehydration furnished bis-oxazole **84**. HF-mediated cleavage of the acetonide, generation of the free acid from the resultant alcohol through a two-step oxidation process, Et_2NH-induced lysis of the Fmoc protecting group and final intramolecular macrolactamization provided the expected lactam. Hydrogenolysis-mediated benzoxy deprotection and concomitant oxidation of the indoline to the oxindole, and selective protection of the phenolic hydroxy group provided intermediate **85**. A five-step reaction sequence as described above furnished diazonamide A (**47**) (Scheme 14).

In summary, the obvious difference between the two Nicolaou syntheses is the reversed order of the construction of the daunting macrocyclic domains of diazonamide A (**47**). The initial synthesis installed the macrolactam ring first, followed by photoinduced HBr elimination for the heterocyclic 12-membered ring. The subsequent synthesis constructed the heterocyclic core first, which featured a



Scheme 12 Second retrosynthetic analysis of diazonamide A

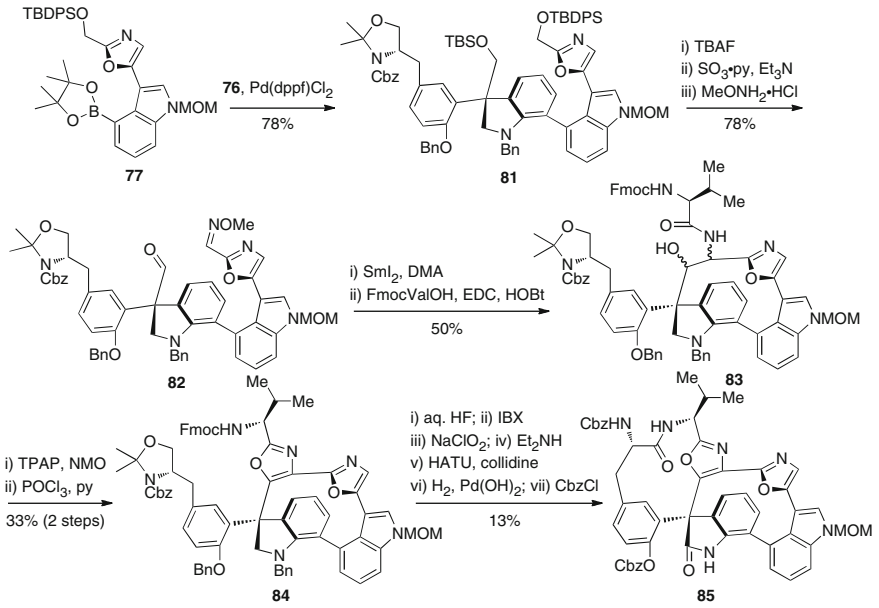


Scheme 13 Preparation of fragment 76

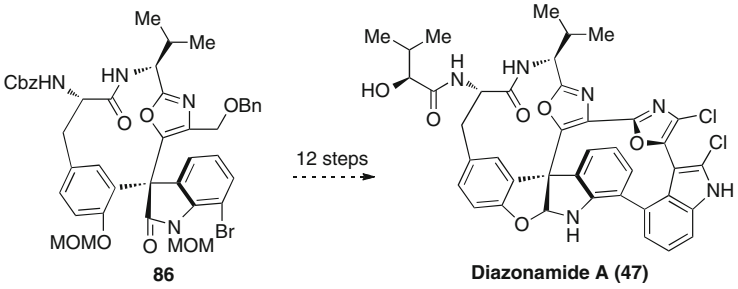
Suzuki coupling and a heteropinacol coupling/oxime-cleavage cascade reaction, followed by a similar macrolactamization for the remaining 12-membered ring.

2.3.4 Formal Synthesis by Magnus and Coworkers

In 2007, Magnus and coworkers reported a formal synthesis of diazonamide A (**47**) [41], which takes advantage of intermediate **86** reported by Nicolaou and coworkers previously [39] (Scheme 15).

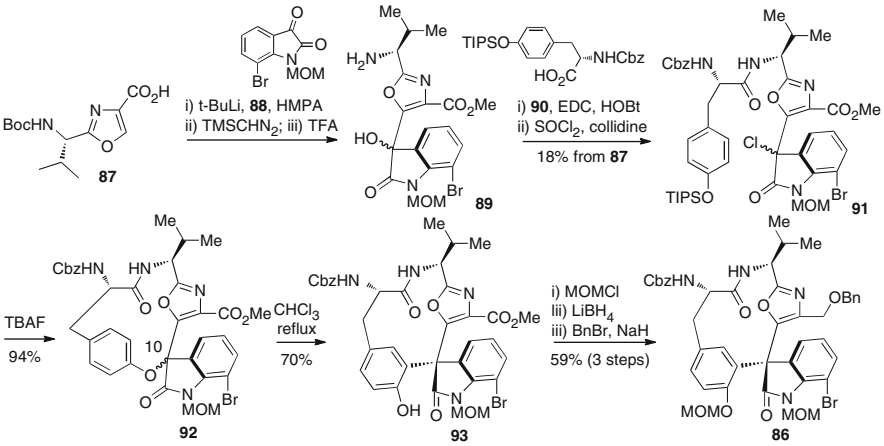


Scheme 14 Completion of the total synthesis of diazonamide A (47)



Scheme 15 Magnus' intermediate for synthesis of diazonamide A (47)

The synthesis of **86** commenced with oxazole carboxylic acid **87**. Base-catalyzed lithiation and coupling with isatin **88** followed by methyl ester formation and Boc deprotection provided tertiary alcohol **89**. A second coupling of the amine **89** with carboxylic acid **90** followed by chlorination afforded chloride **91**. Treatment of **91** with TBAF gave a 1:1 mixture of *O*-aryl ether **92** (C10) in excellent yield. Refluxing **92** in chloroform resulted in the formation of **93** (70%, with 30% of the isomer), which was subjected to a three-step reaction sequence to furnish intermediate **86** (Scheme 16).



Scheme 16 Magnus' synthesis of intermediate 86

2.3.5 Formal Synthesis by Sammakia and Coworkers

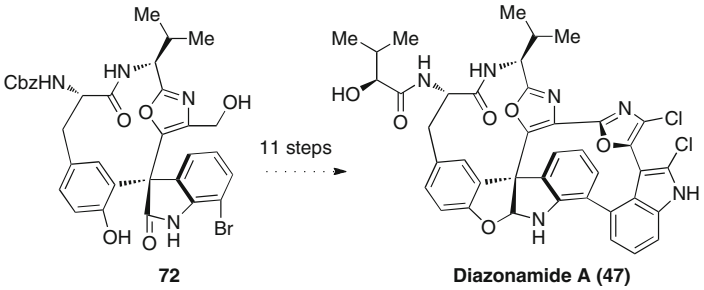
In 2010, Sammakia and coworkers reported a formal synthesis of diazonamide A (**47**) [42], which employs intermediate **72** as previously synthesized by Nicolaou and coworkers [39] (Scheme 17).

The synthesis of **72** started with methyl ester **65**. Addition of **65** to 7-bromoisatin (**67**) afforded tertiary alcohol **94**. A two-step reduction followed by coupling with aminooxazole **95** provided amide **96**. The key base-mediated intramolecular cyclization gave **97**, which was converted to the corresponding carboxamide using Parkin's catalyst **98**. A subsequent SmI_2-mediated reduction furnished primary alcohol **72**, which could be converted to diazonamide A (**47**) in eleven steps (Scheme 18).

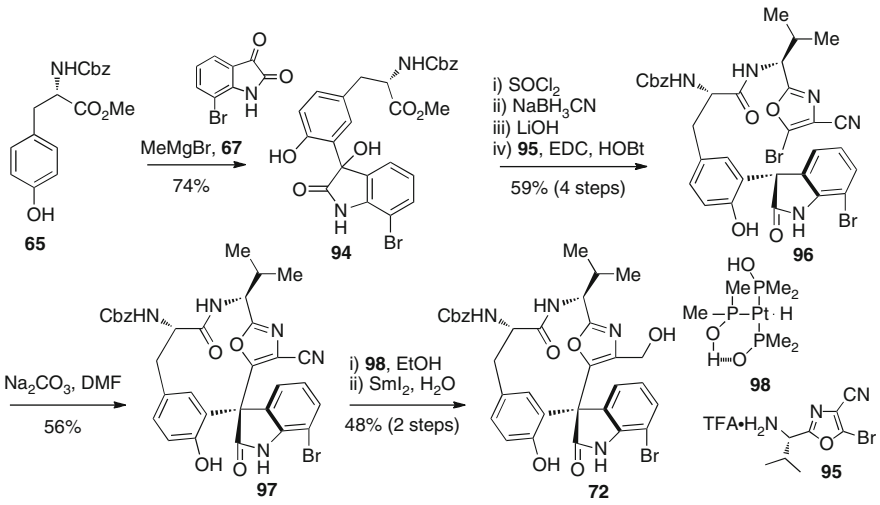
2.4 Minfiensine

Minfiensine (**99**) [43] exemplifies a variety of indole alkaloids containing the novel 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole ring skeleton. These include minfiensine (**99**), vincorine (**100**) [44], corymine (**101**) [45], and echitamine (**102**) [46] (Fig. 4). They exhibit a number of impressive biological activities, including significant anticancer activity [47]. Since the first characterization of the first akuammiline alkaloid member echitamine (**102**), more than 80 years ago, only a few successful syntheses of this challenging tetracyclic system have been reported.

Minfiensine (**99**) was first synthesized by Overman and coworkers in 2005 [48] (Scheme 19). Their synthesis commenced with acid-catalyzed transamination of



Scheme 17 Sammakia's intermediate for synthesis of diazonamide A (47)



Scheme 18 Synthesis of Intermediate 72 for diazonamide A

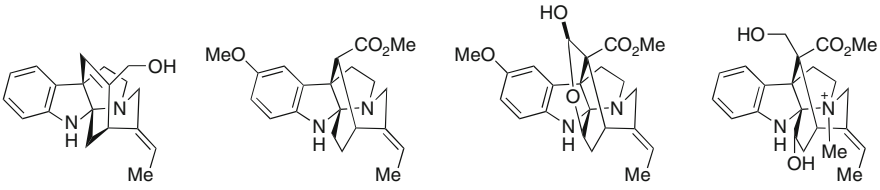
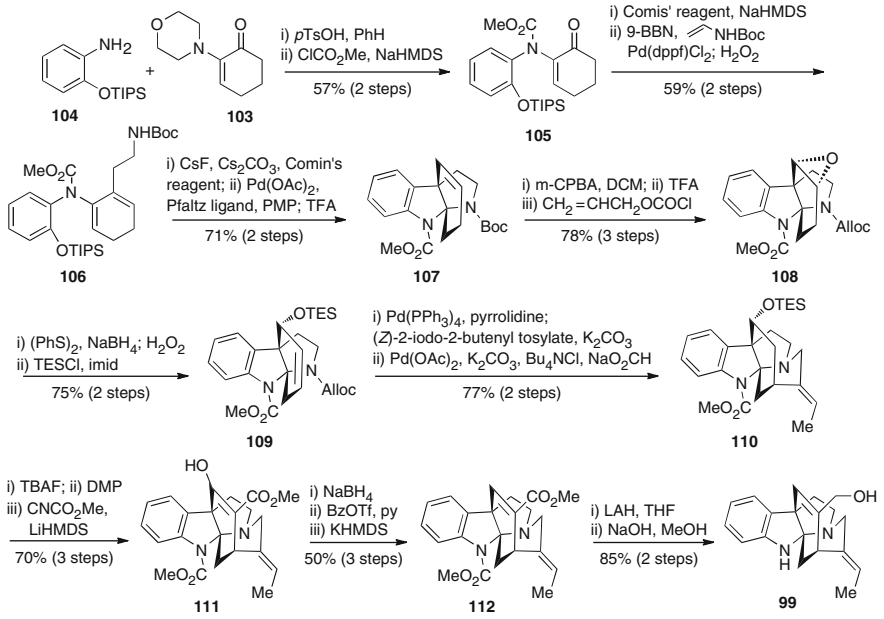


Fig. 4 Minfiensine (99), vincorine (100), corymine(101), and echitamine (102)

enamine **103** with aniline **104**, and a subsequent selective nitrogen protection afforded carbamate **105**. A two-step triflation with Comins' reagent and Suzuki coupling gave intermediate **106**, which underwent the pivotal asymmetric Heck cyclization through a triflate intermediate.

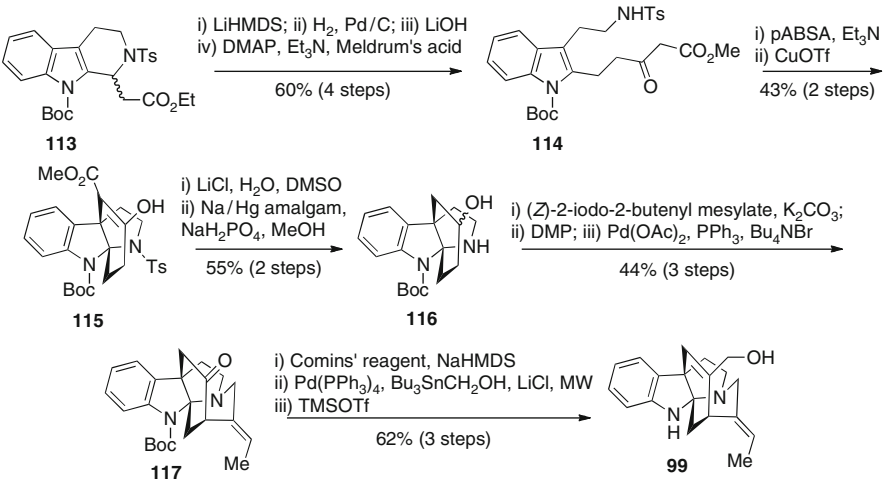


Scheme 19 Total synthesis of minfiensine (99) by Overman and coworkers

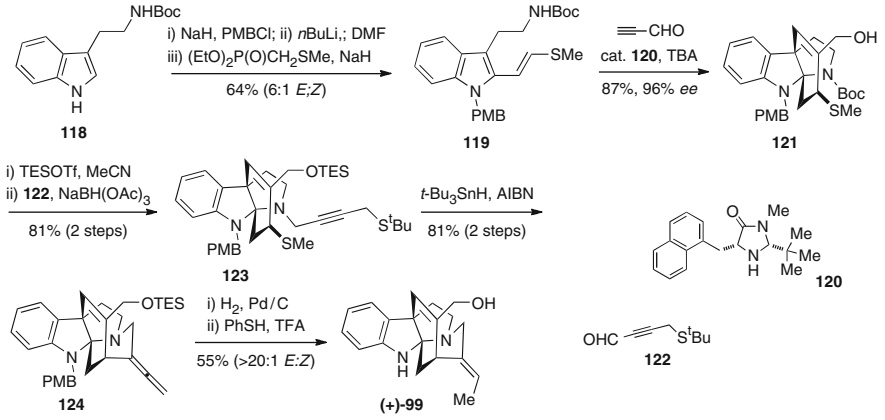
Treatment with excess trifluoroacetic acid furnished the (dihydroiminoethano) carbazole **107** in 71% overall yield. Epoxidation of the alkene followed by a two-step protecting group modification gave epoxide **108**, which underwent an oxidative epoxide opening followed by silyl protection to give silyl ether **109**. Alloc deprotection, alkylation with (*Z*)-2-iodo-2-butenyl tosylate, followed by an intramolecular Heck reaction delivered pentacyclic diamine **110**. A three-step formation of the β-ketoester **111** followed by a three-step reduction process afforded ester **112**, which underwent a reduction and deprotection sequence to provide minfiensine (**99**). A sequential catalytic asymmetric Heck-*N*-acyliminium ion cyclization for the delivery of the enantiopure 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole is the highlight of the synthesis.

In 2008, Qin and coworkers [47] reported their approach to minfiensine (**99**) (Scheme 20), which followed upon their synthesis of vincorine (**100**) [49]. Beginning with tetrahydrocarboline **113**, a base-mediated ring opening, reduction of the double bond, and hydrolysis followed by condensation with Meldrum's acid afforded keto ester **114**. α-Diazo β-keto ester formation followed by a CuOTf-catalyzed cascade reaction afforded tetracycle **115** as the enol isomer. Krapcho decarbomethoxylation and reduction of the ketone was accompanied by cleavage of the tosyl group to give amine **116**. Selective amine alkylation and reoxidation of the alcohol to the ketone was followed by an intramolecular α-vinylation to provide pentacyclic **117**. Triflate formation using Comins' reagent, microwave-assisted hydroxymethylation, and final deprotection gave minfiensine (**99**) (Scheme 20).

In 2009, MacMillan and coworkers reported their asymmetric synthesis of minfiensine (**99**) in only nine steps [50] (Scheme 21). This route commenced with tryptamine derivative **118**, and a three-step transformation afforded vinyl sulfide **119**. A pivotal Diels-Alder cyclization cascade using catalyst **120** and tribromoacetic acid provided tetracycle **121** in both excellent yield and selectivity. Simultaneous *N*-Boc deprotection and primary alcohol protection followed by reductive amination with sulfide **122** gave **123**, which underwent radical cyclization using bulky *t*-Bu_3SnH to give the corresponding allene **124**. Regio- and diastereoselective allene hydrogenation followed by protecting group removal gave minfiensine (**99**). A unique cascade reaction for the installation of the central tetracyclic



Scheme 20 Total synthesis of minfiensine (99) by Qin and coworkers



Scheme 21 Total synthesis of (+)-minfiensine (99) by MacMillan and coworkers

pyrroloindoline framework and a 6-*exo*-dig radical cyclization for the final piperidinyl ring highlight the synthesis.

2.5 Stephacidin B

2.5.1 Introduction

Stephacidin B (**125**) and stephacidin A (**126**), [51] (Fig. 5) are indole alkaloids structurally related to the cytotoxic marine natural product avrainvillamide (**127**) [52, 53] (Fig. 5). They were first isolated in 2001 from a culture broth of *Aspergillus ochraceus* WC76466, a mitosporic fungus isolated from light brown clay collected from Sirsagani, India, by Qian-Cutrone and coworkers at Bristol-Myers Squibb. A combination of NMR spectroscopy and X-ray crystallography was used to elucidate the structure of stephacidin B, without the establishment of the stereochemistry. The unprecedented structural architecture of stephacidin B provides a new level of complexity within prenylated indole alkaloids from fungi. Both of the indole moieties are present in rare oxidation states. Indeed, whereas *N*-methoxyindole alkaloids have been isolated sporadically, very few *N*-hydroxyindoles and indole nitrones have been discovered in natural sources [54].

Both **126** and **125** demonstrated in vitro cytotoxic activity against various human tumor cell lines; IC_{50} values of **126** were in the one-digit micromolar range for ovarian, colon, breast, and lung cancer cell lines, while **125** showed a 5- to 30-fold higher activity. The strongest cytotoxicity was observed with testosterone-dependent prostate LNCap cancer cells with an IC_{50} value of 0.06 μM [54, 55]. Both stephacidin B (**125**) and avrainvillamide (**127**) inhibited the growth of cultured human cancer cells ($IC_{50} \sim$ 50–100 nm), LNCap cancer cells ($IC_{50} \sim$ 40–330 nm), βT-549 cancer cells ($IC_{50} \sim$ 300–700 nm), T-47D cancer cells ($IC_{50} \sim$ 30–300 nm), and MALME-3M cancer cells ($IC_{50} \sim$ 100–600 nm). But **125** always showed at least twofold higher activity than **127** [56].

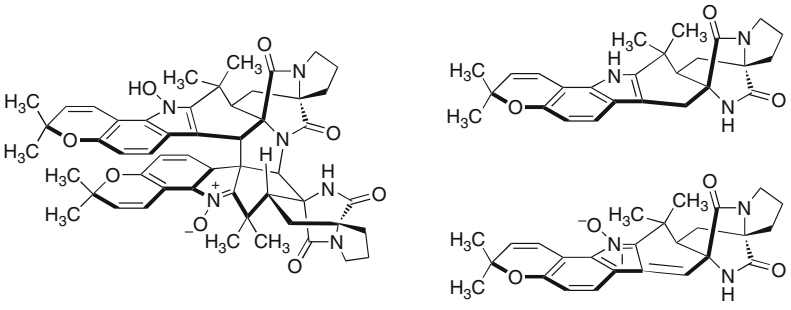


Fig. 5 Stephacidin A (126), Stephacidin B (125) and Avrainvillamide (127)

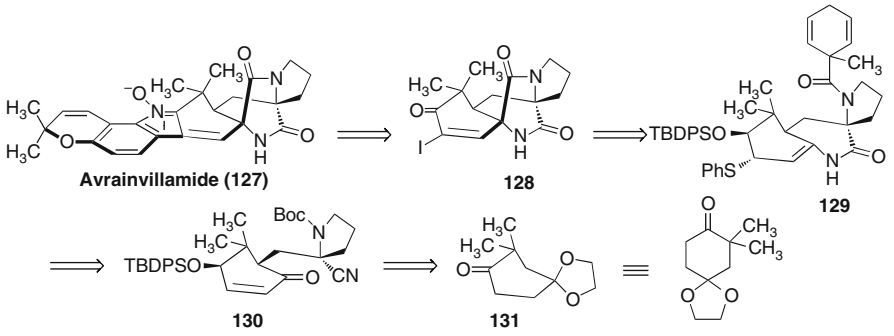
Biosynthetically, **125** is considered to be a dimer of **127**, which itself could be an oxidation product of **126**. The manner in which two avrainvillamide units are linked strongly indicates a dimerization mode that has not yet been described for indole alkaloids. Initiation of the dimerization by a hetero-Michael addition reaction sets the stage for the synthesis of **125**. Until now, three syntheses of stephacidin B (all based on the dimerization of avrainvillamide) have been accomplished, by Myers et al. [55], Baran et al. [57, 58], and Williams et al. [59].

2.5.2 Synthesis by Myers and Coworkers

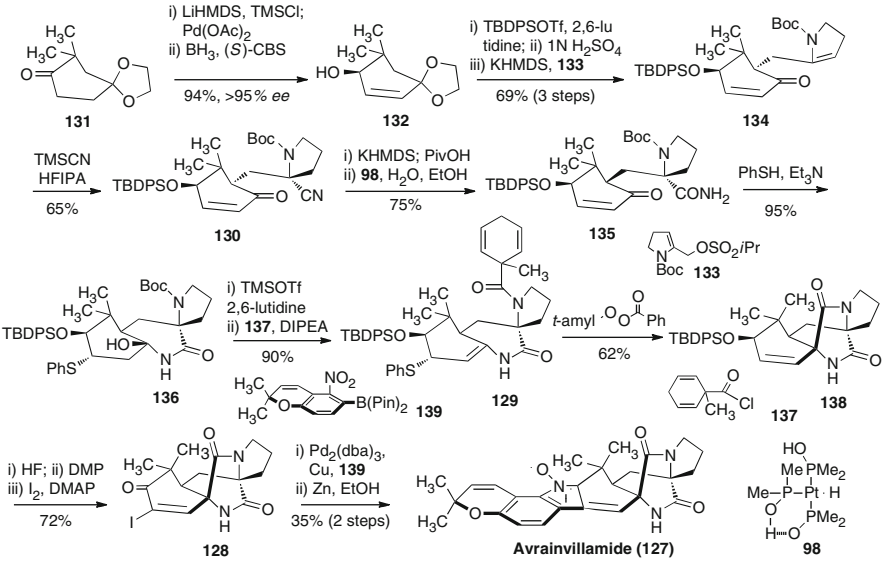
The previously developed methodology by Myers et al. [60], which entailed a sequence to access the 3-alkylidene-3*H*-indole-1-oxide moiety present in **127**, demonstrated the capability of this indole nucleus to act as a Michael acceptor.

Retrosynthetically, a base-catalyzed dimerization of **127** would afford stephacidin B. Avrainvillamide (**127**) was simplified as vinyl iodide **128** by cleavage of the dihydropyrano [2,3-*g*]indole-1-oxide moiety and palladium mediated coupling. An aminoacyl radical addition from **129** gave access to **128**, while **129** could be derived from cyanide **130** through a hemiaminal formation/dehydration and conjugate addition. Finally, Strecker-like reaction of ketone **131** would fulfill nitrile **130** [55] (Scheme 22).

Beginning with cyclohexanone **131**, palladium-mediated oxidation through its trimethylsilyl enol ether followed by Corey-Bakshi-Shibata (CBS) asymmetric reduction afforded (*R*)-allylic alcohol **132** in >95% *ee*. Silyl protection, and ketal hydrolysis followed by base-mediated alkylation using the novel electrophile **133** gave dihydropyrrole derivative **134** as a single diastereomer. Subsequent hexafluoroisopropanol (FHIPA) mediated Strecker-like hydrogen cyanide addition gave the *N*-Boc amino nitrile **130**. Epimerization of the α-carbon of ketone **130** followed by conversion of the nitrile to the corresponding primary amide under the platinum catalyst **98** of Ghaffar and Parkins gave **135**. Treatment of **135** with thiophenol and triethylamine was accompanied by cyclic hemiaminal formation to afford **136**.



Scheme 22 Retrosynthetic analysis of stephacidin B by Myers and coworkers



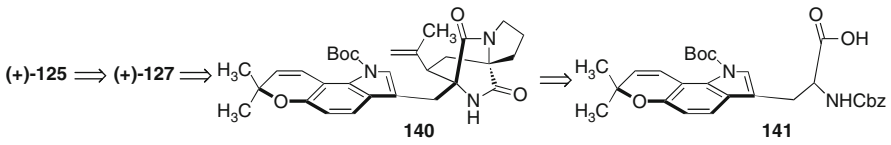
Scheme 23 Total synthesis of stephacidin B by Myers and coworkers

Dehydration of **136** in the presence of TMSOTf and 2,6-lutidine accompanied by Boc deprotection and followed by acylation of the pyrrolidinyl amino group with acyl chloride **137,** gave acyl radical precursor **129**. Thermolysis of amide **129** with *tert*-amyl peroxybenzoate produced tetracyclic product **138**, representing the bridged core of stephacidin B. A three-step transformation followed by Suzuki coupling reaction between the resulting α-iodoenone **128** with arylboronic acid derivative **139**, and subsequent reduction in the presence of activated zinc afforded avrainvillamide (**127**). Treatment with triethylamine provided the dimeric stephacidin B (**125**) (Scheme 23).

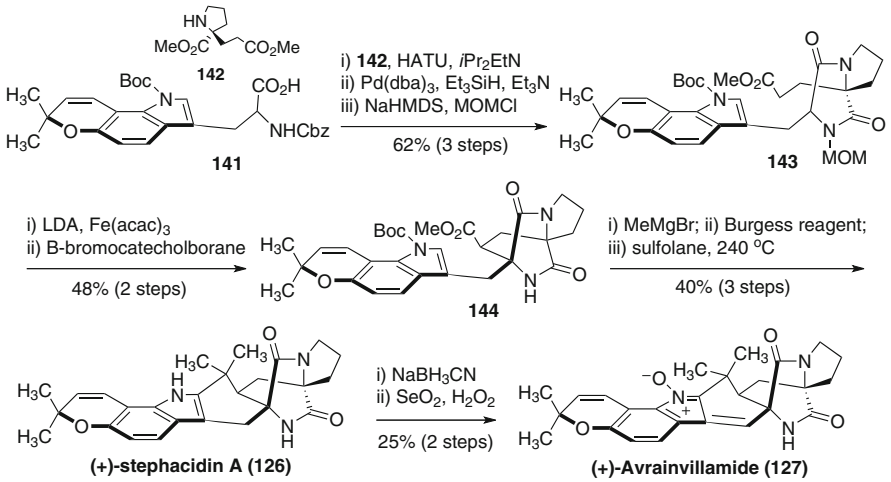
2.5.3 Synthesis by Baran and Coworkers

The approach of Baran and coworkers features the fact that stephacidin A (**126**), which is a reduced monomer biogenetically related to stephacidin B (**125**), can be oxidized to avrainvillamide (**127**). The retrosynthetic analysis fundamentally differs from that of Myers in that the indole nucleus is already present in the starting material. Thus, one stereocenter is in the starting material and the other two stereocenters are installed simultaneously [54, 58] (Scheme 24).

The synthesis commenced with indole **141**, which was coupled to proline ester **142**. Chemoselective removal of the Cbz group was accompanied by diketopiperazine ring formation, and MOM protection gave bislactam **143**. Metal-mediated oxidative coupling, which is seldom used in synthesis and never for such challenging targets, was used to gain access to the bicyclo[2.2.2]diazaoctane moiety **144** in a



Scheme 24 Retrosynthetic analysis of Baran's synthesis of stephacidin B

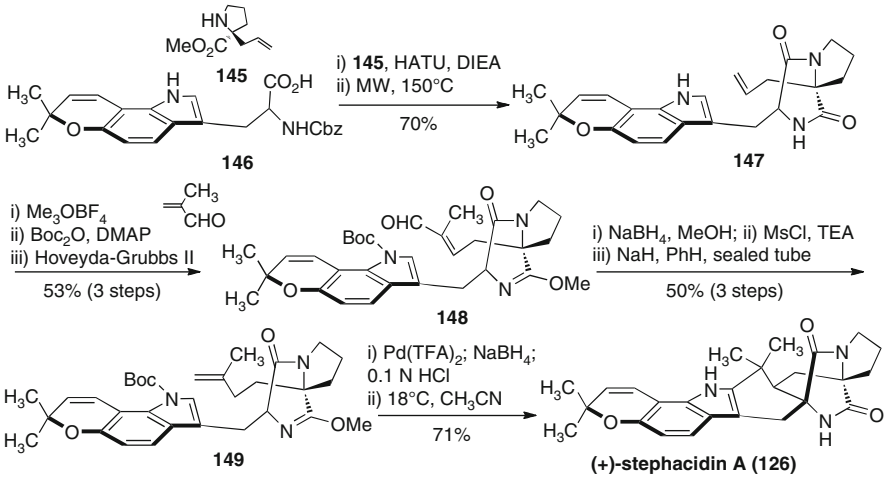


Scheme 25 Total synthesis of stephacidin B by Baran and coworkers

stereocontrolled manner. Subsequent reaction with methyl Grignard reagent followed by thermal removal of the Boc group, was accompanied by thermal indole annulation to provide stephacidin A (**126**) in 45% yield. A Gribble reduction of the indole ring and chemoselective oxidation gave avrainvillamide (**127**), which dimerized to stephacidin B (**125**) in the presence of triethylamine (Scheme 25). The newly employed selenium- and tungsten-based protocols to generate chemoselectively an unsaturated nitrone group from an easily accessible indoline highlight this convenient synthesis of stephacidin B (**125**).

2.5.4 Synthesis by Williams and Coworkers

In 2007, Williams and coworkers reported their independent synthesis of stephacidin B (**125**) [59]. Their key feature is the novel S_N2' cyclization to form the [2.2.2] bridged bicyclic ring system. The synthesis commenced with the coupling between (*R*)-proline methyl ester **145** and indole carboxylic acid **146**. Microwave-mediated ring closure provided the diketopiperazine ring system **147**. A two-step protection sequence followed by Grubbs olefin cross-metathesis gave aldehyde **148**, which was converted to alkene by a standard sequence to provide **149** as a single



Scheme 26 Total synthesis of stephacidin B by Williams and coworkers

diastereomer. Treatment of **149** with $Pd(TFA)_2$ and $NaBH_4$, followed by washing with 0.1 N HCl, and subsequent heating afforded stephacidin A (**126**). A similar reaction sequence to Baran's synthesis above led to stephacidin B (**125**) (Scheme 26).

2.6 Yatakemycin

Yatakemycin (**150**) (Fig. 6), which was isolated from *Streptomyces* sp. TP-AO356 by Igarashi and coworkers in 2003, is the most potent member of a class of antitumor compounds that includes duocarmycin A, duocarmycin SA, and CC-1065 [61, 62]. The remarkable antitumor activity of yatakemycin results from a sequence-selective DNA allylation at the activated cyclopropane. Unlike CC-1065 and duocarmycin SA, yatakemycin presents DNA-binding subunits flanking each side of the alkylation subunit [63]. The nature of the interaction of yatakemycin with DNA and its related potent antitumor activity has attracted a great deal of attention. Boger and coworkers revised the structure of yatakemycin during their first total synthesis [62]. Fukuyama and coworkers reported a second total synthesis in 2006 [64].

Boger's synthesis commenced with the preparation of the left-hand fragment **155**. A sequence of phenol protection of **151**, aldehyde oxidation, Curtius rearrangement, tosylation, nitro reduction, Boc protection, and $Pb(OAc)_4$ mediated oxidation afforded quinodiimide **152**. A key Diels-Alder reaction gave **153** in good yield. Treatment of **153** in a sequence of oxonolysis, aromatization, Boc deprotection, cyclization to the lactam, *N*-tosyl removal, indole reduction, and selective Boc protection afforded **154**. Conversion of the lactam to the

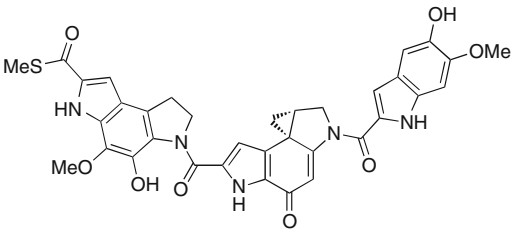
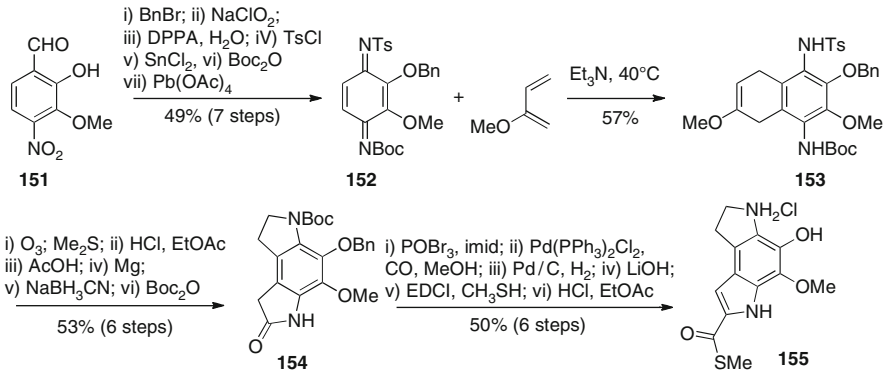


Fig. 6 Yatakemycin (150)

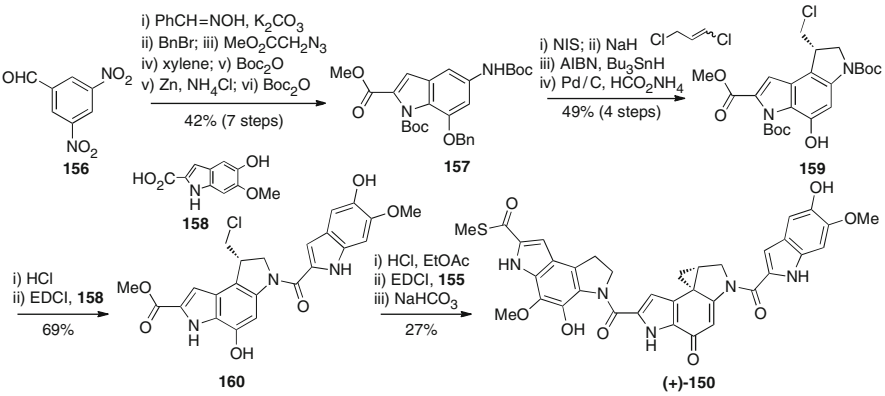


Scheme 27 Preparation of fragment 155

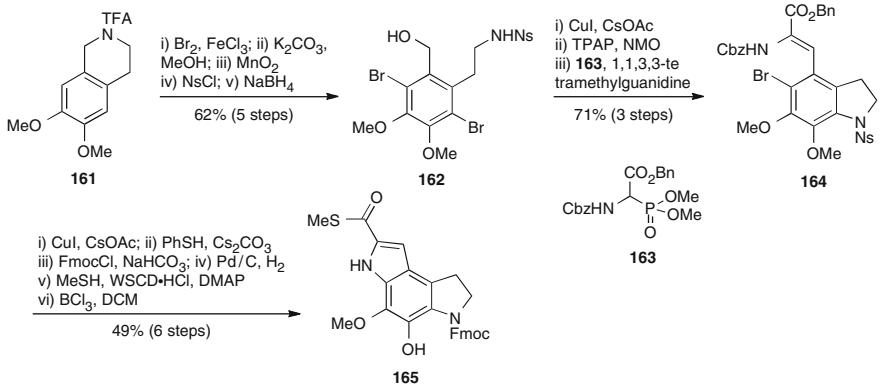
corresponding bromoindole, cross coupling to give the methyl ester, benzyl ether hydrogenolysis, ester hydrolysis, coupling of the resulting acid with CH_3SH, and final Boc deprotection provided fragment **155** in good yield (Scheme 27).

The middle fragment **159** was prepared from dinitrobenzaldehyde **156**. Nucleophilic displacement of a nitro group and in situ elimination for the correspond phenol, phenol protection, aldehyde condensation with methyl azidoacetate, Hemetsberger-Rees thermolysis to the indole, Boc protection, nitro reduction, and a second Boc protection gave indole derivative **157**. Regioselective iodination, *N*-alkylation with 1,3-dichloropropene followed by 5-*exo-trig* free radical ring closure, and subsequent benzyl ether hydrogenolysis provided fragment **159**. EDCI mediated coupling of fragment **159** with indole-2-carboxylic acid **158** afforded intermediate **160**. A second coupling of **160** with left-hand fragment **155** followed base catalyzed cyclopropanation furnished yatakemycin (**150**) (Scheme 28).

In 2006, Fukuyama and coworkers reported their independent synthesis of yatakemycin (**150**) [64]. The preparation of the left-hand fragment **165** started with dimethoxybenzene derivative **161**. Dibromination of **161** in the presence of $FeCl_3$, removal of the TFA group, and oxidation provided a dihydroisoquinoline. Treatment with NsCl to form the hemiaminal, and reductive opening using $NaBH_4$ gave cyclization precursor **162**. Amination using CuI to give the desired indoline,



Scheme 28 Total synthesis of yatakemycin (150) by Boger and coworkers



Scheme 29 Preparation of left-hand fragment 165

oxidation of the primary alcohol to the aldehyde, Horner-Wadsworth-Emmons reaction with **163** provided dehydroalanine derivative **164**. A second amination reaction to give dihydropyrroloindole, followed by respective conversion of the Ns and benzyl ester to the Fmoc and methanethiol ether, and regioselective demethylation using BCl_3 furnished fragment **165** (Scheme 29).

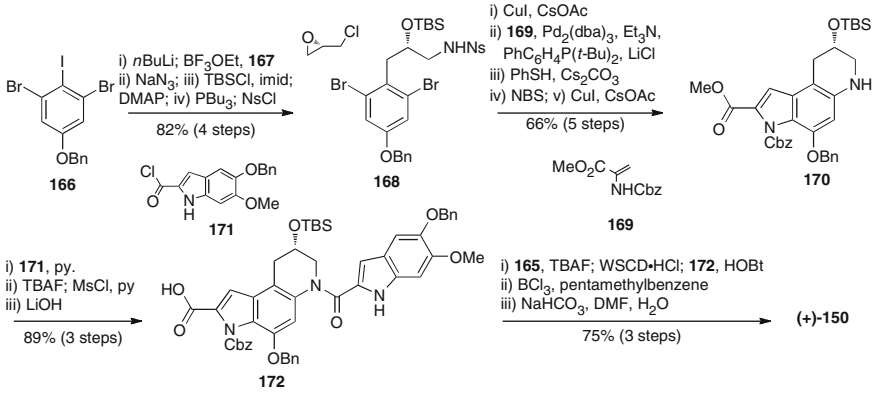
The synthesis of the middle fragment **170** was accomplished starting with 2,6-dibromoiodobenzene derivative **166**. Cleavage of the epoxide in **167** in the presence of BF_3, introduction of an azide group, protection of the resulting alcohol, and a Staudinger reaction afforded intermediate **168**. Intramolecular amination gave the corresponding tetrahydroquinoline. A Heck reaction with alkene **169**, removal of Ns, regioselective bromination, and a second amination provided fragment **170**. Coupling between the middle fragment **170** with right-hand fragment **171** followed by a two-step mesylation and ester hydrolysis gave carboxylic acid **172**. Coupling of **172** with the left-hand fragment **165** followed by benzyl ether deprotection and cyclopropanation furnished yatakemycin (**150**) (Scheme 30).

3 Other Complex Indole Alkaloids

3.1 Chartelline C

The securines, securamines, chartellines, and chartellamides are members of a structurally unique class of natural products isolated from the bryozoa *Chartella papyracea* and *Securiflustra securifrons* by Christophersen and coworkers [65–69] (Fig. 7). Chartellines represent a small family of marine-derived, architecturally unique alkaloids that include chartelline A, chartelline B, and chartelline C, which only differ in the number and position of bromines. Chartelline C (**173**) is composed of indolenine, imidazole, and β-lactam heterocycles arrayed in a dense, π-stacking framework that poses an obvious challenge for its synthesis [70, 71]. Though numerous efforts have been made towards chartelline C (**173**), only Baran and coworkers have reported its synthesis [70, 71].

The synthesis commenced with a site-selective Heck-Sonogashira coupling of the easily prepared indole **174** and known alkyne **175**. Selective reduction of the resulting alkyne **176** to the corresponding *cis* olefin followed by a two-step



Scheme 30 Total synthesis of yatakemycin (150) by Fukuyama and coworkers

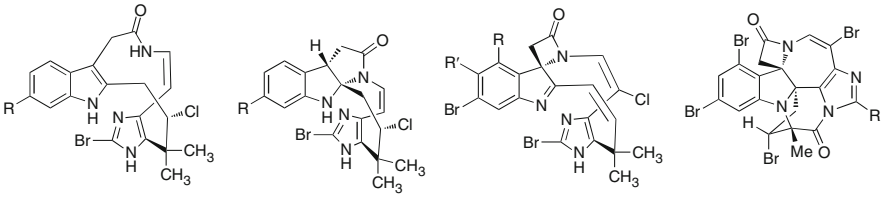
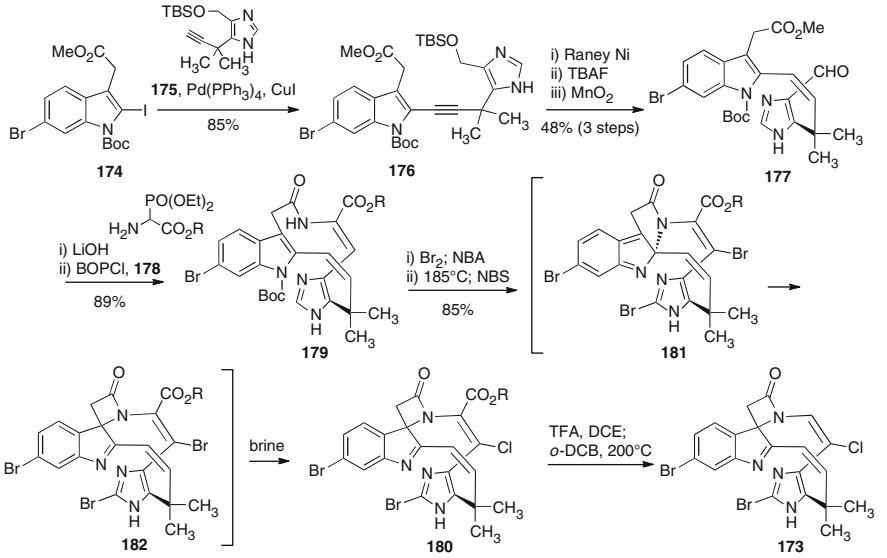


Fig. 7 Securines, securamines, chartellines and chartellamides



Scheme 31 Total synthesis of chartelline C (173)

deprotection and oxidation process afforded aldehyde **177**. Saponification, coupling with amine **178**, followed by intramolecular Horner-Wadsworth-Emmons reaction provided macrocycle **179** with a second *cis* olefin. Chemoselective bromination of **179** followed by NBS-mediated thermolysis furnished β-lactam derivative **180** through intermediate **181** and **182**. Final deprotection of the TMSE ester, and decarboxylation afforded chartelline C (**173**) (Scheme 31).

3.2 Haplophytine

3.2.1 Introduction

Haplophytine (**183**), (Fig. 8), a polycyclic indole alkaloid, was first isolated by Snyder and coworkers in 1952, and identified as the principle bioactive component of the wild Mexican flower *Haplophyton cimicidum* A.D.C. (*Apocynaceae*) [72–77]. Haplophytine is of comparable toxicity to several widely used insecticides, and it was found to be toxic to a wide range of insects including European corn borers, Mexican bean beetle larvae, Colorado potato beetle larvae and adults, grasshoppers, egg-plant lace bugs, and codling moths [75].

The structure of haplophytine was established 21 years after its first isolation and original formula assignment. The correct molecular structure was determined by high-resolution mass spectrometry, while the full structure was realized by extensive chemical degradation, spectroscopy, and X-ray crystallographic studies from the groups of Cava, Yates, and Zacharias [76, 77].

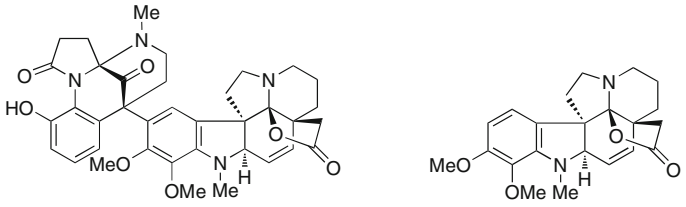


Fig. 8 Haplophytine (183) and Aspidophytine (184)

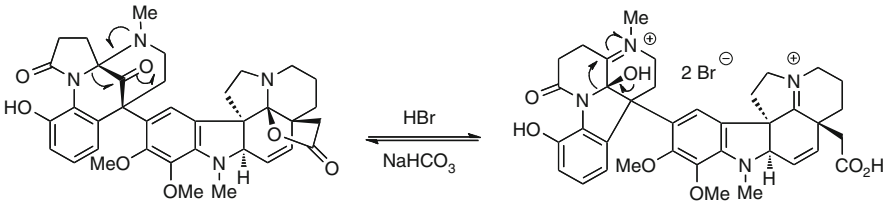
Haplophytine possesses an intriguing polycyclic array of ten rings, six stereocenters (five of which are quaternary), and a highly congested C–C bond connecting the two district halves of the molecule. The left domain possesses a bicyclo [3.3.1] skeleton that includes a bridged ketone, and no synthesis of this domain is known to date, despite numerous efforts. The right indolic domain is known as aspidophytine (**184**), which incorporates a fused lactone. So far, five syntheses of aspidophytine have been accomplished, pioneered by Corey and coworkers [78–82].

In this chapter, only the two syntheses by Fukuyama, Tokuyama et al. [83, 84] and Nicolaou, Chen et al. [84, 85] will be detailed. The left domain of haplophytine undergoes skeletal rearrangement to give the corresponding dihydrobromide **185** under acidic conditions [76, 77], while basic conditions reverse the reaction to recover haplophytine (Scheme 32). This phenomenon plays an important role in the synthesis of haplophytine by both research groups.

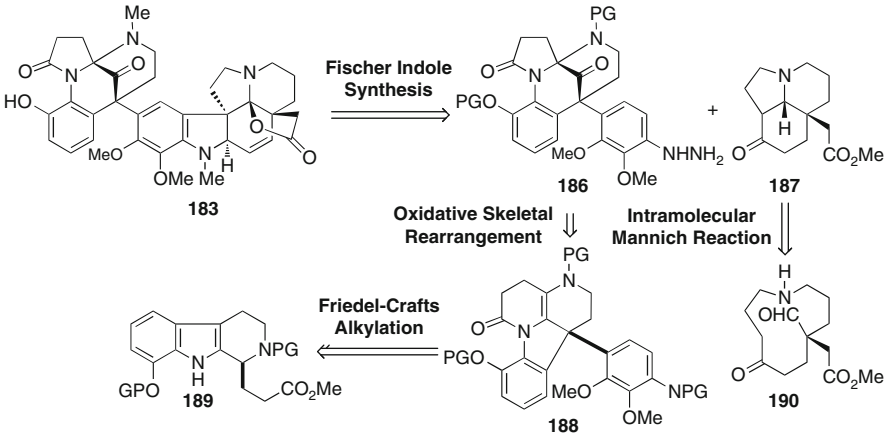
3.2.2 Synthesis by Fukuyama, Tokuyama and Coworkers

The approach to haplophytine proposed by Fukuyama and Tokuyama et al. did not rely on the synthesis of aspidophytine previously reported [75]. One of the main synthetic problems was the connection of the left-hand segment to the indole moiety of aspidophytine. Retrosynthetically, Fischer indole synthesis of the fully elaborated left-hand fragment **186** and the tricyclic ketone **187** gave haplophytine. **186** was generated through oxidative skeletal rearrangement from precursor **188**, which was accessible from indole **189** by Friedel-Crafts alkylation. Optically active ketone **187** was assembled through a stereoselective intramolecular Mannich reaction from aldehyde **190** (Scheme 33).

The preparation of ketone **187** commenced with the stereoselective construction of the quaternary carbon center by asymmetric Michael addition using a thioacrylate. Reduction of the resulting cyclopentanone **192** and mesylation provided the mesylate as a mixture of diastereomers. Chemoselective coupling of the thioester with an alkylzinc reagent gave ketoimide **193**. Ketalization and elimination of the mesylate afforded cyclopentene **194**. Conversion of the phthalimide into the Ns-amide, cleavage of the cyclopentene ring by ozonolysis, and reduction with $NaBH_4$ provided diol **195**. Regioselective sulfonylation of the less sterically hindered alcohol, oxidation of the remaining alcohol, and intramolecular *N*-alkylation of



Scheme 32 Haplophytine and haplophytine dihydrobromide

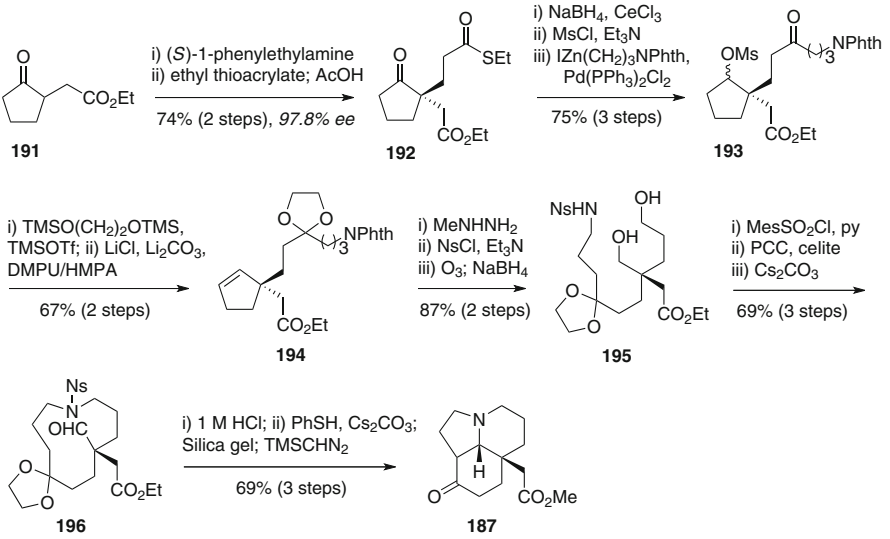


Scheme 33 Retrosynthetic analysis of haplophytine

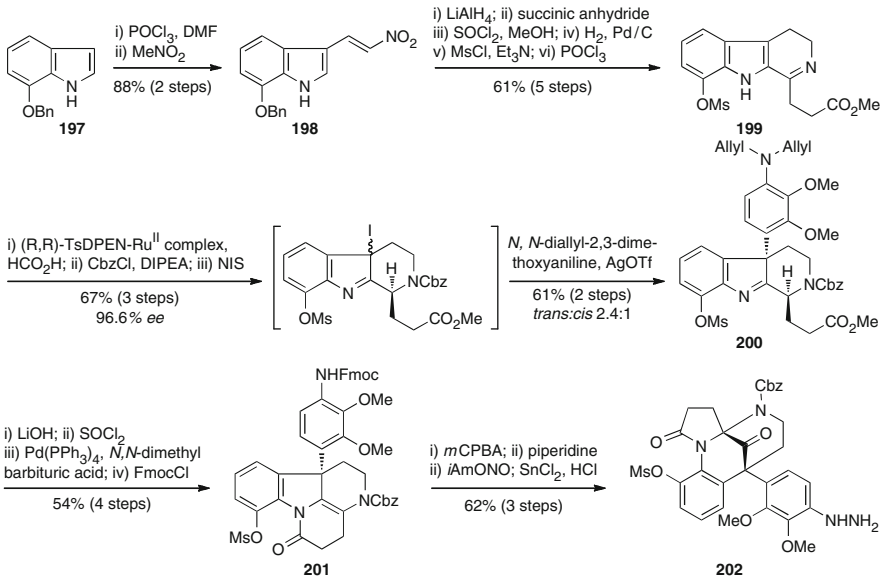
the Ns-amide gave the 11-membered amine derivative **196**. Further acidic cleavage of the acetal, removal of the Ns group, and intramolecular Mannich cyclization furnished the desired tricyclic ketone **187** as a single isomer (Scheme 34).

Synthesis of left-hand segment began with 7-benzyloxyindole **197**. A Vilsmeier-Haack formylation followed by condensation afforded nitroalkene **198**. Reduction, acylation with succinic anhydride, and subsequent Bischler-Napieralski cyclization provided dihydro-β-carboline **199**. Noyori asymmetric reduction of **199**, further treatment with *N*-iodosuccinimide, followed by activation with silver triflate in the presence of dimethoxy-*N*,*N*-diallylaniline furnished the desired coupling product **200**. Subsequent saponification and cyclization via a ketene intermediate gave the rearrangement precursor **201**. Oxidative skeletal rearrangement initiated by *m*-CPBA followed by removal of the Fmoc group and conversion of the aniline to the hydrazine furnished Fischer indole precursor **202** (Scheme 35).

Fischer indole condensation of hydrazine **202** and ketone **187** gave the corresponding indolenine **203**. Conversion of **203** to the conjugated imine, removal of the Cbz group by BBr_3, followed by a one-pot 1,2-reduction of the imine and reductive

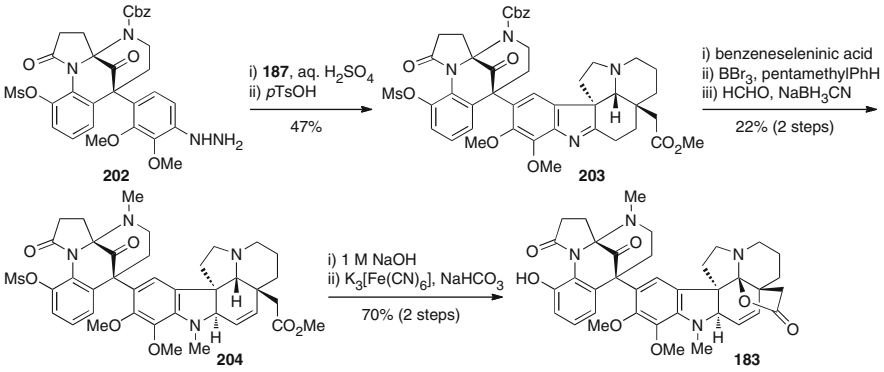


Scheme 34 Synthesis of tricyclic ketone 187



Scheme 35 Synthesis of the left-hand segment 202

methylation of two secondary amino groups led to intermediate **204**. Finally, basic hydrolysis and subsequent formation of the lactone ring furnished natural (+)-haplophytine (**183**) (Scheme 36).



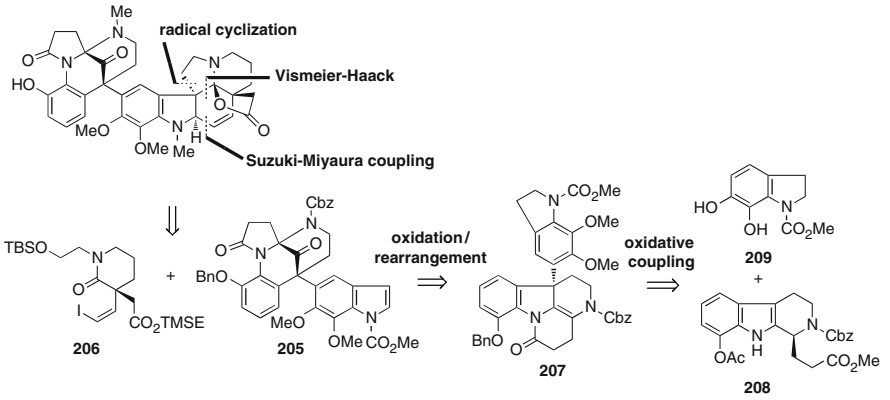
Scheme 36 Completion of the synthesis of haplophytine (183)

3.2.3 Synthesis by Nicolaou, Chen and Coworkers

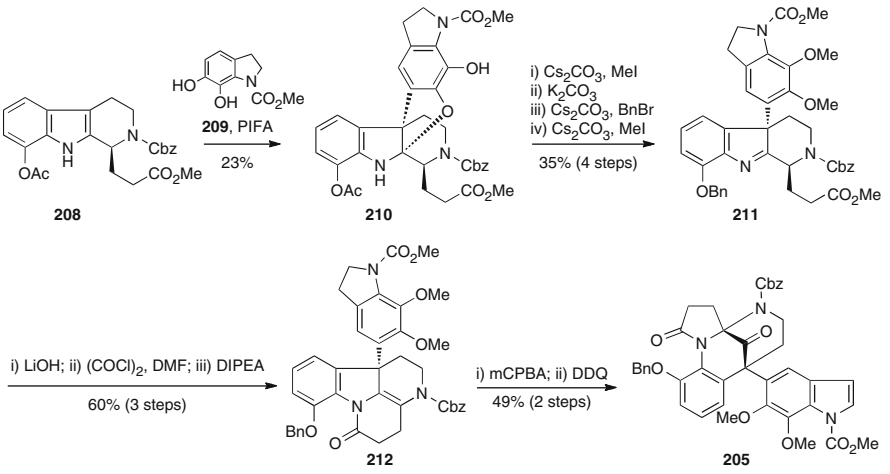
At about the same time, Nicolaou and Chen et al. independently reported the synthesis of haplophytine [85]. Retrosynthetically, haplophytine was envisioned by a sequence of Suzuki-Miyaura Coupling, Vilsmeier-Haack reaction, and radical cyclization from indole **205** and vinyl iodide **206**. The left-hand domain **205** could arise through the oxidative skeletal rearrangement of enamine **207**, which could be obtained from the oxidative coupling of tetrahydro-*β*-carboline **208** and diphenol **209** (Scheme 37).

Tetrahydro-*β*-carboline **208** was prepared in a fashion similar to that of intermediate **189**. Coupling of **208** to diphenol **209** was perhaps the most difficult step in bridging the two halves of haplophytine. Selective phenolic methylation, conversion of the acetate to the benzyloxy group, and rupture of the superfluous *N,O*-acetal afforded imine **211**. Hexacyclic bisenamine **212** was realized through a three-step sequence of saponification, acid chloride formation and based catalyzed cyclization. Similarly, *m*-CPBA mediated rearrangement followed by DDQ oxidation afforded indole **205** (Scheme 38).

A Suzuki-Miyaura coupling between borate **213**, which was derived from indole **205** and vinyl iodide **206**, *N*-methylation, treatment of the resulting lactam with Tf_2O, and $NaBH_4$ reduction of the corresponding iminium salt gave piperidine **215**. Selective desilylation of **215**, conversion of the primary alcohol to a xanthate ester, and radical cyclization using $n Bu_3SnH$ in the presence of AIBN provided nonacycle **216**. With the entire carbon skeleton in place, desilylation with TBAF followed by in situ treatment with $K_3[Fe(CN)_6]$ afforded the desired decacyclic lactone **217**. Removal of the benzyl and Cbz groups, and direct access to haplophytine by *N*-methylation failed. However, selective silylation, and reductive *N*-methylation followed by in situ reoxidation of the resulting carboxylic acid with $K_3[Fe(CN)_6]$ was successful. Final desilylation with TBAF provided haplophytine (**183**) (Scheme 39).



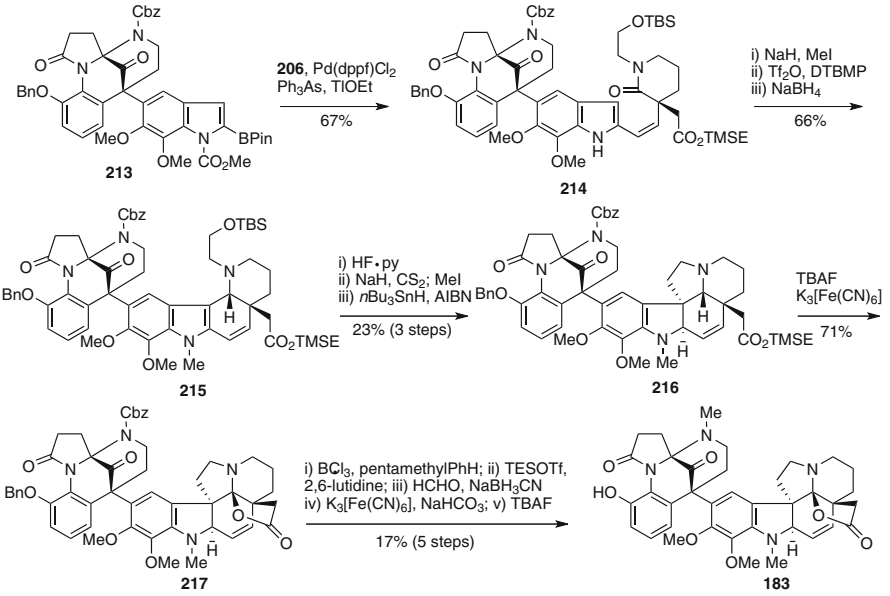
Scheme 37 Retrosynthetic analysis of haplophytine (183)



Scheme 38 Synthesis of the left-hand domain 205

3.3 Kapakahine B

Kapakahine B (**218**) (Fig. 9), a cyclic indole peptide isolated from the marine sponge *Cribrochalina olemda* by Scheuer and coworkers, shows modest anti-leukemia activity (IC_{50} = 5.4 μM, P388 murine leukemia cells), while the structurally related kapakahine F (**219**) (Fig. 9) is inactive [86–88]. Further investigations with this sponge identified kapakahines A–G. Limited quantities of these natural products obtained from isolation (e.g., 0.3 mg and 0.8 mg of **218** and **219** isolated from 840 g and 4.0 kg of sponge material, respectively) have prevented a complete understanding of their biological activity and mode of action [86–88].



Scheme 39 Completion of the synthesis of haplophytine (183)

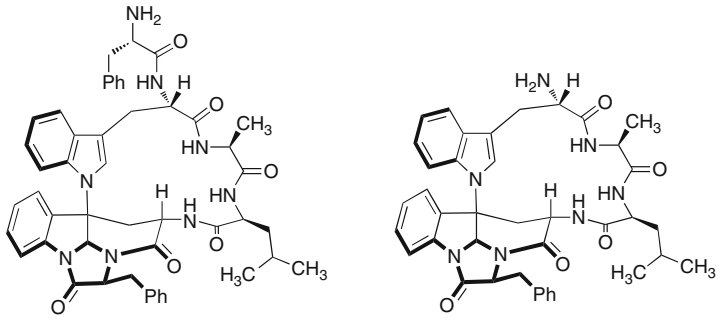
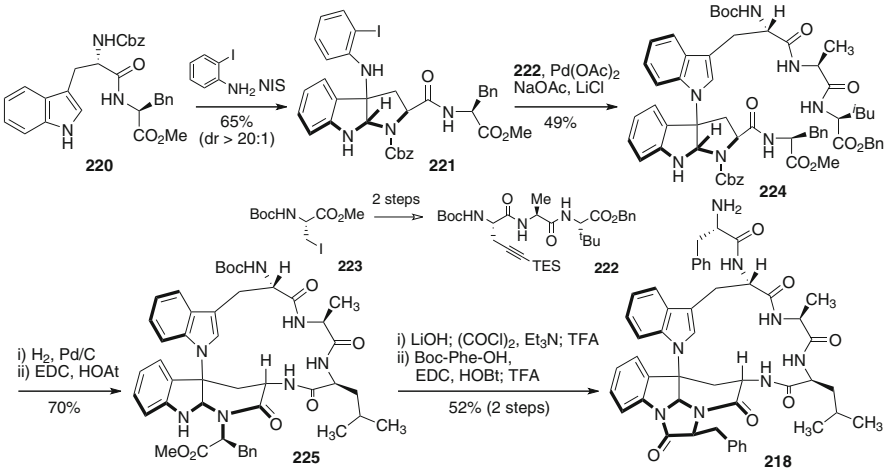


Fig. 9 Kapakahine B (218) and Kapakahine B (219)

Structurally, **218** and **219** feature a heptacyclic ring system, containing a twisted 16-membered macrocycle, a hindered quaternary center linking two tryptophan residues and a strained α-carboline. Recently, Baran and coworkers reported the first synthesis of kapakahines B and F by a diastereoselective, oxidative N–C bond formation and a late-stage shift of structural topology [89].

Their synthesis began with protected dipeptide **220**, reaction of which with *o*-iodoaniline and *N*-iodosuccinimide in the absence of an acid-scavenger afforded the indole-aniline coupled product **221** as a single diastereomer. Larock annulation of **221** with tripeptide **222** obtained in two steps from serine-derived **223** through



Scheme 40 Total synthesis of kapakahine B by Baran and coworkers

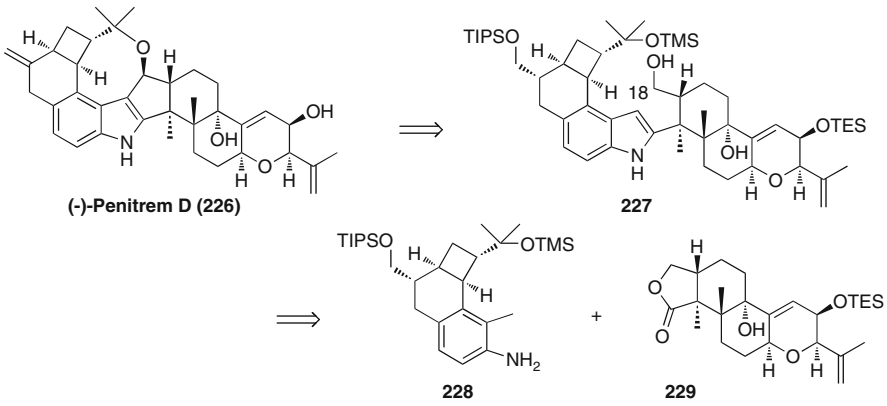
Knochel's method provided the pentameric peptide **224**. Hydrogenation followed by treatment of the resulting amino acid with EDC and HOBt afforded macrocycle **225**. Hydrolysis of methyl ester **225**, and imidazolone formation via the acid chloride, followed by Boc deprotection provided kapakahine F (**219**) in significant quantity. Final coupling of **219** with Boc-Phe-OH followed by Boc removal afforded kapakahine B (**218**) (Scheme 40).

3.4 (-)-Penitrem D

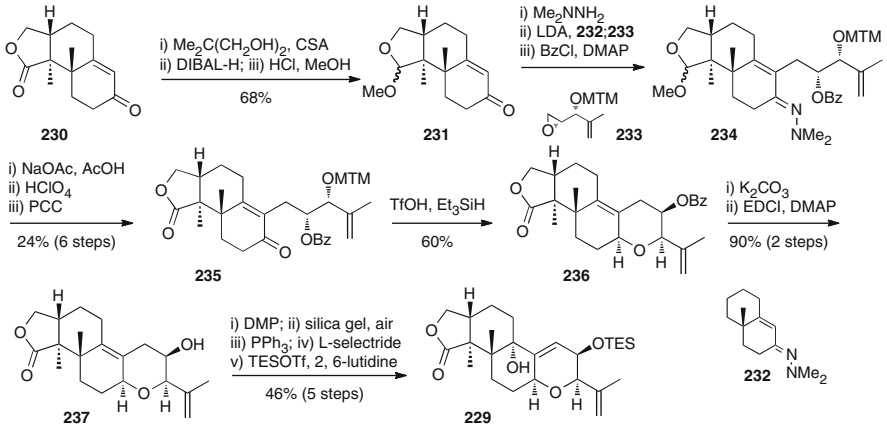
Penitrem D (**226**) (Scheme 41) is one member of the penitrem family, which is a small family of structurally complex tremorgenic mycotoxins, and was isolated from the ergot fungus *Penicillium crustosum* by Steyn and coworkers in 1981 [90].

Penitrem D (**226**) possesses a number of intriguing structural elements, including a highly substituted indole core, a cyclobutane moiety, an eight-membered cyclic ether, nine fused rings, eleven stereogenic carbons, and two allylic hydroxyl groups. Retrosynthetically, oxidation of the C(18) primary hydroxyl in **227**, followed by an acid-promoted cyclization-gramine fragmentation/addition cascade would afford penitrem D. Intermediate **227** should be derived from the union of the fully elaborated western and eastern hemispheres **228** and **229** [91].

Beginning with lactone **230**, a three-step sequence furnished acetal **231** as a mixture of diastereomers. Conversion of **231** to the corresponding hydrazone followed by metalloenamine coupling with epoxide **233** in the presence of **232** afforded **234**. Hydrolytic removal of the hydrazone and acetal followed by oxidation provided lactone **235** as a single diastereomer. Treatment of **235** with TfOH in the presence of Et_3SiH for the cyclized *cis*-pyran **236**, which underwent base-



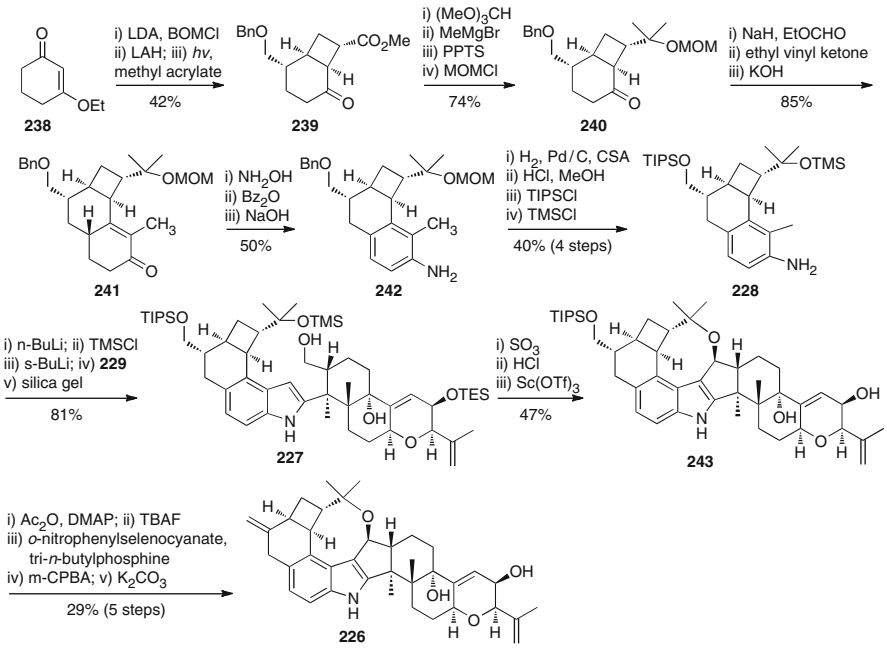
Scheme 41 Retrosynthetic analysis of penitrem D (226)



Scheme 42 Synthesis of eastern hemisphere 229

mediated hydrolysis to remove the benzoyl group accompanied by partial hydrolysis of the lactone followed by relactonization, resulted in lactone **237**. Dess-Martin oxidation, installation of the tertiary alcohol, and a two-step selective reduction and protection furnished eastern hemisphere **229** (Scheme 42).

The western segment **228** was obtained in thirteen steps from cyclohexenone **238**. Alkylation with LDA and benzyl chloromethyl ether, subsequent reductive enone transposition with $LiAlH_4$, followed by intermolecular [2+2]-photocycloaddition gave cyclobutane derivative **239**. Ketalization with trimethylorthoformate, treatment with excess methylmagnesium bromide, PPTS deketalization and the final MOM protection afforded ketoalcohol **240**. Robinson annulation gave enone **241**, and aromatization using benzoic anhydride followed by hydrolysis of the corresponding benzamide provided free amine **242**. Benzyl ether and MOM deprotection and final two-step selective silyl protection furnished segment **228** [92] (Scheme 43).



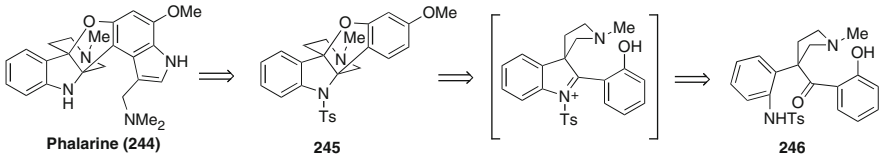
Scheme 43 Completion of the synthesis of penitrem D (226)

With both hemispheres **228** and **229** in hand, treatment of the TMS derivative of **228** with *s*-BuLi, followed by addition of **229** resulting in acylation and subsequent in situ hetero-Peterson olefination provided **227**. Parikh-Doering oxidation, selective removal of the TMS and TES groups, followed by treatment with $Sc(OTf)_3$ in benzene provided indole **243**, assembling the AF ring system and installing the complete penitrem D carbon skeleton. Selective acylation, TIPS removal, selenation of the resulting primary alcohol, oxidative elimination and final hydrolytic removal of the acetate furnished (-)-penitrem D (**226**) (Scheme 43).

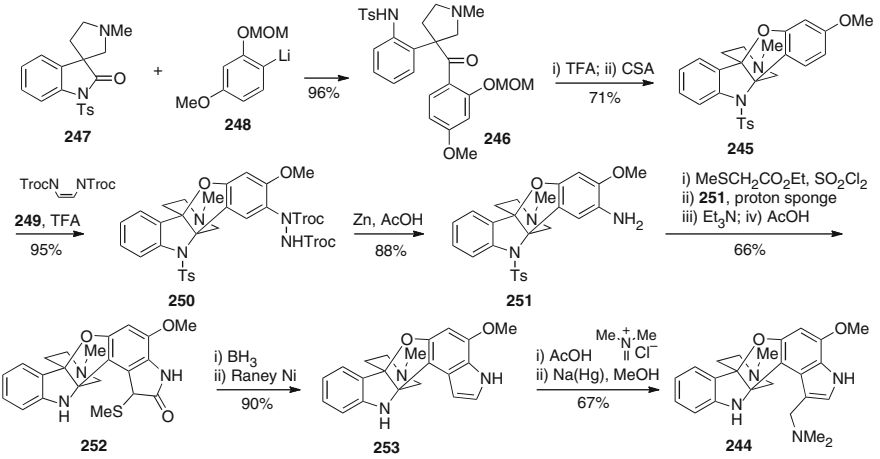
3.5 Phalarine

Phalarine (**244**) (Scheme 44), an indole alkaloid with a novel furanobisindole structure, was isolated from blue canary grass *Phalaris coerulescens* by Colegate and coworkers in 1999 [93]. Recently, Danishefsky and coworkers reported the first synthesis of this indole alkaloid through a novel rearrangement from azaspiroindolenine (derived from **246**) to precursor **245** [94, 95] (Scheme 44).

Coupling of oxindole **247** and the lithio derivative **248** (generated from the corresponding bromo compound) afforded ketone **246**, which underwent the anticipated rearrangement to give the phalarine precursor **245** in 72% yield. Treatment of **245** with azodicarboxylate derivative **249** afforded adduct **250**, which provided



Scheme 44 Retrosynthetic analysis of phalarine (244)



Scheme 45 Total synthesis of phalarine (244) by Danishefsky and coworkers

amine **251** by reduction. Subjection of amine **251** to thiomethylacetic acid ethyl ester followed by treatment with sulfuryl chloride provided oxindole **252**. Conversion of oxindole **252** to bisindole **253**, followed by a critical reaction with *N*,*N*-dimethylmethylene ammonium chloride produced a gramine intermediate. Subsequent cleavage of the sulfonamide function gave phalarine (**244**) (Scheme 45).

3.6 Quadrigemine C and 11,11'-Dideoxyvertillin A

Quadrigemine C (**254**) [96] and 11,11'-dideoxyvertillin A (**255**) [97] are representative of a remarkable series of tryptamine-derived plant alkaloids that link together two to eight pyrrolidinoindoline units, such as the monomer okaramine N (**256**) [98], dimer ditryptophenaline (**257**) [99, 100] and 11,11'-dideoxyverticillin A (**255**) [97], trimer idiospermuline (**258**) [101], and tetramer psycholeine (**259**) [96], together with an exceptional member of this family psychotrimine (**260**) [102–104] (Fig. 10).

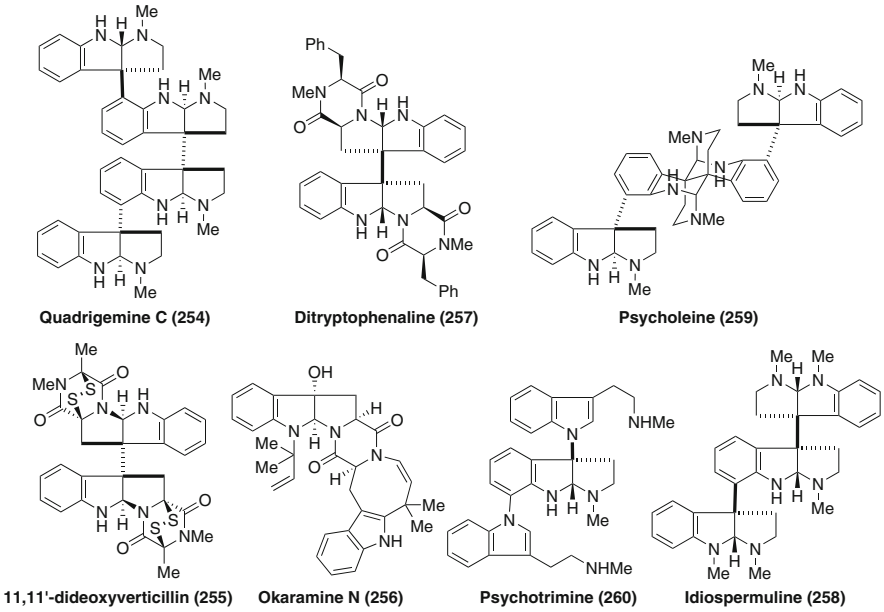
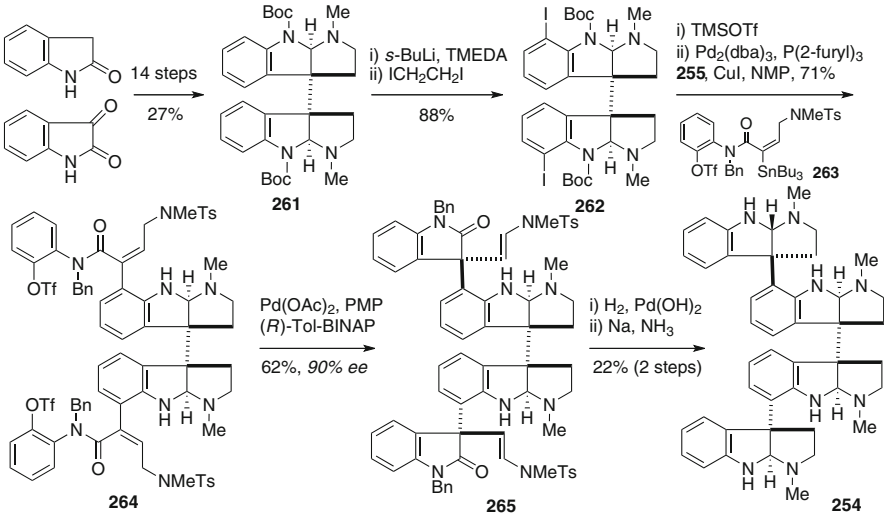


Fig. 10 Quadrigemine C (254), 11,11'-dideoxyverticillin (255) and analogs

First described in 1987 from an extract of *Psychotria oleoides* found in New Caledonia [105], quadrigemine C (**254**) was subsequently isolated from *Psychotria colorata*, a plant used by indigenous people of the Amazon for treating pain [106]. In 1992, Sevenet and coworkers proposed the relative and absolute configuration of quadrigemine C (**254**) and psycholeine (**259**) [107], isolated from the same extract. Quadrigemine C (**254**) is reported both to exhibit significant antibacterial and analgesic activity and, like **259**, to be a weak antagonist of the SRIF (somatostatin) receptor [96]. Its high-order polypyrrolidinoindoline structure, contiguous stereogenic quaternary carbons, and the stereogenic diaryl quaternary carbons exemplified the formidable synthetic challenges. Overman and coworkers accomplished the synthesis of quadrigemine C (**254**) and psycholeine (**259**) based on the chemistry they developed previously.

Beginning with Boc-protected meso-chimonanthine (**261**), which was previously prepared in fourteen steps and 27% overall yield from commercial available oxindole and isatin, a double ortho-lithiation of **261** with *s*-BuLi followed by quenching with 1,2-diiodoethane delivered diiodide **262**. TMSOTf-mediated cleavage of Boc followed by chemoselective double Stille cross-coupling with stannane **263** gave meso dibutenanilide **264**. The pivotal catalyst-controlled dual Heck cyclization of **264** afforded dioxindole **265**, which underwent double bond reduction, followed by treatment with excess of sodium in ammonia to furnish quadrigemine C (**254**) in 22% yield from **265**. Acid-catalyzed isomerization of **254** provided synthetic psycholeine (**259**) in 38% yield (Scheme 46).



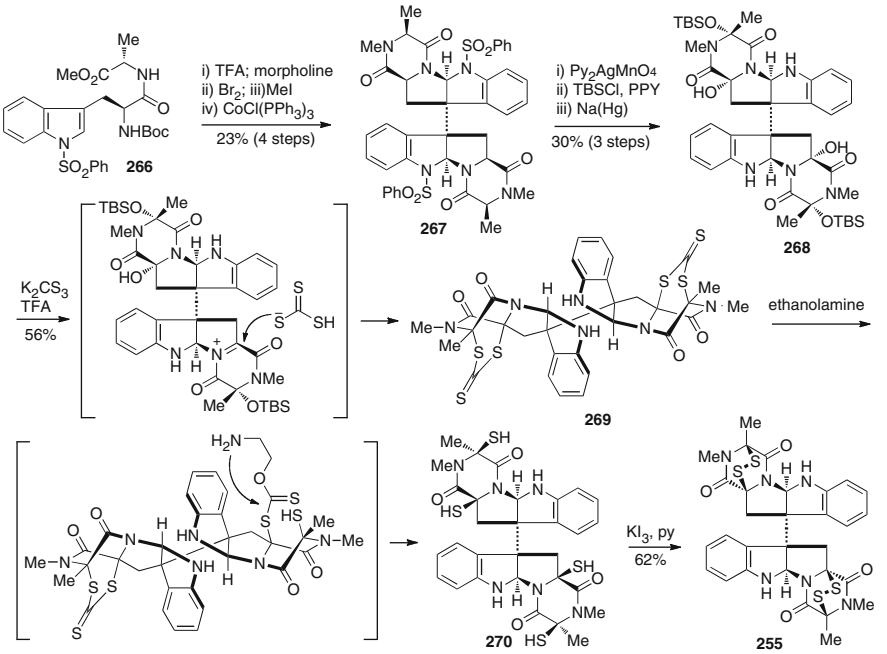
Scheme 46 Total synthesis of quadrigemine C (254) by Overman and coworkers

The structurally related fungal metabolite 11,11'-dideoxyverticillin A (**255**) is a member of the epidithioketopiperazine alkaloids, the alkaloids which have interested a number of research groups in view of their complex architecture and rich biological activity. The main difference between **255** and, for example, ditryptophenaline (**257**) is the incorporation of tetrathiane, which poses a daunting synthetic challenge because of the sterically congested stereogenic centers and the highly acid-, base-, and redox-sensitive functional groups. The first total synthesis of any member of this family was described by Movassaghi and coworkers [97].

Their synthesis commenced with indole amide **266**. Treatment of **266** with TFA, cyclization with morpholine, bromination for the formation of monomeric tetracyclic bromide, *N*-methylation and key reductive dimerization catalyzed by CoCl $(PPh_3)_3$ provided dimeric octacyclic intermediate **267**. Tetra-*n*-butylammonium permanganate-mediated α-methine carbon oxidation generated the tetraol as a single diastereomer, which was followed by selective protection of the diol, and reductive elimination of the sulfone to give bis-protected tetraol **268**. Treatment of **268** with potassium trithiocarbonate and trifluoroacetic acid formed bisdithiepanethione **269**. Further treatment of **269** with ethanolamine gave diaminotetrathiol **270**, which on addition potassium triiodide provided (+)-11,11'-dideoxyverticillin A (**255**) (Scheme 47).

3.7 Welwitindolinone A

Welwitindolinone A isonitrile (**271**) [108], one of several related oxindole-containing alkaloids, such as hapalindole (**272**) [109, 110], fischerindole (**273**) [108], and ambiguine H (**274**) [111, 112], was isolated from blue-green algae by Moore



Scheme 47 Total synthesis of (+)-11,11'-dideoxyverticillin (255)

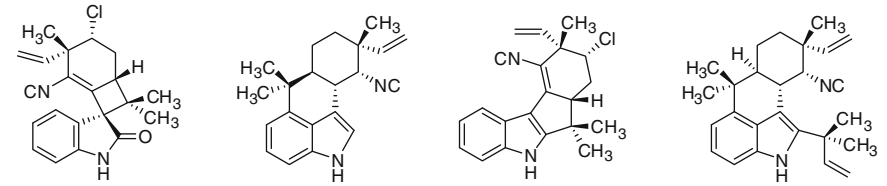
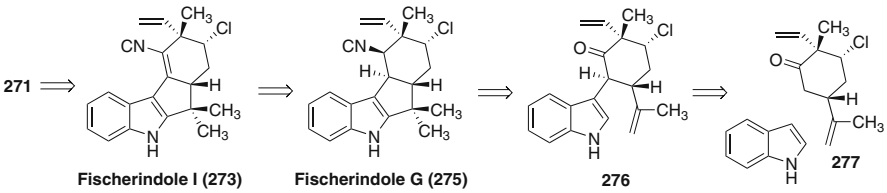


Fig. 11 Welwitindolinone A isonitrile, hapalindole, fischerindole, and ambiguine H

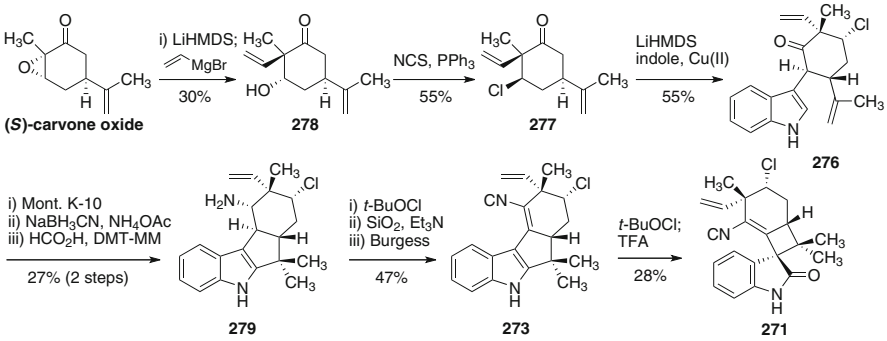
and coworkers in 1994 [108] (Fig. 11). The intriguing antifungal biological activity and the densely packed and diverse array of synthetically challenging functional groups attracted the attention of a number of different research groups. However, to date only two syntheses have been accomplished, by Baran et al. [113, 114] and Wood et al. [115].

3.7.1 Synthesis by Baran and Coworkers

Retrosynthetically, a synthesis of **271** was envisaged from **273** based on a rare oxidative ring contraction to form the four-membered ring. Dehydrogenation of the



Scheme 48 Retrosynthetic analysis of welwitindolinone A isonitrile by Baran and coworkers



Scheme 49 Total synthesis of welwitindolinone A isonitrile by Baran and coworkers

cyclohexane of fischerindole G (**275**) would provide **273**, which in turn was accessible from **276** by Friedel-Crafts alkylation. Direct indole coupling reaction with chloroketone **277** resulted in the formation of **276** [114, 115] (Scheme 48).

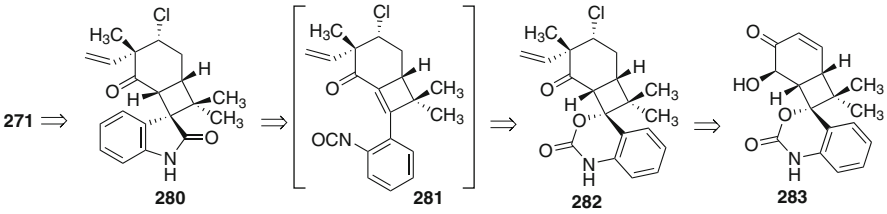
The synthesis commenced with (*S*)-carvone oxide. Enolization with LiHMDS followed by addition of vinylmagnesium bromide furnished neopentyl alcohol **278**, albeit in low yield. Chlorination using NCS and PPh_3 afforded chloroketone **277**, which underwent oxidative coupling reaction with indole to give **276** as a single diastereomer. Friedel-Crafts cyclization furnished the fischerindole skeleton under the action of montmorillonite K-10, followed by reductive amination to afford amine **279**. Formylation of **279** followed by treatment with t-BuOCl in the presence of Et_3N, and subsequent exposure to the Burgess reagent provided (-)-fischerindole I (**273**) in 47% overall yield from **279**. Final treatment of **273** with *t*-BuOCl in THF followed by exposure to a mixture of TFA in THF and H_2O afforded (+)-welwitindolinone A isonitrile (**271**) and in both an enantioselective and protecting-group-free synthesis (Scheme 49).

3.7.2 Synthesis by Wood and Coworkers

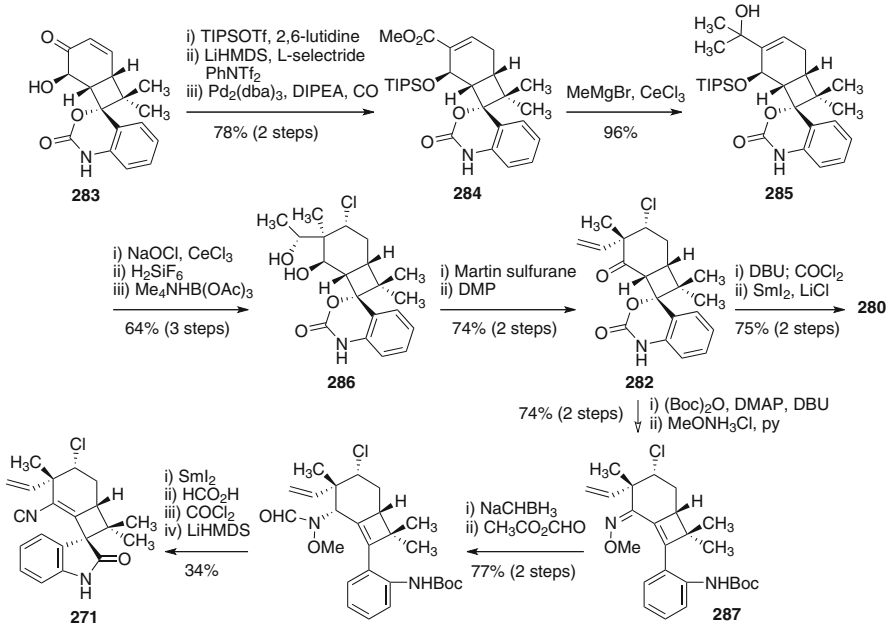
Wood and coworkers reported their independent synthesis of welwitindolinone A isonitrile (**271**) [112], which featured a SmI_2-mediated generation of

a spiro-oxindole **280** from cyclic urethane **282** via aryl isocyanate **281**. Urethane **282** was derived from hydroxy-enone **283** (Scheme 50).

Beginning with the known hydroxy enone **283** (prepared in six steps and 56% overall yield), a two-step sequence involving alcohol protection and enol triflate formation followed by Pd-catalyzed CO insertion in the presence of methanol provided enoate **284**. Treatment of **284** with excess MeMgBr gave **285** and NaOCl and $CeCl_3$-mediated rearrangement of the corresponding chloro-ketone was followed by a two-step desilylation and ketone reduction to afford diol **286** as a single diastereomer. Selective dehydration of **286** using Martin sulfurane followed by Dess-Martin oxidation gave ketone **282**, which underwent DBU-mediated CO_2 elimination to give isocyanate **281**. SmI_2-mediated oxindole formation furnished **280**, which proved to be a remarkably stable intermediate. Therefore,



Scheme 50 Retrosynthetic analysis of welwitindolinone A isonitrile by Wood and coworkers



Scheme 51 Total synthesis of welwitindolinone A isonitrile by Wood and coworkers

an alternative pathway featuring a one-pot Boc protection and CO_2 elimination of **282** followed treatment with methoxylamine afforded oxime **287**. However, SmI_2-mediated oxindole formation of **287** was also unsuccessful. Another alternative route featuring a six step sequence involving reduction of oxime **287**, formylation, removal of protecting groups, formation of the isocyano-isocyanate, and final base induced oxindole formation using LiHMDS completed the synthesis of welwitindolinone A isonitrile (**271**) (Scheme 51).

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