Topics in Current Chemistry 373

Thomas Wirth *Editor*

Hypervalent Iodine Chemistry

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373
Topics in Current Chemistry

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Thomas Wirth
Editor

Hypervalent Iodine Chemistry

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Preface

Hypervalent iodine chemistry has received widespread recognition by chemists during the last decade. This book is an update on the current state-of-the-art, including the use of traditional reagents in novel reactions which further highlight the potential of hypervalent iodine reagents as mild, selective and environmentally benign reagents. The development of novel hypervalent iodine reagents with altered reactivities now allow transformations which, only a decade ago, would have been unthinkable. These developments have led to special issues in journals and increased frequencies of conferences dedicated to this subject. They have also attracted young researchers to join the field and further develop the chemistry by means of their creativity and imagination. The compilation of current topics assembled in this book is a testimony to the many scientists who have contributed to the rapid development of hypervalent iodine chemistry in the past decade. The book should serve as a current dictionary and as a source of inspiration for research. I am very grateful to many distinguished colleagues who have contributed with their expert knowledge to make this comprehensive compilation on hypervalent iodine chemistry possible.

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Contents

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Hypervalent Iodine-Induced Oxidative Couplings (New Metal-Free Coupling Advances and Their Applications in Natural Product Syntheses)

Toshifumi Dohi and Yasuyuki Kita

Abstract Recently, hypervalent iodine reagents have been extensively used in organic synthesis. A variety of reactions available for natural product syntheses have been developed using phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), and other iodine(III) and (V) reagents. These reactions are expected to have applications in pharmaceutical and agrochemical processes because of their safety, mild reaction conditions, and high yields of pure products. Under such considerations, this chapter focuses on the oxidative coupling reactions of hypervalent iodine reagents found in total syntheses of biologically active natural products and their related compounds.

Keywords Hypervalent iodine reagents • Natural products • Oxidative coupling • Total synthesis

Contents

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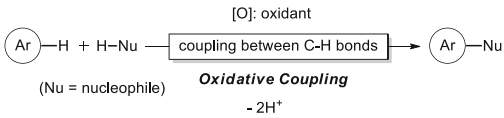
1 Introduction

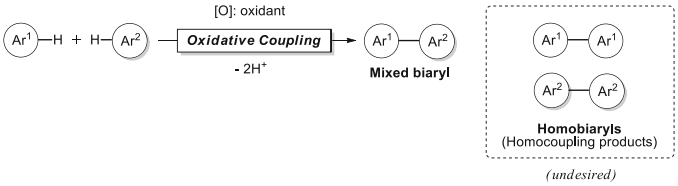
The cross-coupling reactions discovered by Japanese chemists in the twentieth century can provide powerful tools for the construction of complex molecules in organic synthesis. In general, these cross-couplings using organometallic compounds (e.g., [M]=[Zn], Negishi; [B], Suzuki, etc.) with organic halides in the presence of some transition metal catalysts, such as palladium complexes, have been used for the effective formation of new carbon–carbon bonds [1–4]. Although the methods can afford target products in high yields and with good selectivities, these typically require the stoichiometric activated coupling substrates, that is, the metal- and halogen-functionalized organics, and thus produce metallic salts as waste and byproducts from the reactions. The use of these organometallic starting materials is, therefore, not ideal and efficient when considering environmental concerns and practical factors. In addition, the preparation of pre-activated substrates often requires several synthetic operations.

In the concept of green and sustainable chemistry, much effort should be dedicated to the development of more direct cross-coupling reactions. In theory, the oxidative coupling (Scheme 1) is a straightforward route which can reduce the number of synthetic steps by avoiding the preparation of pre-activated substrates. Besides, this strategy involves less waste material generation regarding metal salts. Under such situations, new oxidative coupling methods that directly use the C–H bond of the two substrates instead of organic halides and organometallic compounds have emerged in recent years, enabling the selective formation of cross-coupling products [5–9].

Herein, the authors describe recent advances in hypervalent iodine-induced oxidative coupling reactions as a new strategic choice for metal-free synthesis, and their early applications in natural product synthesis used as the key reactions are summarized. We first briefly outline the fundamental hypervalent iodine-induced reactions and then illustrate the examples of their application to the syntheses of various biologically active compounds, such as natural products.

Scheme 1 Oxidative coupling strategy





Scheme 2 Oxidative biaryl coupling: general situation

2 Recent New Metal-Free Coupling Advances

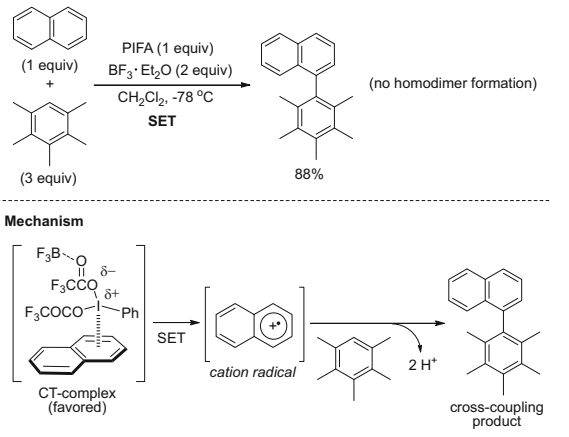
Despite their ideal green chemistry aspect, oxidative couplings employing heavy-metal oxidants have limited synthetic applications regarding chemoselective issues and usually suffer from undesired formation of homo-dimers and uncontrolled over-oxidations. Indeed, studies involving heavy-metal oxidants, electrolytic conditions, and others reported frequent accompanying undesired formation of homodimers and over-oxidations in intermolecular couplings (Scheme 2). Therefore, cross-coupling attempts were rarely reported in the literature during the twentieth century. Early successes include the oxidative cross-coupling of 2-naphthols and naphthyl amines with stoichiometric amounts of copper and iron oxidants ([10–12] and references cited therein), which limited the availability of the substrates to these phenol aromatics showing high sensitivity to induce oxidations.

In 2007, Fagnou and co-workers reported the selective oxidative cross-coupling of indoles or anilines with non-heteroaromatic substrates using palladium salts as catalysts with stoichiometric amounts of copper oxidants [13]. The reaction was performed by the appropriate combination of the catalyst and oxidant, palladium (II) trifluoroacetate (5 mol%) and stoichiometric copper(II) acetate (3 equiv.) at high temperature ($>100°C$). The key to the success of the selective cross-couplings was the selection of the two aromatic substrates having suitable gaps of affinities and reactivities toward the metal catalysts. Thus, excess amounts (30–60 equiv.) of aromatic hydrocarbons were required as coupling partners to react exclusively with indoles over indole homodimerization. Accordingly, the selective cross-couplings between arene molecules with similar characteristics, such as between two aromatic hydrocarbons, are still difficult to achieve by metal-catalyzed oxidative coupling strategies, even after recent advances. Indeed, the reaction of naphthalene with excess mesitylene was not practical in a catalytic system composed of a palladium catalyst with potassium persulfate in the presence of trifluoroacetic acid (TFA) [14, 15], which resulted in low yields of the desired mixed naphthalene-mesitylene biaryl derivative and low turnover numbers (TONs) of the catalyst. In addition, a large amount of an undesired homocoupling product of mesitylene, 2-(3,5-dimethylbenzyl)-1,3,5-trimethylbenzene, was formed. The catalyst combination used by Fagnou's group (palladium(II) trifluoroacetate with copper (II) acetate) even failed and no useful reaction for these aromatic hydrocarbons without heteroatom could be observed. The use of excess metal oxidants, however,

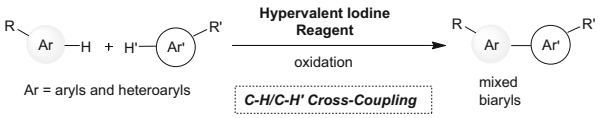
remains a strong contender in the further development of a new oxidative cross-coupling system based on alternative initiators and catalysts.

With the increasing impetus for developing greener synthetic processes, hypervalent iodine reagents have recently received significant attention in organic synthesis as an oxidant by virtue of their low toxicity, controllable reactivity, ready availability, high stability, easy handling, ease of recovery and recyclability, etc. One of the predominant uses of these reagents is replacing the highly toxic heavy-metal oxidizers, i.e., lead(IV)-, mercury(II)-, and thallium(III)-based reagents. Because of their brilliant features, hypervalent iodine reagents are a promising alternative to metal oxidants for developing greener oxidations, the utility of which is already documented in several books and comprehensive reviews ([16] and references cited therein) [17, 18]. Extensive applications as stoichiometric oxidants were found to mediate a wide array of bond-forming reactions and other oxidative transformations, and the synthetic versatility of these reagents has been expanding day by day. For example, oxidation of phenols and related reactions induced by phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have been used for many total syntheses of biologically important natural products and their pivotal intermediates. The pentavalent iodines, Dess–Martin periodinane (DMP) and its precursor, 2-iodoxybenzoic acid (IBX), are widely known as mild and selective oxidants for alcohol functionalities. Based on their unique reactivities, a variety of reactions for constructing complex molecules has been developed, and hypervalent iodine reagents are now extensively accepted for use in natural product syntheses. The reactions using hypervalent iodine reagents can also be utilized for pharmaceutical and agrochemical processes because of their safe and mild reaction conditions.

Regarding the first discovery of the oxidative cross-coupling of aromatic compounds in hypervalent iodine chemistry, we met in 2008 the very exciting success of the oxidative cross-couplings between naphthalenes and alkylbenzenes based on the single-electron-transfer (SET) oxidation strategy [19]. It was a combination of a hypervalent iodine reagent, specifically PIFA, and, for its activation, a Lewis acid, boron trifluoride diethyl etherate. Surprisingly, when the naphthalene and mesitylene, as shown in Scheme 3, were mixed with the activated hypervalent



Scheme 3 First report of metal-free oxidative cross-biaryl-coupling



Scheme 4 Oxidative cross-biaryl-couplings using hypervalent iodine reagent

iodine reagent, the desired cross-coupling was found to occur exclusively, producing the naphthalene-mesitylene biaryl in high yield. Thus, the problematic homocoupling observed in the palladium-catalyzed strategy [14, 15] was apparently suppressed by using the iodine reagent.

Inspired by this elegant success, the authors have pioneered the metal-free oxidative cross-coupling reactions of various electron-rich aromatic compounds (Ar-H) to date using hypervalent iodine reagent (Scheme 4). Indeed, several types of the new oxidative aromatic coupling methods for access to mixed biaryls in high yields with perfect cross-coupling selectivities were realized based on different types of the aromatic ring activation in the mechanisms [20–28]. These research results have been summarized regularly by us since 2011 [29, 30] and others [31–33] as accounts and reviews.

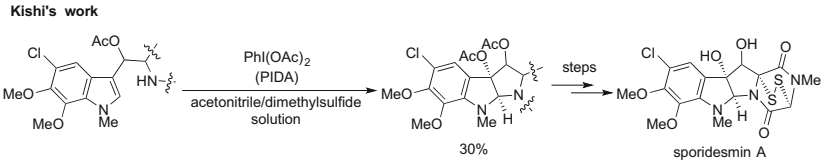
The oxidative coupling strategies with hypervalent iodine reagents were originally used for aromatics in intramolecular reactions without causing issues of homodimer formation, and several applications of total syntheses of natural products are present in the literature. In the following sections, the authors describe the oxidation couplings of aromatic compounds in natural product synthesis together with a brief introduction of their background regarding the establishment of the fundamental reactions.

3 Oxidative Couplings in Natural Product Synthesis

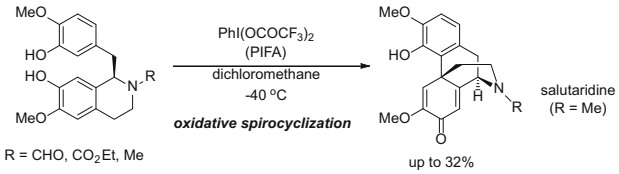
Hypervalent iodine reagents have recently received a great deal of attention in organic synthesis, not only as a mild, safe, and economical alternative to heavy metal reagents, but also because of their variety of unique reactivities applicable to natural product syntheses. Pioneering studies on hypervalent iodine-induced reactions toward total syntheses of several natural products were reported by Kishi and co-workers in the 1970s [34]. Based on the hypervalent iodine-induced oxidative cyclization, a formal stereospecific synthesis of sporidesmin A, a toxic metabolite of *Pithomyces chartarum*, was accomplished, albeit in low yield from the key reaction of the tryptamine derivative at the indole ring (Scheme 5).

Other early applications of hypervalent iodine reagents in natural products are the total syntheses of bioactive alkaloids, by Szantáy's and White's groups in early 1980s, such as salutaridine (Scheme 6), (–)-codeine, and 6a-epipretazettine [35–37]. Although these involved pioneering studies on phenolic coupling reactions, they had not received much attention because of their low yields of the chemical processes (up to 32% yield).

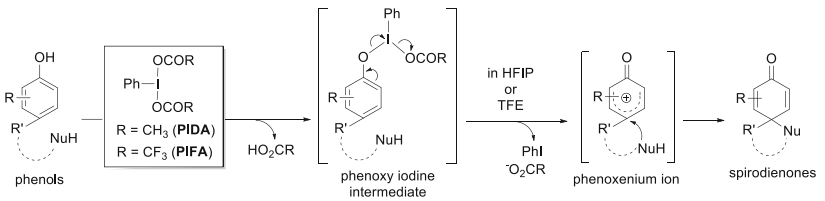
This situation dramatically changed when the efficient phenolic oxidation protocol was developed by Kita and co-workers using a specific hypervalent iodine



Scheme 5 Kishi's early work



Scheme 6 Early report by Szántay

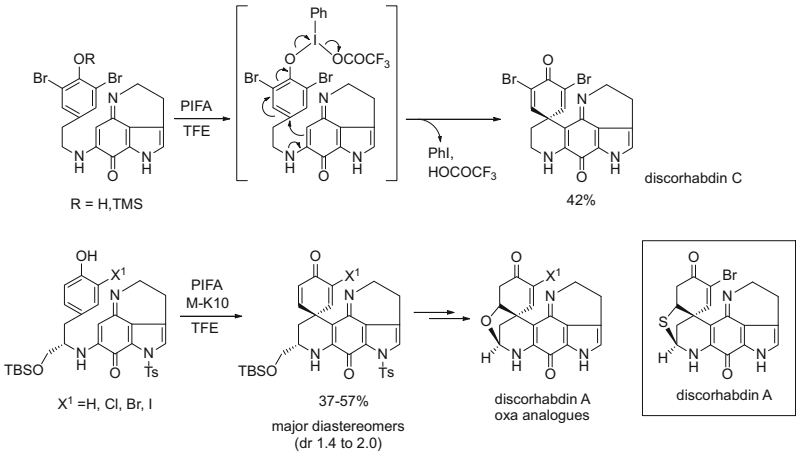


Scheme 7 Hypervalent iodine-induced oxidative dearomatization of phenols leading to spirodienones

reagent, PIFA, in polar solvents [38]. In particular, remarkable improvements of the reaction yields were demonstrated by changing the solvent to polar and weakly nucleophilic solvents, such as 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) [39–41].

In the 1980s Kita's group introduced these fluoroalcohols to perform the dearomatizing oxidations of phenols using hypervalent iodine reagents for the purpose of synthesizing spirodienones [38]. For the oxidation of phenols using hypervalent iodine reagents (Scheme 7), i.e., PIDA and PIFA, the reactions are typically explained by the two-electron-transfer processes that involve the initial ligand exchange at the iodine(III) centers. PIDA and PIFA react with phenolic oxygens to give the phenoxyiodine(III) intermediates. The excellent leaving ability of the high-valent iodine atoms to produce more stable iodobenzene can smoothly generate the phenoxenium ions in the polar solvents, HFIP and TFE, which are then trapped by various concomitant nucleophiles to complete the dearomatizations.

With these discoveries as a turning point, PIDA and PIFA have started to play particularly important roles in reproducing the biomimetic phenolic oxidation processes under mild conditions, which can be applied to the total synthesis of natural products and their pivotal intermediates having the spirodienone moieties



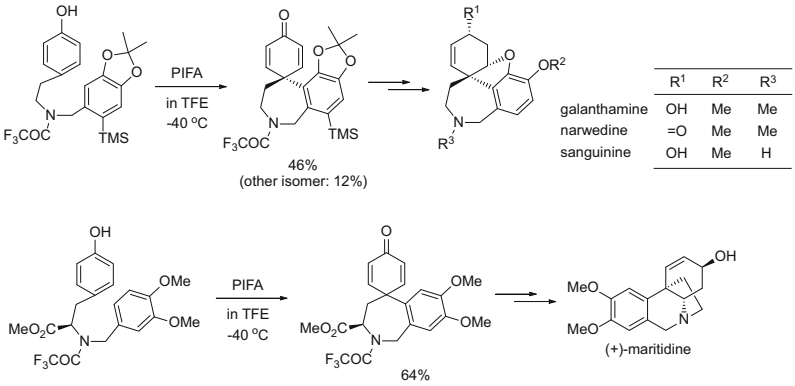
Scheme 8 Total synthesis of discorhabdins by the dearomatizing spirocyclization strategy

[42–47]. After this significant improvement, there are many applications of hypervalent iodine reagents in syntheses of complex molecules.

For example, a variety of natural products bearing spirocyclic systems exist, and many of them are biosynthetically formed by oxidative spiroannulation processes. Hypervalent iodine(III) reagents are thus considered as one of the most effective oxidants for these oxidation processes. Several efficient methods for PIFA-induced spiroannulation reactions of phenols [48, 49] towards the total synthesis of discorhabdin alkaloids [50, 51] and their oxa-analogues have been published [52, 53], which were accomplished via hypervalent iodine oxidation of phenols or *O*-trimethylsilylated phenol derivatives to the azacarbocyclic spirodienones as a key step (Scheme 8).

The similar treatment of the norbelladine derivatives using PIFA proved to be a mild and efficient method for preparing the core structures of *Amaryllidaceae* alkaloids (Scheme 9), such as galanthamine for the treatment of Alzheimer's disease and related alkaloids, i.e., narwedine, norgalanthamine, sanguinine, lycoramine, and maritidine, by dearomatizing carbon–carbon bond formations at the spiro centers [54, 55].

The two most successful areas in oxidative coupling for natural product syntheses include the transformations of aromatic compounds as the key steps. These are classified into (1) phenol oxidative couplings and (2) oxidative functionalizations of other aromatics. The former category is further divided into phenol couplings with or without dearomatizations. In turn, the latter oxidative aromatic substitutions include umpolung strategies regarding aromatic rings or nucleophiles by activations of hypervalent iodine reagents. Category (1) typically includes phenoxyiodine (III) intermediates during the activations of phenol rings during oxidation. In general, the reactivity of hypervalent iodine species depends greatly on the reaction conditions. Indeed, a hypervalent iodine reagent, specifically PIFA, can be extensively utilized as an efficient and selective SET oxidizing agent, enabling formation



Scheme 9 Total synthesis of galanthamine and related alkaloids

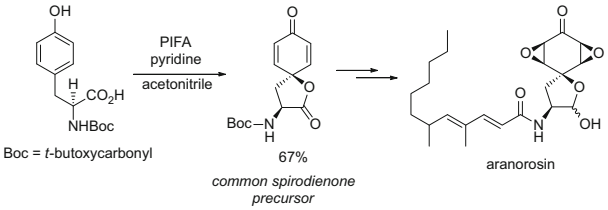
of the charge transfer complex (CT-complex) with aromatic coupling substrates [56, 57], utilized for natural product synthesis in oxidative functionalizations. In category (2), the electrophilic activation of nucleophiles includes the generation of nitrenium ions by the treatment of *N*-methoxyamides with hypervalent iodine reagents, which are captured by intra- and intermolecular aromatic groups for nitrogen bond formation [58, 59]. In the following sections, some aspects of hypervalent iodine-induced oxidative coupling reactions used as the key reactions for the total syntheses of selected natural products are highlighted.

3.1 Phenol Oxidative Couplings

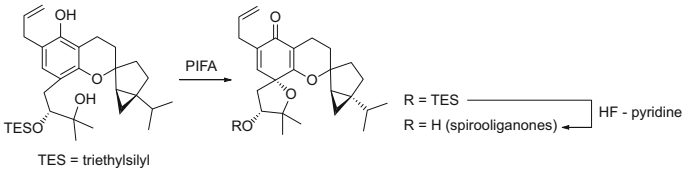
3.1.1 Phenol Dearomatizative Couplings

Utilizing this effective dearomatizing spirocyclization in polar solvent using PIFA or PIDA [38], the total synthesis of the antibiotic aranorosin was accomplished by Rama Rao [60], Wipf [61], and McKillop [62] via the construction of the spirolactone structure as a common intermediate, as shown in Scheme 10.

In addition, Wipf and co-workers achieved the total syntheses of (–)-stenine [63], palmarumycin CP1 [64], and (±)-deoxypreussomerin A [65] by utilizing the hypervalent iodine-induced spirocyclization for substituted phenols carrying nucleophilic side-chains at suitable positions. Similarly, the phenol dearomatization protocols involving intermolecular introductions of oxygen nucleophiles at the *para* and *ortho* positions of the phenol functionality accompanying spirocyclizations were widely applied for many total syntheses of natural products, as reported by Hoshino, Gurjar, Pettus, Katoh, Nicolaou and Chen, Sorensen, Myers, and Ley, respectively, for production of araplysillin-I [66], gymnastatin A [67], epoxysorbicillinol and bisorbicillinol [68], (±)-geodin [69], (+)-haplophytine [70, 71], isotarins E and F [72], cortistatins [73, 74], and (+)-clavolonine [75].



Scheme 10 Diastereoselective spirocyclization for the total synthesis of aranorosin



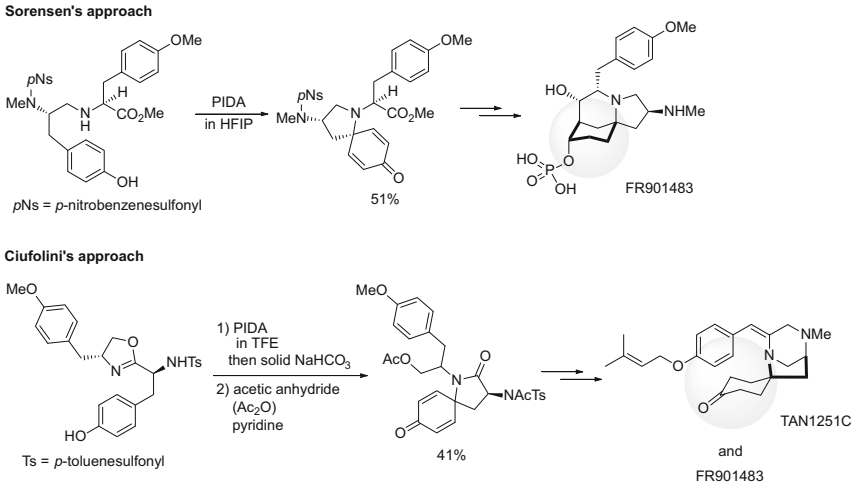
Scheme 11 Application for spirooliganones total synthesis

A more recent report includes the biomimetic total syntheses of potent antiviral spirooliganones A and B utilizing the phenol oxidative dearomatization/spirocyclization to build the spiro-fused cyclohexadienone/tetrahydrofuran moiety (Scheme 11) [76].

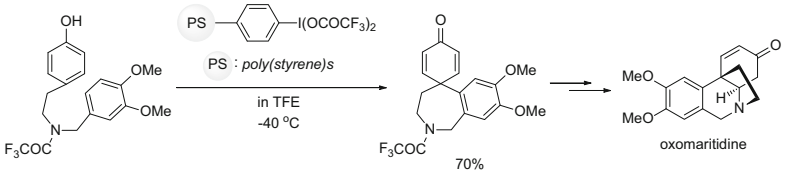
Oxidative dearomatizations with introduction of nitrogen nucleophiles are rather rare in reports. Sorensen and co-workers describe the total synthesis of a powerful immunosuppressant (FR901483) by oxidative aza-spiroannulation with PIDA in HFIP followed by an intramolecular aldol addition (Scheme 12, top) [77]. Similar to Sorensen's procedure, Honda and co-workers completed the formal total synthesis of enantiopure (–)-TAN1251A by dearomatizing spirocyclization reaction of the enantiopure chiral phenol substrate with high stereocontrol at the diastereomeric spiro center [78].

Independently, Ciufolini and co-workers reported the total syntheses of FR901483 and TAN 1251C by utilizing an oxazolidine as a selective nucleophile enabling similar aza-spirocyclizations (Scheme 12, bottom) [79]. The same research group succeeded in several total syntheses by analogous ways using sulfonamide groups instead of the oxazolines for the constructions of nitrogen-containing spiro centers found in the related natural products having the himandrine cores [80–82]. Similar cyclizations leading to spirodienone lactams [83, 84] involving nitrenium ion generation by oxidation of the cation-stabilizing methoxy and phthalimide nitrogen groups were reported by Wardrop [85, 86] in the total syntheses of the muscarinic M_1 receptor antagonist (−)-TAN1251A from *L*-tyrosine and (±)-desmethyl amino FR901483.

Working on the industrial production of galanthamine (see Scheme 9), Node and co-workers improved the yield of this phenolic coupling reaction by employing more suitably protected norbelladine-type derivatives as the intermediates [87]. Later, Shair and co-workers revealed that this synthetic strategy is applicable



Scheme 12 Oxidative spirolactamization examples

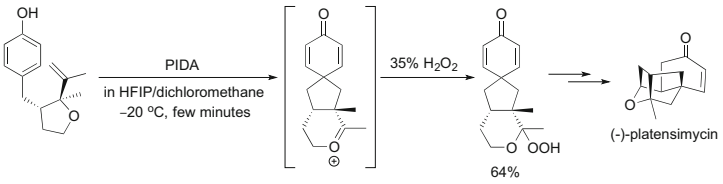


Scheme 13 Utilization of polymer-supported reagent

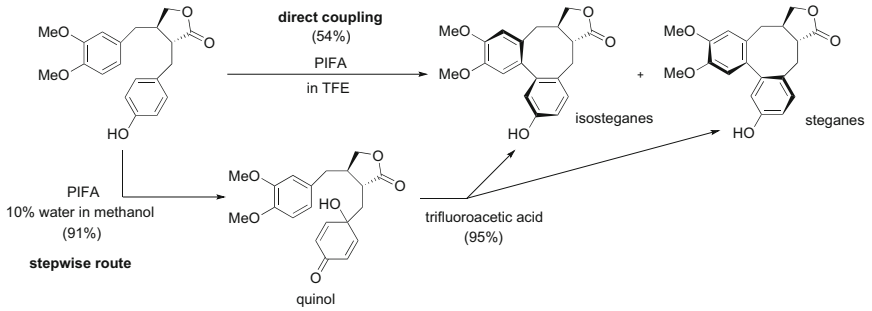
to solid-phase synthesis using the tagged phenols on insoluble poly(styrenes) [88]. Various galanthamine-like molecules with biological properties beyond those of the original natural products were successfully identified from the synthesized compounds.

Utilization of recyclable polymer-supported hypervalent iodine reagents meets the recent demand in constructing practical and industrial processes of natural product synthesis, other bioactive compounds, and related fine chemicals. The polymer-supported hypervalent iodine reagents, poly(diacetoxyiodo)styrene (PDAIS) and polybis(trifluoroacetoxyiodo)styrene (PBTIS), are very useful for these types of reactions, which were reported by Ley and co-workers. The efficient syntheses of (±)-oxomaritidine and (±)-epi-maritidine were established based on the green polymer reagent methodology [89] (Scheme 13). It is impressive to note that this research group has realized an elegant total synthesis of both enantiomers of plicamine employing solid-supported reagents in all the synthetic steps [90, 91].

More recently, large-scale synthesis of (+)-maritidine through organocatalytic methodology was accomplished by the first versatile C–C bond-forming reactions based on a reoxidation system of hypervalent iodine reagent at low temperatures consisting of a urea–hydrogen peroxide adduct and trifluoroacetic anhydride [92].



Scheme 14 Platensimycin synthesis via C-C bond-forming spirocyclyzation

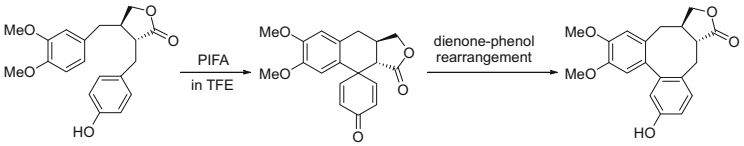


Scheme 15 Direct and indirect routes to steganes by hypervalent iodine oxidations

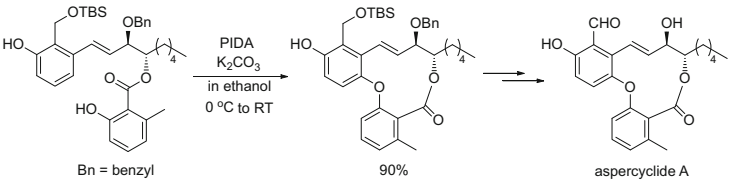
An oxidative Prins-pinacol tandem process mediated by hypervalent iodine reagent was recently established by the Canesi group [93] and it was used for the formal synthesis of (–)-platensimycin (Scheme 14) [94]. The strategy allowed rapid access to the highly functionalized spirocyclic core present in the target natural product.

3.1.2 Other Couplings Without Dearomatization

In contrast to the abundance of synthetic applications of phenol dearomatization strategies using hypervalent iodine reagents, the oxidative couplings of phenols without dearomatization seldom appear in natural product synthesis and only few examples are present in literature. As a rare example of phenol–phenol cross-couplings in synthesis of naturally-occurring type compounds, Pelter and co-workers reported that PIFA in fluoroalcohol reacts with *trans*-2,3-dibenzyl butyrolactones to produce isosteganes and steganes in 54% yield as a 8:1 (isosteganes:steganes) mixture (Scheme 15) [95]. An alternative synthetic route toward these lignans was also developed by the same group, in which dibenzocyclooctene lignans were obtained in high yields (95%) with a similar product ratio (88:12) via 4-hydroxycyclohexa-2,6-dienones from *trans*-2,3-dibenzylbutyrolactones by treatment with PIDA in aqueous methanol followed by trifluoroacetic acid [96, 97].



Scheme 16 Phenolic coupling example via spirodienone intermediate



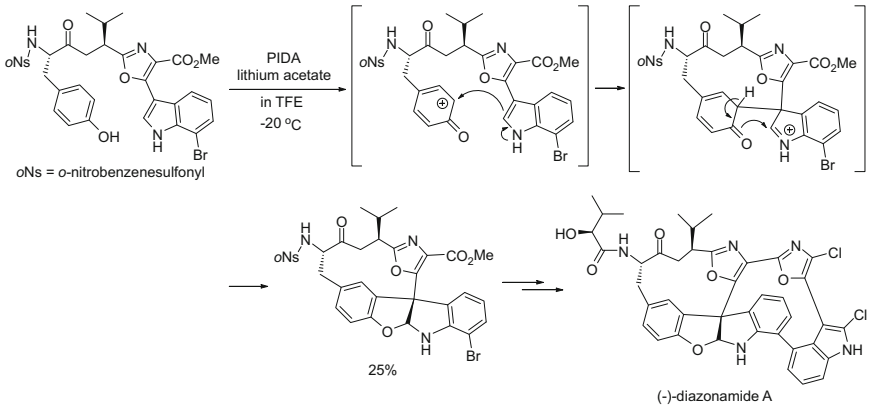
Scheme 17 Oxidative C-O bond forming phenolic coupling for aspercyclide A synthesis

Similarly, the treatment of the dibenzylbutyrolactones with the hypervalent iodine reagent PIFA in TFE gave either the dearomatized spirodienones or the tetrahydrodibenzocyclooctenes after dienone–phenol rearrangement, depending on the reaction time (Scheme 16) [98]. These reactions initially provide the spirodienones, the postulated intermediates in the biosynthesis of these tetrahydrodibenzocyclooctene lignans.

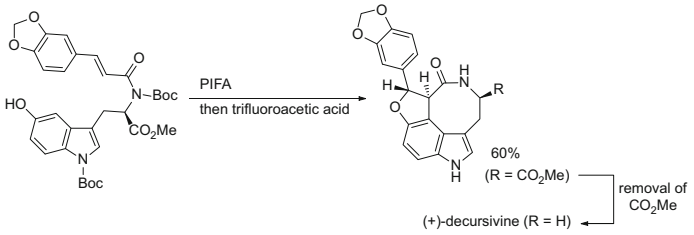
More recently, highly efficient total syntheses of the 11-membered cyclic aspercyclide A and its analogues were accomplished by chemo- and regioselective intramolecular oxidative phenolic coupling between the differently substituted two phenol moieties (Scheme 17) [99].

On the other hand, PIFA-induced oxidation of *p*-methoxy-substituted phenols and corresponding *N*-substituted anilines captured by electron-rich styrenes resulted in new carbon–carbon bond formation via an intermolecular 1,3-cycloaddition, giving *trans*-dihydrobenzofurans stereoselectively [100–102]. In several early reports, the formal syntheses of neolignans, such as kadsurenone and denudatin B, were achieved by this methodology [100, 101]. As reported by Harran and co-workers, this type transformation was recently applied as a key step in (–)-diazonamide A synthesis (Scheme 18) [103]. The operation involved the oxidation of the phenol ring by adding a cold trifluoroethanol solution of PIDA and lithium acetate mixture to produce the cationic phenoxenium ion, which was subsequently trapped intramolecularly by the tethered nucleophilic indole moiety. The resulting cyclohexadienone-linked indoleninium species can cyclize at the phenol oxygen, enabling the rapid construction of the desired linear peptidyl core in high stereo-preference of the undesired diastereomer.

One other application of this phenolic cyclization is the first asymmetric synthesis of a natural indole alkaloid, (+)-decursivine [104]. The key step in this case is the PIFA-mediated oxidative [3+2] cycloaddition of 5-hydroxy tryptophan with a



Scheme 18 Phenolic [3+2] coupling during the total synthesis of diazonamide A



Scheme 19 Application to decursivine total synthesis

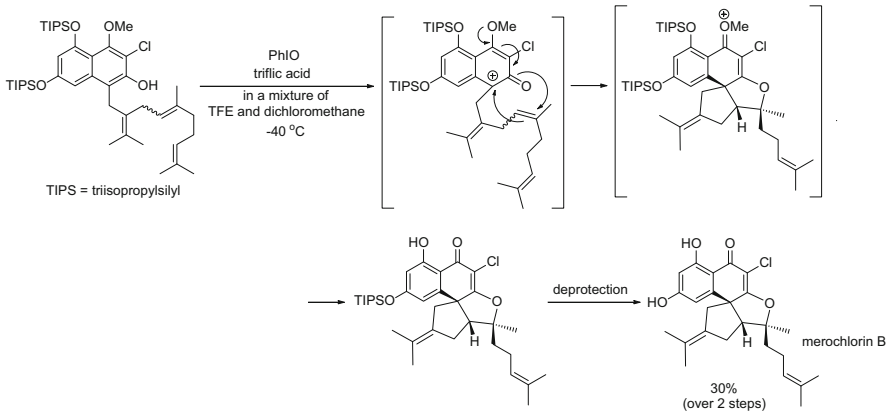
substituted cinnamamide in an intramolecular manner with high diastereoselectivity (Scheme 19).

Similar cyclizations were also successful for the construction of the highly strained core of *ent*-(−)-azonazine, an unusual marine natural cyclopeptide containing a rigid transannular 10-membered ring [105, 106]. After the completion of the total synthesis, the revised structure of (+)-azonazine was correctly assigned by comparing the diastereomeric and enantiomeric synthetic samples.

In addition, Trauner and co-workers recently presented the short total synthesis of racemic merochlorin B by means of this biomimetic [3+2] cationic condensation between phenol ring carbons and the internal nucleophilic alkene moiety mediated by hypervalent iodine reagents (Scheme 20) [107].

3.2 Oxidative Aromatic C–H Functionalizations

As noted in the introduction section, natural product syntheses involving oxidative functionalizations of aromatics are classified into two categories based on the

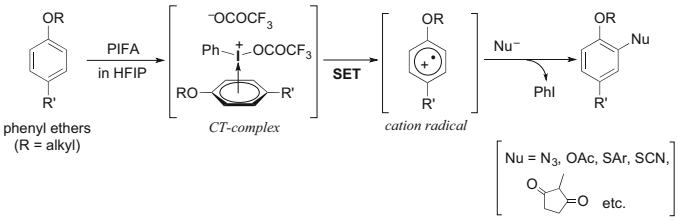


Scheme 20 Application to merochlorin B total synthesis

activation modes: (1) aromatic ring umpolung and (2) umpolung of nucleophiles. These are discussed in the following sections.

3.2.1 Aromatic Ring Activation Strategies

The reactivity of hypervalent iodine species depends greatly on the reaction conditions, and the reagents are now extensively recognized as an efficient and selective single-electron-transfer (SET) oxidizing agent. Indeed, hypervalent iodine(III) reagents can induce SET oxidizing events toward various electron-rich aromatic compounds if treated under specific reaction conditions [56, 57]. Kita and co-workers reported in 1990 the novel aromatic substitution of *p*-substituted phenyl ethers (R=alkyl) by azide (N_3^-) using a hypervalent iodine(III) reagent (PIFA) in a highly polar but low nucleophilic fluoroalcohol solvent, HFIP or TFE (Scheme 21) [108]. It was known that phenyl ethers are generally inert to iodine(III) reagents and would not react at the protected phenol functionality via the reaction mechanism involving phenoxyiodine(III) intermediates (see Scheme 7). This unusual phenomenon indicated that a new mechanism leading to the substitution products is involved in these reactions. Based on detailed UV and ESR spectroscopic studies, the generation of aromatic cation radicals induced by the SET oxidation through the complexation of the phenyl ether rings and PIFA was established [109]. The reactive cationic intermediate was then effectively trapped by various nucleophiles (N_3^-, AcO^-, ArS^- [Ar=aryl], SCN^-, and β-dicarbonyl compounds, etc.), furnishing the oxidative aromatic substitution events to produce a variety of *p*-substituted electron-rich phenyl ethers. That is the first case confirming the presence of a cation radical intermediate during the hypervalent iodine-mediated oxidations, and the organoiodine compounds, specifically PIFA, were suggested to have excellent SET oxidation abilities for these electron-rich aromatic rings.

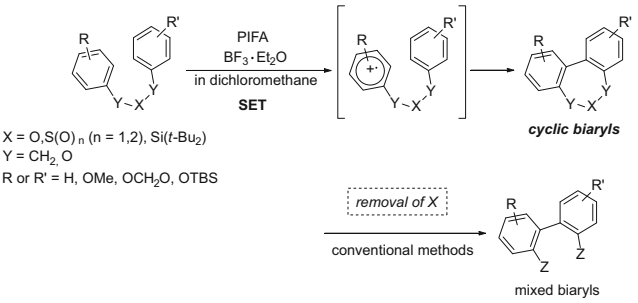


Scheme 21 Oxidative nucleophilic aromatic substitutions by single-electron-transfer (SET) process

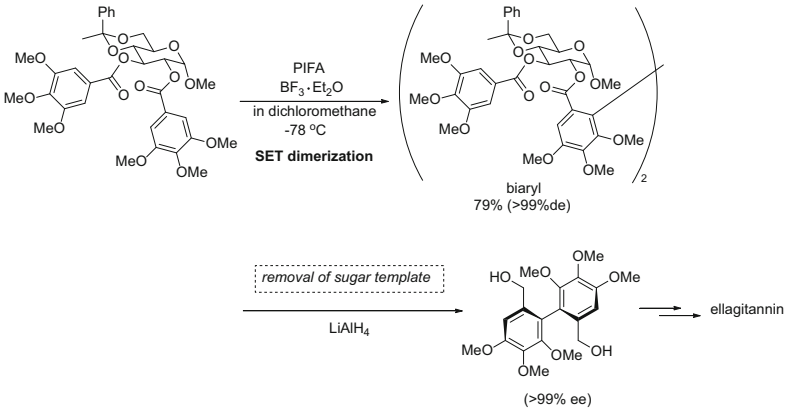
During the CT-complexation of hypervalent iodine reagents to aromatic rings, the acid additives could enhance the cationic characteristics of the iodine atom by coordinating to the trifluoroacetoxy ligand, enhancing the SET oxidizing ability as a result of the smooth interaction with the aromatic rings. Typical examples include the classical boron trifluoride–diethyl etherate ($BF_3{\cdot}Et_2O$) and trimethylsilyl triflate as well as the soft solid acids, such as heteropoly acids (HPA) and other solid clay catalysts. This alternative activation of PIFA has significant advantages in controlling the reactivity of the reagent and the reaction course. For example, in the reactions of methoxy-substituted bisaryl substrates, the use of HPAs as an activator of PIFA interestingly showed a remarkable difference to $BF_3{\cdot}Et_2O$ and the exclusive formation of the morphinandienone-type product was found by using the former new reagent combination (PIFA–HPAs) [110]. By this second activation strategy with acids, the same research group then extended the SET oxidizing processes to affect intramolecular oxidative biaryl couplings. The biaryl structures are present as a central building block in not only a large numbers of bioactive natural products, such as polyketides, terpenes, lignanes, coumarins, flavonoids, tannins, and many alkaloids, but also artificial ligands of metal catalysts used in asymmetric synthesis. In particular, the newly developed biaryl synthetic methods utilizing oxygen-, sulfur-, and silicon-tethered templates could provide a practical route to multi-substituted biaryls (Scheme 22) [111, 112]. The dibenzoheterocyclic structures of the cyclized products were easily cleaved by common deprotecting procedures to give both symmetrical and unsymmetrical biaryls.

This type of biaryl coupling reaction was also successful in an intermolecular fashion for electron-rich, nucleophilic phenyl ethers and alkyl arenes, which directly gave the self-coupling products, i.e., the corresponding biphenyl and binaphthyl dimers [113, 114]. When utilizing a chiral template for the phenol ether couplings, synthesis of enantiomerically pure ellagitannin precursors was unexpectedly accomplished as a result of the diastereoselective biaryl coupling reactions induced by the PIFA–$BF_3{\cdot}Et_2O$ combination (Scheme 23) [115]. In this reaction, high diastereomeric excess of the biaryl was observed when using α-D-glucose derivatives as chiral templates.

The SET aromatic substitution processes were also found in the synthetic courses of some non-natural and naturally-occurring molecules having important and diverse biological actions. For example, an extension of the intramolecular biaryl coupling with the PIFA-$BF_3{\cdot}Et_2O$ combination appeared for the short and



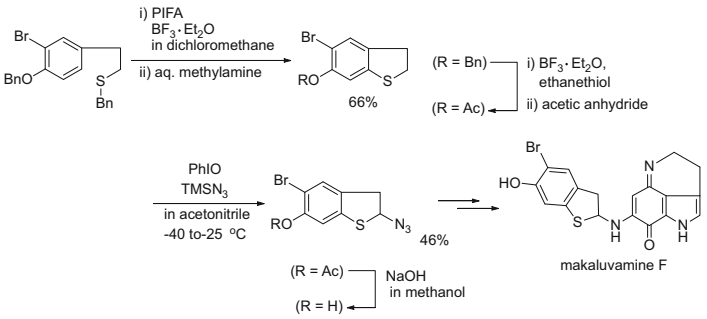
Scheme 22 Synthetic routes to mixed biaryls by tether strategy



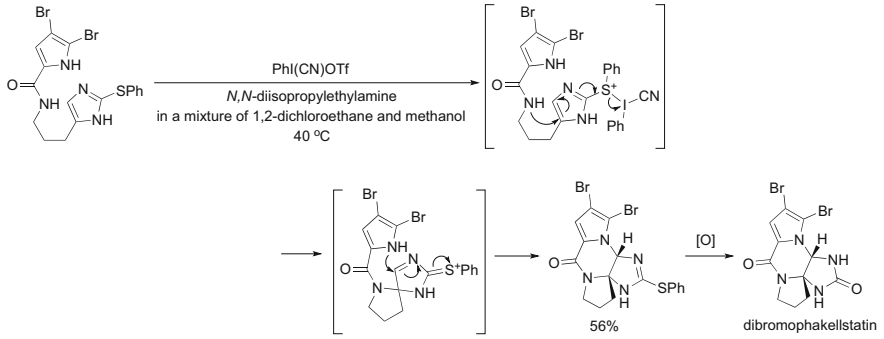
Scheme 23 Chiral sugar template for asymmetric ellagitannin synthesis

efficient constructions of benzo[*c*]phenanthridines and phenanthridinones en route to some biologically active isoquinoline alkaloids [116]. Aiming at the rebeccamycin synthesis, similar application of the PIFA–Lewis acid system was reported by Faul and co-workers for the synthesis of the core indole[2,3-*a*]carbazole parts by the intramolecular coupling reaction of bisindolylmaleimides [117]. Concise synthesis of a promising antiviral agent, michellamine A, was accomplished by Bringmann and Tasler via the oxidative biaryl coupling reaction of korupensamine A using PIFA as an alternative choice to the toxic lead tetraacetate [118].

In addition, this type of aromatic ring activation by the SET oxidation strategy using hypervalent iodine reagents was utilized for the total synthesis of a sulfur-containing pyrroloiminoquinone alkaloid, (±)-makaluvamine F [119–121]. The reaction for the construction of the α-amino dihydrobenzothiophene part involved the efficient cyclization of the benzyl thioether. Hypervalent iodine reagent was iteratively utilized for the successive oxidative transformation, that is, the azidation at the α-position of the sulfur group of the dihydrobenzothiophene via a Pummerer-like mechanism (Scheme 24).



Scheme 24 Oxidative C-S coupling during makaluvamine F total synthesis

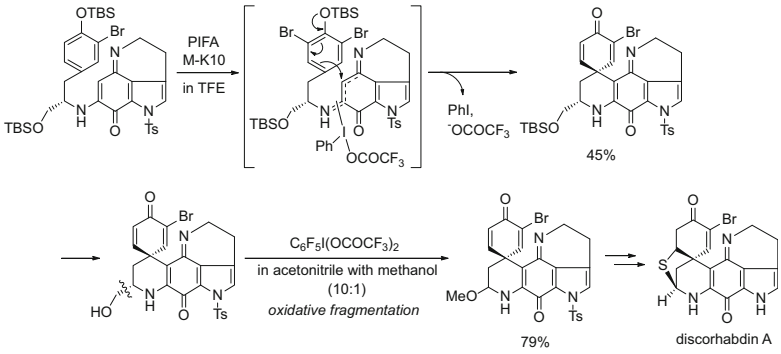


Scheme 25 Aromatic pummerer strategy for the total synthesis of dibromophakellstatin

Other examples of natural product syntheses involving unique aromatic ring activation by hypervalent iodine oxidation were found in the report by Feldman's group. It is interesting that the oxidative cyclization of a phenylthiolated dihydrooroidin derivative triggered by the extended additive Pummerer mechanism for the sulfenylated imidazole ring were described (Scheme 25). [122, 123]. The effective transformation using a specific reagent, PhI(CN)OTf, for producing the sulfonium intermediate served as the biomimetic approach to the marine alkaloids, (±)-dibromophakellstatin and its family.

3.2.2 Nucleophile Umpolung Strategies

The carbon–carbon bond-forming spirocyclizations of phenols leading to dearomatized spirodienones by activating the phenol groups [38] were first reported by Kita's group for the total synthesis accessing discorhabdin C, an antitumor marine alkaloid (see Scheme 8) [48, 49]. The success of the total synthesis of the more complex sulfur-linked discorhabdin A was later reported by the same group using other activation strategies based on the diastereoselective oxidative



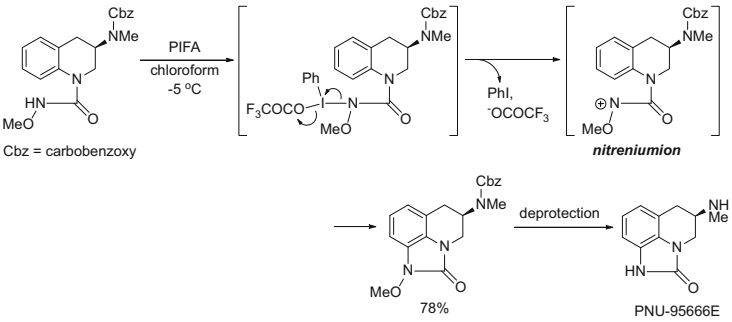
Scheme 26 Enamide ketone activation for the construction of discorhabdin core structure

spirocyclization of corresponding phenolic precursors with hypervalent iodine reagents (Scheme 26) [124, 125]. The phenol functionality of the phenethylaminoindole compound was protected by the *tert*-butyldimethylsilyl (TBS) group followed by the oxidative spirocyclization with PIFA by activating the iminoquinone enamide moiety, instead of the phenol ring, in a fluoroalcohol (TFE) to provide the desired spiro pyrroloquinolinedione skeleton of the natural product.

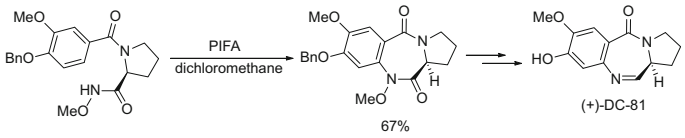
One other important example of the electrophilic activation of nucleophiles in natural product synthesis was established for the carbon–nitrogen bond formations to produce electron-rich aromatic rings, which included treatment of *N*-methoxyamides with PIFA for generating electron-deficient nitrogen species, which are nitrenium ions. Hence, the in situ-formed amido-λ^3-iodane species having a suitable cation-stabilizing group, such as a methoxy group, on the nitrogen at the amide groups would spontaneously release the nitrenium intermediates. The reactive nitrogen cationic species can then react intra- or intermolecularly with nucleophilic aromatic rings and other π-nucleophiles [58, 59]. This nitrogen umpolung strategy was successfully applied by Kikugawa [83, 84] and Wardrop [85, 86] independently for the oxidative couplings of *N*-methoxyamides with an extensive series of aromatic rings and for the oxidative dearomatizing spirolactamizations.

Utilizing this *N*-oxidation process involving nitrenium ions, the construction of the enantiomerically pure tricyclic structure was achieved by the PIFA-induced oxidative cyclization of the *N*-methoxy amide from D-phenylalanine (Scheme 27) [126]. The synthesized PNU-95666E is a selective and high-affinity artificial agonist at the dopamine D2 receptor subtype, and thus serves as a potential agent for treating Parkinson's disease.

Similarly, this *N*-activation coupling was used for synthetic access to the antitumor antibiotic DC-81 (Scheme 28) [127]. The key cyclization step represents the generation of an *N*-acyl nitrenium intermediate and its successive intramolecular trapping by the aromatic ring system.



Scheme 27 Generation of nitrenium ion and its application for total synthesis



Scheme 28 Application of the nitrenium ion strategy for the synthesis of DC-81

In recent years, Olofsson's group has largely been contributing to the significant improvements of classically reported nucleophilic substitution reactions utilizing diaryliodonium(III) salts by further improving the reaction conditions. The investigations regarding the base, solvent, temperature, and reaction time have defined the conditions for the use of potassium *tert*-butoxide for the *O*-arylation of phenols in tetrahydrofuran and for carboxylic acids in refluxing toluene, enabling very efficient and practical metal-free *O*-arylations of a wide scope of phenols and carboxylic acids under mild conditions. Along with the synthetic advances for their preparations, diaryliodonium(III) salts are increasingly used in organic synthesis as versatile arylating agents with broad applications for constructing complex molecules [128, 129]. These contributions in the new metal-free coupling reaction areas are comprehensively described in other chapters of this book. More detailed summaries of the applications of hypervalent iodine reagents in entire natural product synthetic areas are available in several review articles by several groups, including ours [47, 130–134].

4 Conclusion

A variety of biologically active natural products have now been synthesized by the use of hypervalent iodine-induced reactions. The development of the oxidative coupling reactions, which are applicable to natural product syntheses, in this area have become more and more important and useful in the practical productions of chemical, pharmaceutical, and agrochemical products because of their versatility,

mild reactivity, ready availability, high yields, and safety. One of the goals of recent research is replacing rare metal-using methods by hypervalent iodine chemistry. To realize this, further advances of the catalytic oxidative couplings of hypervalent iodine reagents, likewise the metal-catalyzed methods, are required for developing more practical synthetic procedures. The metal catalyst-free coupling studies under the organocatalysis of hypervalent iodine species in combination with practical terminal oxidants in stoichiometric amounts are now important in this field, and recently the authors presented the first success of catalytic oxidative cross-coupling methods [135]. This is realized once by the fine design of the specific 2,2-′-diiodobiphenyl catalysts which can produce in situ highly reactive μ-oxo hypervalent iodine species [136, 137] (related reagent [138, 139]). The report is the first one of the oxidative cross-coupling of aromatic compound under the organocatalysis in the intermolecular manner. In future stages such catalyst-controlled methods are expected to become an active field as a new opportunity for developing greener synthetic methods in metal-free cross-coupling strategy. Indeed, oxidative aromatic substitutions by nitrogen groups via the formation of nitrenium ions introduced in Sect. 3.2.2 seem to be nicely reproducible in catalysis by utilizing the high-performance iodine catalysts with peracetic acid as a stoichiometric practical oxidant [140–142]. Fortunately, the catalytic utilization of hypervalent iodine reagent is possible in theory when the released iodoarene is successfully reoxidized in situ into the hypervalent iodine species, and many phenolic oxidation systems using hypervalent iodine reagents discussed in Sect. 3 have just faced such criteria to become new organocatalytic protocols [143–146]. The new catalytic advances appearing in the oxidative cross-couplings surely contribute to sustainability of the methods for manufacturing important biaryl compounds found in various fine chemicals. With such contributions, the chemistry of hypervalent iodines continues to make an impact in the twenty-first century of organic synthesis.

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Phenol Dearomatization with Hypervalent Iodine Reagents

Stéphane Quideau, Laurent Pouységu, Philippe A. Peixoto, and Denis Deffieux

Abstract This chapter highlights recent developments in phenol dearomatization using organoiodane reagents and a selection of applications in natural product synthesis.

Keywords Cyclohexadienones • Iodanes • Natural product synthesis • Phenol dearomatization • Quinones and quinols • Spirocyclizations

Contents

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1 Phenol Dearomatization: A Powerful Strategy in Organic Synthesis

Organic chemists have long held the view that aromatic and heteroaromatic compounds constitute an abundant and valuable source of carbon-based (hetero)cyclic building blocks for the rapid construction of complex molecular architectures and that their dearomatization is arguably the most versatile strategy to exploit fully their potentiality for chemical transformations [1–10]. Phenols and indoles are the typical (hetero)aromatic starting materials that have served over the years for the development of dearomatization protocols, and numerous methodological tactics have thus been implemented to accomplish this chemical task by relying on, inter alia, oxygenation, dehydrogenation, reduction (hydrogenation), halogenation, arylation, allylation, alkynylation, alkylation, and cycloaddition reactions using various organic, inorganic, (organo)metallic, (organo)halogen, or enzymatic oxidizing, reducing, halogenating, coupling, and atom-transfer reagents and catalysts, not forgetting electrochemical means [1–8]. The added value for organic synthesis of dearomatizing (hetero)aromatic compounds is that some of their constituting planar carbon atoms can be converted into stereogenic centers, whose three-dimensional configuration can be controlled by adopting asymmetric protocols either using starting materials with chiral appendages or using chiral reagents, catalysts, or additives [1–8]. Phenols are unarguably the most frequently utilized aromatic compounds for dearomatization in the synthesis of complex natural products, and the application of such a strategy for the construction of key intermediates or for the elaboration of final products often mimics the manner through which these natural products are biosynthetically generated. Depending on their substitution pattern and functionalities, phenols can be dearomatized into various reactive species such as quinones, quinone methides, and other (possibly chiral) cyclohexadienones (Fig. 1). Generally speaking, phenols are mildly acidic electron-rich aromatic nucleophiles. They are highly sensitive to one-electron oxidation into delocalized phenoxy radical species, and can also be converted into cationic electrophiles of the phenoxenium type or equivalents thereof by two-electron oxidation or activation through the use of "phenolophile" (oxidizing) metal- or halogen-based reagents. Their non-aromatic cyclohexadienone tautomers can also be stabilized through the formation of transition metal–arene complexes, which can then render them prone to cycloaddition and nucleophilic addition processes. All of these different facets of the chemical reactivity of phenols can be exploited for their dearomatization (Fig. 1) [11–15].

This review is devoted to an overview of phenol dearomatization and its application in natural product synthesis through the use of a special class of "phenolophile" reagents that has attracted much attention in recent years, the hypervalent iodine reagents. These polyvalent iodine compounds, also called iodanes, are oxidizing electrophiles that can mediate a wide number of diverse chemical transformations not only of (hetero)aromatic compounds, but also of inter alia alkenes, alkynes, alcohols, sulfides, amines and amides, (enolizable) carbonyl

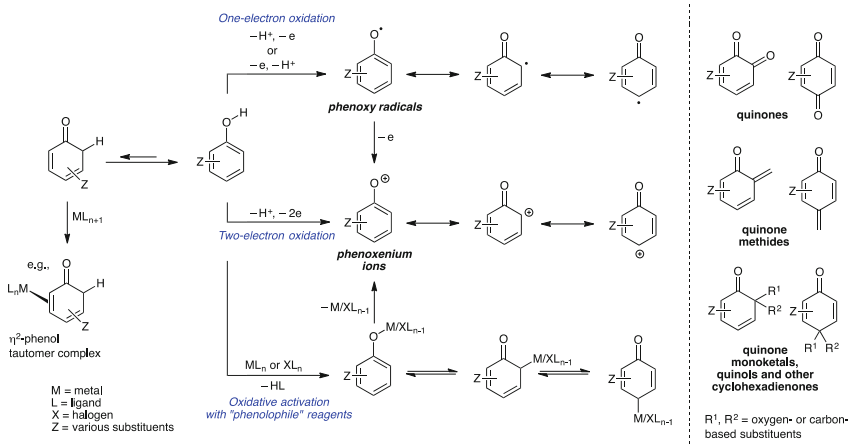

Fig. 1 Various facets of the dearomatization of phenols

compounds, and alkylarenes [16–27]. As metal-free reagents with aptitudes to remain operational under mild and environmentally friendly reaction conditions, with reactivity criteria similar to those of (toxic) transition metals, and with the possibilities of making them chiral and being used as catalysts, iodanes offer convenient alternatives and new solutions for the modern practice of organic synthesis [16–27]. Their utilization in the dearomatization of phenols has been the topic [7, 28, 29] or subtopic [1–3, 19–26] of several recent review articles, so this review only highlights a selection of research work published for the most part since 2010 and only concerns the use of organo-λ^3- and -λ^5-iodanes. Their mechanistic implications in phenol dearomatization processes is not discussed, as these aspects still today remain mostly speculative, including various hypothetical depictions based on either ionic associative or dissociative, ligand coupling, or radical reaction paths. A general description of possible ionic and ligand coupling pathways is schematized in Fig. 2. All these hypotheses are feasible, but depend greatly on the nature of the iodane used, on the reactivity of its ligands (nucleophilicity and nucleofugality), on the nature of the starting phenol (substitution pattern and electronic demand), on the reactivity (nucleophilicity) of the intervening species leading to dearomatization, and on the reaction conditions, notably on the type of solvent(s) used. As of today, most mechanistic depictions given in the literature are based on chemists' interpretations of their experimental observations rather than on accurate potential energy-based examinations of reaction coordinates.

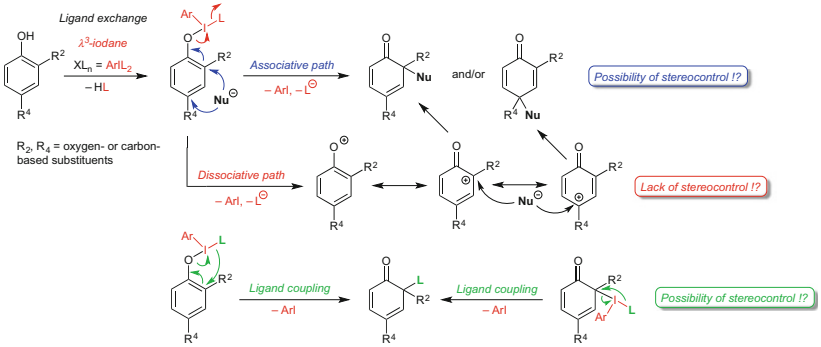

Fig. 2 Examples of possible mechanistic options for phenol dearomatization using organo-λ^3-iodane reagents

2 Organoiodane-Mediated Dearomatization of Phenols into Quinonoids

2.1 Synthesis of Quinones

The simplest dearomatizing transformation of phenols is their conversion into *ortho*- or *para*-quinones by oxygenation and/or dehydrogenation reactions. Hypervalent iodine(III) and iodine(V) reagents (i.e., λ^3- and λ^5-iodanes) have often been used to mediate these reactions, and related reports continue to appear in the literature. For example, Harvey and co-workers utilized the λ^3-iodane [bis(trifluoroacetoxy)iodo]benzene (**BTI**) and the λ^5-iodane 2-iodylbenzoic acid (**IBX**) to oxidize a series of polycyclic aromatic phenols (e.g., **1a**–**f**) into quinones [30]. Treatment of these arenols with **IBX** in dimethylformamide (DMF) systematically afforded the corresponding expected *ortho*-quinones **2a**–**e** [31, 32], whereas oxidations of the same phenolic compounds with **BTI** in aqueous DMF either led to the corresponding *para*-quinones, when their formation was structurally possible (i.e., **3a**–**d**), or to the same *ortho*-quinones as those produced using **IBX**, when *para*-positions were blocked by their implication in the polycyclic arene ring system, such as for **1b** and **1f** leading to **2a** and **2e**, respectively (Fig. 3) [30].

Kita's group recently reported on the advantage of using the μ-oxo-bridged version of **BTI** to oxidize phenols and naphthols into quinones in aqueous media [33]. Soluble in water in contrast to **BTI**, this reagent [μ-oxobis(trifluoroacetoxyiodobenzene), **μ-oxoBTI**] also possesses a more pronounced electrophilic character in comparison to **BTI**. The oxidation of naphthol **1a** into the *para*-quinone **3a** using **μ-oxoBTI** in aqueous acetonitrile was much faster and higher yielding than using **BTI** under similar reaction conditions (Fig. 4). Many other phenols, naphthols, 1,4-hydroquinones, and monomethylated variants thereof were also converted in high yields into their corresponding *para*-quinones [33]. Even using only half of an equivalent of this bis-λ^3-iodanyl reagent in water, the

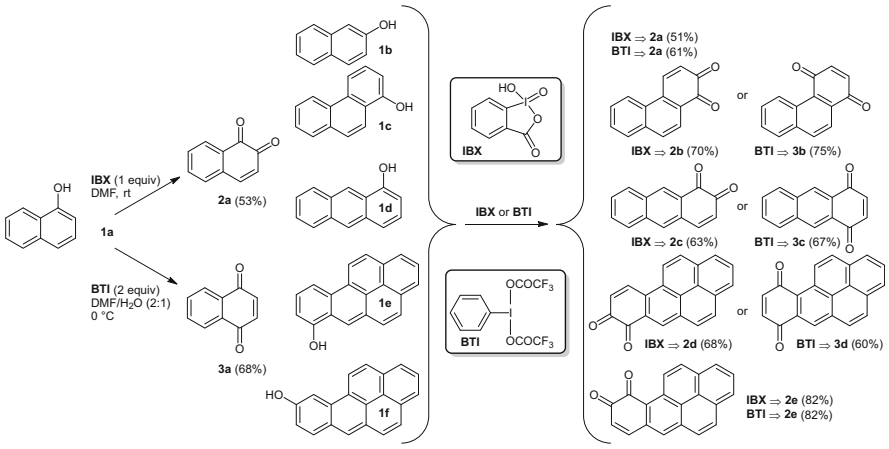

Fig. 3 IBX- or BTI-mediated oxygenation of polycyclic arenols into *ortho*- or *para*-quinones

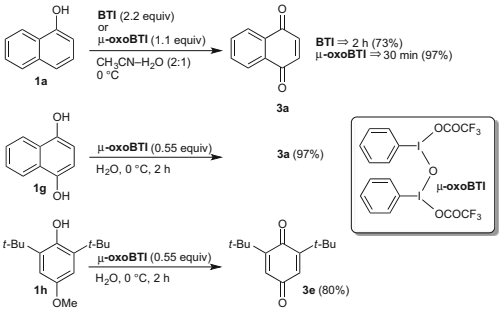

Fig. 4 Kita's μ-oxoBTI-mediated oxidation of naphthols and phenols into *para*-quinones in aqueous media

1,4-hydroquinone **1g** and the hydroquinone monomethyl ether **1h** were converted into the *para*-quinones **3a** and **3e** in high yields (Fig. 4).

Ishihara's group also recently reported the catalytic use of sodium salts of 2-iodobenzenesulfonic acids in the presence of Oxone® as co-oxidant to oxidize polycyclic arenols and simpler phenols into *ortho*-quinones in good to high yields under optimized non-aqueous conditions [34]. The λ^5-iodanes 2-iodylbenzenesulfonic acids (**IBS**) [35, 36] that are thus generated in situ by the action of Oxone®, such as the **5-Me-IBS**, regioselectively convert naphthols [including 2-methoxy-1-naphthol (**1i**)] [37], phenanthrols, or simple phenols into *ortho*-quinones, as exemplified in Fig. 5, except in the case of 3-methoxy-1-naphthol (**1k**), for which the oxidation was *para*-selective as a likely consequence of a directing effect of the electron-donating *meta*-methoxy group [34].

The rich topic of the utilization of *ortho*- and *para*-quinones in chemical synthesis falls outside the scope of this review, but there is a quite elegant and

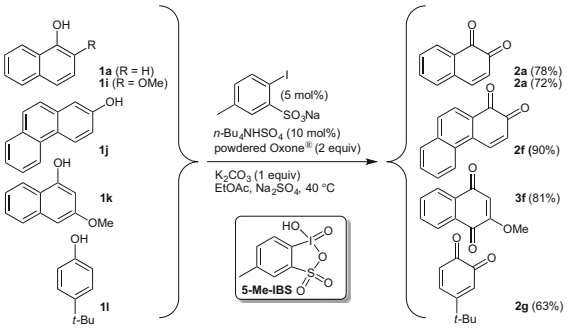

Fig. 5 5-Me-IBS-catalyzed oxidation of arenols into quinones

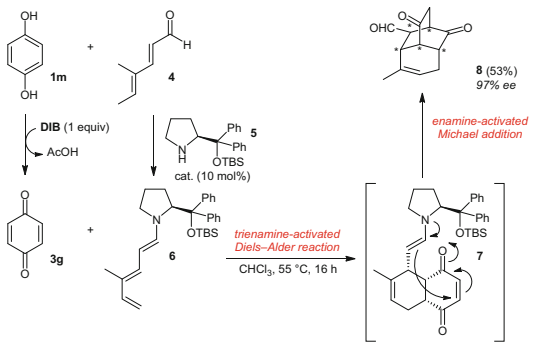

Fig. 6 Example of a combined DIB-mediated dearomatization and organocatalyzed trienamine/enamine-activated asymmetric Diels–Alder/Michael cascade reaction of 1,4-hydroquinones and dienals into highly functionalized natural product-relevant tricycles

recent exploitation of 1,4-benzoquinone that deserves to be highlighted herein. Coeffard, Greck, and co-workers reported an asymmetric oxidative organocatalytic three-bond-forming one-pot transformation of 1,4-hydroquinones and dienals into functionalized tricyclic systems in the presence of the λ^3-iodane (diacetoxyiodo) benzene (**DIB**) reagent and chiral diarylprolinol silyl ether catalysts [38]. As exemplified in Fig. 6, **DIB** was used to dehydrogenate the 1,4-hydroquinone **1m** into the benzoquinone **3g**, and the chiral proline-based catalyst **5** served to activate the starting dienal **4** toward an asymmetric Diels–Alder/Michael cascade reaction with **3g**, which gave rise to the formation of the natural product-related five-stereocenter-containing tricyclic system **8** in a relatively good yield with excellent stereoselectivity [38].

2.2 Synthesis and Applications of Quinone Monoketals

Simple quinone monoketals, such as dimethyl ketal variants of type **9**/**10** (Fig. 7), constitute the second most often used group of simple quinonoids in synthesis. They are usually described as monoprotected or "masked" forms of their quinone counterparts, with which they share some of the basic reactivity features related to the

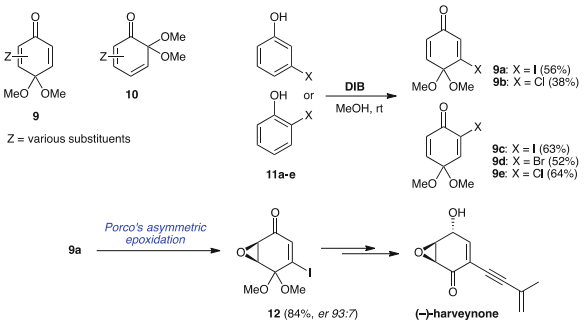

Fig. 7 Methoxylative dearomatization of halogenated phenols into halo-*para*-quinone monoketals

electrophilic character and propensity toward cycloaddition of their dienone motifs. Usually more stable than their quinone counterparts, they are conveniently prepared by alkoxylative dearomatization of phenols using λ^3-iodane reagents such as **DIB** or **BTI** in the corresponding alcohol solvent [11, 12, 39]. Among the new additions to this chemistry is a report by Taylor [40], in which he describes the synthesis of halo-*para*-quinone monoketals of type **9** using **DIB** in MeOH (Fig. 7). The iodo-*para*-quinone dimethyl ketal **9a** was then regio- and stereoselectively oxygenated to deliver the epoxide **12** en route to the fungal metabolite, (–)-harveynone [40].

One of the most innovative exploitations of *para*-quinone monoketals of type **9** was reported in 2011 by Kita's group to prepare polyoxygenated polyaryls [41, 42]. Masked *para*-benzoquinones (MPBs) are potent electrophiles that can be subjected to direct and conjugate nucleophilic additions or direct nucleophilic substitutions. Rarer are examples of conjugate SN_2'-type nucleophilic substitutions [43]. This is what Kita's group managed to implement with MPBs, which were generated from phenols or 4-methoxyphenols using **DIB** in methanol, and various methyl aryl ethers or phenols as nucleophiles in the presence of Montmorillonite clays as mild Brønsted acid activators in a mixed 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)/CH_2Cl_2 (10:1) solvent system. For example, the naphthoid MPB **9f** reacted accordingly with the 3,5-dihydroxybenzoate **14** to furnish the biarylic gilvocarcin core **15** (Fig. 8) [41]. Kita and co-workers went on to construct polyoxygenated oligoaryl compounds such as the teraryl **18**, which was obtained by resubmitting the initially formed 4-methoxyphenolic biaryl **16** to a second methoxylative phenol dearomatization–SN_2'-type substitution sequence using 1,3,5-trimethoxybenzene **17**. Higher oligoaryls such as **19** and **20** were then obtained by combining, respectively, the biaryl **16** with its corresponding *para*-quinone monoketal **9g**, and the teraryl **18** with the same MPB **9g** (Fig. 8) [42].

A couple of years later, Peddinti made similar observations on the electrophilic reactivity of *ortho*-quinone monoketals of type **10** [44]. Various 4-substituted 2-methoxyphenols **21** were converted into such masked *ortho*-benzoquinones (MOBs) [39], again using **DIB** in MeOH, in the presence of electron-rich arenes for constructing unsymmetrical polyoxygenated biaryls by conjugate additions at position 3 or 5 of the MOB's dienone system. In fact, the Lewis acid activation of these intended coupling reactions between MOBs **10a–d** and

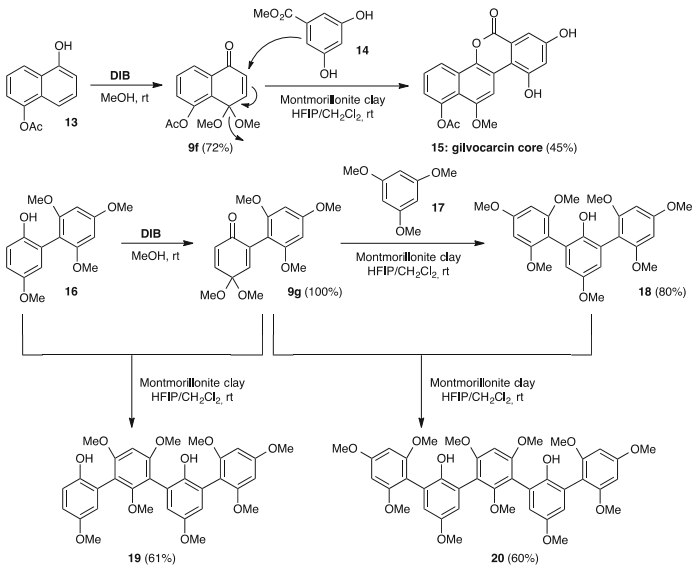

Fig. 8 Kita's *para*-quinone monoketal-based synthesis of polyoxygenated oligoarenes

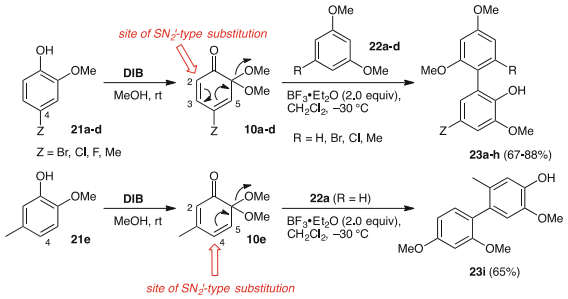

Fig. 9 Peddinti's *ortho*-quinone monoketal-based synthesis of polyoxygenated biarenes

1,3-dimethoxybenzenes **22a–d**, using BF_3 etherate, led to the formation of biaryls **23**, which instead resulted from vinylogous SN_2'-type substitutions at position 2 (Fig. 9). Higher yields of analogous biaryls were even obtained when using 2-naphthol derivatives as nucleophiles, and the use of a 4-unsubstituted MOB **10e** confirmed this reactivity preference for SN_2'-type substitutions over Michael-type additions under these reaction conditions – 1,3-dimethoxybenzene (**22a**) attacked **10e** at its position 4 to furnish the biaryl **23i** in 65% yield (Fig. 9) [44]. It is true that MOBs often and usually react as Michael acceptors, as again also evidenced by Peddinti's group using *S*-based nucleophiles in their recently reported method for the synthesis of diaryl and alkyl aryl sulfides [45]. Indeed, there are only rare examples of SN_2'-type substitution reactions in MOB chemistry, but precedents

do exist for C–C bond-forming reactions with and without Lewis acid mediation, as previously reviewed [11].

The most productive application of MOBs in chemical synthesis is unquestionably their utilization in Diels–Alder reactions, and the most prolific researcher and frontrunner for this chemistry is indisputably Liao, who has spent the last 30 years or so investigating the various aspects of the behavior of MOBs (an acronym he first introduced in the literature) in these [4+2] cycloadditions [39]. Peddinti, one of Liao's former co-workers, has also today taken up the torch and has reported other extensions of this chemistry, for example, by using the four 4-halogenated MOBs **10a–c/f** in inverse-electron-demand Diels–Alder reactions with a large excess of several electronic-rich as well as electron-deficient dienophiles **24** to furnish bicyclo[2.2.2]octenones of type **25** in good to high yields in an *endo*-selective manner (Fig. 10) [46].

Peddinti also reported a simple and efficient one-pot synthesis of benzoxazolic bicyclo[2.2.2]octenones **29–31** by subjecting 2-methoxy-substituted phenolic aldimines of type **26** to a similar treatment with **DIB** in the presence of the same kind of dienophiles **24**, or furans, in MeOH [47]. This clever domino reaction starts with a **DIB**-mediated oxidative cyclization of the phenolic aldimines into the phenolic benzoxazoles **27**, which are then converted, with a second equivalent of **DIB**, into the MOBs **28** that are finally trapped with excess of dienophile to furnish selectively the expected [4+2] cycloadducts **29–31** (Fig. 11) [47].

Liao is also still active in this field, as he reported in 2014 an elegant and rapid access to the natural product-related tricyclic decahydrophenanthrene skeleton by subjecting various 2-methoxyphenols **21** to **DIB**-mediated methoxylative dearomatization/Diels–Alder cascade reactions using 1-vinylcyclohexenes **32** in excess [48]. Interestingly, the MOB intermediates of type **10** reacted with those vinylcyclohexenes either as dienes to furnish the expected bicyclo[2.2.2]octenones of type **33**, or as dienophiles to furnish directly decahydrophenanthrenes of type **34** (Fig. 12). The bicyclo[2.2.2]octenones **33** could be converted into the corresponding decahydrophenanthrenes through a thermally-induced Cope rearrangement. For example, the bicyclo[2.2.2]octenone **33a** was converted into the decahydrophenanthrene **35** in quantitative yield (Fig. 12) [48].

The above examples of intermolecular Diels–Alder reactions should not let us forget that MOBs and other *ortho*-quinone monoketals, and their *ortho*-quinol

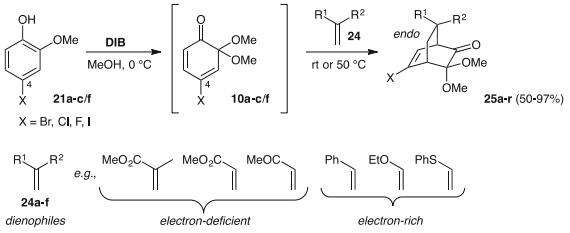

Fig. 10 Inverse-electron-demand *endo*-Diels–Alder reactions between 4-halo-*ortho*-quinone monoketals and various dienophiles

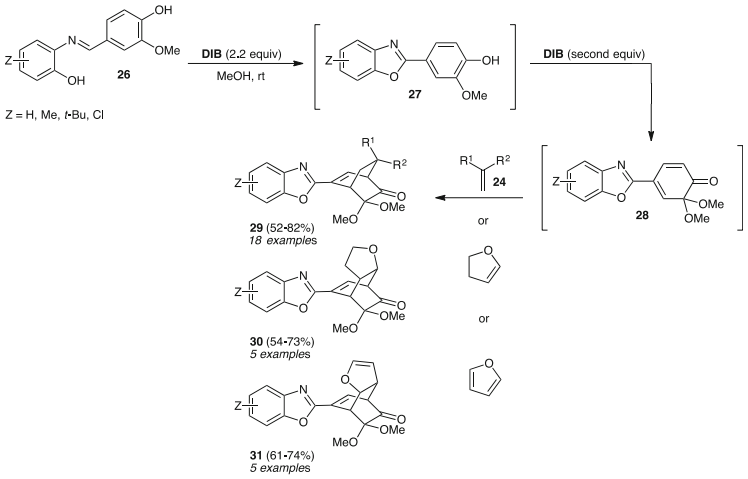

Fig. 11 Peddinti's synthesis of benzoxazolic bicyclo[2.2.2]octenones

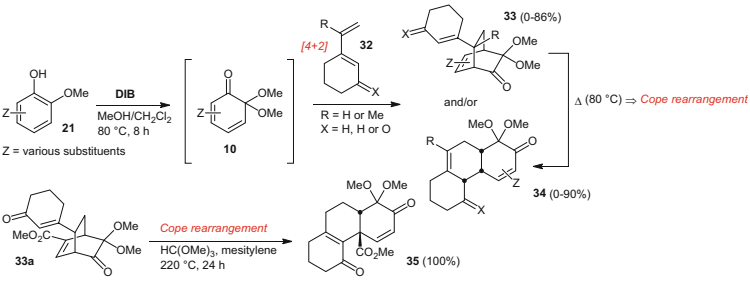

Fig. 12 Liao's DIB-mediated methoxylative phenol dearomatization/Diels–Alder cycloaddition cascade reactions with vinylcyclohexenes, and conversion of bicyclo[2.2.2]octenones into decahydrophenanthrenes through Cope rearrangement

variants (see below), have a highly pronounced tendency to self-dimerize spontaneously, even at room temperature. This self-dimerization can be circumvented, blocked, or at least retarded by using any other reaction partner in excess, as in most of the cases highlighted above, or by the presence of certain substituents, such as a bulky group or a halogen atom at the MOB's position 4, or even just a small alkyl or alkoxy group at their position 5; for previous discussions on these issues, see [49]. Nevertheless, the self-dimerization is a highly valuable process, which is at the origin of the biosynthesis of several natural products (see below) [29, 49]. In this vein, Chittimalla recently reported the self-dimerization of simple MOBs bearing a fluorine or bromine atom at their position 3 [50]. Again, these MOBs were generated by a DIB-mediated methoxylative dearomatization of 5-fluoro/bromo-2-methoxyphenols. For example, the 3-fluorinated MOB **10g** cyclodimerized to furnish the bicyclo[2.2.2]octanone **36** in high yield (Fig. 13). This homodimeric

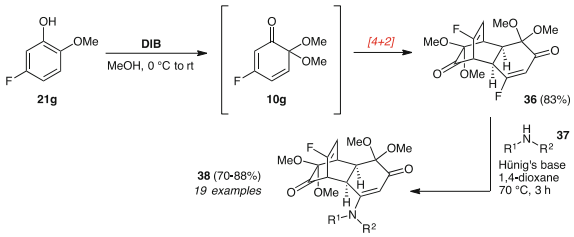

Fig. 13 DIB-mediated methoxylative phenol dearomatization/Diels–Alder cyclodimerization cascade reaction of 5-fluoro-2-methoxyphenol, followed by substitution of the vinylic fluorine atom by conjugate addition/elimination reactions with amines

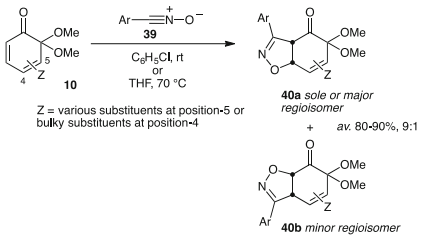

Fig. 14 Isoxazolines synthesis through 1,3-dipolar [3+2] cycloaddition reactions between *ortho*-quinone monoketals and benzonitrile oxides

compound was then subjected to a series of conjugate addition/elimination reactions at its fluorinated vinylic position with various primary and cyclic secondary amines **37** in the presence of Hünig's base to afford the corresponding aminated heterodimers **38** in good to high yields (Fig. 13) [50].

Another aspect of the versatile reactivity of *ortho*-quinone monoketals was exploited by Chittimalla's and Suzuki's groups [51, 52], who reported examples of [3+2] cycloaddition reactions involving non-dimerizing MOBs of type **10** and benzonitrile oxides **39**. The reactions are site- and regioselective, primarily affording isoxazolines **40**, as a result of the 1,3-dipolar cycloaddition of the nitrile oxides to the MOBs' 2,3-C–C double bond (Fig. 14).

MOBs can also be used to construct highly substituted α-tropolones, as recently demonstrated by Herzon and Kats-Kagan [53], who prepared several bicyclo[4.1.0] heptanes from their brominated parent **43a**, which was generated by a regioselective cyclopropanation of the dimethylketal MOB **42**, itself made by a **DIB**-mediated methoxylative dearomatization of the 4-bromophenol **41**. Heating these bicyclo[4.1.0]heptanes in THF at 70°C was sufficient to provoke their ring expansion rearrangement into the α-tropolones **44** in high yields (Fig. 15). A bis (bicyclo[4.1.0]heptane) variant of type **43** was thus converted into a bis(tropolone) derivative displaying the core structure of the antitumoral marine products gukulenins [53].

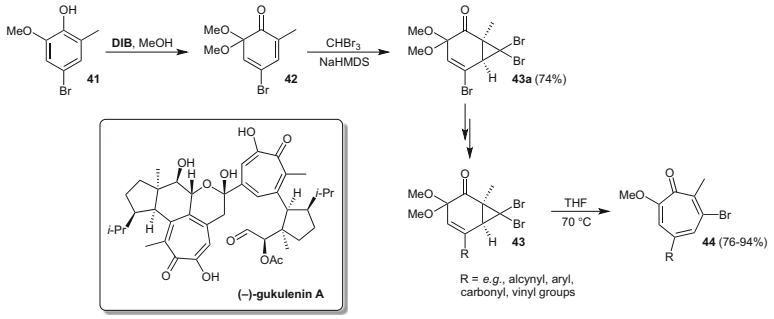

Fig. 15 Synthesis of α-tropolones from *ortho*-quinone monoketals

2.3 Synthesis and Applications of Quinols

Next in this survey of recent developments of iodane-mediated dearomatization of phenols into quinonoids are the synthesis and applications of quinols, which regroup different cyclohexa-2,5- and -2,4-dienones bearing a hydroxy group at position 4 or 6, respectively, (i.e., **45** and **46**), including their corresponding ethers and esters **45′** and **46′** (Fig. 16). In line with the current efforts toward the development of iodane-catalyzed reactions, Yakura reported an efficient method to prepare *para*-quinols of type **45** such as the 4-aryl-4-hydroxycyclohexa-2,5-dienones **45a** from 4-arylphenols **47** using catalytic amounts of 4-iodophenoxyacetic acid **48** as iodane precursor and Oxone® as terminal oxidant (Fig. 16) [54]. Also, more recently, Harned devised the chiral iodoarene **50** to be used in concert with *m*-CPBA as terminal oxidant for catalytic asymmetric dearomatization of phenols of type **49** into *para*-quinols of type **45**, albeit in moderate yields and enantiomeric excesses (Fig. 16) [55]. However, most chemists interested in exploiting the reactivity of *para*-quinols in subsequent transformations still today mainly rely on the stoichiometric use of commercially available iodanes.

For example, Fan and co-workers developed a one-pot procedure to prepare *meta*-indolylphenol derivatives of type **54** by subjecting 4-substituted phenols **51** to a **DIB**-mediated methoxylative dearomatization in the presence of indoles **53** and a catalytic amount of 4-methylbenzenesulfonic acid (TsOH) (Fig. 17) [56]. The **45′**-type *para*-quinol methyl ether intermediates **52** served as Michael acceptors for acid-catalyzed C–C bond-forming indole additions, the products of which then underwent direct methanol additions and re-aromatization via methanol and water eliminations (Fig. 17). Li and Fan then also relied on a **DIB**-mediated methoxylative phenol dearomatization to prepare rapidly **45′**-type *para*-quinol methyl ethers **56** bearing an alkynyl motif at their position 2. Then the use of a Pd(II) catalyst in the presence of an alkene of type **57** and an amine of type **58** induced oxocyclization, C–C coupling with the alkene, C–N bond-forming conjugate addition of the amine onto the *para*-quinol moiety, and a final re-aromatizing elimination to furnish the 3,4-difunctionalized benzofurans **59** in good yields

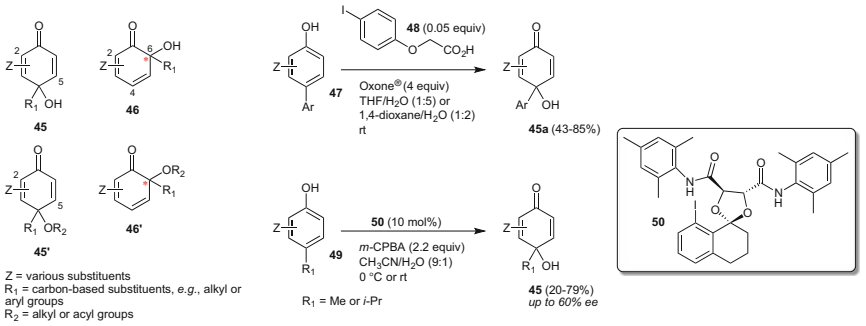

Fig. 16 Yakura's iodane-catalyzed synthesis of *para*-quinols and Harned's asymmetric version

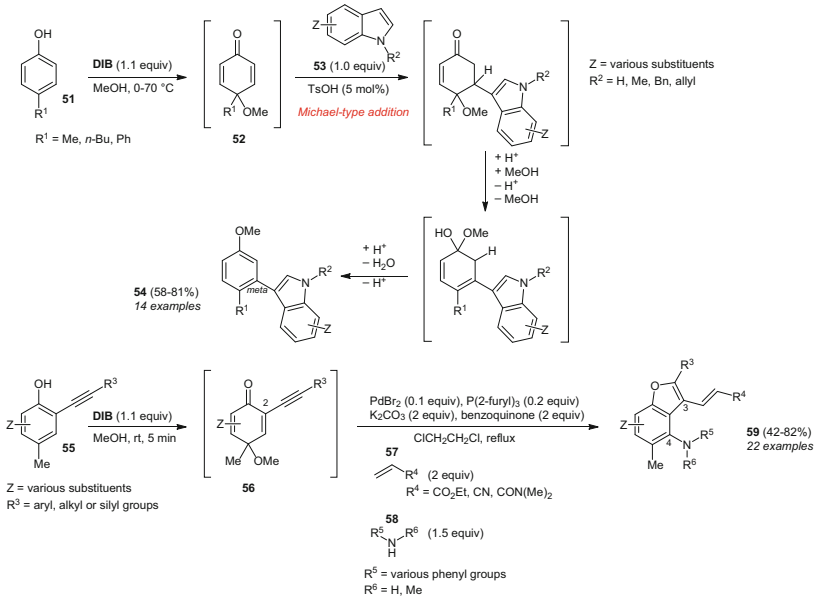

Fig. 17 Fan's syntheses of *meta*-indolylphenol methyl ethers and 3,4-difunctionalized benzofurans

(Fig. 17) [57]. The use of this outstanding **DIB**-mediated phenol dearomatization/Pd-catalyzed domino reaction sequence was then also further extended to build polycyclic benzofurans [57]. Fan had also earlier described a related method using the same initial **DIB**-mediated phenol dearomatization tactic in the presence of indole nucleophiles and an Ag(I) catalyst to prepare 4-indolylbenzofurans from 4-alkyl-2-alkynylphenols [58].

The dearomatization of 4-substituted phenols into *para*-quinols can also be implemented to desymmetrize achiral cyclohexa-2,5-dienone cores, as recently reviewed by Harned and Canesi [59, 60]. For example, You's group has reported

several versions of the application of such a desymmetrization strategy using chiral catalysts. The **45′**-type *para*-quinol ethers **60**, which were generated from phenols of type **51** using **DIB** in the presence of glycol in CH_2Cl_2, could then be annulated via an intramolecular C–O bond-forming Michael addition, whose induction and enantioselectivity were controlled by chiral binaphthyl phosphoric acids such as **61** (Fig. 18). The 1,4-dioxane products **62** were obtained in good to high yields with enantiomeric excesses up to 95% [61]. Later on, Ye's group developed a similar oxa-Michael addition-based method using chiral diamine catalysts to desymmetrize efficiently various *para*-quinol ethers of type **60** and related *para*-quinone monoketals [62], which were made according to You's **DIB**-mediated protocol. Another of You's desymmetrizing methods made use of phenolic biaryls **51a** tethered to a bisphenylsulfonyl methylene motif [63]. A **DIB**-mediated methoxylative dearomatization afforded the **45′**-type *para*-quinol ethers **63**, which were then desymmetrized through a C–C bond-forming Michael addition by the action of the cinchonine-derived urea catalyst **64a** to furnish the diterpenoid-related tricyclic cyclohexenones **65** in high yields and enantiomeric excesses (Fig. 18) [63]. The thiourea analogue **64b** was used to catalyze aza-Michael reaction variants such as that involving the **45**-type *para*-quinol **66**, which was generated by a **DIB**-mediated hydroxylative dearomatization of the aminophenol

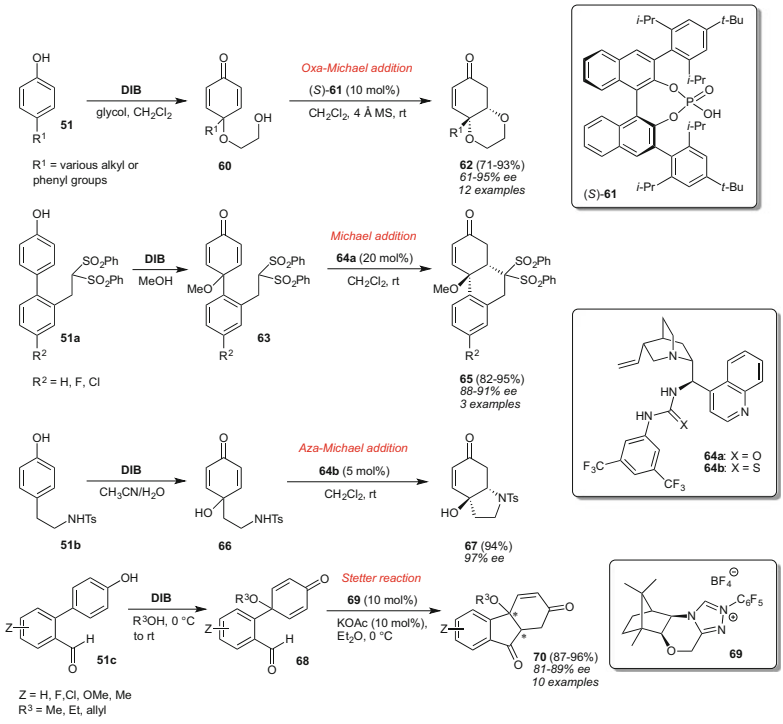

Fig. 18 Examples of You's methods for desymmetrization of achiral *para*-quinols

51b in aqueous acetonitrile [64]. The resulting pyrrolidine derivative **67** was obtained in 94% yield with an *ee* of 97% (Fig. 18). Adaptation and further optimization of this phenol dearomatization/thiourea-catalyzed asymmetric aza-Michael reaction sequence also led to the preparation of morpholine derivatives in high yields and enantiomeric excesses [64]. Furthermore, inspired by Rovis' earlier work [65], You's group more recently also reported a desymmetrization of *para*-quinol ethers based on an intramolecular version of the Stetter reaction [66]. This N-heterocyclic carbene-catalyzed umpolung transform was used to construct tricyclic carbocycles **70** in high yields and enantioselectivities from **45′**-type *para*-quinol ethers **68** using the D-camphor-derived triazolium salt **69** as a chiral catalyst (Fig. 18) [66].

Harned and co-workers also relied on **DIB**-mediated hydroxylative phenol dearomatization in aqueous acetonitrile to prepare *para*-quinols of type **45**, which were then acylated with malonic acid monoesters such as **72** [67]. The resulting cyclohexa-2,5-dienones **73** thus tethered to an activated methylene group were treated with Cs_2CO_3 in acetonitrile to induce intramolecular Michael addition reactions. The bicyclic lactone products **74** were obtained with very good to complete regioselectivity in good to high yields as single *cis*-fused diastereomers (Fig. 19). The *para*-quinol esters of type **73** that bore a bromine atom at their position 2 underwent a subsequent cyclopropanation (not shown) via intramolecular nucleophilic substitution between the malonate-derived methanetriyl center and the brominated center [67]. Attempts to desymmetrize the *para*-quinol esters **73** using a *Cinchona* alkaloid-based ammonium salt as phase-transfer catalyst during the Michael (and cyclopropanation) reactions gave rise to the expected products with only moderate but promising enantioselectivities [67].

Later on, Harned's group explored another desymmetrization method based on a Pd-catalyzed acetoxylation-cyclization of **45′**-type alkyne-tethered cyclohexa-2,5-dienones **75**, which were generated by a **DIB**- or **BTI**-mediated dearomatization of *para*-substituted phenols **51** in the presence of propargyl alcohol or but-2-yn-1-ol as solvent (Fig. 20). The control of stereoselectivity of the Pd-catalyzed cyclization event was brought by the use of the pinene-derived bipyridine ligand **76**, but enantiomeric excesses of only up to 62% could be obtained for the formation of the bicycles **77** [68]. An extension of this exploratory work was later reported by Sasai and co-workers, who used their SPRIX ligand **78** under oxidative conditions to generate α-acetoxylated variants of **77** (i.e., **79**) with *ee* values up to 82% (Fig. 20) [69].

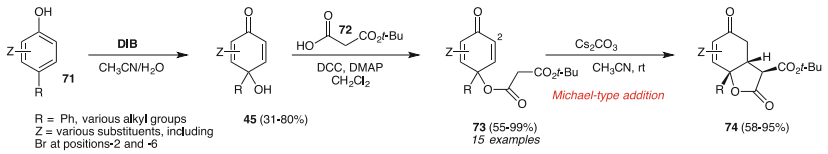

Fig. 19 Harned's synthesis of bicyclic lactonic cyclohexenones

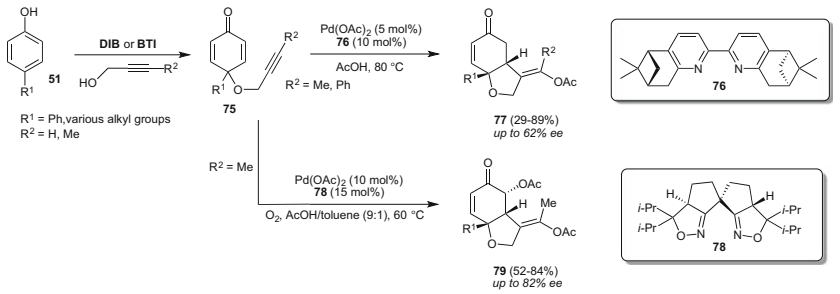

Fig. 20 Harned's and Sasai's Pd-catalyzed asymmetric cyclizations of alkyne-tethered cyclohexa-2,5-dienones

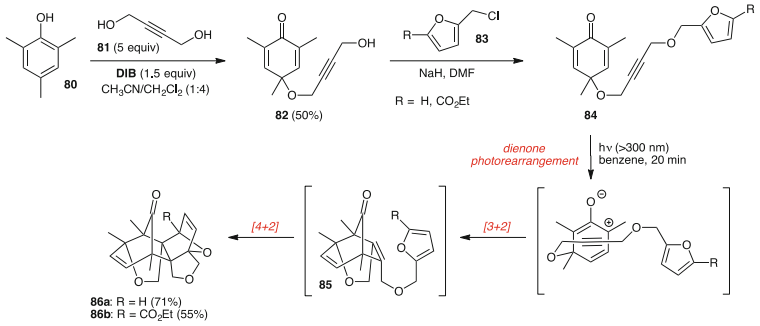

Fig. 21 Porco–Stephenson's tandem dienone photorearrangement-[3+2]/[4+2] cycloadditions

In their remarkable work on the use of tandem dienone photorearrangement-cycloaddition of alkenyl and alkynyl ether-tethered cyclohexa-2,5-dienones for the rapid construction of complex polycyclic bridged molecular frameworks, Porco, Stephenson, and co-workers also rely heavily on **DIB**-mediated phenol dearomatization to produce the requisite *para*-quinol and *para*-quinol ether substrates [70]. The most outstanding example of this work is the use of *para*-quinol alkynol ethers tethered with furfuryl ethers in [3+2]/[4+2] cycloadditions. The **DIB**-mediated dearomatization of 2,4,6-trimethylphenol **80** with an excess of 1,4-butynediol **81** furnished the **45′**-type *para*-quinol ether **82**, which was then etherified with the furfuryl chlorides **83**. The resulting *para*-quinol alkynyl furfuryl bisethers **84** were then irradiated to induce the dienone photorearrangement-[3+2] cycloaddition with the alkynyl unit into compounds **85**, which then underwent a [4+2] cycloaddition involving their furanyl unit as diene to afford the polycyclic bridged compounds **86a/b** in good isolated yields as single diastereomers (Fig. 21) [70].

It is clear that the recent literature on the chemistry of cyclohexa-2,4-dienones of the *ortho*-quinol type **46** is much less abundant than that of *para*-quinols of type **45** (Fig. 16). This can perhaps be mainly attributed to added technical difficulties in

handling *ortho*-quinols, which are less stable than their *para*-quinol counterparts and more susceptible to undergo inter alia transpositions and cycloaddition processes. Nevertheless, *ortho*-quinols have one particular advantage over *para*-quinols; they are systematically chiral by virtue of their stereogenic C6 center. Efforts have been made to develop chiral iodane reagents capable of transferring an oxygen atom at the 2-alkylated position of arenols. In this context, λ^5-iodanes of the iodyl type, such as 2-iodylbenzoic acid (**IBX**) or its stabilized (non-explosive) version (**SIBX**) [37], have clearly demonstrated their faculty to respond to the regioselectivity criterion [31, 32, 71, 72]. In 2009, we developed an asymmetric hydroxylative phenol dearomatization (HPD) reaction using the chiral iodobinaphthyl (*R*)-**88**, which was oxidized in situ with *m*-CPBA to convert 2-methylnaphthol **87** into the **46**-type naphthoid *ortho*-quinol (*S*)-**89** with 50% *ee* (Fig. 22) [73]. Unfortunately, the iodobinaphthyl **88** could not be oxidized ex situ into any iodane species using *m*-CPBA, and the nature of the reacting iodane (i.e., λ^3 or λ^5) at play in this transformation could not be firmly established [73].

At the same time, Birman reported on a chiral oxazoline-containing aryl-λ^5-iodane reagent (*S*)-**91**, which was generated from the corresponding iodoarene using dimethyldioxirane (DMDO) in acetone [74]. It was then successfully used to convert a short series of 2-methylphenols **90a–c** in 1,2-dimethoxyethane (DME) into **46**-type *ortho*-quinols **92a–c**, which spontaneously cyclodimerized at room temperature to furnish the expected bicyclo[2.2.2]octenones **93a–c** in poor to good yields with *ee* values up to 77% (Fig. 23) [74]. In 2014, we reported on the performances of new chiral C_2-symmetrical binaphthylic and biphenylic bis(λ^3-iodanes) and bis(λ^5-iodanes), generated from their corresponding diiodobiarenes using DMDO in acetone, in asymmetric HPD reactions [75]. The best reagent, the bis(iodyl) compound **94**, used in CH_2Cl_2 at –40°C, furnished **89** (Fig. 22) in 40% yield with 73% *ee*. It is in HPD/[4+2] cascade reactions of 2-alkylphenols **90b–f** that **94** best performed, affording bicyclo[2.2.2]octenones **93b–f**, such as natural (+)-bis(carvacrol), its enantiomer, and its regioisomer (+)-bis(thymol) in 68–77% yields and *ee* values up to 94% (Fig. 23) [75].

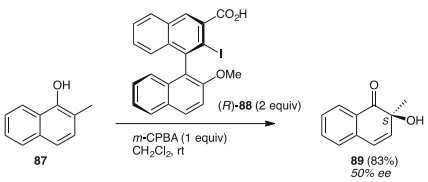

Fig. 22 Quideau's asymmetric hydroxylative naphthol dearomatization via an in situ *m*-CPBA-mediated generation of a chiral binaphthyl iodane

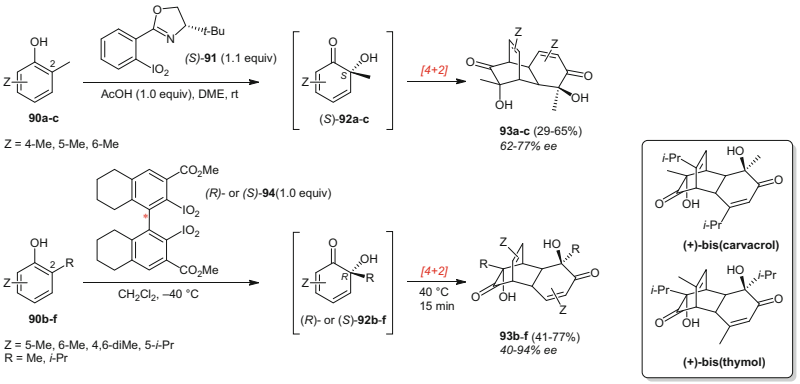

Fig. 23 Birman's and Quideau's asymmetric hydroxylative phenol dearomatization/Diels–Alder cyclodimerization cascade reaction

3 Organoiodane-Mediated Dearomatization of Phenols into Spirocycles

The iodane-mediated oxidative dearomatization of phenols tethered at their position 2 or 4 to motifs bearing nucleophilic or pronucleophilic centers constitutes a convenient access to spirocyclic cyclohexadienones, including spirocyclic variants of quinols. Oxo-, aza-, and carbo-spirocyclization have often been implemented by this tactic for a long time, but new applications and further extensions of this chemistry continue to be reported. **DIB** and **BTI** are among the most frequently used iodane reagents to mediate these spirocyclizations, but other λ^3-iodanes have also given satisfaction. Kita and co-workers have notably advocated the use of the **μ-oxoBTI** reagent (see Fig. 4) over that of **BTI** or **DIB** to produce spirocyclic cyclohexadienones [76]. For example, the phenolic biarylic carboxylic acid **95** can be spirocyclized into **96** using **μ-oxoBTI** in acetonitrile in 99% yield, whereas the use of **BTI** afforded this spirolactonic *para*-quinol ester in a much lower yield under the same reaction conditions (Fig. 24). The **μ-oxoBTI** reagent was also used in fluorinated alcoholic solvents [i.e., HFIP or 2,2,2-trifluoroethanol (TFE)] to induce rapidly high-yielding aza- and carbo-spirocyclizations of phenols **97** and **99** into spirocycles **98** and **100**, respectively (Fig. 24) [76].

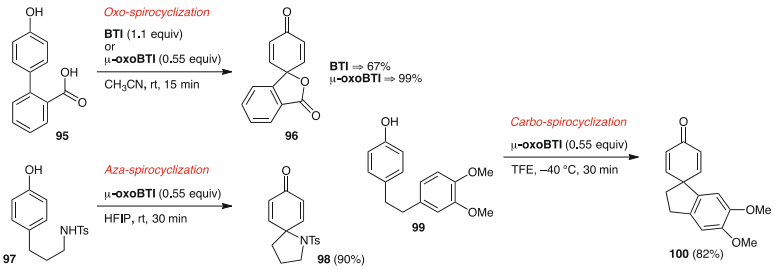

Fig. 24 Kita's μ-oxoBTI-mediated oxo-, aza-, and carbo-spirocyclization

3.1 Oxo-Spirocyclization into Spirocyclic Quinol Variants

In an elegant adaptation of their λ^3-iodane-mediated oxidative dearomatization/transition metal-catalyzed oxocyclization of 2-alkynylphenols in tandem with conjugate addition of amines (see Fig. 17) for the synthesis of furoquinolinones [77], Fan and co-workers this time relied on iodosylbenzene (**PhIO**), in place of **DIB**, in TFE to convert the phenolic propanoic acid alkynyl derivatives **101** quickly into the spirolactonic *para*-quinol esters **102**. These were immediately treated with a Pd-based catalyst in the presence of aromatic amines in refluxing 1,2-dichloroethane to induce a sequence of events encompassing the oxocyclization into the benzofuran moiety, conjugate addition of the amines, re-aromatizing lactone opening of the resulting intermediates **103**, and lactamization into the final 3,4-dihydrofuro-[2,3-*h*]quinolin-2(1*H*)-ones **104** in moderate to high yields (Fig. 25) [77].

One of the most significant advances in oxo-spirocyclization via phenol dearomatization has been Kita's asymmetric synthesis of spirolactonic *ortho*-quinol esters **108** from naphthols of type **105** using catalytic amounts of the spirobiindane-based chiral bis(iodoarene) **106a** in the presence of *m*-CPBA as oxidant and AcOH for in situ generation of the corresponding λ^3-iodane catalyst **107a** [78]. Under these conditions, naphthols **105a/b** were converted into the spirolactones **108a/b** in good yields with good enantiomeric excesses (Fig. 26). Using 0.5 equiv. of the bis-λ^3-iodane reagent **107a** in $CHCl_3$ at –50°C, naphthols of type **105** were similarly spirolactonized with *ee* values up to 86% [78]. Kita's group more recently reported on new developments of this oxo-spirocyclizing naphthol dearomatization and found that *ortho*-substituted spirobiindanes gave superior results in terms of enantioselectivity under catalytic conditions. The best results were obtained using the spirobiindane **106b** in $CHCl_3$ at 0°C; the spirolactones **108a/b** were obtained in much higher yields with 87% and 82% *ee* (Fig. 26) [79].

Ishihara and Uyanik also worked on this enantioselective oxo-spirocyclization using different and more conformationally flexible chiral λ^3-iodane catalysts generated in situ from lactate-based iodoarenes of type **109** and *m*-CPBA [80]. Enantiomeric excesses up to 92% could be obtained under Kita's conditions for the conversion of **105a** into **108a** using the iodoarene **109** (Fig. 26). Ishihara and

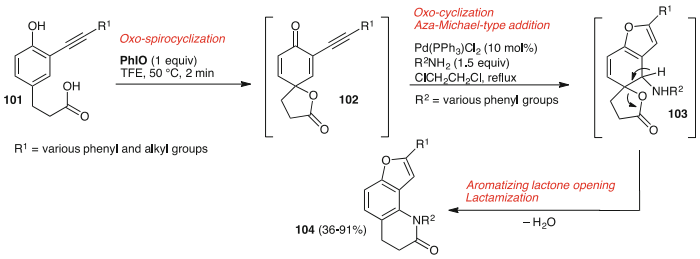

Fig. 25 Fan's synthesis of furoquinolinone derivatives

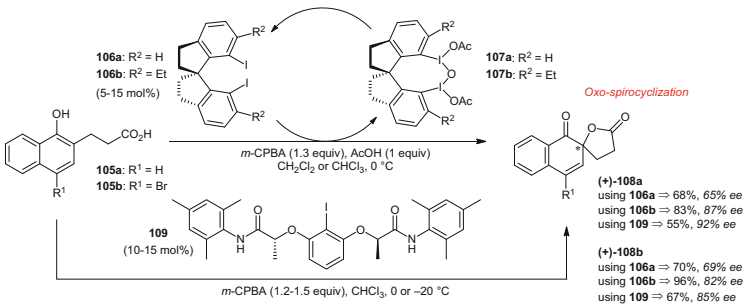

Fig. 26 Kita's and Ishihara's catalytic asymmetric dearomative spirolactonization of naphthols

co-workers went on to perform the same kind of oxo-spirocyclization on simple phenols, such as **110**, using other variants of their designed flexible chiral C_2-symmetric iodoarene [81]. The 2-aminoalcohol-based iodoarene **111** was found to be the best pre-iodane catalyst for the dearomative spirolactonization of phenol **110** into **112** (Fig. 27). The presence of a simple alcohol such as MeOH or EtOH, or, in some other cases, HFIP, was found crucial to improve both chemical yields and levels of enantioselectivity, and the best result was obtained using 25 equiv. of MeOH in CH_2Cl_2 (Fig. 27). The authors proposed that MeOH can be mounted, through ligand exchange, onto the λ^3-iodanyl center of the reaction intermediate generated between the *m*-CPBA-oxidized iodoarene **111** and the starting phenol, and that the moderate nucleofugality of MeOH, used in excess, would favor the formation of the methoxylated intermediate, more prone to follow an associative (and enantioselective) reaction pathway instead of a dissociative (racemic) alternative pathway (see Fig. 2) [81].

Another different C_2-symmetric iodoarene system, based on an all-carbon and quite rigid *anti*-dimethanoanthracene core, was recently described and tested by Ibrahim for catalytic asymmetric Kita's spirolactonization [82]. For example, the *para*-methylated variant of the iododimethanoanthracene **113** in a 2:1 $CHCl_3$/CH_3NO_2 solvent mixture at –20°C converted the 4-brominated variant of naphthol **105** (i.e., **105b**) into the corresponding spirolactone **106b** in 63% yield with 67% *ee* (best *ee*) (Fig. 28). The use of the *para*-methoxylated variant of **113** under the same

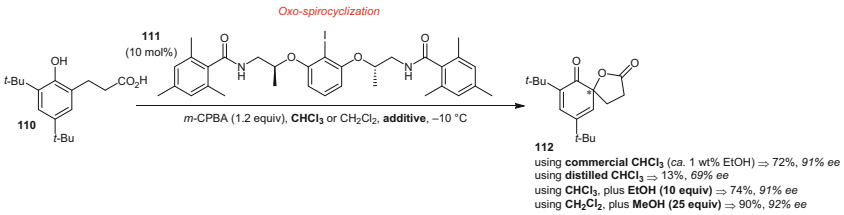

Fig. 27 Ishihara's catalytic asymmetric dearomative spirolactonization of phenols

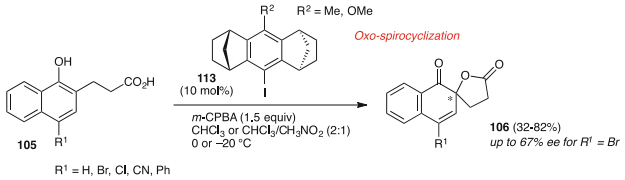

Fig. 28 Ibrahim's catalytic asymmetric dearomative spirolactonization of naphthols

conditions enabled the chemical yield of this conversion to increase to 82% (best yield), but the *ee* dropped to 53% [82].

3.2 Aza-Spirocyclization

One of the long-time frontrunners of the developments of iodane-mediated phenol dearomatization reactions for aza-spirocyclization and applications in the synthesis of alkaloids is Ciufolini, who notably reported in 2010 two related full accounts of this chemistry using phenolic sulfonamides [83, 84]. One of the technical objectives of Cuifolini's group has notably been to replace the use of the fluorinated alcoholic solvents HFIP and TFE, which had been first recognized by Kita to be the solvents of choice for **DIB**-, **BTI**-, or Koser's [hydroxy(tosyloxy)iodo]benzene **HTIB**-mediated transformations [85, 86], by more conventional and less expensive solvents to conduct these oxidative amidation reactions on a large scale. Thus, Liang and Ciufolini found that neat trifluoroacetic acid (TFA) constitutes an appropriate medium for the preparation of aza-spirocycles **115** and **117** from *para*- and, albeit to a lesser extent, *ortho*-phenolic sulfonamides **114** and **116** (Fig. 29) [83]. Ciufolini's group also developed different approaches, based on intramolecular Michael addition and cycloaddition reactions, to desymmetrize aza-spirocyclic cyclohexa-2,5-dienones of type **115** within the framework of their alkaloid synthesis goals [83, 84]. For example, the aza-spirocyclohexa-2,5-dienone methylsulfonamide **115b** was treated with the base LiHMDS at –100°C to furnish, after silylation, a 14:1 mixture of the diastereomeric Michael cycloadducts **118a** and **118b** in 78% yield. The major product was then further transformed to complete a synthesis of the lepadiformine analogue **119** (Fig. 29) [83].

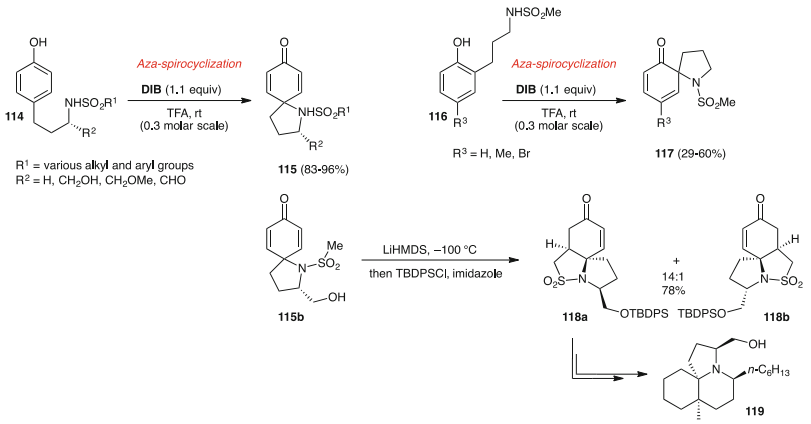

Fig. 29 Ciufolini's synthesis of aza-spirocycles from *para*- and *ortho*-phenolic sulfonamides and desymmetrization en route to the synthesis of a lepadiformine analogue

3.3 Carbo-Spirocyclization

Recent developments in iodane-mediated carbo-spirocyclizing phenol dearomatization include methodologies that also led to aza-spirocycles. For example, Zhang and co-workers reported the preparation of β-lactam spirocyclohexa-2,5-dienones **121** from phenolic amides of type **120** bearing an active methylene center, using **DIB** in the presence of copper(II) sulfate and DMAP as a base (Fig. 30) [87]. Moreover, the phenolic benzyl amide homologue **122** gave rise to the formation of the carbo-spirocyclic pyrrolidone derivative **123** (Fig. 30). The use of the copper salt was found compulsory to mediate these C–C bond-forming reactions with active methylene species [87].

Nachtsheim and co-workers utilized phenolic benzamido-acrylates of type **124** to construct carbo-spirocycles **125** [88]. They relied on the use of **BTI** in propionitrile at 90°C to activate the phenols toward the anticipated dearomative spirocyclization, hoping that the carbon-based enamide nucleophilic unit would be the major actor of this intramolecular event. However, the yields of the desired products hardly passed beyond 50%, notably because an unexpected competitive oxo-spirocyclization took place to furnish the δ-spirolactone **126** (Fig. 31). The yield of **126** could even be optimized up to 70% by performing the reaction with the isopropyl ester **124c** (i.e., R=*i*-Pr) in TFE at 0°C in the presence of TFA (2 equiv.). These conditions completely shut down the formation of the corresponding spirolactam **125** [88]. The use of other λ^3-iodane reagents, such as **DIB** and Koser's **HTIB** reagent, was also attempted, but **BTI** turned out to be by far the best reagent for this oxo-spirocyclization.

In a related study, Yu and co-workers had also selected the use of **BTI** over that of **DIB** to convert 4-hydroxyphenyl *N*-phenylbenzamides such as **127a** into oxindolic spirocyclohexa-2,5-dienones such as **128a** (Fig. 32) [89]. These authors

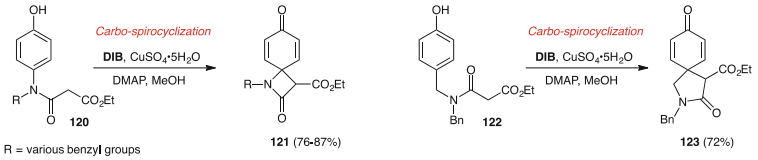

Fig. 30 Zhang's synthesis of β-lactamic and pyrrolidonic spirocyclohexa-2,5-dienones

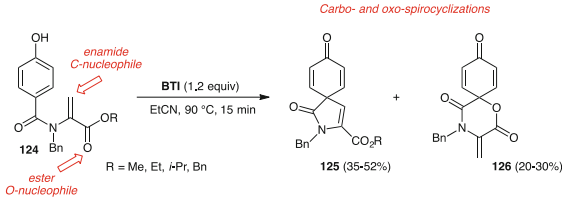

Fig. 31 Nachtsheim's dearomative carbo- and oxo-spirocyclizations from phenolic benzamido-acrylates

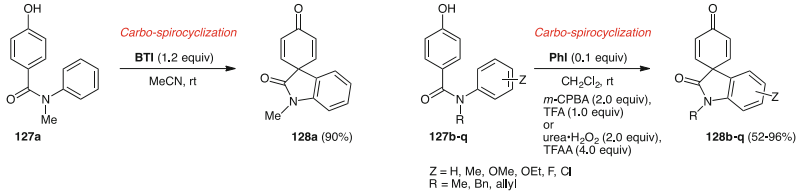

Fig. 32 Yu's synthesis of cyclohexa-2,5-dienonyl spirooxindoles

then relied on the use of 0.1 equiv. of iodobenzene in the presence of a co-oxidant (i.e., *m*-CPBA or urea•H_2O_2) and TFA or its anhydride (TFAA) to mediate the same transformation in a catalytic manner in good to excellent yields (Fig. 32) [89].

Oxindolic spirocyclohexa-2,4-dienones can also be prepared from 2-hydroxyphenyl *N*-phenylbenzamides, as reported by Du, Zhao and co-workers [90]. For example, the phenolic *N*-phenylbenzamide **129** was converted into the spirooxindole **130** in 74% isolated yield using **BTI** in CH_2Cl_2 at 0°C (Fig. 33). A chiral iodane-catalyzed variant of this transformation was recently reported by Gong and co-workers, who utilized Ishihara's chiral iodoarene **109** (Fig. 26) in the presence of *m*-CPBA in CH_3NO_2 for converting a series of 1-hydroxy-*N*-(2-naphthalenyl)-2-naphthamides **131** into the spirooxindoles **132** in relatively good yields and with high to excellent levels of enantioselectivity (Fig. 33) [91]. The addition of TFE and water to the reaction mixture was crucial to reach these levels of chemical yields and enantiomeric excesses. As did Ishihara and Uyanik [81], Gong hypothesized that both TFE and/or water can be mounted onto the λ^3-iodanyl center through ligand exchanges and that their moderate

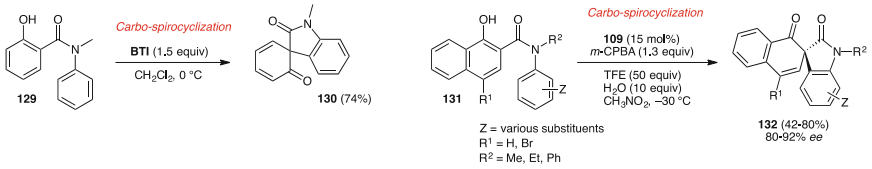

Fig. 33 Du–Zhao's synthesis of cyclohexa-2,4-dienonyl spirooxindoles and Gong's catalytic asymmetric variant

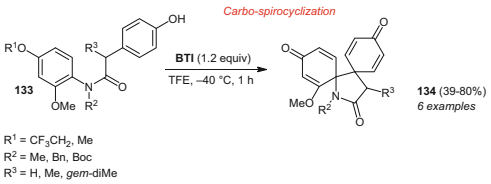

Fig. 34 Chabaud–Guillou's synthesis of lactamic 1,2-dispirodienones

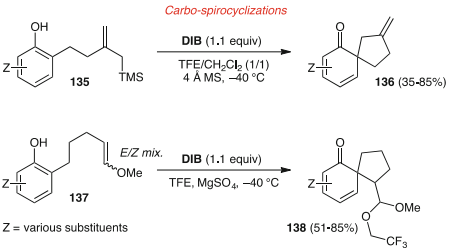

Fig. 35 Wang's *ortho*-dearomatizations of phenols into spiro[4,5]decanyl ring systems

nucleofugality would then favor an associative reaction pathway over the cationic dissociative alternative (see Fig. 2), which would lead to racemic products [91].

Another interesting case of carbo-spirocyclization of phenolic substrates is that reported by Chabaud and Guillou on the conversion of *para*-hydroxy acetanilides of type **133** into 1,2-aza/carbo-dispirodienones **134**, using **BTI** in TFE at –40°C (Fig. 34) [92]. This is the first example of a synthesis of 1,2-dispirodienones via a λ^3-iodane-mediated phenol dearomatization.

An access to all-carbon spirobicycles from phenols *ortho*-tethered to allylsilane or vinyl ether units has recently been reported by Wang and co-workers [93]. Using **DIB** in a TFE/CH_2Cl_2 solvent mixture at –40°C, the phenolic allylsilanes of type **135** were converted into spirobicycles **136** in moderate to high yields (Fig. 35). Intermolecular versions of such a Hosomi–Sakurai-type reaction between oxidatively activated arenols and allylsilanes had previously been described for the preparation of 6-allylcyclohexa-2,4-dienone and 4-allylcyclohexa-2,5-dienone derivatives [94, 95]. Similarly, under slightly modified reaction conditions, the phenolic methyl vinyl ethers of type **137** afforded the spirobicycles **138**, whose methyloxonium reaction intermediates were trapped by TFE to forge their acetal moiety (Fig. 35) [93].

Canesi's group had also earlier described access to all-carbon spirobicycles from phenols *para*-tethered to an allylic alcohol or ether unit, or an acetylenic variant [96]. These transformations, which were depicted as following in a dissociative pathway (see Fig. 2) and thus involving passage through phenoxenium ions such as **141a–c** (Fig. 36), can be regarded as oxidative Prins–pinacol tandem rearrangement sequences. Using **DIB** in a HFIP/CH_2Cl_2 solvent mixture at –20°C, phenols of type **139a/b** were thus oxidatively activated to allow their alkenyl or alkynyl silyl ether tethers to participate quickly (2 min) in carbo-spirocyclization and ring contraction events for affording the functionalized spiro[4.5]decanes **143a/b** in moderate to good yields. This elegant methodology was then applied to the phenolic allylic cycloalkyl ether **139c** to give the cyclohexa-2,5-dienone intermediate **144**, which was quickly peroxidized in situ to furnish **145** en route to the (–)-platensimycin core **146** [96, 97] (Fig. 36).

In the same vein, Canesi's group also reported a method to prepare spiro[5.5] undecanyl ring systems **150** from phenols **147** *para*-tethered to a free alkyne moiety [98]. The phenoxenium ions **148** undergo carbo-spirocyclization into the vinyl cations **149**, which are then trapped by solvent-derived nucleophiles to furnish the spirobicycles **150** in good yields (Fig. 37) [98].

The last example that deserves to be highlighted in this section on spirocyclization is the **DIB**-induced domino reaction described by Fujioka, Kita, and co-workers [99] (Fig. 38), who utilized phenolic cyclobutanols of type **151** in aqueous HFIP with the aim of producing spiroketonic cyclohexadienones of type **153** through a 1,2-cycloalkyl shift analogous to the **DIB**-mediated Wagner–

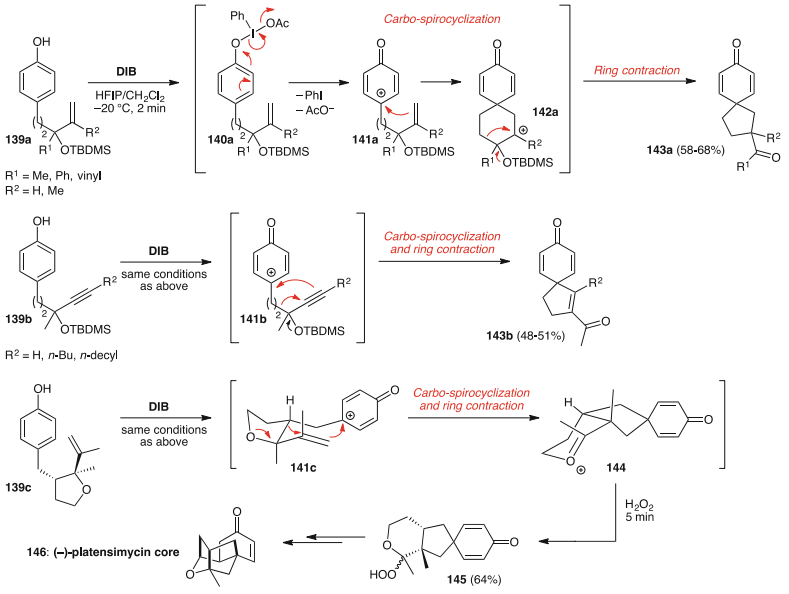

Fig. 36 Canesi's *para*-dearomatizations of phenols into spiro[4.5]decanyl ring systems and formal synthesis of (–)-platensimycin

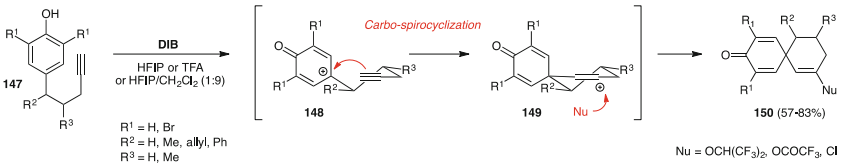

Fig. 37 Canesi's *para*-dearomatization of phenols into spiro[5.5]undecanyl ring systems

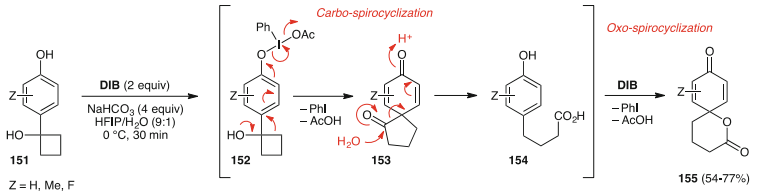

Fig. 38 Fujioka–Kita's synthesis of lactonic spirocyclohexa-2,5-dienones from 1-(4-hydroxyaryl) cyclobutanols

Meerwein transpositions performed by Canesi and co-workers under quasi-identical reaction conditions [100]. However, the presence of water caused the opening of the cyclopentanone unit of **153** with rearomatization of the phenolic moiety. The resulting phenolic carboxylic acids **154** were then oxo-spirocyclized with a second equivalent of **DIB** to furnish the lactonic spirocyclohexa-2,5-dienones **155** [99] (Fig. 38).

4 Organoiodane-Mediated Phenol Dearomatization in Natural Product Synthesis

Organoiodane-mediated phenol dearomatization processes are today regularly used in the synthesis of complex natural products. Of course, chemists who developed these methodologies are first in line to apply them to the total or formal chemical syntheses of natural products or, at least, to the construction of their main cores. The above highlights of Taylor's synthesis of (–)-harveynone [40], Kita's synthesis of the glivocarcin core **15** [41], Liao's synthesis of terpenoid-related tricyclic decahydrophenanthrenes [48], Herzon and Kats-Kagan's synthesis of the bis (tropolone) core of gukulenins [53], Ciufolini's synthesis of the lepadiformine analogue **119** [83], Canesi's synthesis of the platensimycin core **146** [96, 97], and our own synthesis of (+)-bis(carvacrol) [75] (see Figs. 7, 8, 12, 15, 23, 29 and 36) have already illustrated the utility of organoiodane reagents in promoting phenol dearomatization as a valuable tactic in organic synthesis. Several additional applications have recently been reported, not only by researchers well versed in

hypervalent iodine chemistry, but also by an increasing number of organic chemists heavily involved in natural product total synthesis research programs.

4.1 Synthesis of Alkaloids

In his approach toward the synthesis of the alkaloid himandrine [101, 102], Ciufolini applied his oxidative phenol (spiro)amidation reaction, using **DIB** in TFA, to the chiral dienyl sulfonamide **156** to generate the aza-spirocycle **157**, which was then heated in added toluene (reflux) to furnish the *endo*-Diels–Alder cycloadduct **158** as the major regioisomer. An epimerization occurred in situ to deliver the himandrine-like *trans*-decaline system **159** in a combined yield of 32%, together with the epimerized minor Diels–Alder regioisomer [101] (Fig. 39).

In 2015, Ciufolini's group reported yet another application of the oxidative amidation of a phenol in the context of their total synthesis of members of the *Erythrina* alkaloid family [103]. The chiral phenolic oxazoline **160** was converted, in a remarkably good yield using **BTI** in HFIP, into the spiro-piperidinic cyclohexa-2,5-dienone **161**, which was desymmetrized during the subsequent intramolecular diastereoselective acid-catalyzed oxa-Michael-type addition of the amino-tethered alcohol, followed by a classical hydrogenation, to afford the morpholinic intermediate **162** in high yield. This compound was then elaborated in 10–12 steps to (+)-3-demethoxy-erythratidinone and (+)-erysotramidine [103] (Fig. 40). In 2014, a racemic synthesis of erysotramidine was

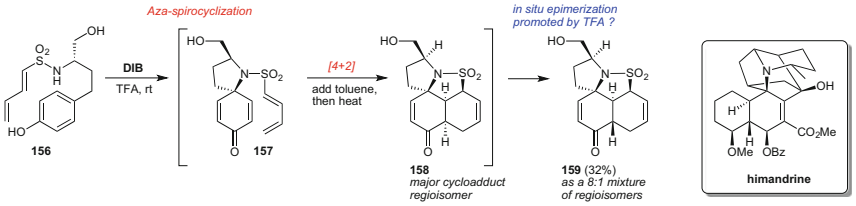

Fig. 39 Ciufolini's approach to the himandrine core

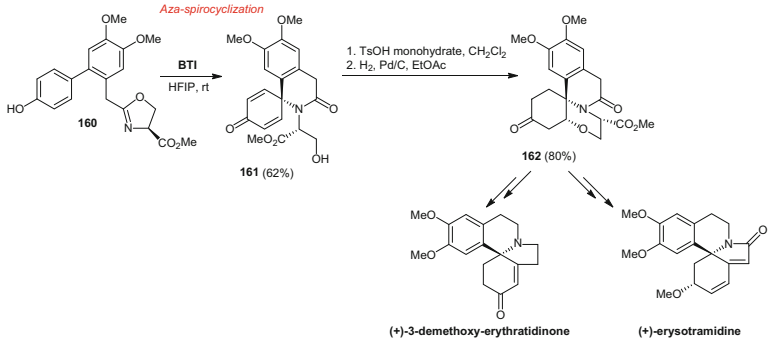

Fig. 40 Ciufolini's oxidative phenol amidation in the total synthesis of *Erythrina* alkaloids

also described by Canesi and co-workers, who relied on **DIB**- and **BTI**-mediated methoxylative phenol dearomatization processes to construct this alkaloid [104].

The same year, Canesi's group reported an asymmetric synthesis of the levorotatory enantiomer of the *Amaryllidaceae* alkaloid fortucine [105]. The L-tyrosine-derived phenol **163** was treated with **DIB** in HFIP to induce an oxo-spirocyclization into the *para*-quinolic lactone **164**, which was treated with methanolic KOH to mediate both the opening of the lactone unit and an aza-Michael addition of the amide onto the cyclohexa-2,5-dienone moiety in high yield and stereoselectivity. The resulting aza-bicyclic intermediate **165** was then converted in 11 steps into (–)-fortucine (Fig. 41). This first asymmetric synthesis of fortucine led to the correction of the absolute configuration of the natural (+)-fortucine [105].

Another recent and outstanding achievement of Canesi's group is their version of a synthesis of *rac*-isostrychnine in only nine steps starting from the readily available phenol **166**, which was first converted into the phenolic amide **167** (Fig. 42) [106]. This compound was subjected to a **DIB**-mediated methoxylative phenol dearomatization to afford the *para*-quinol ether **168**, the amide function of which was then engaged in an intramolecular aza-Michael addition onto its cyclohexa-2,5-dienone moiety to forge the fused bicyclic system **169** en route to isostrychnine, which was obtained after six additional steps (Fig. 42) [106]. Canesi's group also reported several elegant applications of the phenol dearomatization-induced processes of their own invention in natural product synthesis, such as in

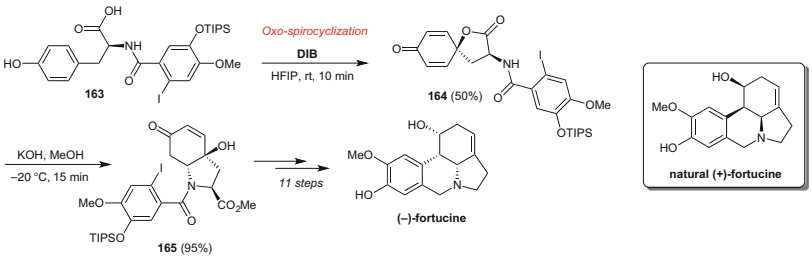

Fig. 41 Canesi's asymmetric synthesis of (–)-fortucine

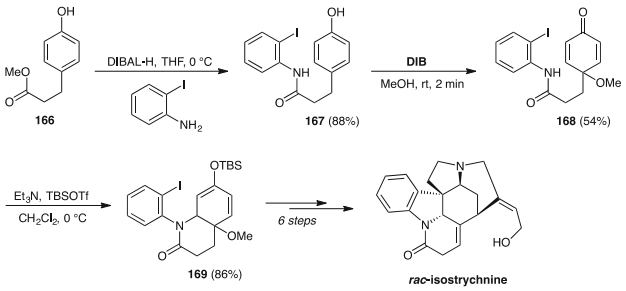

Fig. 42 Canesi's synthesis of *rac*-isostrychnine

their formal synthesis of (–)-platensimycin (Fig. 36) [96, 97]. They further took advantage of λ^3-iodane-induced activation of phenols *para*-tethered to unsaturated alcoholic units to set up various pinacol-type 1,2-alkyl and 1,3-allyl shifts, as well as 1,3-alkyne shifts [100, 107]. For example, treating the phenolic alkyne **170** with **DIB** in HFIP promotes a 1,3-alkyne shift to produce, via the phenoxenium-type half-chair transition state **171**, the allenyl cyclohexa-2,5-dienone **172** in good yield (Fig. 43). This compound was then elaborated in four steps to the functionalized tricyclic core **173** of *Aspidosperma* alkaloids, and seven additional steps led to the natural hexacyclic acetylaspidoalbidine (Fig. 43) [107]. Furthermore, Canesi's group developed an interesting oxidative *ipso*-rearrangement of phenolic alkyldiarylsilyl ethers [108], which they exploited to transfer one aryl group from the silicon atom to the phenolic carbon center bearing the silyl ether side-chain to accomplish a total synthesis of the alkaloid sceletenone. The phenolic *tert*-butyldi (4-methoxyphenyl)silyl ether **174** was quickly treated with **DIB** in HFIP to promote the transfer of one 4-methoxyphenyl group to the oxidatively activated phenolic *para*-position, with concomitant attack of some HFIP onto the silicon atom (Fig. 44). The resulting cyclohexa-2,5-dienone **176** was then converted in five and six steps into racemic *O*-methylsceletenone and sceletenone [108].

In 2013, Fan's group reported a formal synthesis of *rac*-morphine [109], for which the phenolic alkyl aryl ether **177** served as a precursor of an oxidative dearomative *ortho-para* phenolic coupling reaction which was promoted by **DIB** in HFIP to afford the *carbo*-spirocyclic cyclohexa-2,5-dienone **178** (Fig. 45). This

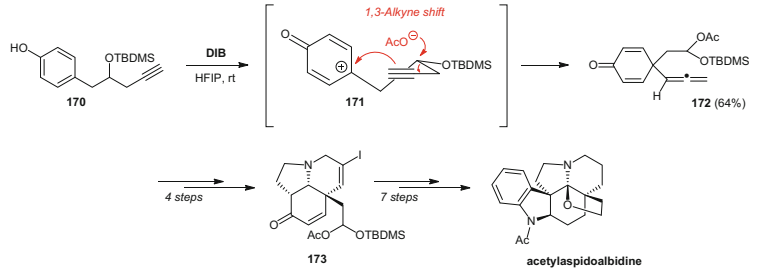

Fig. 43 Canesi's synthesis of acetylaspidoalbidine via an oxidative phenolic 1,3-alkyne shift

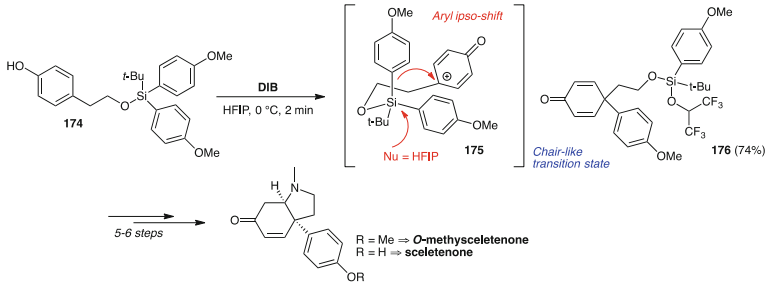

Fig. 44 Canesi's synthesis of sceletenone via an oxidative phenolic aryl *ipso*-shift

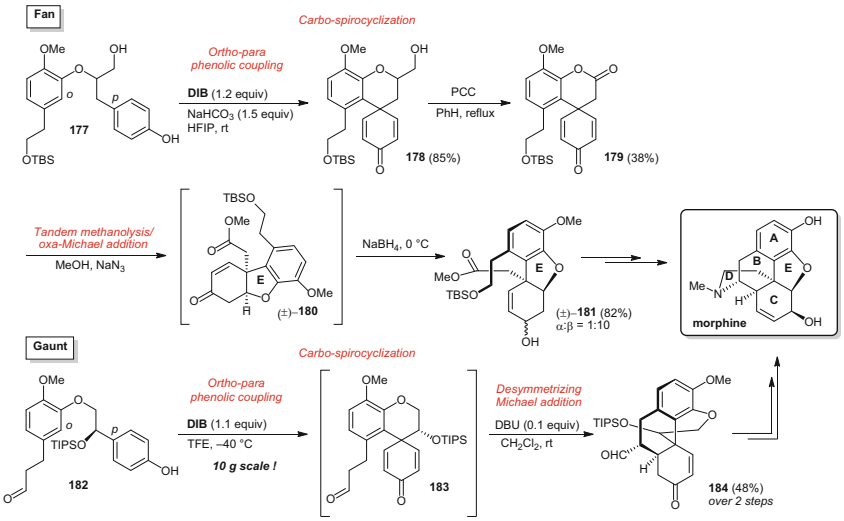

Fig. 45 Fan's racemic formal and Gaunt's enantioselective formal synthesis of morphine

compound was transformed into the lactone **179**, which was then subjected to a tandem methanolysis/oxa-Michael addition sequence to construct the morphine five-membered oxo-ring E. The resulting compound **180** was diastereoselectively reduced in the same pot using sodium borohydride to afford the allylic alcohol **181** in a good yield as a 1:10 α/β epimeric mixture (Fig. 45), en route to *rac*-morphine via Hudlicky's advanced precursor [109]. In 2014, Gaunt's group disclosed a gram scale enantioselective formal synthesis of morphine [110], for which a similar *ortho-para* phenolic coupling carbo-spirocyclizing reaction was performed on the phenolic alkyl aryl ether **182** using **DIB** in TFE (Fig. 45). The resulting cyclohexa-2,5-dienone **183** was directly treated with a catalytic amount of DBU to promote a desymmetrizing diastereoselective Michael addition, which afforded **184** as a single diastereomer featuring the ABC ring system and three of four morphine ring junction stereocenters [110]. A total synthesis of *rac*-codeine for which an early phenolic biaryl intermediate was dearomatized into a *para*-quinol methyl ether using **DIB** in methanol had also been reported by Metz and co-workers in 2011 [111].

Another domino application of an oxidative carbo-spirocyclization and an aza-Michael addition was developed by She and co-workers to construct the core skeleton of the *Amaryllidaceae* alkaloids tazettine and 6a-epipretazettine. In 2013, they disclosed their approach that requires the phenolic amide **185** as key precursor of the intended carbo-spirocyclization [112]. Both **DIB** and **BTI** were first used to mediate this oxidative *para-para* phenolic coupling reaction, but the more electrophilic Kita's **μ-oxoBTI** reagent (see Fig. 4) in TFE gave higher yields. The addition of potassium hydroxide in the reaction mixture then promoted the aza-Michael addition to furnish the known tazettinone intermediate **187** in 72% yield as a single diastereomer (Fig. 46) [112].

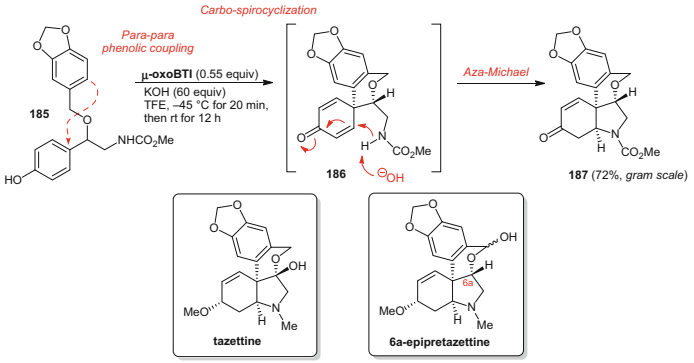

Fig. 46 She's formal syntheses of *rac*-tazettine and *rac*-6a-epipretazettine

Still in 2013, Fan and co-workers also described a remarkable total synthesis of a series of montanine-type *Amaryllidaceae* alkaloids [113]. The homochiral cherylline-type phenolic isoquinoline precursor **188** was treated with **DIB** in methanol in the presence of TFE to generate the *ortho*-quinone dimethyl monoketal **189**, which underwent in situ a fully diastereoselective intramolecular aza-Michael addition to furnish exclusively the pivotal pentacyclic 5,11-methanomorphanthridine **190** in good yield. Diastereoselective ketone reductions then afforded the separable alcohols **191a/b**, which were independently converted in one to two simple steps into *inter alia* (–)-manthidine, (–)-brunsvigine, (–)-coccinine, (–)-montanine, and (–)-pancracine (Fig. 47) [113].

The same year, Rodrigo and Assoud also disclosed the results of their investigations on asymmetric access to allylated phenanthrofurans via intramolecular Diels–Alder processes [114]. The homochiral phenolic ether **192** was treated with **DIB** in MeOH to furnish a mixture of the two *ortho*-quinone monoketals **193a/b** (ca. 2:1), which spontaneously underwent intramolecular [4+2] transformations (Fig. 48). The major diastereomer **193a** led to an unseparable mixture of *endo*-adducts **194a/b** in a combined yield of 64%. This mixture was further processed, involving a thermally induced Cope rearrangement of **194b** into **194a**, to afford the acetoxy phenanthrofuran **195** in 70% yield. This compound was then converted into the levogyre morphine-type indolinocodeine **196** (Fig. 48) [114].

In their outstanding efforts toward the synthesis of the *Lycopodium* alkaloid lycopladine H from 2011 to 2015, Weinreb's group started by constructing the bicyclo[2.2.2]octanone core via a **DIB**-mediated methoxylative dearomatization of the 2-methoxyphenol **197** [115]. The resulting *ortho*-quinone monoketal (or MOB) **198** could thus be generated in high yield and was sufficiently stable to be isolated, thanks to the presence of the bromine atom at position 4, which efficiently blocked the cyclodimerization of the species. However, Weinreb decided to treat **198** in situ with nitroethylene to afford the [4+2] cycloadduct **199** in a quasi quantitative yield as a single regio- and stereoisomer [115, 116]. This nitro compound was then subjected to a Henry reaction with paraformaldehyde in the presence of

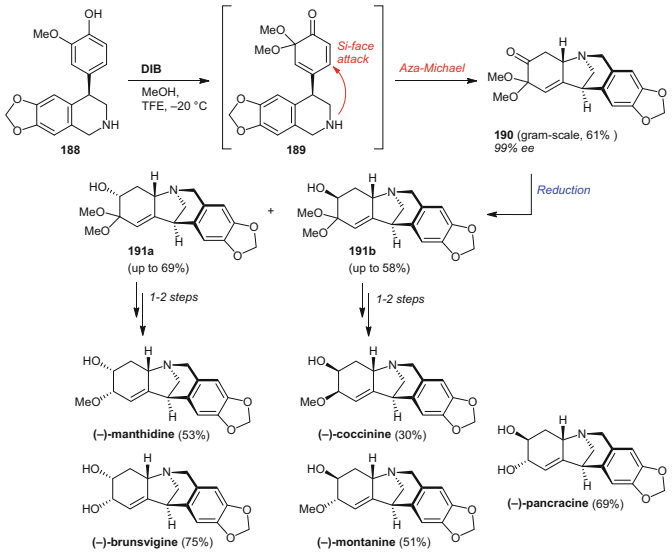

Fig. 47 Fan's bioinspired synthesis of montanine-type *Amaryllidaceae* alkaloids

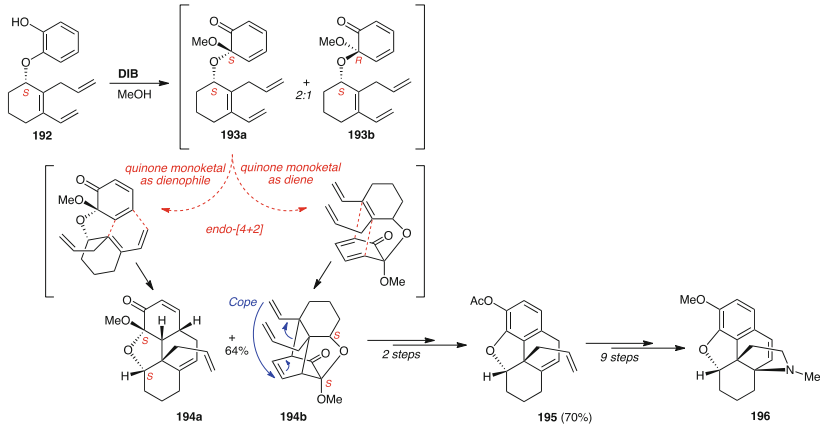

Fig. 48 Rodrigo–Assoud's asymmetric synthesis of a morphine-type indolinocodeine

triethylamine to afford the *endo* hydroxymethylated product **200** in 82% yield [115]. A highly efficient reduction protocol was applied to convert **200** into **201**, which was converted in several steps into **202**, one alcohol-to-ketone oxidation away from lycopladine H (Fig. 49) [117].

A first asymmetric synthesis of the antimalarial indole alkaloid (+)-decursivine was reported in 2011 by Li and co-workers [118]. To construct the eight-membered ring lactam of this target, they used **BTI** in HFIP to promote a highly

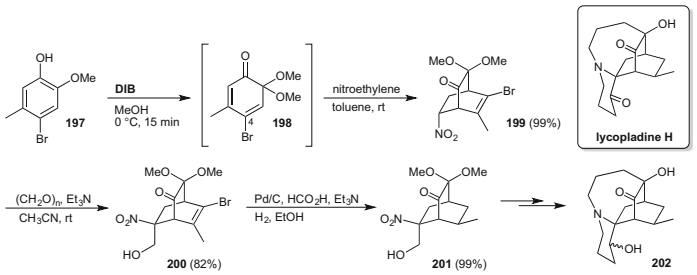

Fig. 49 Weinreb's synthesis of the lycopladine H framework

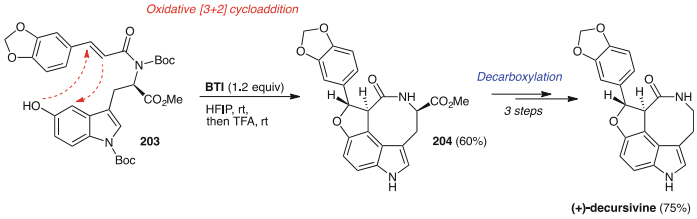

Fig. 50 Li's first asymmetric synthesis of (+)-decursivine

diastereoselective intramolecular [3+2] cycloaddition of the phenolic tryptophan cinnamide **203** (Fig. 50). TFA was used to cleave the *N*-Boc groups and afford the dihydrobenzofuran **204**, which was then decarboxylated to furnish (+)-decursivine in a good yield [118].

The first total syntheses of the marine bromotyrosine-derived alkaloid subereamollines A and B were also described by Ley's group in 2011 [119]. Access to the spirocyclohexadienylisoxazoline core of the targets was ensured by a **DIB**-mediated oxo-spirocyclization of the phenolic oxime methyl ester **205**, followed by a diastereoselective ketone reduction of the resulting *ortho*-quinol **206** (Fig. 51). The methyl ester **207** was then converted in two steps into *rac*-subereamolline A or B. Both racemates were then separated into their respective enantiomers by chiral HPLC [119].

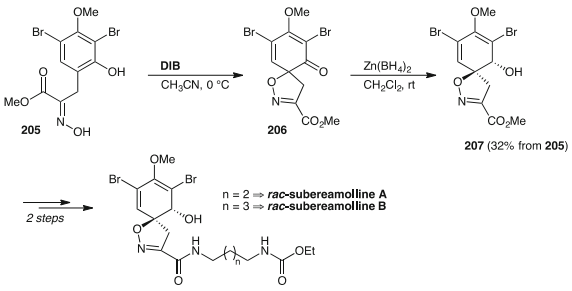

Fig. 51 Ley's synthesis of subereamollines A and B

4.2 Synthesis of Steroids and Terpenoids

In 2010, Myers described a comprehensive route for the synthesis of the alkaloidal steroids cortistatins from the common azido alcohol precursor **210** [120], whose oxabicyclo[3.2.1]octane system was elaborated by a **BTI**-mediated oxidative dearomatizing oxocyclization of the phenolic intermediate released from the desilylation of **208** (Fig. 52), in a manner similar to that previously used by Sarpong and others, reviewed in [29]. The resulting cyclohexa-2,5-dienone **209** was converted in three steps into the azido alcohol **210**, which then served as a pivotal intermediate for the parallel syntheses of cortistatins A, J, K, and L (Fig. 52) [120].

Efforts toward the synthesis of the antitumoral diterpenoid maoecrystal V have also relied on iodane-mediated phenol dearomatization tactics. In 2010, Nicolaou and Chen had reported an access to a functionalized maoecrystal V core via a **BTI**-mediated methoxylative dearomatization of the phenolic bicyclo[2.2.2]octanone **211** [121]. Upon hydrogenation of the resulting *para*-quinone monoketal **212**, the desired diketone **214** was obtained together with the rearomatized compound **213** in a combined yield of 99%. This 4-methoxyphenolic compound could be recycled into the dienone **212** by treating it with **BTI** under the same conditions as for **211**. The diketone **214** was then saponified and subjected to a triple alkylation process using $ClCH_2I$ in the presence of potassium *tert*-butoxide and 18-crown-6 to deliver the enone lactone **216**, which features the entire maoecrystal V ring framework (Fig. 53) [121]. Later on, Chen continued this synthesis work using the *para*-quinone monoketal **212**, which was transformed in a different manner into a further advanced precursor of maoecrystal V with the correct stereochemistry at the C5 center [122]. In a different approach toward the maoecrystal V core, Zakarian and Gu utilized the 2-ethoxyphenolic intermediate **217** which was dearomatized into the *ortho*-quinone monoketal **218** in high yield [123]. This compound was then treated with acryloyl chloride or 2-chloroethanesulfonyl chloride to generate the acrylate **219a** or the vinylsulfonate **219b** as substrates for intramolecular Diels–Alder processes. Thermal activation of these cycloadditions afforded the bicyclo[2.2.2] octanonic lactone **220a** in quasi quantitative yield or sulfonate **220b** in 60% yield (Fig. 53) [123].

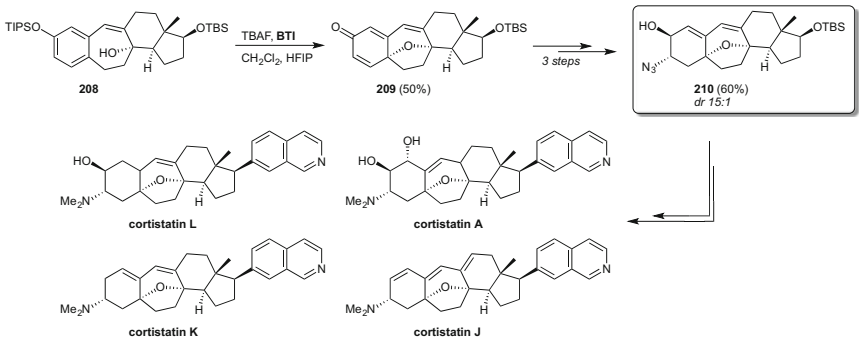

Fig. 52 Myers' synthesis of cortistatins A, J, K, and L

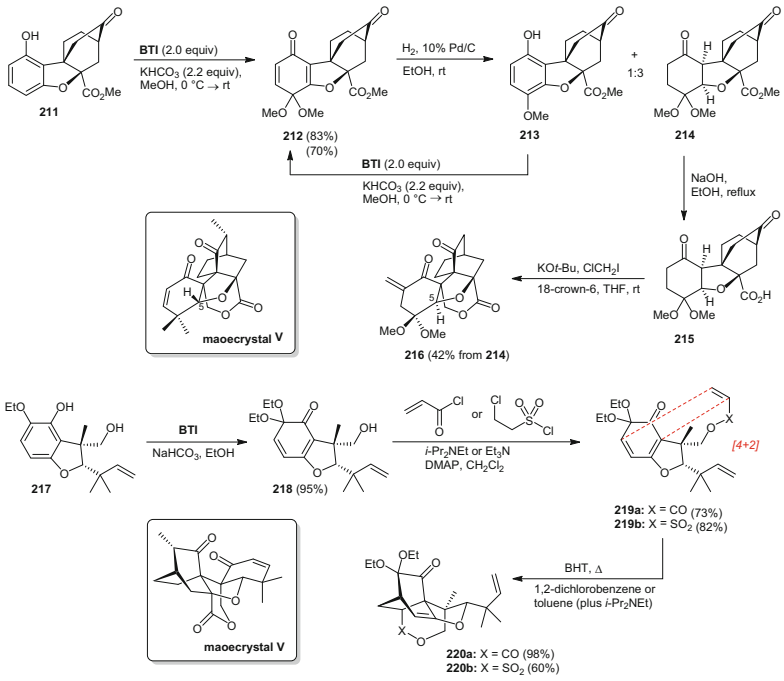

Fig. 53 Nicolaou's, Chen's, and Zakarian's studies toward the synthesis of maoecrystal V core structures

In 2014, two first enantioselective syntheses of (–)-maoecrystal V were reported by Zakarian and by Thomson, and were published back-to-back in the *Journal of the American Chemical Society* [124, 125]. Both syntheses include a key step involving an organoiodane-mediated phenol dearomatization. Zakarian adapted his intramolecular Diels–Alder (IMDA) method for the construction of the

bicyclo[2.2.2]octanone ring system (see Fig. 53) by performing the **BTI**-mediated dearomatization on the 2-ethoxyphenolic intermediate **221** (*dr* 20:1). The resulting *ortho*-quinone diethyl monoketal **222** was then silylated with vinyldimethylchlorosilane to afford the IMDA precursor **223**. The Diels–Alder reaction proceeded as expected to furnish the bicyclo[2.2.2]octanone **224**, which was converted into (–)-maoecrystal V in 14 steps (Fig. 54) [124]. In Thomson's synthesis, a phenol dearomatization served to forge the central tetrahydrofuran ring. The homochiral phenolic intermediate **225** was treated with **DIB** to promote the dearomative cycloetherification into **226** in 95% yield [125]. This *para*-quinol ether was then converted into (–)-maoecrystal V in nine steps (Fig. 54) [125].

Intramolecular Diels–Alder reactions of *ortho*-quinone monoketals into bicyclo[2.2.2]octane ring systems were also used by Chen's group in the three syntheses of the Fab-inhibitory antibiotic platencin (and analogues thereof) that they reported in 2011 [126]. For example, inspired by Liao's work, they prepared the phenolic (*R*)-alcohol **227** (90% *ee*), which was treated with **DIB** in MeOH to afford the *ortho*-quinone dimethyl monoketal **228**. This MOB was heated in toluene to trigger its [4+2] cycloaddition, which preferentially occurred via a chair-like transition state displaying the OH group in an equatorial orientation (see **228** in Fig. 55) to furnish

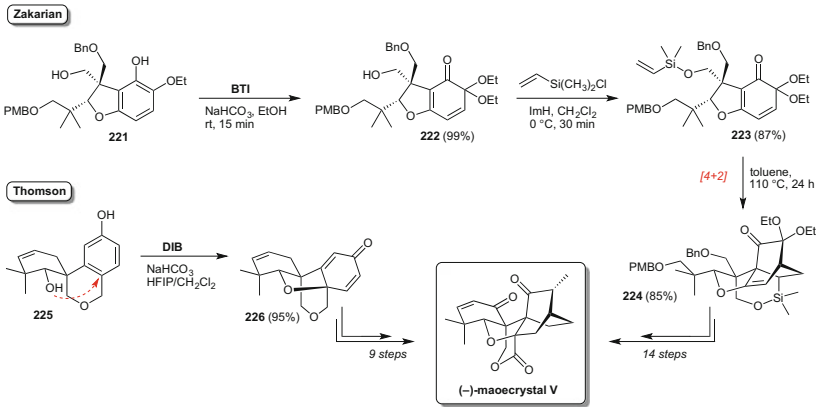

Fig. 54 Zakarian's and Thomson's enantioselective syntheses of (–)-maoecrystal V

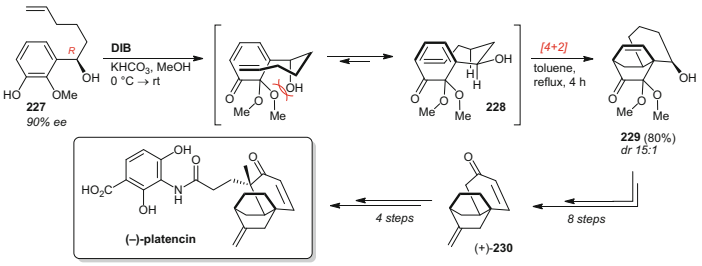

Fig. 55 Chen's synthesis of platencin

the cycloadduct **229** with high diastereoselectivity. This bicyclo[2.2.2]octanenone was then converted into the tricyclic enone **230** en route to (–)-platencin [126].

In 2012, Fukuyama's group reported a novel synthesis route to the spiro-β-lactonic sesquiterpene (–)-anisatin, and they also relied on the construction of a bicyclo[2.2.2]octane system via a **DIB**-mediated methoxylative phenol dearomatization followed by an intramolecular Diels–Alder reaction [127]. The homochiral phenolic dihydrobenzofuran propargyl ether **231** thus afforded, via the *ortho*-quinone monoketal **232** and treatment of its intramolecular [4+2] epimeric cycloadducts with camphorsulfonic acid in MeOH, the bicyclo[2.2.2] octanedienone **234** as a single diastereomer (Fig. 56). Further transformation of **234** gave the vinyl **235**, whose trisubstituted double bond bridge was oxidatively cleaved by mild ozonolysis to furnish the ketoaldehyde **236**, en route to (–)-anisatin [127].

Fukuyama's group employed related tactics to construct the north part of lepenine in their first asymmetric total synthesis of this complex alkaloidal diterpenoid, which they disclosed in 2014 [128]. The phenolic advanced intermediate **237** could not be directly converted into the *ortho*-quinone monoketal **238** using **DIB** in methanol, as the presence of the tertiary amine perturbed the action of the iodane reagent. However, passage by the corresponding ammonium salt solved this issue, and hence **238** was obtained in high yield (Fig. 57). It was then subjected

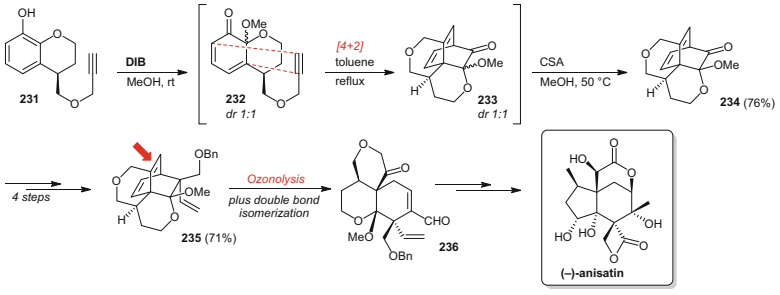

Fig. 56 Fukuyama's synthesis of (–)-anisatin

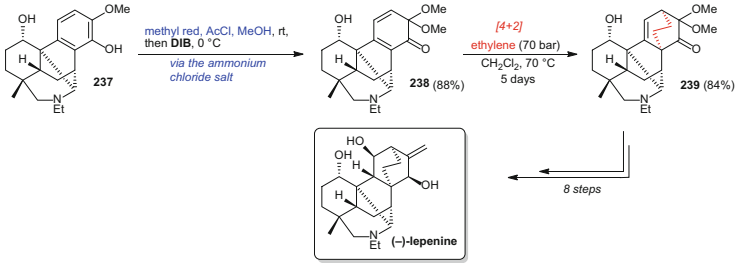

Fig. 57 Fukuyama's synthesis of (–)-lepenine

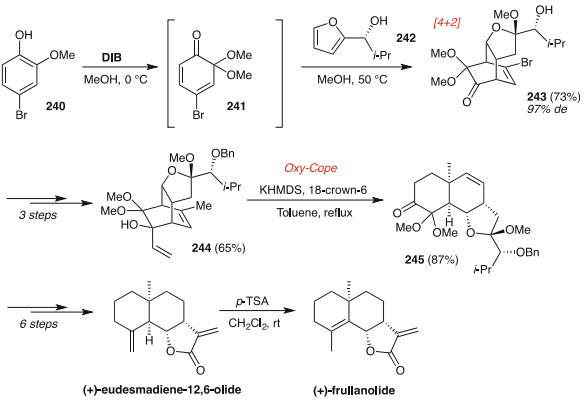

Fig. 58 Liao's asymmetric syntheses of (+)-eudesmadiene-12,6-olide and (+)-frullanolide

to an intermolecular Diels–Alder reaction with ethylene to build the bicyclo[2.2.2] octenone **239**, which was converted into (–)-lepenine in eight steps [128].

In 2013, Liao reported the first asymmetric total syntheses of the sesquiterpenoid lactones (+)-eudesmadiene-12,6-olide and (+)-frullanolide, which were based on an initial dearomatization of 4-bromo-2-methoxyphenol **240** into the corresponding MOB **241** (Fig. 58) [129]. An asymmetric Diels–Alder reaction with the chiral furan (*R*)-**242** furnished the bicyclo[2.2.2]octenone **243** in good yield with high chemo-, regio-, and stereoselectivities. This compound was further transformed in a few steps to reach (+)-eudesmadiene-12,6-olide, whose *cis*-decalin core was elaborated by a high-yielding anionic oxy-Cope rearrangement of the allylic alcohol **244** (Fig. 58) [129].

An oxidative phenolic [3+2] cycloaddition tactic was employed by Trauner's group in 2014 to accomplish a short racemic biomimetic synthesis of the antibiotic terpenoid merochlorin B [130]. After having unsuccessfully tried lead(IV) reagents to provoke the desired [3+2] cycloaddition of the prenylated naphthol **246**, Trauner identified iodosylbenzene (**PhIO**) and trifluoromethanesulfonic acid, generating in situ the Koser's reagent variant [PhI(OH)OTf], as a suitable λ^3-iodane for the intended purpose. The naphthol **246** thus likely gave rise to the cationic carbospirocyclized cyclohexadienonyl intermediate **247**, which then suffered the nucleophilic addition of the ketone to complete the [3+2] cycloaddition process (Fig. 59). A final desilylation of the resulting compound **248** furnished *rac*-merochlorin B as a single diastereomer in 30% yield over these two steps [130].

In 2014, Canesi's group also reported on a remarkable application of their chemistry that enabled them to develop an asymmetric synthesis of the tetracyclic main core of kaurane diterpenes [131]. The phenolic non-conjugated enyne **249** was elaborated to fulfill the reactivity and stereochemistry requirements of the intended oxidative cationic polycyclization [132], in tandem with a pinacolic transposition. After chlorination of the benzylic alcohol of **249** with inversion of configuration, the use of **BTI** rapidly promoted this dearomative tandem process, which thus

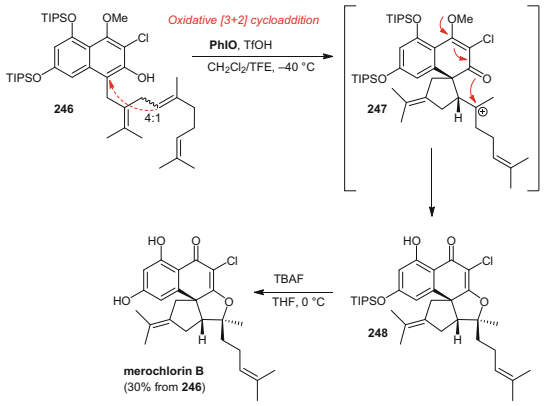

Fig. 59 Trauner's synthesis of *rac*-merochlorin B

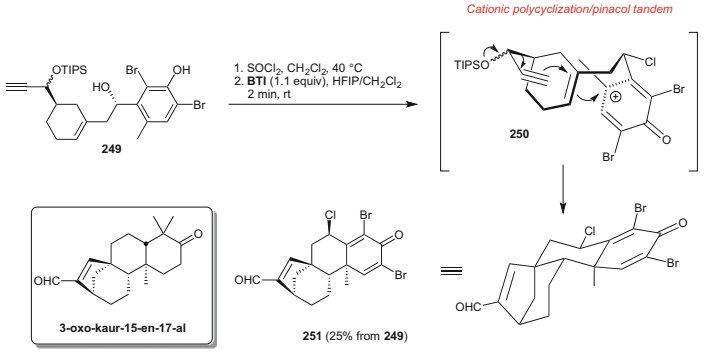

Fig. 60 Canesi's asymmetric synthesis of the terpenoid kaurane core

furnished in a single operation the kaurane-like tetracycle **251** in 25% from **249** (Fig. 60) [131].

The first total synthesis of (–)-incarviatone A was described by Li, Lei, and co-workers in 2015 [133]. Only 14 steps were necessary to accomplish this synthesis of such a complex natural product, and one of the key steps was the **DIB**-mediated hydroxylative dearomatization of the diastereomeric phenols **252** into the *para*-quinols **253**, which were next coupled with the vinyl boronic ester (*R*)-**254** (Fig. 61). The β-epimer of the resulting diastereomeric *para*-quinols **255** was then converted into (–)-incarviatone A in a one-pot operation via an outstanding (and biomimetic) triply cyclizing cascade reaction, which involved an oxa-Michael addition to the cyclohexa-2,5-dienone unit, an aldol reaction to forge the central six-membered carbocycle and a second oxa-Michael addition of the C_{15}-oxygen atom to the remaining enone unit. Incarviatone A was thus obtained in 46% yield, together with the regioisomeric product **256** in 19% yield, which resulted from the major α-epimer of **255** with which the aldol reaction was followed by a competing oxa-Michael addition of the C_{17}-oxygen atom (Fig. 61). The fact that incarviatone

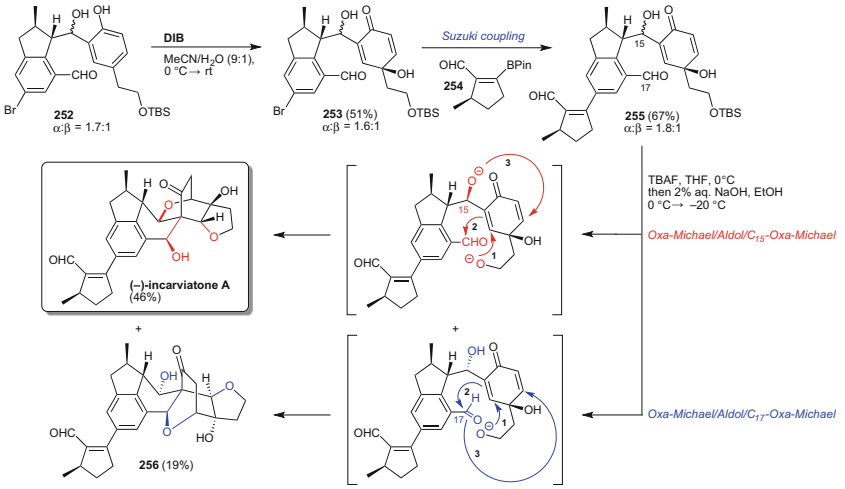

Fig. 61 Li-Lei's enantioselective synthesis of (–)-incarviatone A

A was preferentially produced was a result of the facile, albeit reversible, epimerization at the C-15 center via a retro-aldol/aldol sequence under the alkaline conditions used [133].

4.3 Synthesis of Polyketides

Following up on their synthesis of (–)-harveynone (see Fig. 7) [40], Taylor and co-workers disclosed in 2011 their synthesis of other epoxy-*para*-quinone natural products [134], such as the fungal SDEF 678 metabolite, a regioisomer of harveynone, for which the epoxidation occurred on the trisubstituted double bond. The *para*-quinone monoketal **9a** was prepared by a double oxidation of 3-iodophenol using **DIB** in MeOH (see Fig. 7), the enyne moiety was installed via a Stille reaction, and the disubstituted double bond of the resulting quinone monoketal **257** was temporarily masked using a Diels–Alder reaction with cyclopentadiene in the presence of Corey's chiral oxazaborolidine/triflic acid adduct to furnish the *endo*-cycloadduct **258**, which was unfortunately essentially racemic (Fig. 62). The epoxidation could then be directed on the trisubstituted double bond during the elaboration of the epoxide **259**, which was then heated in diphenyl ether to furnish the SDEF 678 metabolite via a retro-Diels–Alder reaction (Fig. 62). Other natural and analogous epoxyquinones also featuring a trisubstituted epoxide, the speciosins A–D, were similarly synthesized [134].

In a continuation of their work on the synthesis of azaphilone natural products and derivatives [135], Porco and co-workers disclosed in 2012 the synthesis of azaphilone-based chemical libraries [136]. Phenolic *ortho*-alkynylbenzaldehydes **260** were cycloisomerized via a gold(III) catalysis in the presence of TFA to afford

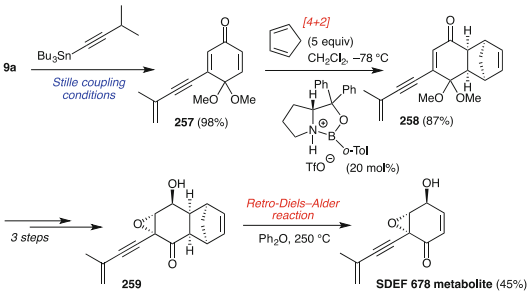

Fig. 62 Taylor's synthesis of the fungal epoxyquinone SDEF 678 metabolite

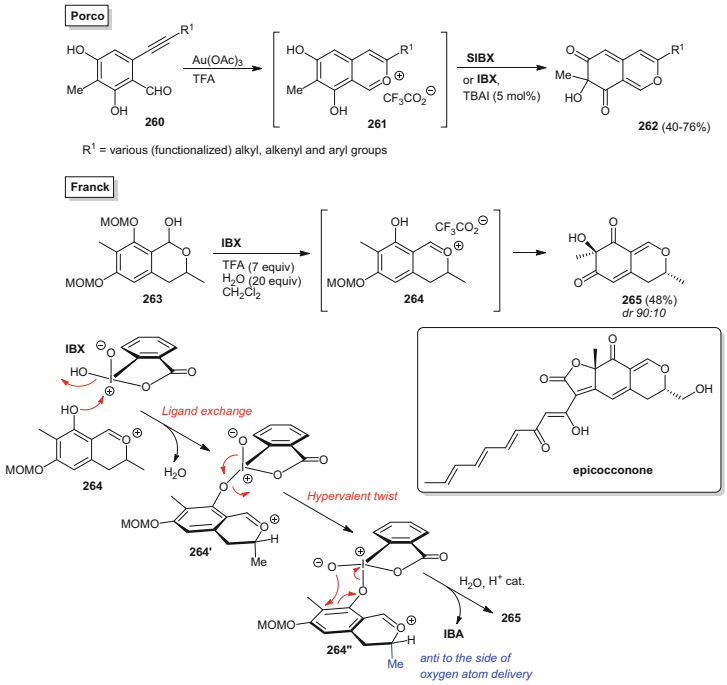

Fig. 63 Porco's synthesis of pyranic azaphilone scaffolds and Franck's diastereoselective synthesis of the epicocconone-related dihydropyranic azaphilone core

2-benzopyrylium salts of type **261**. These salts were directly treated with the λ^5-iodanes **SIBX** or **IBX** [plus a catalytic amount of tetrabutylammonium iodide (TBAI)] to dearomatize their phenolic moiety and deliver the azaphilone scaffolds of type **262** (Fig. 63) for further structural diversifications [136].

IBX was also used, albeit without TBAI, by Franck and co-workers in their elaboration of the dihydropyranic azaphilone-related core of the fungal epicocconone in a highly diastereoselective manner [137, 138]. The best result

was obtained by treating the MOM-bisprotected phenolic hemiketal **263** in CH_2Cl_2 with TFA, which generates in situ the mono-deprotected oxonium ion **264**, and IBX (2 equiv.) in the presence of water. Under these conditions, the hydroxylated dearomatized product **265** was obtained in 48% yield in a 90:10 diastereomeric ratio (Fig. 63). This remarkable remote control of diastereoselectivity (i.e., over five bonds) was rationalized by internal delivery of the oxygen atom of the **IBX**-derived unit coordinated to the free phenolic position of **264** (i.e., after ligand exchange between **IBX** and **264** into **264′** and a hypervalent twist into **264″**) [73], *anti* to the methyl group of its dihydropyran ring [137, 139]. TFA would then promote cleavage of the second MOM group and the hydrolytic release of the major diastereomer **265** together with 2-iodosylbenzoic acid (**IBA**) (Fig. 63).

More recently (2014), Porco's group reported their racemic synthesis of the sorbicillinoid polyketide sorbiterrin A [140], for which they first prepared the acetylated natural *ortho*-quinol sorbicillinol **267** from the acetylated sorbicillin **266**. The dearomatization was induced by the use of **BTI** in aqueous acetonitrile and encompassed a regioselective hydrolytic shift of the nucleophilic acetyl group to the oxidatively activated *para*-position of the starting phenol (Fig. 64). A thermolysis of **267** with 4-hydroxypyrone **268** in the presence of silica gel provoked a Michael addition cascade that resulted in the high-yielding formation of the desired spiro epimers **269**, en route to 3-*epi*-sorbiterrin A and/or sorbiterrin A [140].

Following up on their work on the synthesis of aculeatins, Yung-Sing Wong and co-workers disclosed in 2011 their enantioselective synthesis of the related amomols [141]. The chiral phenolic ketone (–)-**270** was treated with **DIB** in CH_2Cl_2 in the presence of MeOH. The nucleophilic ketone oxygen trapped the oxidatively activated phenolic *para*-position to generate the highly electrophilic spirocyclohexa-2,5-dienonic oxo-carbenium cation **271**, which was, in turn, trapped by MeOH to furnish both (–)-amomol A and (+)-amomol B in 15 and 21% yields, respectively (Fig. 65) [141].

Harned's group had also earlier (2011) reported one of their contributions to the synthesis of sorbicillinoid natural products, which concerns the synthesis of sorbicillactones [142]. The phenol **272** was first trimethylsilylated, as this silyl aryl ether gave higher yields upon dearomatization, which was performed on an

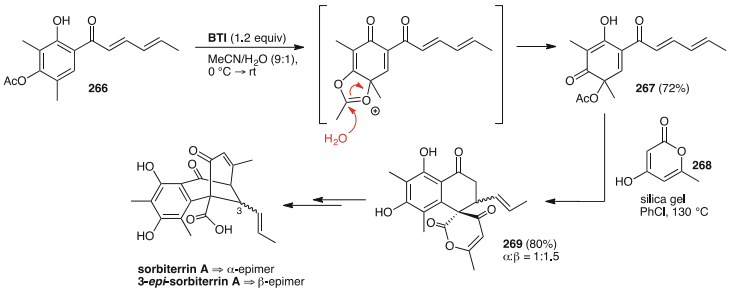

Fig. 64 Porco's synthesis of (±)-sorbiterrin A and its C3 epimer

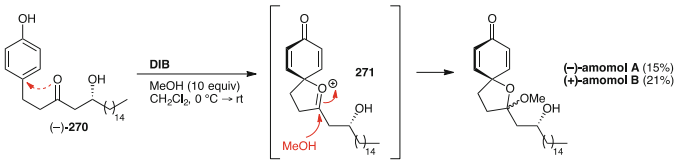

Fig. 65 Wong's enantioselective synthesis of amomols A and B

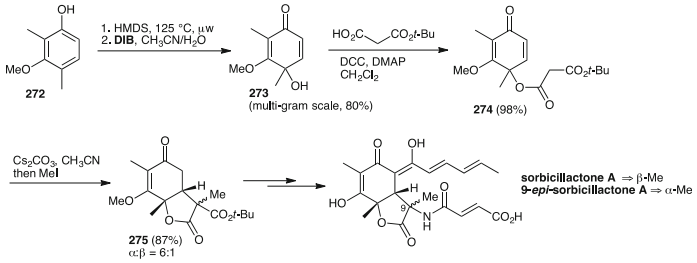

Fig. 66 Harned's synthesis of (±)-sorbicillactone A and its C9 epimer

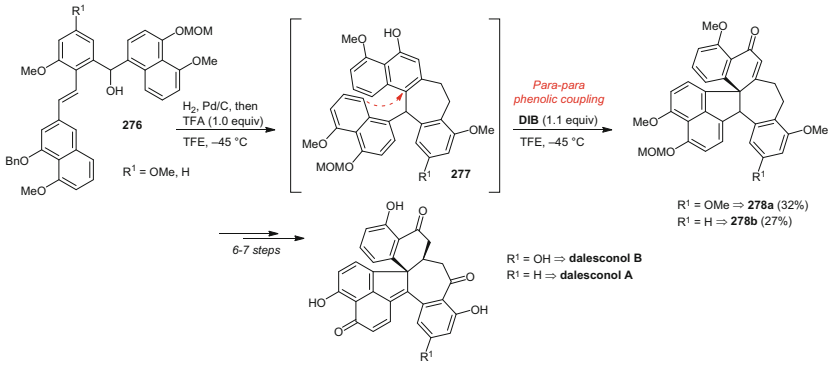

Fig. 67 Snyder's total syntheses of dalesconols A and B

8-gram scale using **DIB** in aqueous acetonitrile. The resulting *para*-quinol **273** was acylated with a malonic ester to give **274**, which was then cyclized and methylated to the *cis*-fused bicyclic lactones mixture **275**, en route to 9-*epi*-sorbicillactone A or sorbicillactone A (Fig. 66) [142].

For their 2010 synthesis of the immunosuppressive polyketides dalesconols A and B [143], Snyder and co-workers developed an outstanding one-pot cascade to forge the bicyclo[5.3.0]decanyl core of these targets from the judiciously functionalized and protected precursors **276**. The ultimate addition of **DIB** in TFE at low temperature served to transform in situ the phenols **277** into the five-membered carbo-spirocyclic cyclohexa-2,5-dienone intermediates **278**, which were then efficiently converted into dalesconols A and B (Fig. 67) [143].

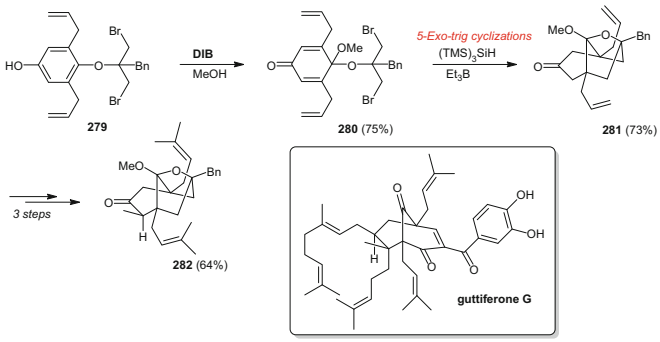

Fig. 68 Njardarson's synthesis of the guttiferone bicyclic core

In 2011, an elegant access to the bridged bicyclic core of the guttiferone family of polyketides was described by Njardarson and colleagues [144]. Judiciously designed for the purpose, the bisallylated bisbrominated phenolic ketal **279** was converted into the *para*-quinone monoketal **280**, which was then subjected to radical cyclization conditions that furnish the bicycle **281** as the sole product via two consecutive 5-*exo*-trig cyclizations (Fig. 68). This compound was then further transformed to afford the bisprenylated bicyclic motif **282** displaying the core structure of the guttiferones [144]. The same year, Snider and Yu disclosed their results on the synthesis of the fungal *ortho*-quinone spirolactonic monoketal maldoxin and several other congeners [145]. The ultimate step of the synthesis of maldoxin was a high-yielding **DIB**-mediated dearomatizing oxo-spirocyclization of the phenolic carboxylic acid dihydromaldoxin (Fig. 69) [145]. Maldoxin was then engaged with the isopropenylallene **283** in a Diels–Alder reaction, during which maldoxin mainly reacted as a diene component to furnish at 60°C a mixture of bicyclo[2.2.2]octenes **284**–**286** [146]. The structure of the cycloadduct **284** closely resembles that of natural chloropestolide A. At 75°C, the cycloadduct **285** was not observed, as it was fully converted into the ene reaction product **286**, which displays the skeleton of chloropupukeanolide D (Fig. 69) [146].

A very short synthesis of *rac*-incarviditone and *rac*-incarvilleatone was reported in 2012 by Lawrence and co-workers [147], who first prepared on a multigram scale rengyolone in three steps from tyrosol via a **DIB**-mediated hydroxylative dearomatization into the *para*-quinol **287** and an oxa-Michael addition. The resulting (±)-rengyolone was then biomimetically dimerized under mildly basic conditions simply using a catalytic amount of potassium carbonate to furnish (±)-incarviditone in 19% yield via a homochiral oxa-Michael/Michael domino reaction, and (±)-incarvilleatone in 23% yield via a heterochiral oxa-Michael/Michael/aldol domino reaction (Fig. 70) [147].

In 2015, Shi-Shan Yu and co-workers relied on a **SIBX**-mediated HPD/[4+2] cascade reaction of a 1:1 mixture of enantio-enriched 2-allylphenolic benzopyran and benzofuran derivatives **288** and **289** to synthesize both illicidione A and illihendione A [148]. Both starting phenols were dearomatized into the *ortho*-

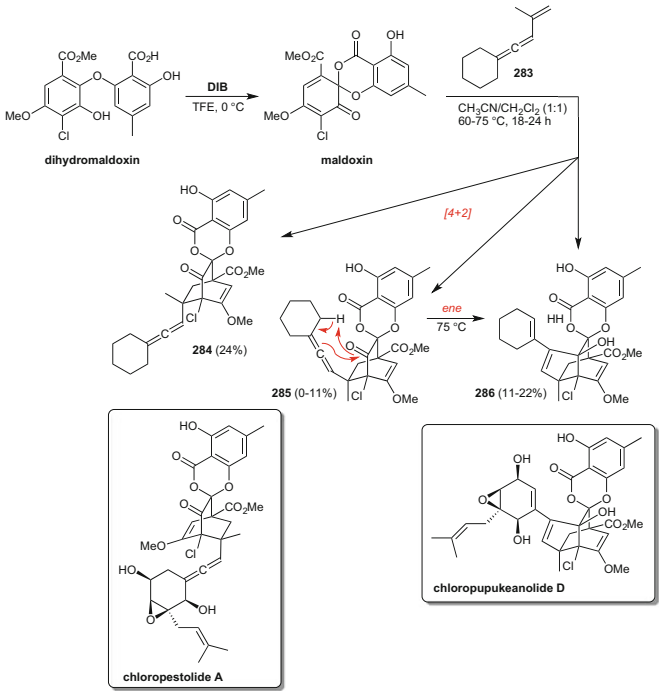

Fig. 69 Snider's synthesis of maldoxin and analogues of chloropestolide A and chloropupukeanolide D

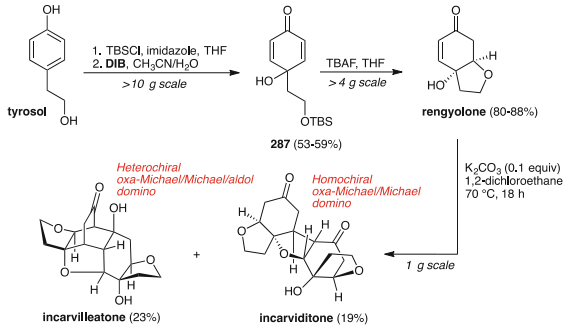

Fig. 70 Lawrence's synthesis of *rac*-incarviditone and *rac*-incarvilleatone

quinols **290** and **291**, respectively, with full control of the configuration at their hydroxylated C6 centers (Fig. 71). The *ortho*-quinol **290** cyclodimerized to furnish the expected bicyclo[2.2.2]octenone stereoisomer **292** in 37% yield. This yield could be improved up to 53% by performing the same reaction only with **290**. Intriguingly, the *ortho*-quinol **291** could not cyclodimerize and solely acted as a dienophile. In the presence of the *ortho*-quinol **290**, it thus led to the formation of the cycloadduct **293** with the regio- and stereoselectivities expected for this kind of

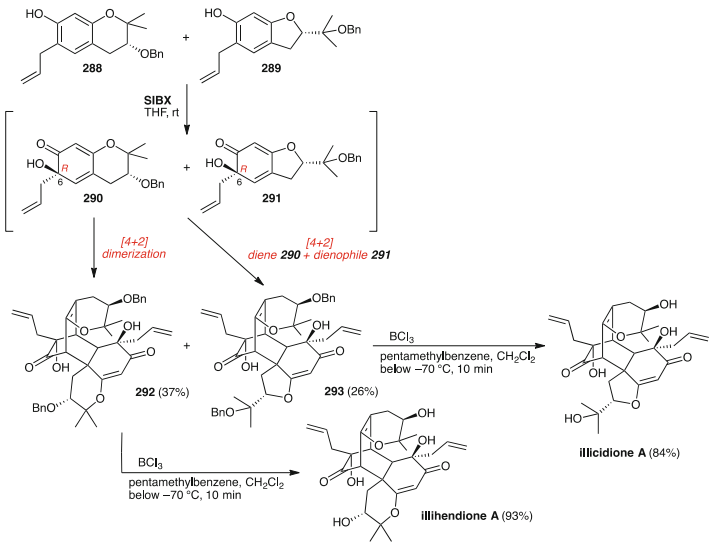

Fig. 71 Shi-Shan Yu's synthesis of illicidione A and illihendione A

[4+2] cycloaddition of *ortho*-quinols [49] (Fig. 71). Both cycloadducts **292** and **293** were finally debenzylated to furnish illihendione A and illicidione A, respectively [148].

5 Conclusions

Several other applications of organoiodane-mediated phenol dearomatization in natural product synthesis have been reported since the writing of this chapter and many more will undoubtedly appear in the literature in the forthcoming years, as this tactic has today amply proven its utility and value for the rapid construction of complex molecular architectures from simple starting phenols and other arenols. The simplest reagents, such as **DIB**, **BTI**, and **(S)IBX**, are the most often used organoiodanes and should certainly remain for a long time the primary tools for many dearomative transformations of phenols. Other more complex organoiodanes with modulated physico-chemical properties and reactivities are also already available and future developments should certainly lead to many more such reagents, notably chiral variants for the stereocontrol of various dearomative bond formations. The implementation of catalytic versions of phenol dearomatization processes unarguably also constitutes an added value, especially in regard to the utilization of these more complex organoiodanes. However, knowledge of the mechanistic implications of either λ^3- or λ^5-organoiodanes in phenol dearomatization, as well as in any other type of transformations, is still in its infancy. Future progress and breakthroughs in the design and applications of

novel organoiodanes are waiting for the acquisition of a precise and detailed knowledge of the reactivity behavior of the hypervalent iodine atom and the ligands it can bear, exchange, or lose, and transfer to a given substrate.

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Oxidative Heterocycle Formation Using Hypervalent Iodine(III) Reagents

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Abstract Hypervalent iodine(III) reagents have been widely exploited in a diverse array of synthetic transformations. This chapter focuses on the general application of hypervalent iodine(III) reagents in the de novo synthesis and in the late stage functionalization of heterocyclic compounds.

Keywords Heterocycles • Hypervalent iodine(III) reagents • Organocatalysis • Oxidative cyclization • Transition metal-free

Contents

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1 Introduction

Heterocyclic compounds represent one of the privileged scaffolds and hence there has been continuous interest in the construction of biologically active heterocycles. The omnipresence of heterocyclic compounds in many natural products and pharmaceutical agents warrants the development of efficient strategies for their synthesis. In this regard, hypervalent iodine chemistry has emerged as an elegant and powerful tool for the construction of a plethora of bioactive heterocyclic compounds and natural products [1, 2]. Recent decades have witnessed a great expansion and significant popularity of hypervalent iodine chemistry because of the ready accessibility, reduced toxicity, high reactivity, impressive functional group tolerance, and environmentally benign nature of hypervalent iodine reagents. Iodine(III) derivatives, such as phenyliodine(III) diacetate (PIDA), phenyliodine(III)-bis (trifluoroacetate) (PIFA), iodosobenzene (PhIO), and [hydroxyl(tosyloxy)iodo]benzene (HTIB, Koser's reagent) have been widely applied in an array of organic reactions including oxidative halogenation of organic substrates, oxidative functionalization of unsaturated compounds, oxidative cationic cyclization, various oxidative rearrangements, and numerous other oxidative transformations leading to the formation of new carbon–carbon, carbon–heteroatom, and heteroatom–heteroatom bonds [3–7]. Besides the formation of several heterocyclic compounds, the aforementioned diverse reactivity of iodine(III) reagents represents an attractive alternative for conventional transition metal catalyzed/mediated coupling reactions. In this chapter we showcase recent significant advances made towards the synthesis of heterocyclic compounds involving hypervalent iodine(III) reagents, based on the type of reactions and patterns of bond formation during the construction of the heterocyclic scaffolds. The first part is devoted to the synthesis of heterocycles through oxidative intra- and intermolecular bond-forming reactions, and the second part describes the direct C–H bond functionalization of heterocycles leading to the formation of new C–C and C–N bonds.

2 Synthesis of Heterocycles via Intra- and Intermolecular Oxidative Bond Formation

2.1 Heterocycles Through Intramolecular Bond Formation

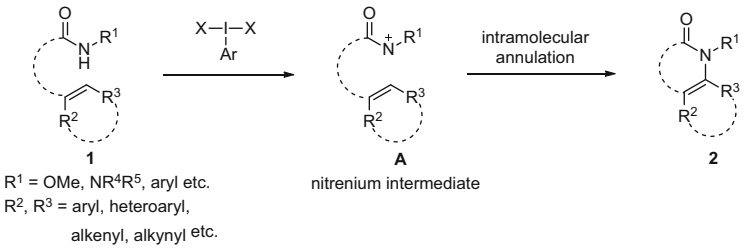
Hypervalent iodine(III) mediated/catalyzed intramolecular oxidative C–H bond functionalization of (hetero)arenes and alkenes has been widely applied in the synthesis of several biologically active heterocyclic scaffolds. This intramolecular oxidative C–H bond functionalization reaction leads to the formation of carbon–carbon and carbon–heteroatom bonds in an efficient manner. Of all bond formation reactions, C–N bond annulations have been exploited most and are of immense

importance because of the wide occurrence of nitrogen-containing compounds as natural products, bioactive molecules, and functional materials [8–10]. In this section, we discuss intramolecular oxidative annulation reactions mediated/catalyzed by hypervalent iodine(III) reagents, based on either the activation mode of the substrate or the common reactive intermediate formed during the reaction.

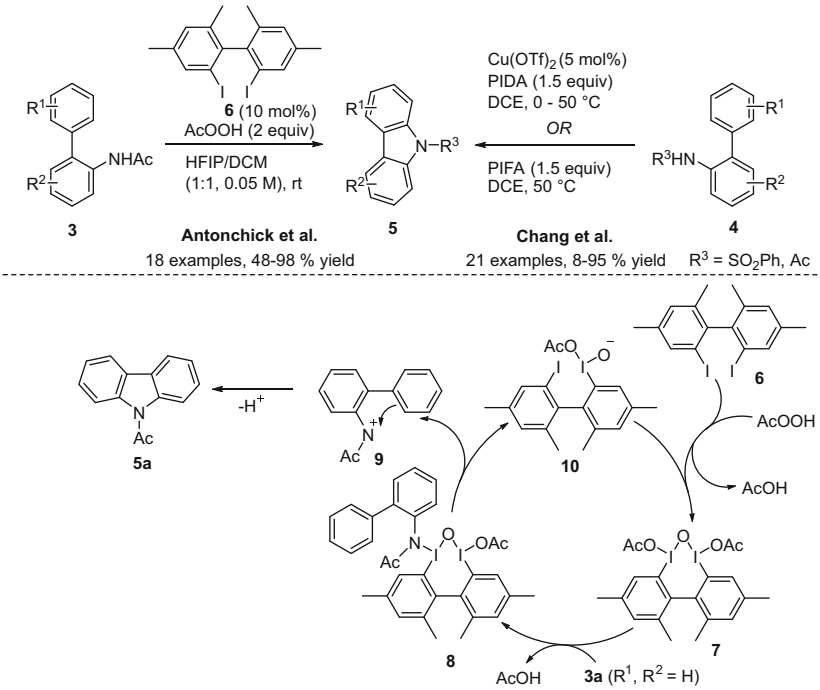
2.1.1 Annulation Through Electrophilic Nitrogen

Hypervalent iodine-induced cationic cyclizations are of particular importance in the synthesis of heterocycles. In the early 1990s, Kikugawa et al. [11] reported that aromatic amides of type **1** undergo a PIDA-mediated intramolecular oxidative C (sp^2)–N bond formation to yield the corresponding heterocycles **2**. Since this early report, many methods constructing diverse heterocycles have been explored in the last two decades [6]. Along these lines, Tellitu, Domínguez, and coworkers [4] reported a series of PIFA-promoted intramolecular amidation reactions leading to various five-, six-, and seven-membered heterocycles. Experimental studies have revealed that these reactions proceed through an ionic mechanism, involving initial generation of *N*-acylnitrenium intermediate **A** from the reaction of the amide with iodine(III) reagent, followed by intramolecular nucleophilic attack by a (hetero) arene or alkene (Scheme 1).

In 2011, Chang et al. [12] showed that the synthesis of carbazoles **5** can be achieved from *N*-substituted aminobiphenyls **4** either by a Cu-catalyzed process using PIDA as an oxidant or under metal-free conditions using *only* hypervalent iodine as the sole oxidant (Scheme 2). However, the yields of the reaction were found to be significantly higher when the Cu(II) catalyst was used in conjunction with hypervalent iodine as compared to metal-free conditions. Meanwhile, using aryl iodide **6** as a catalyst in the presence of peroxyacetic acid, Antonchick and coworkers [13] realized an organocatalytic approach to synthesize carbazoles **5** through intramolecular C–H amination of amide precursor **3** (Scheme 2). Chang and coauthors proposed a radical mechanism whereas, based on several radical trapping experiments, Antonchick's group excluded any possibility of radical intermediates. The authors proposed that initially 2,2′-diiodoarene **6** is oxidized by peracetic acid to generate the oxo-bridged hypervalent species



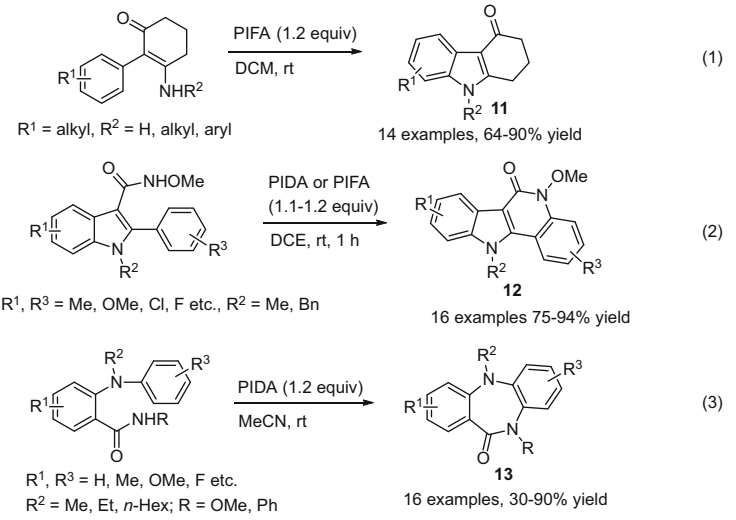
Scheme 1 General scheme describing the oxidative amidation protocol



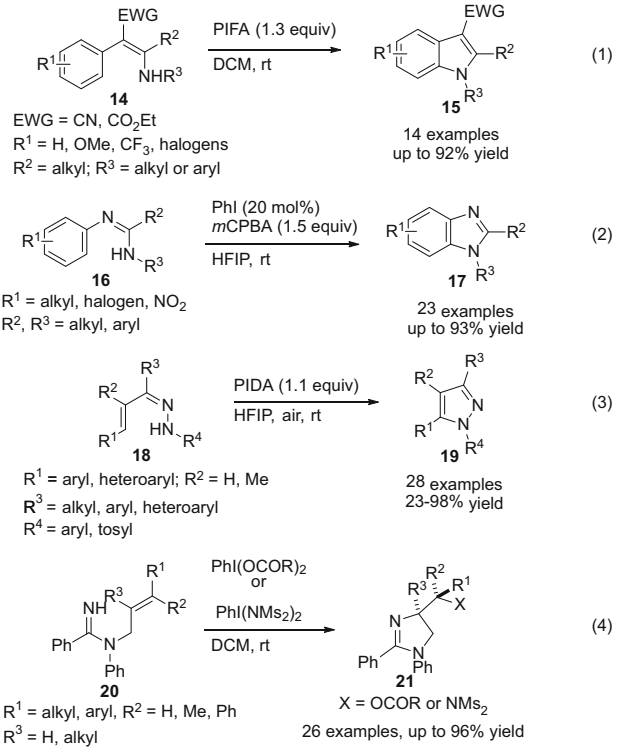
Scheme 2 Carbazole synthesis via oxidative amidation

7 which then reacts with the amide group of **3a** through ligand exchange to form **8** (Scheme 2). Following this, **8** undergoes oxidative cleavage to generate nitrenium ion **9** and iodoarene **10**. Finally, nitrenium ion **9** undergoes electrophilic aromatic substitution to furnish product **5a**, at the same time reoxidizing **10** to **7** to complete the catalytic cycle. This strategy of oxidative intramolecular amidation has found wide application in the synthesis of various heterocycles, including carbazolones **11** [14], indoloquinolinones **12** [15], and 1,4-benzodiazepins **13** [16] (Scheme 3).

The hypervalent iodine(III)-mediated intramolecular amidation protocol was further extended to other substrates, such as enamines **14** (Scheme 4 (1)), amidines **16** (Scheme 4 (2)), and vinyl hydrazones **18** (Scheme 4 (3)). For example, Zhao and coworkers [17] showed that a variety of *N*-arylated and *N*-alkylated indoles **15** can be synthesized by PIFA-mediated intramolecular cyclization of enamine derivatives **14** (Scheme 4 (1)). The authors further showed that functionalized indoles can also be prepared from *N*-aryl enamines by $C(sp^2)$–$C(sp^2)$ coupling in the presence of PIDA as an oxidant [18]. Zhu et al. [19] developed a straightforward approach for the creation of 2-substituted benzimidazoles **17** from easily available *N*-arylamidines **16** using PIDA as an oxidant. Later, the organocatalytic version of the transformation was also realized using iodobenzene as a catalyst and *meta*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant (Scheme 4 (2)) [20]. In an another report, Zhu's group [21] applied a similar strategy to the synthesis of



Scheme 3 Synthesis of carbazolones, indoloquinolinones, and 1,4-benzodiazepines through intramolecular oxidative amination

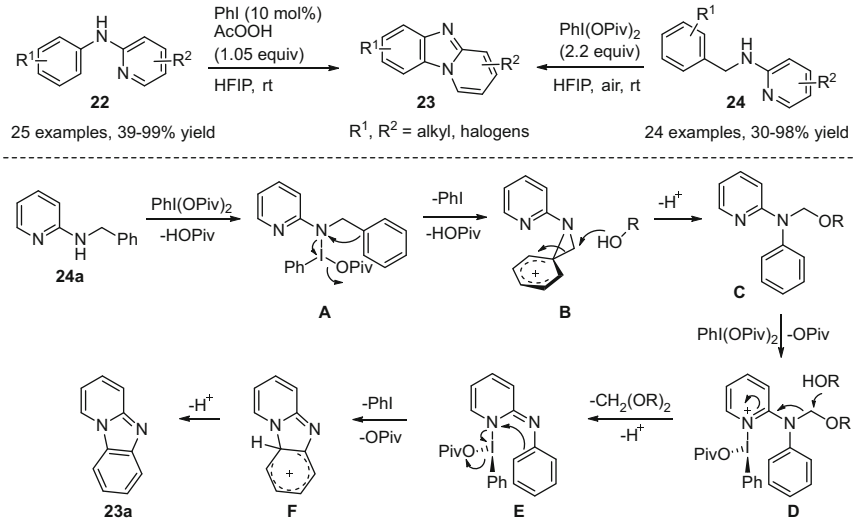


Scheme 4 Synthesis of indoles, imidazoles, pyrazoles, and dihydroimidazoles

structurally diversified pyrazole derivatives **19** through metal-free cycloamination of vinyl hydrazones **18** (Scheme 4 (3)). Analogously, in 2014, Chiba and coworkers reported an efficient hypervalent iodine enabled diastereoselective *anti*-aminooxygenation and *anti*-diamination of *N*-allylamidines **20** for the synthesis of dihydroimidazoles **21** [22].

Zhu and coworkers [23] developed a metal-free intramolecular C-H amination reaction of *N*-aryl-2-aminopyridines **22** catalyzed by a hypervalent iodine(III) species generated in situ from iodobenzene and peracetic acid for the synthesis of pyrido[1,2-*a*]benzimidazoles **23** (Scheme 5). Interestingly, the authors published [24] another paper showing that pyridobenzimidazoles **23** can also be obtained from *N*-benzyl-2-aminopyridines **24** in the presence of $PhI(OPiv)_2$ as a stoichiometric oxidant in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) via an oxidative tandem demethylenation cycloamination reaction (Scheme 5). Based on several mechanistic experiments performed, including crossover experiments and intramolecular competition reactions, the authors proposed a mechanistic pathway for this intriguing oxidative demethylenative C–N bond-forming reaction (Scheme 5). Initial coordination of $PhI(OPiv)_2$ with **24a** generates the electrophilic *N*-iodo species **A**, which then undergoes an *ipso*-S_EAr reaction on the phenyl ring generating the delocalized carbocation **B** (Wheland intermediate). Following this, HFIP undergoes nucleophilic addition on the benzylic carbon in **B**, causing cleavage of the C–C bond to give intermediate **C**, which then reacts with another equivalent of PhI $(OPiv)_2$ to form active complex **D**. Finally, a second nucleophilic substitution by HFIP and subsequent electrophilic annulation on the activated pyridine nitrogen generates intermediate **F** which upon deprotonation forms **23a** (Scheme 5).

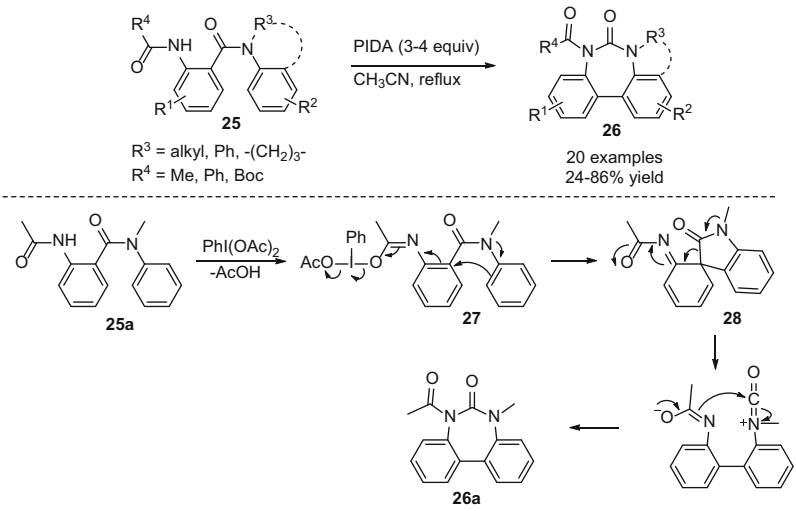
In an interesting report, Shang et al. [25] demonstrated an unprecedented hypervalent iodide-mediated tandem reaction involving cross dehydrogenative



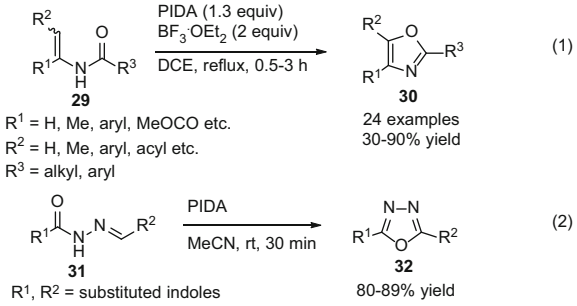
Scheme 5 Synthesis of pyridoimidazoles by Zhu and coworkers

coupling between two aryl groups with concomitant C–O bond cleavage and final intramolecular cyclization leading to the formation of a series of dibenzodihydro-1,3-diazepin-2-ones **26** (Scheme 6). The authors proposed that an initial reaction between **25a** and PIDA led to the formation of intermediate **27** which gives rise to the spiro-intermediate **28** followed by a nucleophilic *ipso* attack of the aniline ring on the electron deficient aromatic carbon of the anthranilic ring in **27**. Finally, ring opening of **28**, assisted by the lone pair on nitrogen, and lactamization provides product **26a** (Scheme 6).

The range of oxidative heterocyclizations was successfully extended to the construction of intramolecular C–O bonds. Zheng et al. [26] showed that enamides **29** can be oxidatively cyclized to functionalized oxazoles **30** using PIDA as an oxidant and $BF_3 \cdot OEt_2$ as a Lewis acid (Scheme 7 (1)). A similar strategy was adopted by Yu and coworkers portraying the synthesis of benzoxazoles in high



Scheme 6 Iodine(III)-mediated synthesis of dibenzodihydro-1,3-diazepin-2-ones

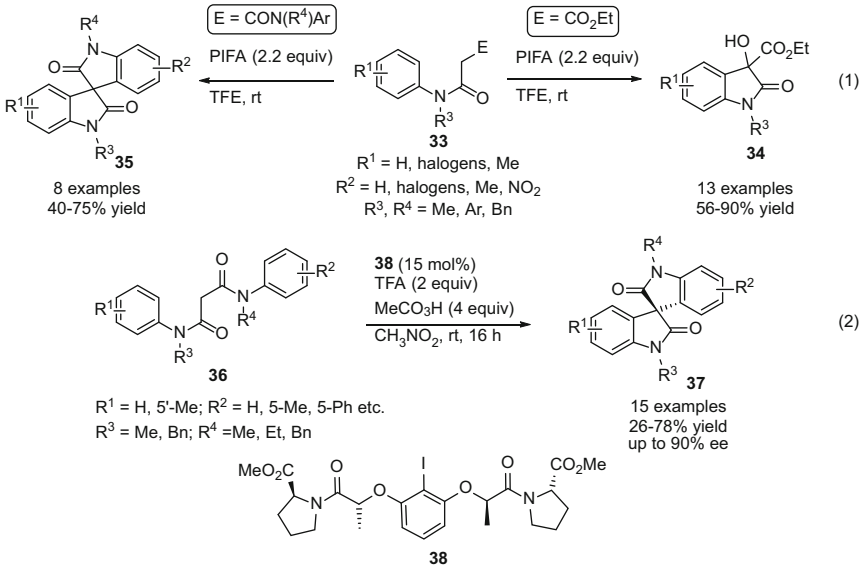


Scheme 7 Synthesis of oxazoles and 1,3,4-oxadiazoles

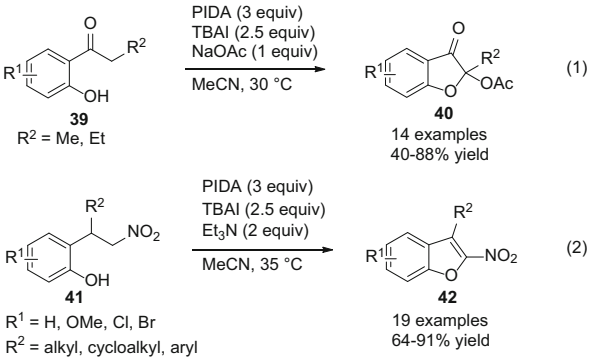
yields [27]. Kumar and coauthors [28] also utilized PIDA-promoted oxidative cyclization of hydrazide–hydrazones **31** to prepare bis(indolyl)-1,3,4-oxadiazoles **32** (Scheme 7 (2)). The authors were able to extend the methodology to the synthesis of 1,2,4-thiadiazoles [29] and 2-arylaminothiadiazoles [30]. In an attempt to expand further the scope of these intramolecular oxidative annulation reactions, successful N–N and N–S bond formation was achieved in the context of the synthesis of several heterocycles such as indazol-3-ones [31], pyrazolin-5-one *N*-oxides [32], 1,2,4-triazolo[1,5-*a*]pyridines [33], benzisothiazol-3-ones [34, 35], and isothiazol-3(2*H*)-ones [36].

2.1.2 Oxidative Annulation of Enolizable Carbonyl Compounds

Hypervalent iodine reagents have successfully been employed in the oxidative functionalization of enolizable carbonyl compounds over the years [6]. This methodology has allowed the construction of diverse C–C bonds in the context of heterocyclic synthesis and has enriched the otherwise rare repertoire of such chemistry. Zhao, Du, and coworkers [37] have recently realized a metal-free PIFA-mediated synthesis of 3-hydroxy-2-oxindoles **34** and spirooxindoles **35** starting from anilide derivatives **33** (Scheme 8 (1)). These processes showcase an oxidative cross coupling between an aromatic carbon and a pendant aliphatic carbon, followed by further oxidative hydroxylation or spirocyclization. Later, the authors extended the same concept to achieve C(sp^2)–C(sp^2) bond formation, where anilide derivatives possessing terminal enol functionality underwent PIDA-



Scheme 8 PIFA-mediated synthesis of oxindoles and spirooxindoles



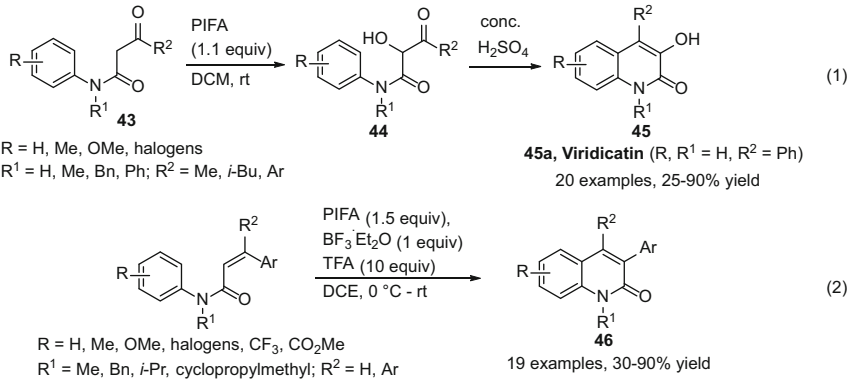
Scheme 9 PIDA/TBAI-mediated synthesis of acetoxybenzofuranones and 2-nitrobenzofuran

mediated annulation and subsequent deacylation to yield important oxindoles [38]. In 2014, Gong and coworkers [39] successfully demonstrated a chiral hypervalent iodine-catalyzed direct intramolecular C–H/C–H coupling of diphenylmalonamides **36** which allowed access to optically active spirooxindoles **37** (Scheme 8 (2)). The hypervalent iodine was generated in situ from the chiral iodine reagent **38** and peracetic acid. This organocatalytic annulation method features the stereoselective functionalization of four C–H bonds and implies that inactive C–H bonds can be functionalized in an enantioselective manner using chiral hypervalent iodine reagents.

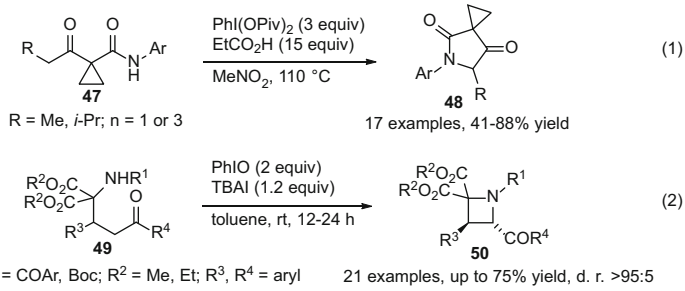
The α-tosyloxylation of enolizable ketones followed by heterocyclization has been utilized in syntheses of several oxygen-containing heterocyclic compounds [6]. Along these lines, Fan and coworkers [40] developed a PIDA/tetrabutylammonium iodide (TBAI)-mediated efficient tandem acetoxylation-cyclization of *o*-acylphenols **39** to deliver α-acetoxybenzofuranones **40** in moderate to good yields (Scheme 9 (1)). The method was successfully extended to *o*-acylanilines, providing a useful route to 2-acetoxy indolin-3-ones [41]. By using a similar approach, Liu et al. [42] developed a PIDA-mediated practical method to prepare a collection of 2-nitrobenzofurans **42** from 2-(2-nitroethyl)phenols **41** (Scheme 9 (2)).

In an analogous manner, biologically active quinolinones were synthesized starting from *N*-phenylacetoacetamides **43** utilizing PIFA as oxidant [43]. In this one-pot reaction sequence, an initially formed α-hydroxylated intermediate **44** underwent dehydrative cyclization to provide quinolinones **45** (Scheme 10 (1)). This strategy allowed authors to prepare viridicatin **45a**, a natural product with potent anti-HIV activity. In addition to the synthesis of 3-hydroxy quinolinones **45**, Zhao's group [44] demonstrated a mechanistically different route towards the synthesis of 3-aryl quinolin-2-ones **46** (Scheme 10 (2)). This simple and metal-free PIFA-promoted and Lewis acid-assisted transformation was realized through simultaneous C–C bond formation and 1,2-aryl migration.

Besides carbon–carbon and carbon–oxygen bonds, a successful carbon–nitrogen bond formation was also achieved utilizing a similar oxidative heterocyclization of enolizable ketones. An efficient synthesis of tetramic acids with a pyrrolidine-2,4-



Scheme 10 PIFA-mediated synthesis of 3-hydroxy and 3-aryl quinolinones



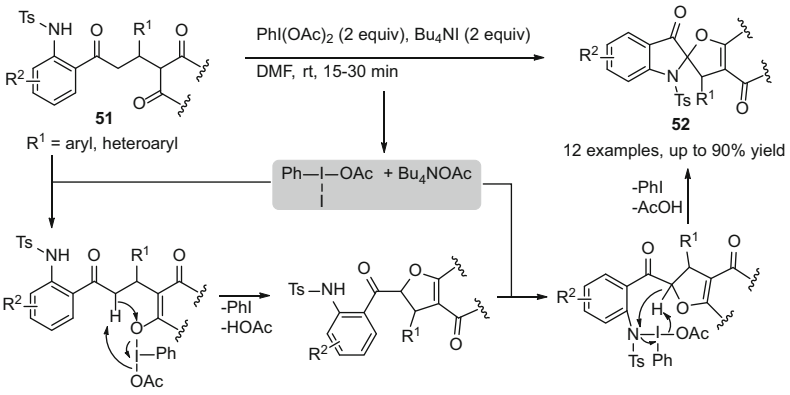
Scheme 11 Synthesis of tetramic acid derivatives and azetidines

dione ring system **48** was developed via intramolecular sp^3 C–H amination of 1-acetyl *N*-aryl carboxamides **47** in the presence of the mild iodine(III) oxidant $PhI(OPiv)_2$ (Scheme 11 (1)) [45]. In 2010, Fan and coauthors [46] reported a PhIO-mediated oxidative cyclization of substrate **49**, a Michael adduct of 2-aminomalonates with chalcones, to afford highly functionalized azetidines **50** with high diastereoselectivity (>95:5) (Scheme 11 (2)). The protocol was successfully adopted for the synthesis of biologically and medicinally important oxetanes [47].

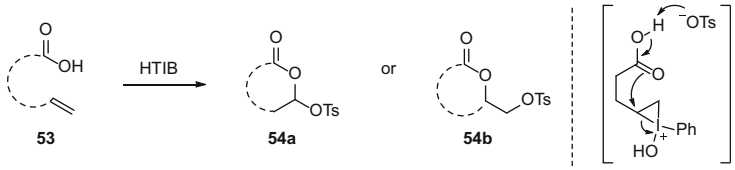
In 2011, Fan et al. [48] developed an efficient PIDA/TBAI-mediated method for constructing oxa-aza spirobicycles **52** from substrates **51**. A reaction pathway shown in Scheme 12 was proposed for this highly interesting tandem C–O/C–N bond-forming reaction.

2.1.3 Annulation via Activation of Double and Triple Bonds

In 1986, Taschner, Koser, and coworkers [49] showed that various olefinic acids **53** in the presence of HTIB lead to the formation of tosyloxylactones **54** via an



Scheme 12 Synthesis of oxa-aza spirobicycles

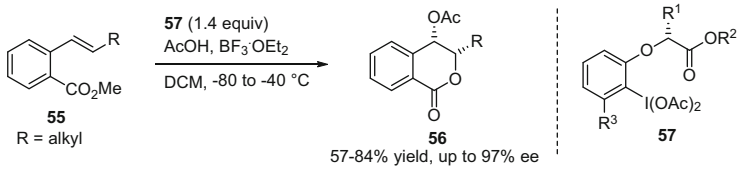


Scheme 13 Lactonization of alkenoic acids using HTIB

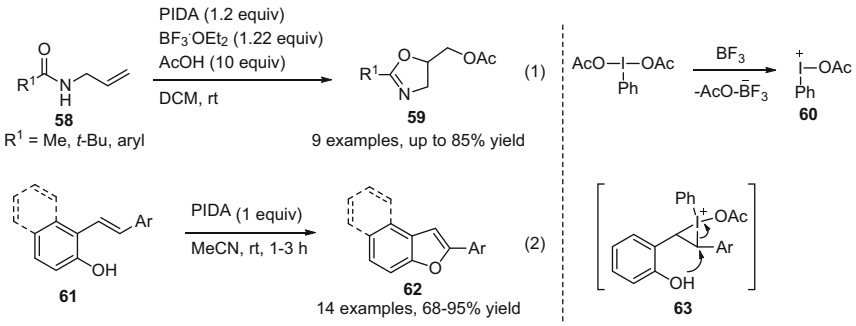
intramolecular oxidative C–O bond formation (Scheme 13). The reaction was proposed to occur via the intermediacy of an iodonium ion which, after its formation, gets intercepted by the pendant carboxylate ion. Thereafter, several examples of such reactions of unsaturated compounds using different hypervalent iodine(III) reagents have been reported [50–52].

In recent years, chiral hypervalent iodine(III) reagents have received immense attention and have been applied extensively in the stereoselective synthesis of heterocycles. In 2010, Fujita et al. [53, 54] documented an enantiodifferentiating *endo*-selective oxylactonization of *ortho*-alkenylbenzoates **55** by using a series of optically active lactate-derived iodine(III) reagents such as **57** (Scheme 14). This stereocontrolled transformation allowed efficient access to optically active 4-oxyisochromanones **56**.

A similar methodology was applied by Moon et al. [55] in the oxidative cyclization of *N*-allylamides **58** to afford oxazolines **59** (Scheme 15 (1)). In this reaction, the electrophilicity of PIDA was enhanced by the addition of Lewis acid ($BF_3 \cdot OEt_2$) to generate the more electrophilic aryliodonium **60**, which then triggered the cyclic iodonium ion formation and cyclization event. Wirth and coworkers [56] demonstrated a convenient PIDA-mediated intramolecular cyclization route to 2-arylbenzofurans **62** starting from *ortho*-hydroxystilbenes **61** (Scheme 15 (2)). The method was subsequently extended to 2-arylnaphthofurans



Scheme 14 Synthesis of optically active 4-oxyisochromanones

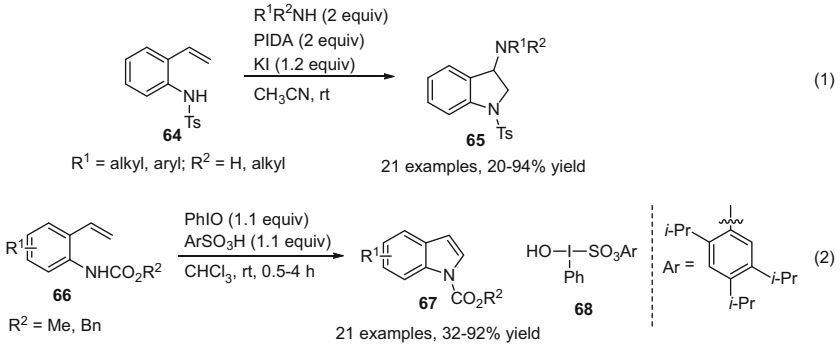


Scheme 15 PIDA-mediated synthesis of oxazolines, benzofurans, and naphthofurans

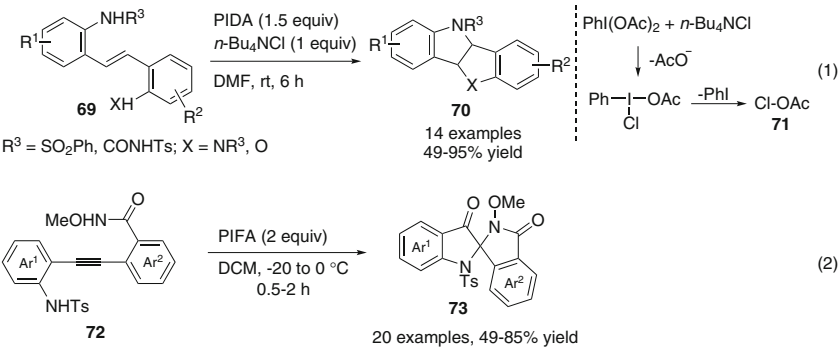
as well. The authors proposed that the reaction is going through the intermediacy of three-membered iodonium ions **63**.

In addition to carboxylic acids and phenols, *N*-centered nucleophiles such as anilides and amides have also been reported to participate in the iodine(III)-mediated oxidative cyclization reaction. Johnston's group [57] developed a PIDA-assisted, combined intermolecular/intramolecular diamination reaction of tosyl-protected 2-vinyl anilines **64** to provide diverse 3-aminoindoline derivatives **65** (Scheme 16 (1)). Based on the mechanistic experiments performed, the authors anticipated that the reaction occurs through the intermediacy of electrophilic nitrogen, generated in situ by the reaction of iodonium ion and primary or secondary amines. Muñiz and coworkers [58] successfully extended the intramolecular amination of alkenes to the synthesis of indoles. The authors showed that 2-vinyl anilines of type **66** can be efficiently transformed to the corresponding indole derivatives **67** employing modified Koser reagent **68** which is generated in situ from 2,4,5-tris-isopropyl benzene sulfonic acid and iodosobenzene (Scheme 16 (2)). The authors showed that this modified Koser reagent **68** can also be generated in situ in a catalytic manner using *m*CPBA as a terminal oxidant.

Chang and coauthors [59] developed a facile intramolecular oxidative diamination of olefins using PIDA and a halide additive such as *n*-Bu_4NCl to furnish diverse bisindolines **70** (Scheme 17 (1)). The authors found that the halide additive was crucial for exerting the high reactivity of the iodobenzene diacetate. Addition of *n*-Bu_4NCl to PIDA released acetyl hypohalite **71** which reacted with olefin **69** to produce a halonium intermediate, which upon consecutive ring opening



Scheme 16 Intramolecular amination in the synthesis of indolines and indoles



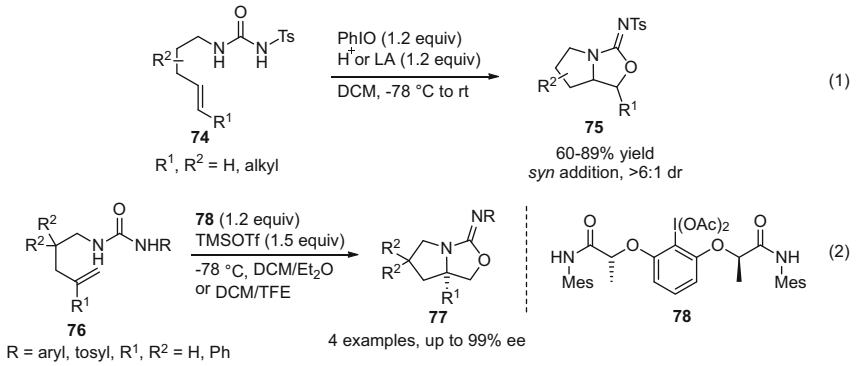
Scheme 17 Oxidative diamination towards the synthesis of bisindolines and spiroheterocycles

and nucleophilic substitution furnished desired bisindolines **70**. Along the same line, Du and coworkers [60] developed a PIFA-mediated cascade annulation protocol for the construction of a series of spiro heterocycles **73** from di-*ortho* substituted diarylacetylenes **72** (Scheme 17 (2)).

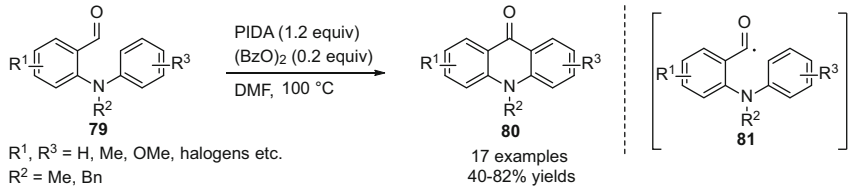
In 2008, Michael and coworkers [61] reported an intramolecular oxyamination of urea derivatives **74** having pendant unactivated alkenes using PhIO as an oxidant and Brønsted or Lewis acid as a promoter to furnish bicyclic isoureas **75** via *syn* addition (Scheme 18 (1)).Farid et al. [62] recently disclosed the asymmetric version of such a transformation. The authors described an efficient chiral hypervalent iodine **78**-mediated oxidative cyclization of alkenyl ureas **76** to optically pure isourea derivatives **77** (Scheme 18 (2)).

2.1.4 Annulation via Intermediacy of Radicals and Radical Cations

In recent years, radical chemistry has evolved as a very powerful tool for the preparation of nitrogen-containing heterocycles involving domino-type radical



Scheme 18 Synthesis of isourea derivatives by oxyamination reaction

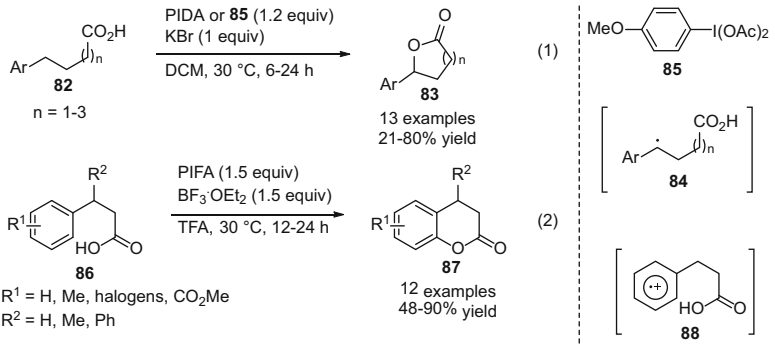


Scheme 19 Intramolecular arene-aldehyde coupling towards acridones

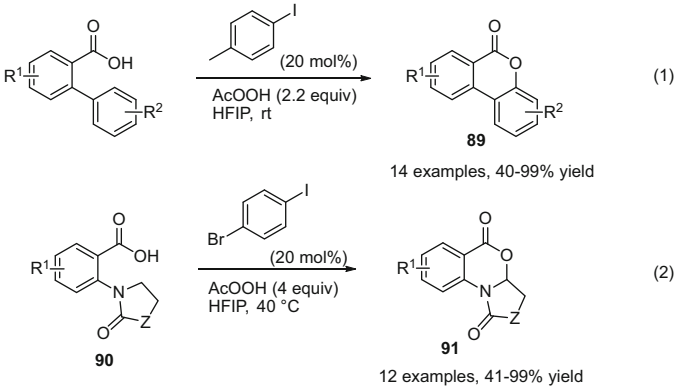
addition/cyclization reactions. In this regard, hypervalent iodine(III) reagents have received wide application as they allow generation of several reactive radicals, such as alkyl, azide, trifluoromethyl, acyloxy, etc., under metal-free conditions which finally lead to oxidative cyclization to afford diverse heterocyclic scaffolds.

Zhao and Du's group [63] developed a metal-free cross-dehydrogenative coupling (CDC) of various 2-(*N*-arylamino)aldehydes **79** for direct aryl-aldehyde C(sp^2)–C(sp^2) bond formation to provide a convenient approach for the synthesis of biologically important acridone derivatives **80** (Scheme 19). PIDA was used in combination with a substoichiometric amount of benzoyl peroxide as radical initiator for this oxidative intramolecular annulation reaction which presumably proceeds via the intermediacy of acyl radicals **81**.

In 2007, Dohi et al. [64] developed a mild oxidative C–H lactonization of carboxylic acids **82** for the direct construction of biologically important aryl lactones **83** using a combination of hypervalent iodine(III) reagent and KBr (Scheme 20 (1)). The reaction went through the generation of benzyl radical **84** which then ensured the successive lactone-forming step. In 2010, Gu and coauthors [65] showed that 3-aryl propionic acids **86** undergo oxidative cyclization to 3,4-dihydrocoumarins **87** in the presence of PIFA as an oxidant and $BF_3 \cdot OEt_2$ as a Lewis acid (Scheme 20 (2)). The authors proposed that radical cation **88**, formed by one electron oxidation by PIFA, initially undergo a nucleophilic attack by the carboxylic acid. Following this, rearrangement of the resulting spirolactone cation and deprotonation generated dihydrocoumarin **87**. Later, Zhao's group [66] adopted



Scheme 20 Synthesis of aryl lactones and dihydrocoumarin derivatives

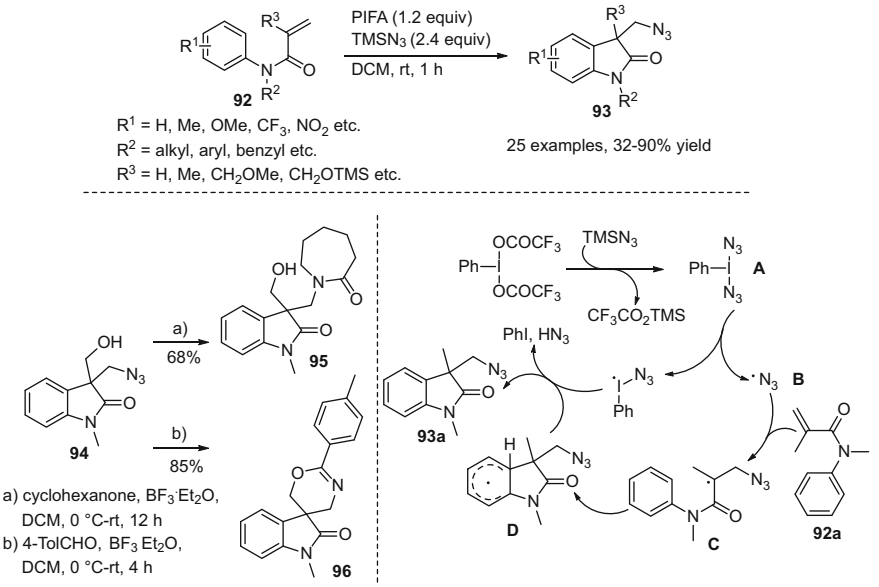


Scheme 21 Organocatalytic synthesis of benzolactone and benzoxazinone derivatives

a similar strategy and showed that coumarin derivatives can be synthesized from phenylacrylic acids by PIDA/I_2-mediated and irradiation promoted oxidative C–O bond formation.

Martin and coworkers [67] have recently developed a mild organocatalytic C (sp^2)–H bond functionalization/C–O bond forming process that provides efficient access to benzolactones **89** (Scheme 21). The authors used 20 mol% of 4-iodotoluene as an organocatalyst in combination with 2.2 equiv. of AcOOH as a terminal oxidant in this intramolecular oxidative coupling reaction. Importantly, the authors successfully extended the methodology to the functionalization of the C (sp^3)–H bond in **90** to obtain diverse benzoxazinone derivatives **91**. Interestingly, in this case 4-bromoiodobenzene was found to be the optimal organocatalyst.

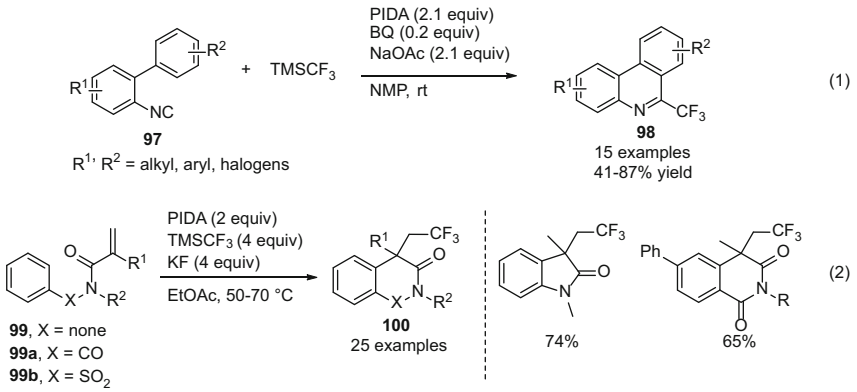
Antonchick's group [68] developed a PIFA-mediated unprecedented and efficient azidoarylation of alkenes which occurs under mild and metal-free reaction conditions and provides a general approach to the synthesis of biologically interesting 2-oxindoles **93** (Scheme 22). In order to demonstrate the potential of the methodology, the authors performed several post-synthetic transformations of the



Scheme 22 Azidoarylation of alkenes towards the synthesis of oxindoles

azide-containing final product. For example, hydroxyl group-assisted Schmidt reaction of product **94** with cyclohexanone and *p*-tolualdehyde provided important heterocycles such as lactam **95** and oxazoline **96**, respectively (Scheme 22). According to the proposed mechanism, initial double ligand exchange between PIFA and $TMSN_3$ would provide intermediate **A**, which then undergoes thermal homolytic cleavage to generate azidyl radical **B** (Scheme 22). This radical **B** then adds to the alkene in substrate **92** to generate a *C*-centered radical **C**, which undergoes intramolecular aromatic substitution to give intermediate **D**. Finally, oxidation and deprotonation of **D** provides oxindole **93a**.

Along these lines, intramolecular trifluoromethylations leading to the formation of several heterocycles, such as phenanthridines and 2-oxindoles, were reported. Zhou and coauthors [69] developed a mild and efficient method for the synthesis of 6-(trifluoromethyl)phenanthridines **98** through oxidative cyclization of 2-isocyanobiphenyls **97** with PIDA and trifluoromethyltrimethylsilane ($TMSCF_3$) under metal-free conditions (Scheme 23 (1)). Soon after, Liu, Tan, and coworkers [70] reported a similar carbotrifluoromethylation of *N*-arylacrylamides **99** for the synthesis of trifluoromethylated oxindoles **100**. The authors showed that, besides *N*-arylacrylamides **99**, α,β-unsaturated imides **99a** and conjugated tosyl amides **99b** were also compatible substrates in this reaction. Mechanistically, on both occasions, the trifluoromethyl radical was generated from $TMSCF_3$ in a similar manner as the azide radical in the azidoarylation process.



Scheme 23 Carbotrifluoromethylation in the synthesis of phenanthridines and oxindoles

2.2 *Synthesis of Heterocycles Through Intermolecular Bond Formation*

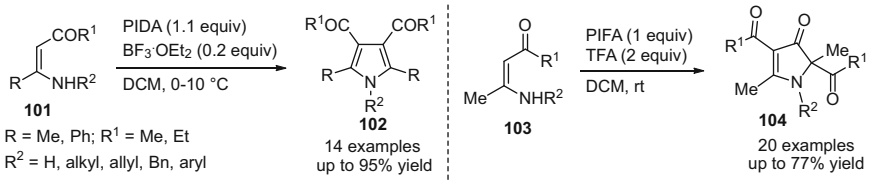
Hypervalent iodine(III)-mediated/catalyzed synthesis of heterocycles is not confined to intramolecular bond formation; in fact, several heterocycles have been synthesized through multiple intermolecular bond-forming reactions.

2.2.1 Intermolecular C–C/C–N Bond Annulation

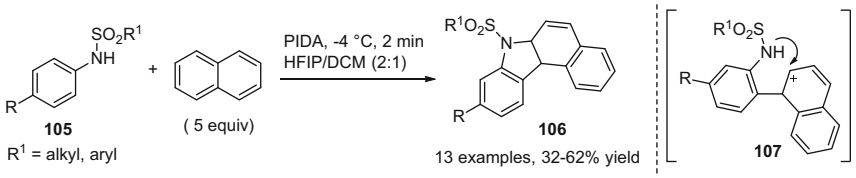
In 2009, Wang et al. [71] demonstrated that enamine esters or ketones **101** undergo oxidative homocoupling in the presence of PIDA and $BF_3 \cdot OEt_2$ to afford symmetric polysubstituted pyrroles **102** (Scheme 24). The authors could show that some non-symmetric pyrroles can also be prepared using this protocol. Similarly, Dong and coworkers [72] developed a PIFA-mediated intermolecular condensation of enaminones **103** for the synthesis of highly substituted pyrrolin-4-ones **104**. The postulated mechanism involves multiple steps: sequential N–C bond cleavage, new N–C bond formation, intramolecular addition reaction, and benzilic acid-type rearrangement (Scheme 24).

Canesi and coworkers [73] recently reported an elegant oxidative dearomatizing formal cycloaddition process between sulfonamides **105** and naphthalene to afford highly fused tetracyclic compounds **106** (Scheme 25). The reaction is postulated to occur via an intramolecular nucleophilic addition of the *N*-moiety to Wheland intermediate **107** generated during the oxidative umpolung activation. The above reaction with slightly modified conditions was successfully applied to the synthesis of dihydrobenzo[*b*,*d*]furan derivatives [73].

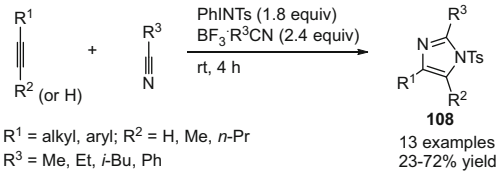
Zhdankin and coauthors [74] developed very recently a metal-free regioselective synthesis of 2,4-disubstituted or 2,4,5-trisubstituted imidazoles **108** using terminal



Scheme 24 Synthesis of polysubstituted pyrrole and pyrrolin-4-one derivatives



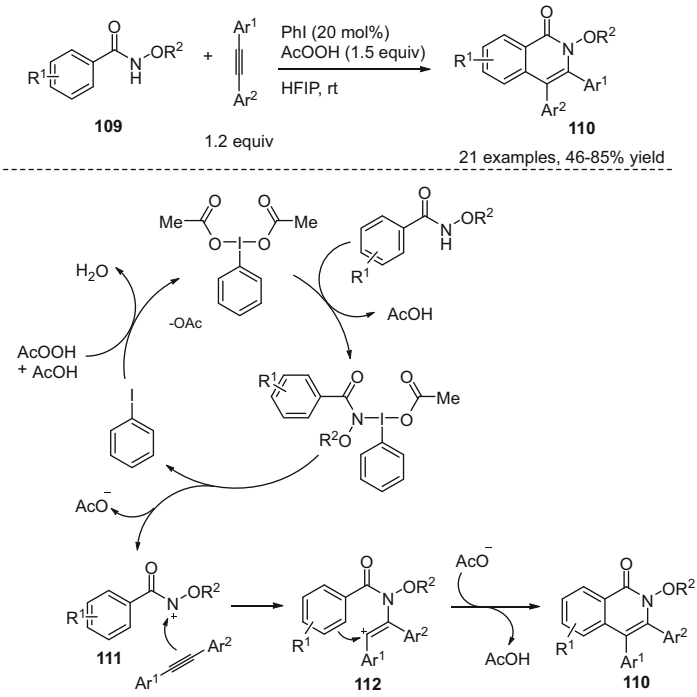
Scheme 25 Synthesis of highly fused indoline derivatives



Scheme 26 Synthesis of highly substituted imidazoles by metal-free [2 + 2 + 1] annulation

or internal alkynes and nitriles in the presence of PhINTs and borontrifluoride · nitrile complexes (Scheme 26). A similar regiochemistry of the product was observed in Saito and coworker's [75] previous report on the synthesis of substituted oxazoles by oxidative [2 + 2 + 1] annulation of alkynes.

Meanwhile, Antonchick and coworkers [76] described a conceptually novel transition metal-free highly regioselective synthesis of diverse isoquinolone derivatives **110**. In this mild iodobenzene-catalyzed annulation process, a series of readily available symmetrical and non-symmetrical internal alkynes were coupled with *N*-alkoxybenzamide derivatives **109** in the presence of peracetic acid as an oxidant (Scheme 27). This result is indeed highly intriguing considering the fact that such annulation reactions have previously been achieved only through expensive transition metal (Pd, Rh, Ni, Ru) catalyzed processes requiring high temperatures, external oxidants, and longer reaction times [77–82]. The mechanistic cycle of this transformation presumably begins with the formation of a nitrenium ion **111**, in a manner similar to that described in Sect. 2.1.1. Following its generation, **111** gets attacked by the alkyne to form vinyl cation **112**, which then undergoes intramolecular Friedel–Crafts reaction to form isoquinolone **110**. Zhu, Zheng, and coworkers [83] have reported a similar oxidative annulation reaction using stoichiometric amounts of PIFA in the presence of trifluoroacetic acid (TFA).

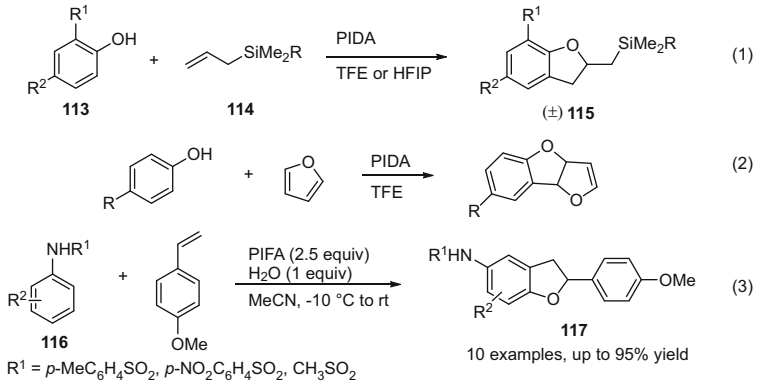


Scheme 27 Synthesis of isoquinolone via organocatalytic annulation of benzamides and alkynes

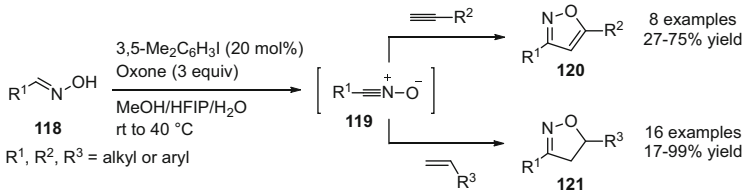
2.2.2 Intermolecular C–C/C–O Bond Annulation

The research group of Canesi [84] found that several dihydrobenzofurans **115** can be synthesized in moderate to good yields by treating substituted phenols **113** with allyltrimethylsilanes **114** and PIDA via an oxidative formal (2 + 3) cycloaddition (Scheme 28 (1)). A formal (2 + 3) cycloaddition between furan and substituted phenols was also realized using PIDA as an oxidant (Scheme 28 (2)) [85–87]. In this "aromatic ring umpolung" process, PIDA oxidizes phenols to the corresponding phenoxenium ions, a very electrophilic species which reacts with various nucleophiles leading to the formation of diverse core structures prevalent in many natural products [87]. Along these lines, Fan and coworkers [88] documented an efficient one-pot PIFA-mediated oxidative heteroannulation of *N*-sulfonylaniline derivatives **116** with styrenes for the synthesis of 5-aminocoumaran derivatives **117** (Scheme 28 (3)).

The in situ generation of nitrile oxides **119** and subsequent intra- or intermolecular 1,3-dipolar cycloaddition reactions with alkenes and alkynes represent one of the most exploited strategies for the preparation of diverse isoxazoline **121** and isoxazole **120** derivatives. Ciufolini et al. [89] reported that PIDA in combination with a substoichiometric amount of TFA efficiently oxidize aldoximes **118** to nitrile oxides **119**, which were trapped in situ with olefins to afford



Scheme 28 Oxidative cycloaddition reactions for the synthesis of coumaran derivatives



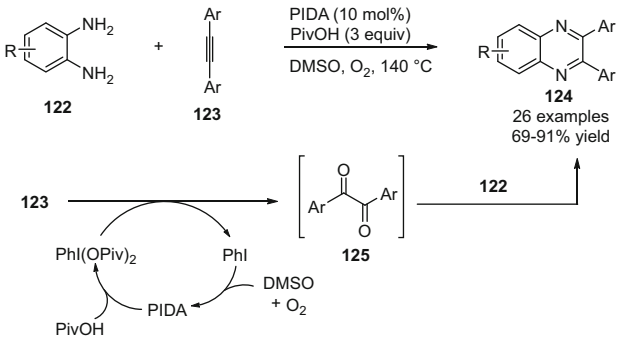
Scheme 29 Organocatalytic synthesis of isoxazolines and isoxazoles

isoxazoline derivatives. Meanwhile, Delft and coworkers [90] demonstrated the use of PIFA for the in situ generation of nitrile oxides from aldoximes and the cycloaddition with alkynes to give 3,5-di- and 3,4,5-tri-substituted isoxazoles in good yields. A similar strategy was applied in the synthesis of benzo[*d*]isoxazole-4,7-diols in aqueous medium via cycloaddition of nitrile oxides and benzoquinone intermediates using PIDA as an oxidant [91].

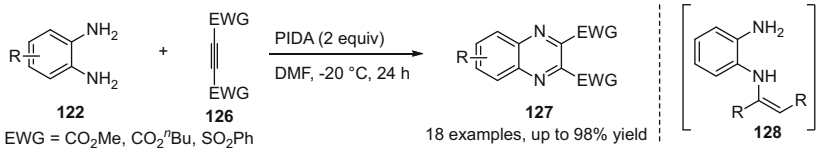
Zhdankin and coauthors [92] showed that nitrile oxides **119** can be generated by hypervalent iodine-catalyzed oxidation of aldoximes **118** using oxone as a terminal oxidant (Scheme 29). These in situ generated nitrile oxides **119** reacted with several alkenes and alkynes to afford the corresponding isoxazolines **121** and isoxazoles **120** in moderate to good yields.

2.2.3 Intermolecular C–N/C–N Bond Annulation

Wang, Chung, and coworkers [93] showed that biologically important quinoxalines **124** can be effectively synthesized via PIDA-catalyzed oxidative coupling between 1,2-diaminobenzenes **122** and internal alkynes **123** (Scheme 30). The authors proposed that $PhI(OPiv)_2$ initially formed from the reaction of PIDA and PivOH, reacts with **123** to produce benzoins **125**, which then undergo subsequent



Scheme 30 Organocatalytic synthesis of quinoxaline derivatives



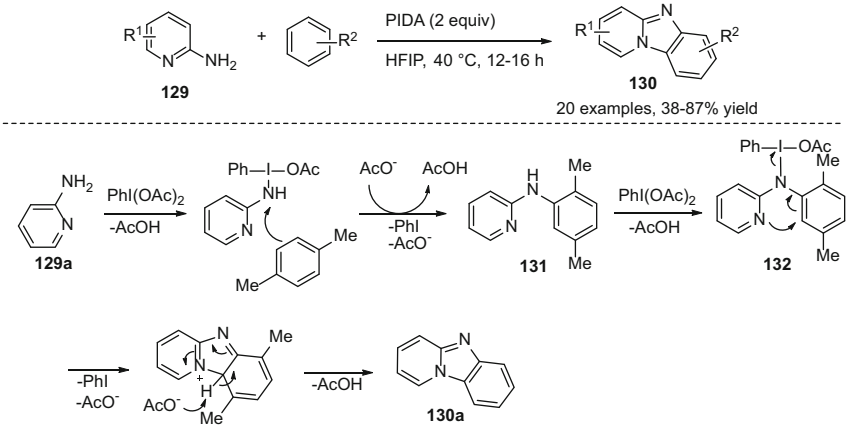
Scheme 31 Oxidative [4 + 2] annulation for the synthesis of quinoxalines

condensation with 1,2-diaminobenzene **122** to afford the desired compounds **124**. The oxidant $PhI(OPiv)_2$ was regenerated in situ by oxidation of iodobenzene in the presence of oxygen and pivalic acid (Scheme 30).

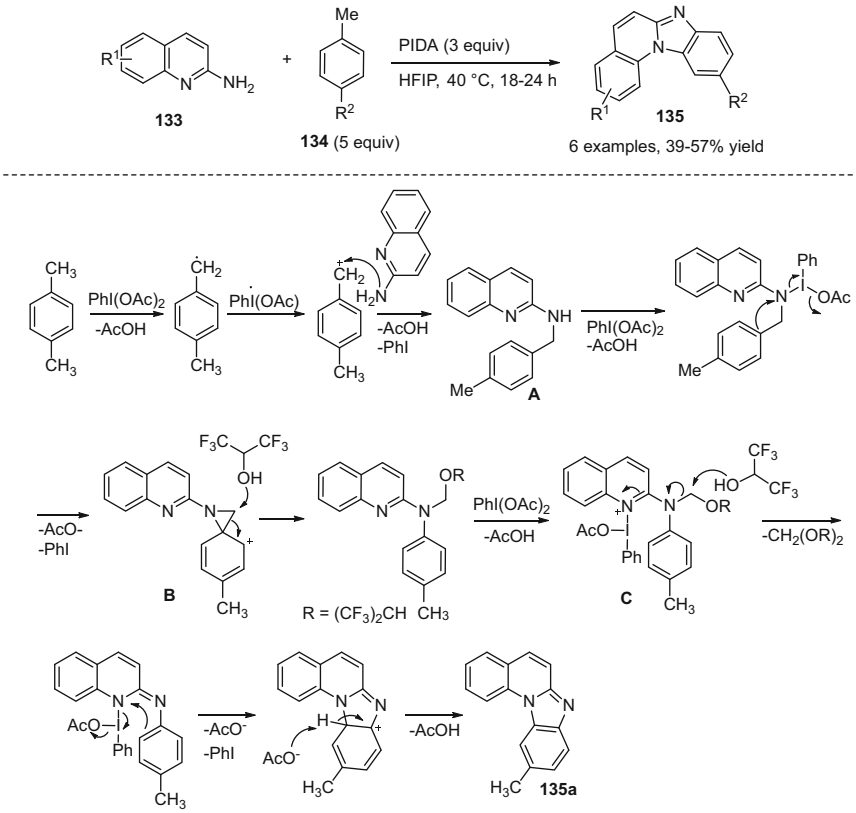
In a different approach, Minakata and coworkers [94] developed a practical and high yielding PIDA-induced oxidative [4 + 2] annulation of *o*-phenylene diamines **122** and electron-deficient alkynes **126** for direct access to quinoxalines **127** bearing two electron-withdrawing groups (Scheme 31). The formation of quinoxalines **127** was proposed to occur via an initial generation of enamine **128**, which was likely to undergo PIDA-mediated oxidative annulation and rearomatization.

Antonchick and coauthors [95] recently developed a novel PIDA-mediated intermolecular annulation of 2-aminopyridines **129** and simple arenes under metal-free conditions to obtain pyrido[1,2-*a*]benzimidazoles **130** which are prevalent in many natural products and pharmaceuticals (Scheme 32). The authors proposed that an initial ligand exchange between PIDA and **129a** followed by nucleophilic attack of arene generates intermediate **131** (Scheme 32). Intermediate **131** reacts afterwards with a second equivalent of PIDA to form **132** which finally undergoes intramolecular annulation with the loss of PhI and AcOH to generate product **130a**.

Interestingly, when the authors used 2-aminoisoquinoline derivatives **133** instead of 2-aminopyridines **129** in the coupling reaction with arene **134**, the annulation product **135** was obtained which lacked one methyl group (Scheme 33) [95]. Essentially, one of the methyl groups of *p*-xylene acts as a traceless directing group in this unprecedented transformation. Based on several control experiments,



Scheme 32 Intermolecular synthesis of pyrido[1,2-*a*]benzimidazoles



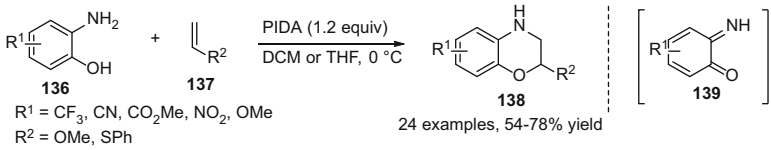
Scheme 33 Synthesis of benzo[4,5]imidazo[1,2-*a*]quinolines

the authors proposed that in the case of **133**, the reaction is initiated by oxidation of the benzylic position of arene **134** through successive single-electron transfer from PIDA to generate a benzylic cation which is attacked by **133** to form benzylic amination product **A** (Scheme 33). Intermediate **A** then reacts with PIDA and subsequently undergoes *ipso* substitution to form cation **B**. The opening of the aziridine ring in **B** by HFIP, followed by reaction with PIDA, provides **C**. Afterwards, nucleophilic attack by HFIP leads to the cleavage of the C–N bond in **C** accounting for the formal loss of a methyl group from the arene substrate. Finally, intramolecular cyclization and rearomatization provides the final product **135a**.

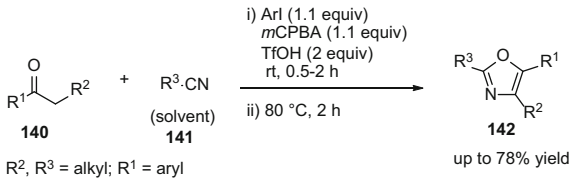
2.2.4 Intermolecular C–N/C–O Bond Annulation

Bodipati et al. [96] showed that the highly reactive *o*-quinone monoamine intermediates **139**, generated by treatment of *o*-aminophenols **136** with PIDA, readily undergo completely regioselective [4 + 2] cycloadditions with vinyl ethers and phenyl vinyl sulfide to afford *N*-unsubstituted-1,4-benzoxazine derivatives **138** (Scheme 34).

As described in Sect. 2.1.2, the α-functionalization (tosylation, triflation) of ketones with hypervalent iodine, followed by nucleophilic attack by diverse nucleophiles in an intramolecular fashion offers a convenient entry to various heterocycles [6]. Such a transformation can also be realized in an intermolecular fashion. Along these lines, Togo and coworkers [97] reported an elegant one-pot synthesis of 2,4,5-trisubstituted oxazoles **142** from alkyl aryl ketones **140** and nitriles **141** via an iodoarene-catalyzed oxidation reaction (Scheme 35). In this reaction sequence, reactive aryliodonium species were generated in situ by the reaction of aryl iodide with *m*CPBA and trifluoromethanesulfonic acid (TfOH). Afterwards, aryliodonium species reacted with alkyl aryl ketone to form a β-keto aryliodonium species.



Scheme 34 Synthesis of 1,4-benzoxazine derivatives



Scheme 35 Synthesis of tri-substituted oxazoles

This iodine(III) species then reacted with **141** to give the corresponding trisubstituted oxazole derivatives **142**.

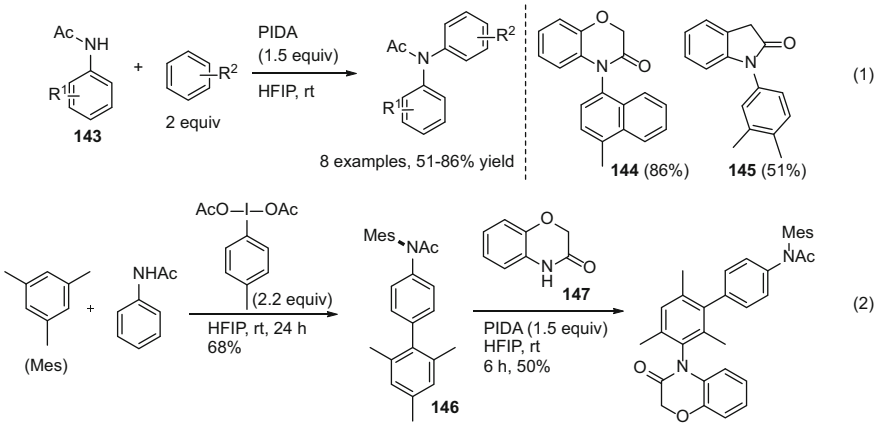
3 Functionalization of Heterocycles

The direct C–H functionalization to install new C–C and C–N bonds provides an alternative to the classical de novo synthesis and renders synthetic routes more straightforward and atom-economical. The late-stage functionalization of heterocyclic compounds and drug candidates has evolved as a powerful strategy for the development of new drugs and methods, and hence such direct manipulations are highly desirable [98]. Lately, several hypervalent iodine(III)-mediated/catalyzed transformations, such as intermolecular amination, cross dehydrogenative coupling (CDC), etc., have been successfully applied in the direct C–H functionalization of several heterocycles and bioactive molecules.

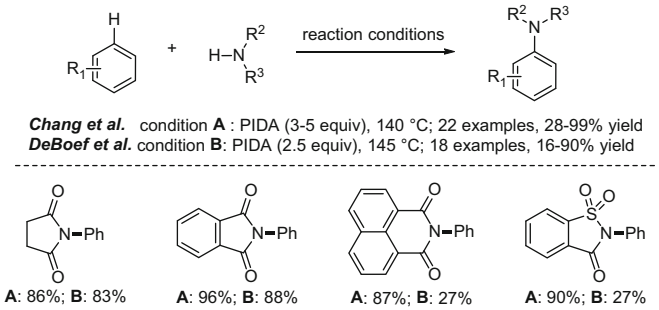
3.1 Functionalization via Intermolecular Oxidative Amination

Intermolecular oxidative amination is one of the most crucial and challenging C–N bond-forming transformations. Substantial progress based on transition metal catalysis has been made in this field, but the corresponding metal-free variant is underdeveloped and highly desirable. In the last decade, iodine(III) reagents have evolved as efficient tools for performing such oxidative intermolecular cross coupling reactions to construct C–N bonds without the aid of any transition metals. In 2002, Kikugawa and coworkers [99] realized a PIFA-mediated *N*-iodophenylation of acetanilide derivatives to provide acetyldiarylamines in moderate to good yields. In a recent development, Antonchick's group [13] demonstrated an example of a direct oxidative C–N bond formation between acetanilide **143** and non-prefunctionalized arenes using PIDA as an oxidant (Scheme 36 (1)). Besides acyclic amides, the authors were able to functionalize several cyclic amides such as 2*H*-1,4-benzoxazin-3(4*H*)-one and oxindoles to furnish the corresponding cross-coupled heterocycles **144** and **145**, respectively, in moderate to good yields. Subsequently, the authors developed a protocol for *para*-selective diarylation of anilides using an excess of *para*-tolyliodonium diacetate as an oxidant [100]. The final products were obtained with high regioselectivity and are amenable for further amination as was demonstrated by the successful amination of **146** by benzoxazinone **147** (Scheme 36 (2)).

Simultaneously, Chang's [101] and DeBoef's group [102] independently reported an intermolecular oxidative amination of simple arenes using PIDA as a stoichiometric oxidant (Scheme 37). The authors were able to arylate several



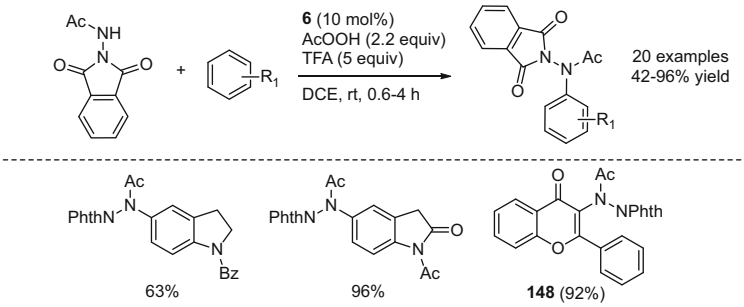
Scheme 36 Metal-free arylation of heterocycles



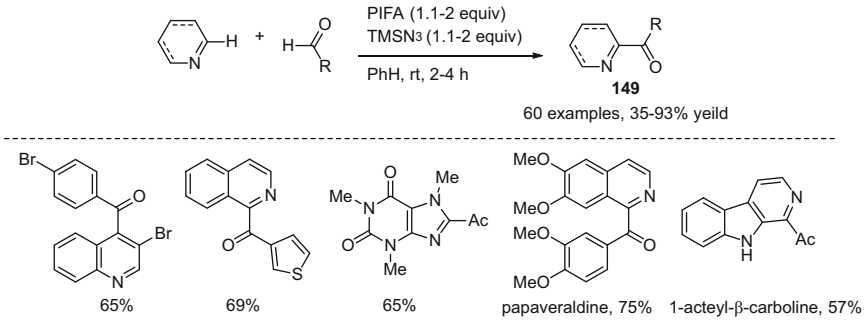
Scheme 37 PIDA-mediated intermolecular arylation of heterocycles

heterocycles to form new C–N bonds under the respective reaction conditions. Interestingly, whereas Chang and coworkers proposed that the reaction could proceed through electrophilic aromatic substitution, DeBoef and coauthors postulated a radical cationic pathway caused by the regiochemical mixture of products.

Unfortunately, all of these amination methods require stoichiometric or more than stoichiometric amounts of hypervalent iodine reagents, which necessitated the development of organocatalytic and mild variants of such transformations. To this end, Antonchick and coworkers [103] disclosed a highly efficient intermolecular process for the introduction of an amine or hydrazine functionality into simple non-prefunctionalized arenes. The method was successfully utilized in the hydrazination of several heterocyclic compounds and biologically active molecules (Scheme 38). For example, late stage functionalization using this organocatalytic method afforded a hydrazinated analogue of Vitamin P **148** in good yield (Scheme 38).



Scheme 38 Organocatalytic hydrazination of heterocycles



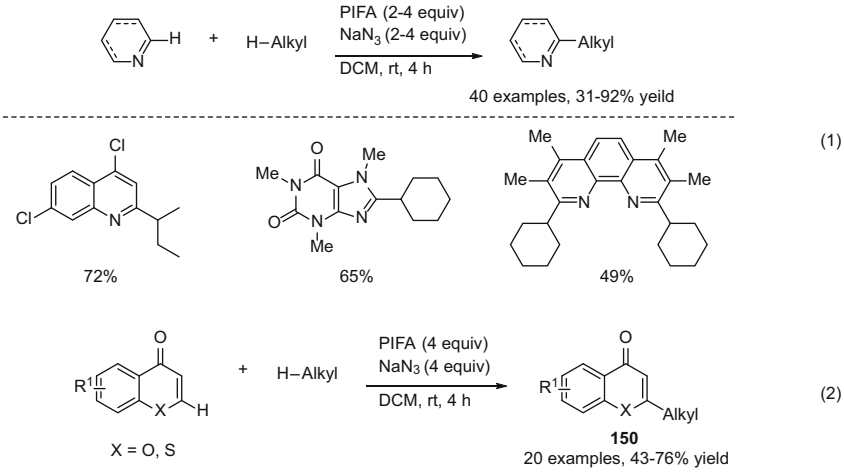
Scheme 39 PIFA-mediated CDC of heterocycles and aldehydes

3.2 Functionalization of Heterocycles via CDC

Hypervalent iodine(III) reagents have recently been applied in the direct functionalization of heterocycles by cross-dehydrogenative coupling reactions leading to the formation of new C–N and C–C bonds.

Antonchick and coauthors [104] developed an efficient and robust PIFA-mediated method for the direct functionalization of heterocycles with aldehydes in the presence of trimethylsilyl azide ($TMSN_3$) as an additive (Scheme 39). Several nitrogen-containing heterocycles, such as quinoline, isoquinoline, quinoxazaline, β-carboline, and caffeine, to name a few, could be successfully cross-coupled to provide the corresponding acylated heterocycles **149** in good yields. Most importantly, the methodology was shown to provide one-step access to many isoquinoline alkaloids such as papaveraldine and pulcheotine which exhibit important biological and medicinal properties.

Afterwards, Antonchick and coworkers [105] successfully extended this methodology to the oxidative cross coupling of heteroarenes and simple unfunctionalized alkanes (Scheme 40 (1)). The new $C(sp^3)$–$C(sp^2)$ bond formation occurred selectively at the electron-deficient site of the arene. The reaction was



Scheme 40 PIFA-mediated CDC of heterocycles and alkanes

found to be very versatile and a range of heterocycles, such as pyridine, quinoxaline, phthalazine, quinazoline, pyrimidine, benzimidazole, purine, and pyridopyrazine, underwent CDC to provide the cross-coupled products in good to excellent yields. The authors have recently shown that (thio)chromones, an important heterocyclic motif, undergoes oxidative cross coupling with several cyclic and acyclic alkanes in a similar manner to provide the corresponding alkylated (thio) chromones **150** (Scheme 40 (2)) [106].

4 Conclusions

In this chapter we describe the recent developments in the field of hypervalent iodine(III)-mediated synthetic transformations and their applications to the synthesis of several heterocycles. The recent surge of hypervalent iodine-based reactions as potential alternatives to transition metal-catalyzed reactions is expected to attract broad research interest and to lead to the development of many more novel synthetic methods. Considering the ready accessibility, environmentally benign nature, and unique oxidizing properties of these reagents, synthesis of more known or novel bioactive heterocyclic compounds through innovative disconnection approaches can be hoped for. In view of economic and environmental considerations, further development of catalytic methods should become an area of major focus, as this would make the process more sustainable. In addition, the development of efficient chiral organohypervalent iodine(III)-catalyzed stereoselective transformations is highly desirable, enriching the already impressive list of synthetic methods based on hypervalent iodine(III) reagents.

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Aminations with Hypervalent Iodine

Kilian Muñiz

Abstract Recent progress in the area of hypervalent iodine-mediated and catalyzed amination reaction of hydrocarbons is reviewed. These reactions comprise processes under both intra and intermolecular control and include the functionalization of aromatic C–H bonds as well as conversion of sp-, sp^2-, and sp^3-hybridized carbon atoms. These developments demonstrate that hypervalent iodine(III) methodology has reached a high level in amination chemistry. The individual reactions are discussed with a focus on mechanistic details and emphasis is made to the underlying hypervalent iodine reagents, for which structural information is available.

Keywords Alkenes • Amination • Arenes • C–N bond formation • Iodine–nitrogen bonds

Contents

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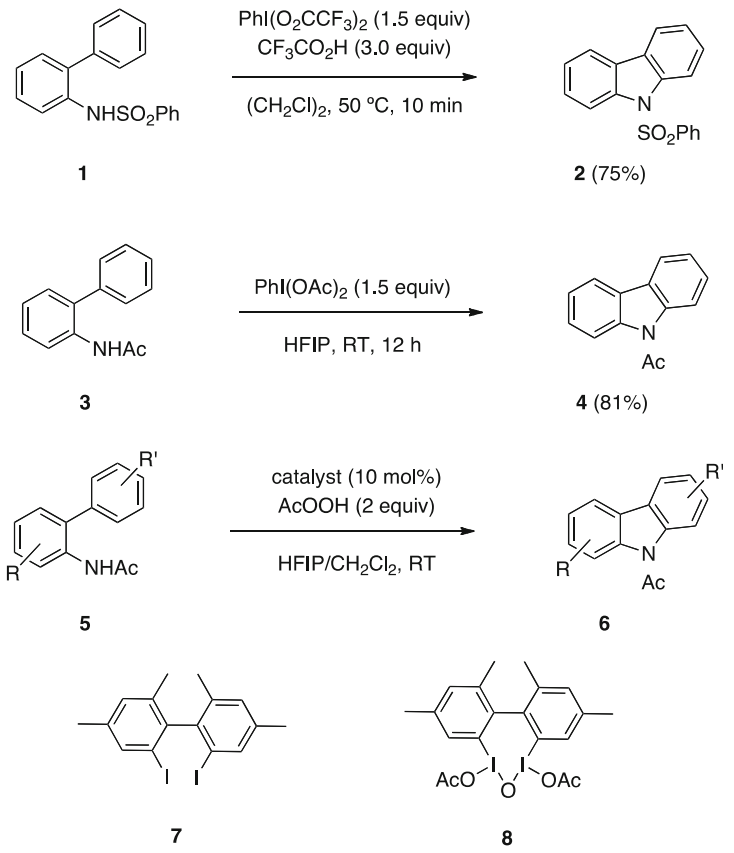
1 Introduction

Hypervalent iodine(III) reagents represent powerful metal-free alternatives in oxidation reactions [1]. In recent years the potential of these reagents to promote conceptually new C–N bond formations has been broadened to a significant extent [1, 2]. This chapter summarizes recent advances in the field of such hypervalent iodine mediated or catalyzed amination reactions, which are based on the oxidizing power of the hypervalent iodine itself. Reactions involving additional transition metal promoters or catalysts are not included. The major aim of this chapter is to summarize new methodology based on hypervalent iodine reagents or catalysts that enable synthetically meaningful transformations in amination chemistry. Examples include the intra- and intermolecular amination of sp^2-hybridized carbons as presented by arenes and heteroarenes, various trifunctionalization reactions of alkenes, and further unique transformations in the area. Although most of the processes employ common hypervalent iodine reagents such as diacetoxyiodobenzene [$PhI(OAc)_2$] and [bis(trifluoroacetoxy)iodo]benzene [$PhI(O_2CCF_3)_2$, PIFA] for an in situ functionalization of the nitrogen partner, recent advances have also provided new preformed reagents, which are discussed within the individual reactions.

2 Csp^2-Amination: Electrophilic Amination of Arenes

The interaction between nitrogen groups and hypervalent iodine(III) reagents usually leads to the formation of a discrete iodine–nitrogen bond, which undergoes heterolytic cleavage to provide an electrophilic nitrogen. The most convenient reactivity that can be employed is the attack of an aromatic system [3, 4]. Such a process has ample opportunity for the synthesis of aniline derivatives or nitrogenated heterocycles as demonstrated in the following. Furthermore, such a direct amination of a Csp^2–H bond under metal-free conditions represents a particularly economic process for heterocycles of pharmaceutical interest as the usual metal trace contamination often encountered in alternative transition metal mediated or catalyzed transformations is absent. In addition, the use of non-prefunctionalized arenes greatly streamlines synthetic chemistry.

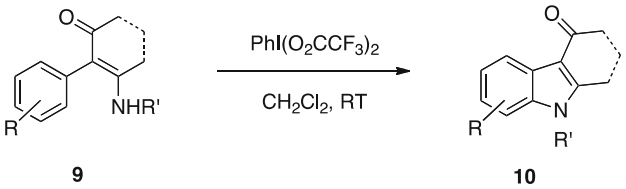


Scheme 1 Stoichiometric and catalytic aromatic amination

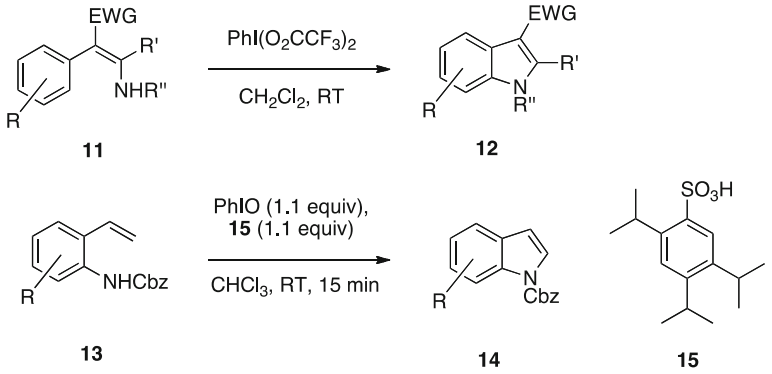
2.1 Intramolecular Reactions

An elegant reaction to underline this conceptual approach is the synthesis of carbazole from 2-amino biphenyl derivatives. For example, during the screening of metal catalyses for this transformation, Chang observed that the transformation from **1** to **2** proceeded readily in the presence of hypervalent iodine reagent itself (Scheme 1) [5].

The reaction was subsequently taken up by Antonchick, who developed suitable conditions for a reaction catalytic in iodine(III) [6]. Initially, the authors could demonstrate that a combination of diacetoxyiodobenzene [$PhI(OAc)_2$] in 1,1,1,3,3,3-hexafluoroisopropanol provided the corresponding carbazole **4** from precursor **3** in 81% isolated yield. Subsequent development of a catalytic transformation identified the sterically congested 1,1-diaryl,2,2-diiodide **7** as the optimum catalyst precursor. This compound is oxidized by peracetic acid under the reaction



Scheme 2 C–H amination for synthesis of annelated indoles



Scheme 3 C–H amination for indole synthesis

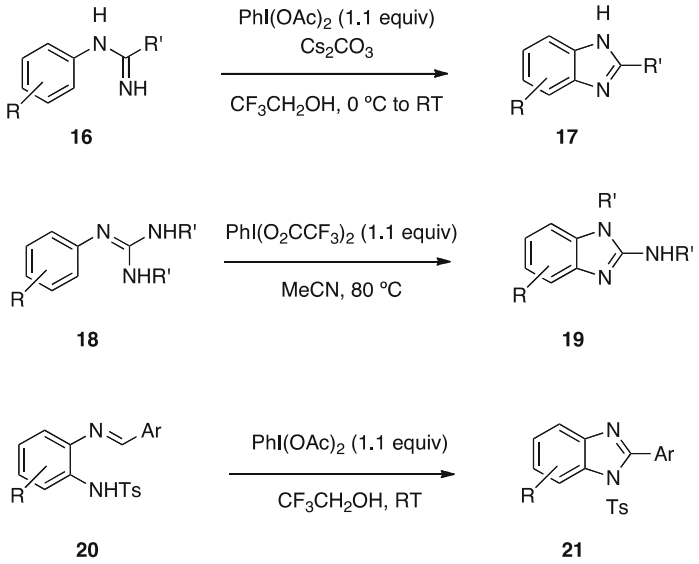
conditions to provide the active μ-oxo-bridged bisiodine(III) catalyst **8** (Kita's catalyst). The authors propose formation of an electrophilic nitrogen from **5** and **8** as the key step, which gives rise to cyclization to carbazole **6** upon nucleophilic attack by the second arene ring.

A related transformation was developed by Ban, who described the cyclization of enaminones **9** to indole derivatives **10** with PIFA as the only oxidizing reagent in dichloromethane under mild conditions (Scheme 2) [7]. The key step again is the formation of an electrophilic nitrogen for cyclization. A related cyclization toward indeno-1,4-diazepinones was also developed.

An interesting indole synthesis was realized by Zhao, who reported the PIFA-mediated cyclization of enamines **11** (Scheme 3) [8]. This reaction toward indoles **12** may rely on an electrophilic nitrogen atom to initiate cyclization or proceed through single electron transfer. Related pyrrole derivatives are also accessible by this method.

In contrast, Muñiz reported an indole synthesis from 2-vinyl anilines **13**, which relies on activation of the alkene moiety by the hypervalent iodine reagent [9]. The reaction employs a sterically congested Koser reagent generated in situ from iodosobenzene and the bulky sulfonic acid **15**. The reaction provides synthetically unique access to 2,3-unsubstituted indoles **14** and can also be conducted under catalytic conditions.

Another direct arene cyclization involves the synthesis of benzimidazoles **17** from *N*-aryl amidines **16** (Scheme 4) [10]. The cyclization proceeds readily with



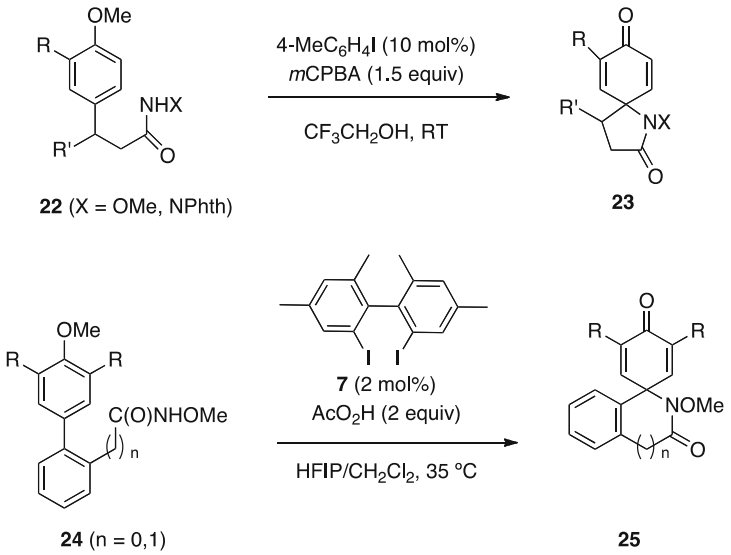
Scheme 4 C–H amination for benzimidazole synthesis

$PhI(OAc)_2$ in trifluoroethanol and in the presence of carbonate base within rather short reaction time and displays a remarkably large substrate scope. Mechanistically, the authors propose an initial interaction between the hypervalent iodine(III) reagent and the amidine nitrogen, which upon homolytic cleavage of the N–I bond initiates the start of a radical-based cyclization onto the arene ring. The reaction can also be conducted as a catalytic transformation using 20 mol% of PhI as catalyst and *m*CPBA as terminal oxidant. For this transformation HFIP is the preferred solvent [11].

Zhang extended this methodology to the cyclization of the corresponding *N*-aryl guanidines **18** to yield 2-aminobenzimidazoles **19**. Although closely related to the previous transformation, the reaction required significantly harsher conditions, including the use of PIFA as iodine(III) reagent [12].

Finally, an alternative intramolecular Csp^2–N bond coupling was described by Mal [13]. In this case, the authors developed conditions for the oxidative addition of an aniline to an imine group within the same molecule **20** to arrive at 2-arylated benzimidazoles **21**. The reaction is of ample scope. The mechanistic details are unclear at present and the authors propose an initial interaction between the tosylamido group and the hypervalent iodine reagent to initiate electrophilic amination chemistry, which is followed by an unprecedented cyclization upon the aldimine group.

Additional cyclization reactions involve the use of *N*-aryl 2-aminopyridines as cyclization precursors, which undergo C–N bond formation upon dearomatization [14–16]. For *N*-biaryl-2-aminopyridines, the cyclization event can be governed by



Scheme 5 Kita-amino-spirolactonization

electronic effects to differentiate between the carbazole formation and the dearomative amination, respectively [17].

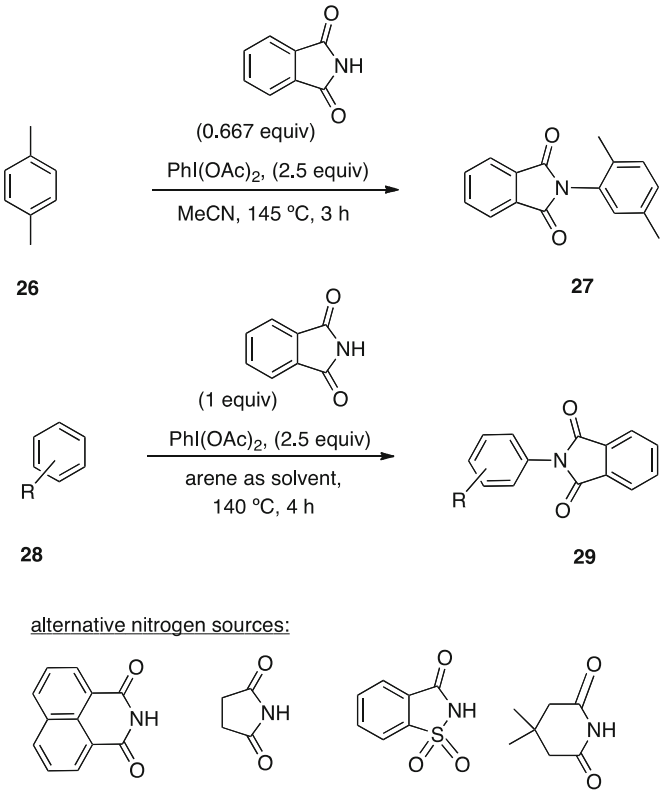
Within his seminal work on catalytic oxidative spiro-cyclization reactions, Kita reported on hypervalent iodine catalyzed lactamization reactions [18, 19]. These reactions lead to de-aromatization throughout the process, but appear to provide valuable entries into C–N bond formation involving congested carbon frameworks.

The initial realization involved a catalytic system of 4-tolyl iodide and *m*CPBA as terminal oxidant, which generates a hypervalent iodine reagent that promotes the formation of a cationic nitrogen. Subsequent nucleophilic attack of the anisole ring engages in C–N bond formation and ultimately in dearomatization.

An advanced catalyst system was provided with the use of the biaryl catalyst **7**, which could be employed at a catalyst loading of only 2 mol% in combination with the benign peracetic acid as terminal oxidant for the conversion of a series of the former substrates **23**. In addition, the reaction could also be employed for the arene-bridged substrates **24**, which led to the formation of six-membered spiro products **25** (Scheme 5) [19].

2.2 Intermolecular Reactions

Stoichiometric intermolecular amination reactions of arenes have been explored to a larger extent recently. Of major interest had been the investigation on the behavior of phthalimide in the presence of hypervalent iodine as oxidation promoter, which was simultaneously reported by DeBoef and Chang (Scheme 6) [20, 21]. The respective reactions of *p*-xylene **26** to 2-phthaloyl xylene **27** and arenes **28** to



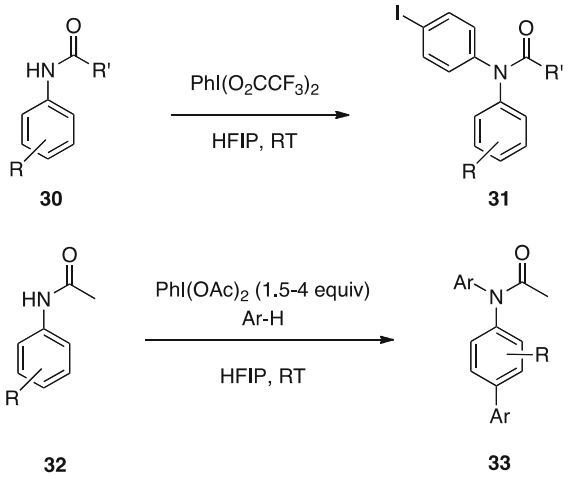
Scheme 6 Intermolecular C–H amination

N-aryl phthalimide **29** are suggested to proceed through a common intermediate generated from (diacetoxyiodo)benzene and phthalimide and which consists of a discrete I–N bond between the phthalimide group and the hypervalent iodine center. Interestingly, the authors provide different subsequent mechanistic accounts for the two similar transformations. Whereas DeBoef favors homolytic cleavage to generate a phthalimido radical [20], Chang proposes heterolytic cleavage to provide a nitrogen-centered cation for an electrophilic aromatic substitution [21]. Such a pathway may be supported by phthalimide containing cationic iodine(III) intermediates detected by Togo and Moriyama [22].

In addition to phthalimide and substituted derivatives, related compounds such as 1,8-naphthimide, succinimide, saccharine, or piperidien-2,6-dione could be used successfully [21].

The field was further advanced with the development of C–N coupling reactions of acetanilides such as **30** and **32** (Scheme 7). First, Kikugawa discovered that these compounds undergo direct coupling with PIFA in hexafluoroisopropanol as solvent and under mild conditions to give arylation products **31** [23]. The reaction is general for donor- and acceptor-substituted starting materials **30**. Formation of the products

Scheme 7 Intermolecular C–H amination of anilines

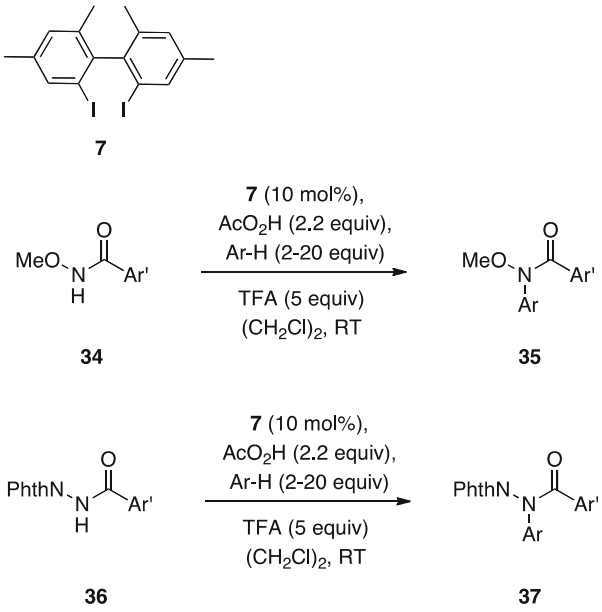


is believed to arise from initial iodine(III)–nitrogen bond formation followed by rearrangement to the final products. Second, a related reaction was developed by Antonchick addressing electron-rich arenes **32** [24]. In this case, double coupling occurred to provide the corresponding product **33** from concomitant C–N and para-selective C–C coupling of the arene with the anilide substrate, when the latter position was available. The reaction was suggested to proceed through oxidation of the amide and the formation of cationic nitrogen. The mesomeric stabilization of the latter provides an electrophilic *para*-position of the arene ring, which initiates C–C coupling. Subsequent further oxidation regenerates the electrophilic nitrogen that engages in C–N bond coupling.

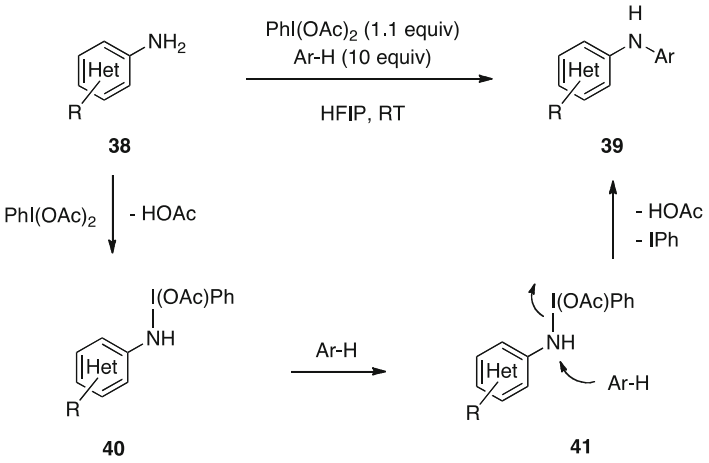
In addition to these reactions, Muñiz reported the intermolecular amination via bistosylimidation of an arene and an indole, respectively, with a preformed hypervalent iodine reagent [9, 25].

The requirement for stoichiometric amounts of iodine(III) reagent has triggered several attempts to develop catalytic reactions of intermolecular C–N bond formation (Scheme 8) [26]. Within this context, Antonchick employed the previously described diaryl-2,2-diiodide **7** as catalyst precursor for an intermolecular C–N bond formation. The reaction employs *N*-methoxy benzamides **34** as nitrogen source and displays a useful scope. Apart from the expected electron-rich arenes, electron-neutral and electron-poor arenes also undergo the C–N bond formation to **35**, in most cases with remarkable regioselectivity. The reaction could be extended to the corresponding *N*-acetamido phthalimide **36**, which showed similar substrate scope. Because of the bulkiness of the phthalimide substituent, high selectivity in favor of the more accessible C–H position of the arene partner was obtained for all coupling events towards products **37**.

Finally, Antonchick extended the scope of iodine-mediated intermolecular arylation reactions to primary amino heterocycles **38** to generate diarylanilines **39** (Scheme 9) [27]. This work is characterized by a broad substrate scope and the toleration of various heterocyclic cores. A mechanistic scenario was suggested that



Scheme 8 Catalytic intermolecular C–H amination



Scheme 9 Catalytic intermolecular C–H amination of anilines

involves an initial interaction **40** between the primary amino group and the hypervalent iodine followed by a scenario **41** of nucleophilic attack of the arene coupling partner at the electrophilic nitrogen.

3 Iminoiodanes for Nitrene Stabilization

The interaction of primary amines and amides is well reported for hypervalent iodine(III) compounds such as iodosobenzene PhIO or related compounds leading to formation of iminoiodanes [1]. These compounds are commonly stabilized by the presence of *N*-acceptor substituents such as sulfonyl groups. For the case of one typical derivative *N*-phenylsulfonylimido iodane $PhSO_2NIPh$, recent theoretical studies question the commonly displayed double bond between iodine and nitrogen, but rather suggest a structural scenario of a single bond character between the iodine and the nitrogen atom for this compound [28].

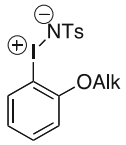
In general, compounds of this type contain a major synthetic drawback as they tend to show low solubility in common organic solvents. As a result, reactions often suffer from prolonged reaction times and incomplete conversions. A solution to overcome this limitation was the introduction of several arene rings with 2-sulfonylated groups [29–31].

A recent improvement was accomplished by Nemykin and Zhdankin, who introduced 2-alkoxyphenyl iminoiodanes **42** (Scheme 10), which displays significantly enhanced solubility and greatly advances the synthetic possibilities of imino-iodanes (see below) [32].

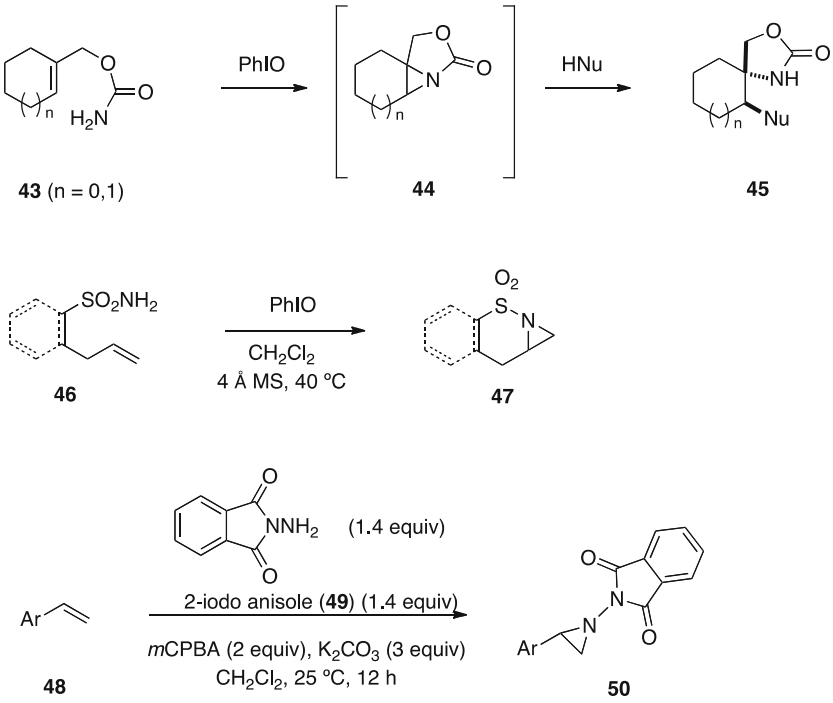
3.1 Aziridination

The formation of stabilized imino-iodanes as nitrene precursors has been exploited widely in aziridination of alkenes. Traditionally, isolated iminoiodanes have been the preferred route toward transition metal mediated or catalyzed aziridination or C–H amination chemistry [33]. Despite the great success in this field, some reports have become available on the corresponding transition metal-free variants. For example, Padwa reported an iodine(III)-mediated aziridination of some carbamates **43** from allylic alcohols that in situ formed the corresponding imino-iodanes. Unexpectedly, these compounds underwent direct aziridination to the putative tricyclic compound **44**, which was subsequently opened by addition of suitable nucleophiles to arrive at the 1,2-difunctionalized product **45** in a completely stereoselective manner (Scheme 11) [34]. This transformation constituted the proof of concept that iodine(III)-mediated aziridination does not necessarily require metal promoters.

Scheme 10 Structure of imido iodane **42**



42



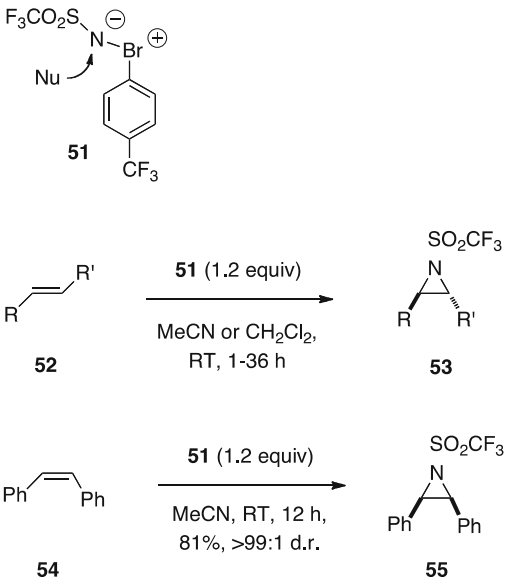
Scheme 11 Aziridination reactions with hypervalent iodine

In a subsequent investigation, Moriarty could demonstrate that primary sulfamides **46** also undergo metal-free aziridination [35]. In these cases, stable aziridines **47** were obtained which could be isolated conveniently. The authors proposed an interesting mechanistic hypothesis of a [2 + 2] cycloaddition to encounter for the overall reaction, although it appears that this proposal has not been discussed further. Subsequent developments include the application of $PhI(OAc)_2$ for intramolecular versions, in particular transannular aziridination reactions, which were of concern in natural product synthesis [36, 37].

A major advance was accomplished with the introduction of hydrazine derivatives by Che, in particular, *N*-amino phthalimide [38]. Although initial work had relied on $PhI(OAc)_2$ as the oxidant, the same group later discovered that a tricomponent system consisting of 2-iodoanisole (**49**), *m*CPBA, and the *N*-amino phthalimide could be employed for an in situ preparation of the required iminoiodane [39]. It is important to note that the final iminoiodane contains a 2-methoxyphenyl substituent, which is in line with the observation from Zhdankin on enhanced solubility of derivatives of the type **42**. Under these conditions, a series of styrenes **48** could be submitted to intermolecular aziridination and provided products **50** under mild conditions and in good to excellent yields.

Curiously at first sight, the reaction could not be conducted as a catalysis using substoichiometric amounts of 2-iodo anisole as catalyst. This context was clarified by Wirth in an elegant study [40]. The authors elucidated a complex mechanism of

Scheme 12 Aziridination reactions with hypervalent bromine



the stoichiometric reaction including the proposal of an aminoiodane intermediate as the crucial species in aziridination. Their studies suggest that it might be challenging to arrive at an oxidant that promotes chemoselective formation of an iodine(III) as a catalyst without engaging in a background reaction of uncatalyzed alkene oxidation.

Efficient aziridination could also be accomplished with the isolated bromine(III) reagent **51** introduced by Ochiai (Scheme 12). This reagent provides entirely stereospecific metal-free formation of aziridines **53** for a series of neutral alkenes **52**. As to a particularly impressive example, (*Z*)-stilbene **54** underwent completely selective formation of the *cis*-2,3-diphenyl product **55**. Although its structural description follows the one discussed before for the iminoiodine derivatives, the nitrogen atom maintains suitable electrophilicity to react with alkenes to engage in the corresponding aziridine formation [41].

In addition to the aziridination, this reagent also performs unprecedented C–H amination reactions of aliphatic hydrocarbons. Although the reaction requires large excess of the alkanes, the mild reaction conditions and high yields are impressive [42].

4 Dual Carbon–Heteroatom Bond Formation

To date, this chemistry remains rather unexplored with respect to the development of related transition metal catalyses [43]. Still, difunctionalization of alkenes with hypervalent iodine reagents has been explored extensively over the past few decades [44], and there are important recent contributions that indicate that hypervalent iodines can indeed serve as suitable chiral reagents or catalysts for enantioselective oxidation of alkenes [43–46].

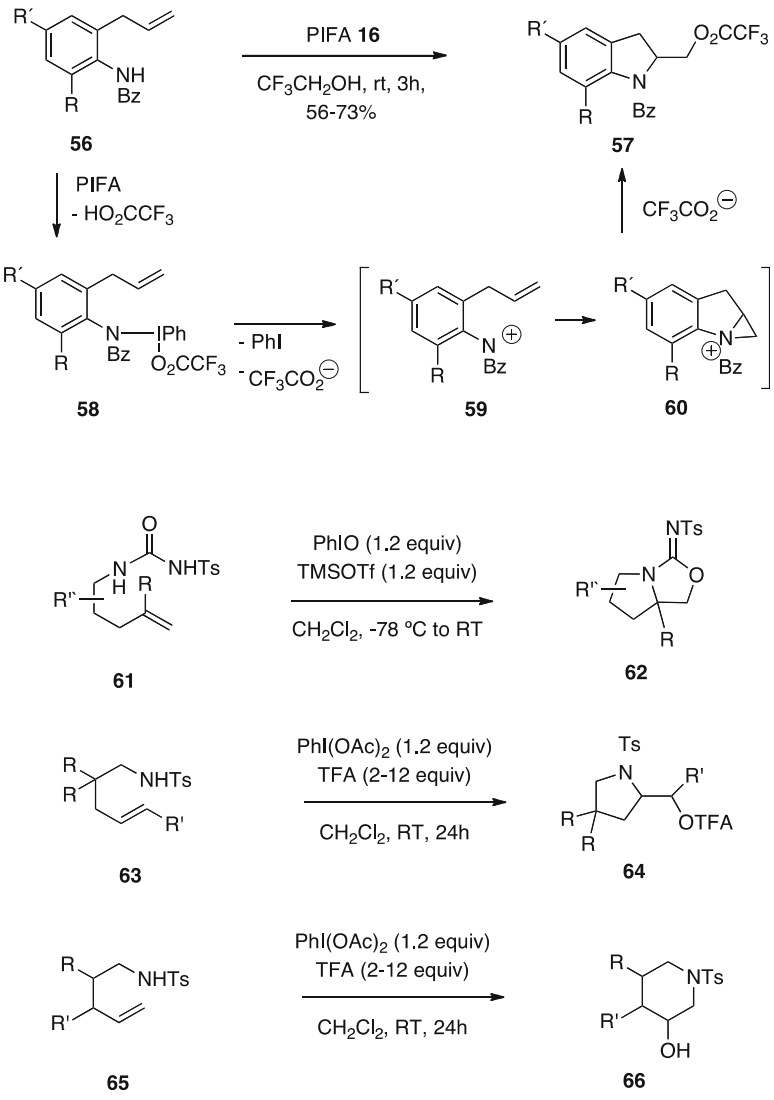
4.1 Vicinal Aminooxygenation

In the area of aminooxygenation reactions, intermolecular reactivity has so far remained elusive. This may be the result of the difficulty in generating efficient regioselectivity control, a problem that is well known from the osmium-catalyzed aminohydroxylation reaction [43]. However, intramolecular iodine(III)-based reactions have become available (Scheme 13).

Most of this work is based on the conceptual use of hypervalent iodine reagents as precursors to electrophilic nitrogen intermediates. This approach was introduced by Domínguez, and has resulted in ample application [47, 48]. Domínguez pioneered PIFA-based intramolecular amination reactions such as the transformation of **56** into aminooxygenation product **57**. This work makes use of the conceptual prerequisite of the in situ formation of I–N bonds as illustrated by intermediate **58**, which undergo heterolysis to form electrophilic nitrogen atom **59** that are attacked nucleophilically by the alkene. The resulting aziridinium intermediate **60** undergoes nucleophilic opening by the trifluoroacetate from the initial PIFA oxidant. The final product **57** constitutes an overall aminotrifluoroacetoxylation and can be easily hydrolyzed to the corresponding free aminoalcohol. Alternatively, suitably prearranged polar groups can promote an intramolecular aziridinium opening as employed in some natural product syntheses [49, 50].

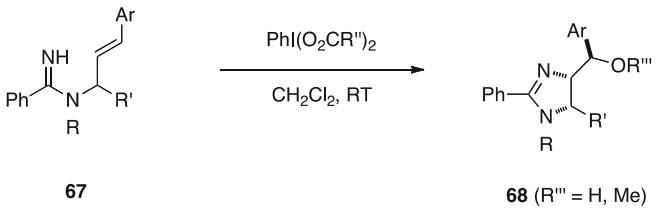
The reaction has recently been developed further by use of the milder reagents PhIO and $PhI(OAc)_2$, respectively, within the iodine(III)-mediated intramolecular pyrrolidine formation from alkenes. For example, the combined use of iodosobenzene and trimethylsilyl triflate generates reaction conditions that enable an efficient aminooxygenation of urea precursors **61**. Because of the acidic reaction conditions, the final carbon–heteroatom bond formation cannot proceed toward diamination, and aminooxygenation products **62** are obtained selectively. The free aminoalcohols are conveniently obtained by acidic cleavage of the cyclic carbamate [51].

An alternative process involves the combination of (diacetoxyiodo)benzene and trifluoroacetic acid (TFA). Under these conditions, the reaction of internal alkenes (**63**, with R′ preferentially phenyl) provides pyrrolidine formation products **64** [52]. These reactions are understood not to require proceeding through oxidation



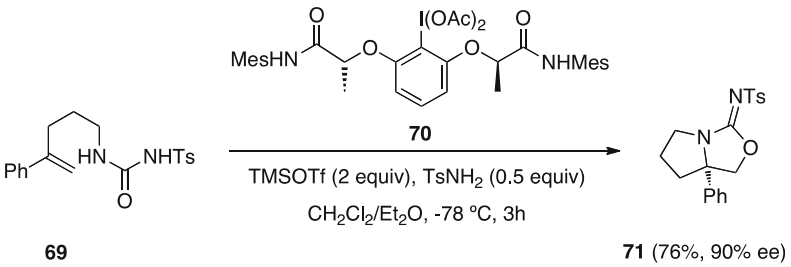
Scheme 13 Vicinal aminooxygenation reactions

of the nitrogen group, but to involve the coordination of alkene to the electrophilic iodine reagent. Under such a scenario, five-membered ring formation proceeds within an *exo*-cyclic pathway followed by nucleophilic replacement at the alkyl-iodine(III) group to arrive at the aminooxygenated product. For terminal alkenes **65** the authors postulate iodine–nitrogen bond interaction leading to an aziridinium intermediate from an electrophilic nitrogen and opening with an oxygen nucleophile to generate piperazine **66**.



67 **68** ($R''' = H, Me$)

Scheme 14 Vicinal aminooxygenation reaction of **67**



69 **71** (76%, 90% ee)

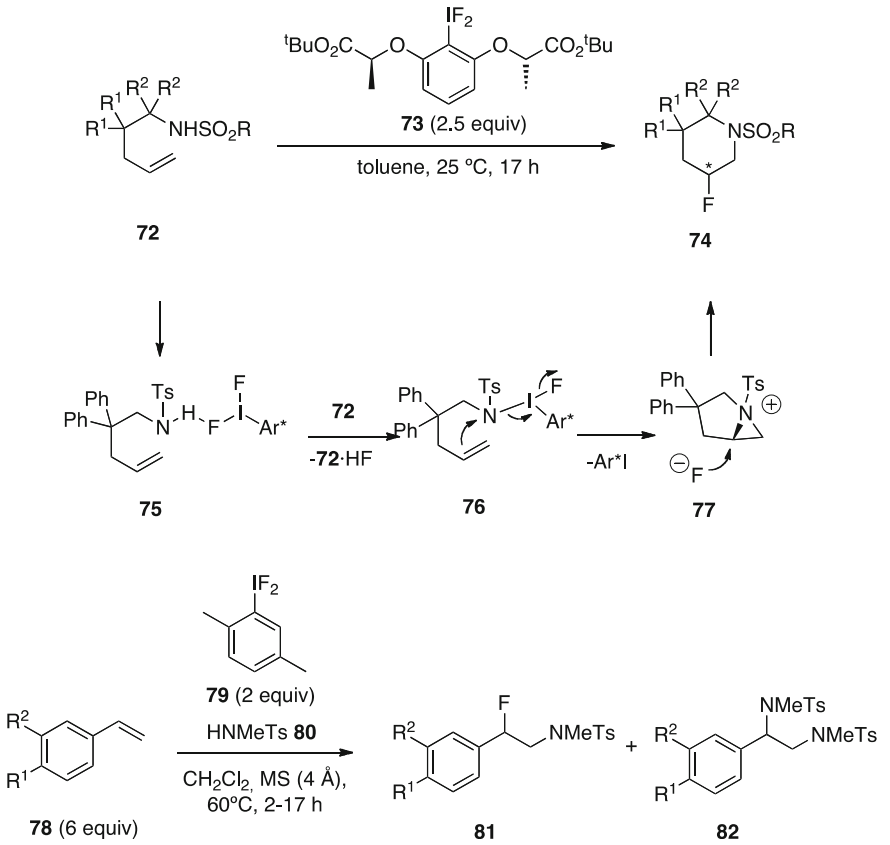
Scheme 15 Enantioselective vicinal aminooxygenation reaction

Alternative pathways were developed by Chiba, who employed amidines **67** as nitrogen sources for an intramolecular aziridination with hypervalent iodine reagents $PhI(OAc)_2$ or PIFA, respectively (Scheme 14) [53]. The resulting aziridinium intermediate then underwent selective ring opening with the present oxygen-based nucleophiles to provide aminoacetoxylation or aminohydroxylation products **68**, respectively. Because of the implemented amidine group, the reaction provides an overall 1,2,3-trifunctionalized scaffold.

Wirth recently demonstrated that an intramolecular reaction could indeed be realized with suitable induction, when a suitable chiral iodine(III) reagent was initially treated with TMS triflate followed by reaction at low temperature (Scheme 15) [54]. Conceptually, this process appears to be different from the usual pathways that originate from electrophilic nitrogen. Instead, the chiral hypervalent Ishihara reagent **70** probably leads to activation of one of the enantiotopic faces of the alkene **69** followed by nucleophilic amination and subsequent reductive de-iodination by oxygenation to arrive at the cyclic aminooxygenation product **71**.

4.2 Vicinal Aminofluorination

The corresponding aminofluorination reaction of alkenes was developed by Nevado (Scheme 16) [55]. Key to its successful realization was the synthesis of the new chiral difluoroiodine(III) reagent **73** based on chiral information by the lactate side chains. It was obtained from the related chiral aryliodide by oxidation with



Scheme 16 Vicinal aminofluorination reactions

Selectfluor in the presence of $Et_3N{\cdot}HF$. This new chiral difluorinated iodine(III) reagent is capable of realizing an oxidative cyclization of alkenes **72** into the corresponding aminofluorinated products **74**. The reaction is characterized by complete *endo*-selectivity leading to exclusive piperidine formation. The reaction already generates high *ee* values, which could be further enhanced upon crystallization. To rationalize for the selective piperidine formation, a deuterium labeling experiment confirmed the involvement of a direct aminofluorination process. It suggests that the overall reaction is initiated via **75** by hydrogen bond assisted ligand exchange at iodine(III) to form the I–N intermediate **76** from **72**. An intermediate such as **76** exercises electrophilic character at nitrogen. Interaction with the nucleophilic alkene provides the commonly accepted aziridinium intermediate **77** followed by nucleophilic fluorination at the internal carbon atom bearing better stabilization of the cationic charge.

Within a complimentary approach, Li has developed conditions for the racemic version of this reaction, which proceeds readily using a combination of

iodosobenzene dipivalate and boron trifluorate together with HF-pyridine in dichloromethane at room temperature [56]. The authors propose a mechanistic pathway identical to the one from the enantioselective variant. This theme was later extended to further aminohalogenation and related difunctionalization reactions as well [57].

The aminofluorination reaction could also be conducted within its intermolecular version [55]. Oxidation of styrenes **78** with excess of the difluoride reagent **79** in the presence of *N*-methyl tosylamide **80** leads to the corresponding aminofluorination products **81** in very good isolated yields and with complete regioselectivity. Drawbacks are that the reaction requires a sixfold excess of starting material to provide reasonable product formation and that the related diamination products **82** were formed as by-products, although in amounts less than 15% yield.

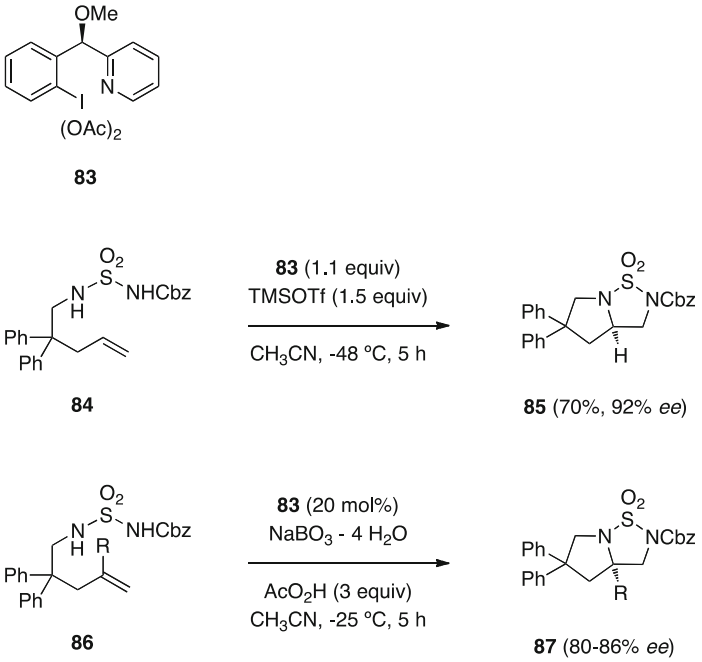
4.3 Vicinal Diamination

Addition of two nitrogen moieties to an alkene was initially reported within the historic diazidonation reaction. In 1986, Moriarty reported such a diazidonation using PhIO as the terminal oxidant in combination with NaN_3 and in AcOH as solvent, which allowed for facile diazidonation of several alkenes [58]. Unfortunately, functional group tolerance was a major problem and, as the consequence of the underlying radical mechanism for the double bond oxidation, the corresponding diazide products were obtained as diastereomeric mixtures. More defined conditions to generate the hypervalent iodine(III) compound $PhI(N_3)_2$ were used by Magnus, which provided an advanced diazidonation protocol [59–62].

The development of suitable conditions for the intramolecular diamination of alkenes using iodine(III) promoters was initially addressed by Wirth within his aminooxygenation reactions. For the case of tosylated urea precursor, the corresponding diamination product could be isolated, but a general profile towards diamination was not reported [54].

A more pronounced solution toward intramolecular diamination was encountered with the development of the new hypervalent iodine reagent **83** using sulfamides as nitrogen sources. In combination with TMSOTf, this reagent is capable of promoting the corresponding diamination of **84** to **85** with excellent enantioselectivity. Furthermore, its amounts can be reduced in the presence of peracetic acid to arrive at an efficient catalytic intramolecular diamination of disubstituted alkenes **86** to products **87**. These reactions show broad substrate scope and proceed with very good yields and with high enantioselectivities. This protocol is currently the best available for enantioselective intramolecular diamination of alkenes, particularly in view of the benign reaction conditions (Scheme 17) [63].

A related achiral approach was employed to explore the diamination of fullerenes with symmetric and non-symmetric sulfamides [64]. A combination of hypervalent iodine reagent and molecular iodine was required. For iodosobenzene, the

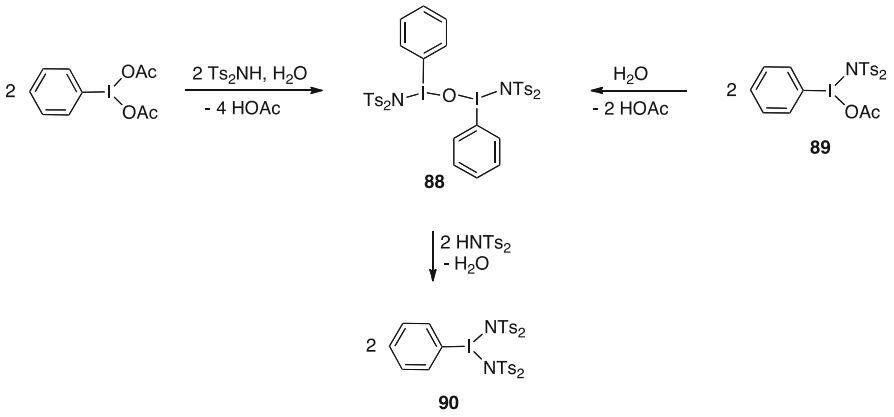


Scheme 17 Intramolecular vicinal diamination reactions

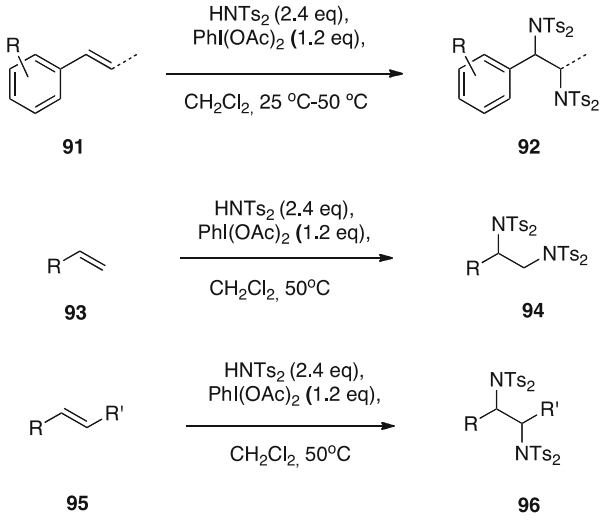
reaction provided clean diamination, although double C–N bond formation to an azafulleroid was encountered for $PhI(OAc)_2$ as the iodine(III) reagent.

Muñiz introduced the use of defined hypervalent iodine(III) reagents **88**–**90** for an intermolecular enantioselective diamination of styrenes [25, 65]. These reactions usually involve an in situ formation of the active reagent $ArI[N(SO_2R)_2]_2$ **90**. The latter can also be prepared independently and stored for those reactions, where required. The general sequence of its independent synthesis resembles the in situ formation. Starting from $PhI(OAc)_2$, exchange of its acetate ligands by hydrolytic amination provides the μ-oxo dimer **88**, which can also be accessed from preformed $PhI(OAc)NTs_2$ **89**. Further protonolysis with $HNTs_2$ finally provides the bisimido iodine(III) species **90**, which was identified as the active reagent in many amination reactions (Scheme 18).

A number of diamination reactions were explored with this reagent including the diamination of terminal alkenes and styrenes, internal symmetric and non-symmetric alkenes, and 1,3-butadienes. Some examples regarding diamination are included in Scheme 19 [66]. Generally, the reaction scope is unusually broad, rendering the $PhI(OAc)_2/HNTs_2$ reagent combination the most versatile diamination protocol available to date. Examples include styrenes **91** derivatives as the preferred substrate class, which forms diamines **92** with complete chemoselectivity and high stereospecificity in the case of internal alkenes.



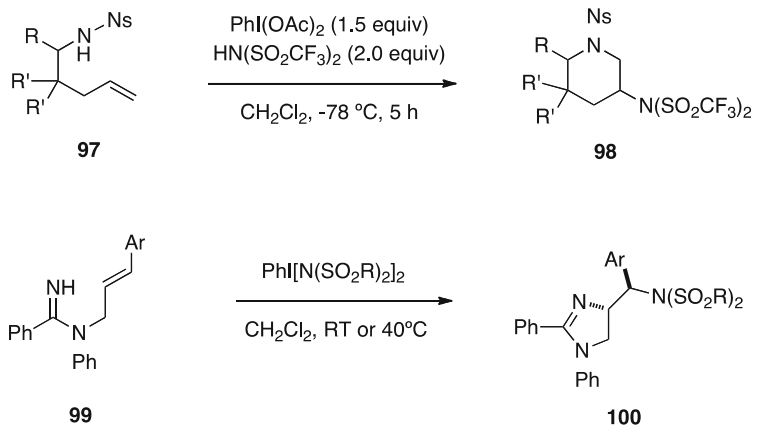
Scheme 18 Synthetic approaches to reagent **90**



Scheme 19 Vicinal diamination reactions

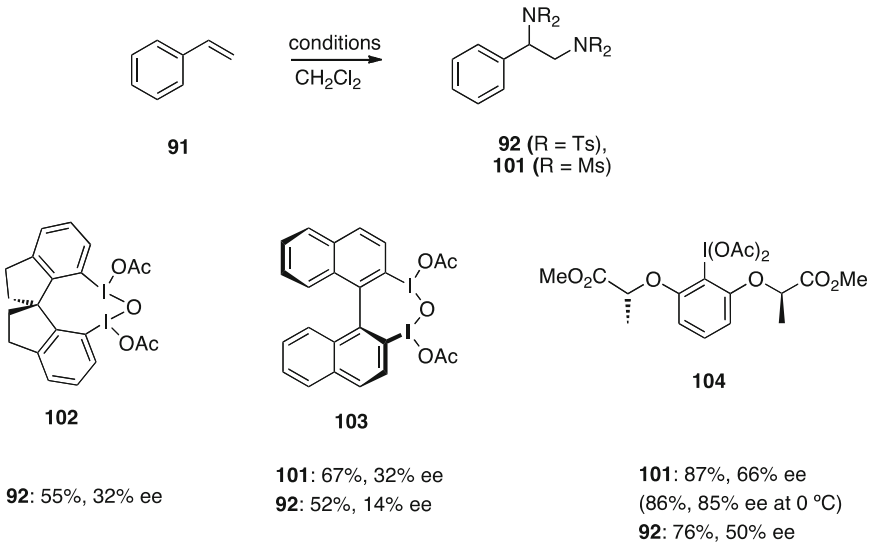
The scope could be extended to the synthesis of products **94** from terminal alkenes **93** of all different types and containing most common functional groups. Importantly, the reaction also tolerates internal alkenes. (*E*)-Configured symmetrically substituted alkenes **95** provide the corresponding *meso*-diamines **96**, whereas unsymmetrically substituted derivatives and cyclic alkenes give access to chiral diamines **96**.

A related reaction was introduced by Blakey, who reported the selective transformation of ω-aminoalkenes **97** into 2-aminated piperidines **98** using $PhI(OAc)_2$ as oxidant and the highly acidic bis(trifluormethylsulfon)imide as Brønsted activator and nitrogen source (Scheme 20) [67]. Although the active iodine(III) reagent remains to be determined, it seems reasonable to assume that the reaction involves



97 **98** **99** **100**

Scheme 20 Vicinal intra/intermolecular diamination reactions



91 **92** (R = Ts), **101** (R = Ms)

102 **103** **104**

92: 55%, 32% ee

101: 67%, 32% ee
92: 52%, 14% ee

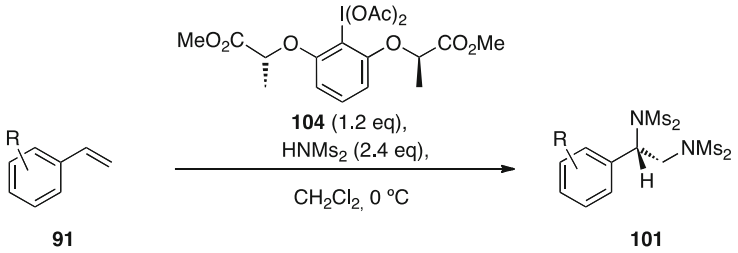
101: 87%, 66% ee
(86%, 85% ee at 0 °C)
92: 76%, 50% ee

Scheme 21 Enantioselective vicinal diamination reactions

interaction between (diacetoxyiodo)benzene and the acidic imide at the outset of the transformation.

Selectivity in favor of five-membered ring formation was reported by Chiba, who employed preformed $PhI[N(SO_2R)_2]_2$ reagents (R = Me, Tol) from Muñiz [53]. The reaction follows the mechanistic pathways of the discussed amino-oxygenation reaction and provides the corresponding diamination products **100** with complete diastereoselective control from amidines **99**.

For a standard substrate such as styrene, enantioselective diamination could be mediated by several hypervalent iodine reagents (Scheme 21) [65, 68]. For example,



Scheme 22 Enantioselective vicinal diamination of styerens

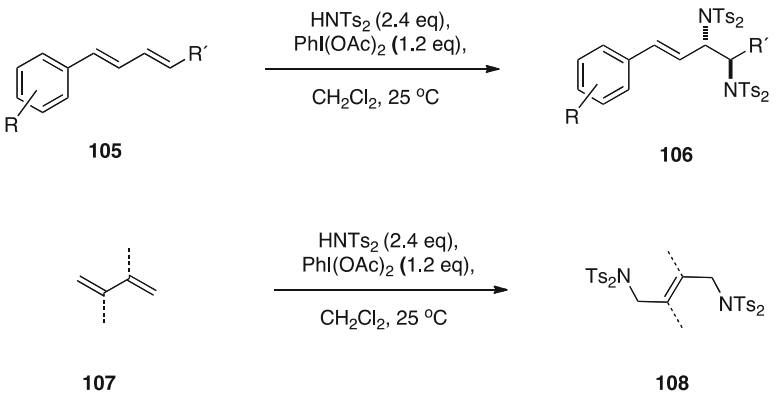
a spiro-reagent **102** led to 32% *ee* with bistosylimide as nitrogen source, whereas for the same transformation the binaphthyl derivative **103** provided only 14% *ee* and 32% *ee* for the corresponding reaction with bismesylimide [65]. Reagent **104** was identified as the most suitable one, leading to 50% *ee* for bistosylimide and 66% *ee* for bismesylimide. The latter value could be increased to 85% for a reaction at lower temperature, and the product **101** was crystallized to enantiomeric purity within a single crystallization.

Under these reaction conditions, a series of styrene derivatives underwent an enanatioselective diamination reaction under metal-free conditions (Scheme 22). A series of substituents and substitution patterns are tolerated and all compounds could be crystallized to enantiomeric purity within a single crystallization step.

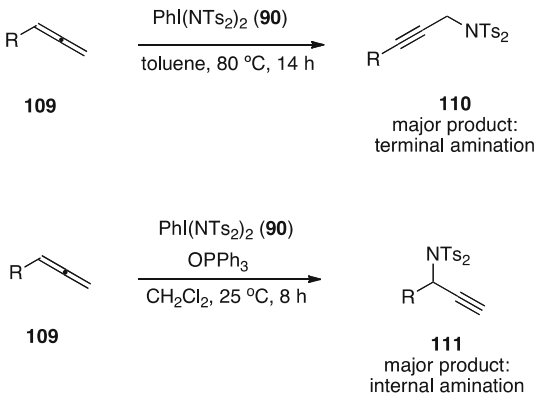
Alternative diamination protocols have recently become available. Within this context, Hong and Johnston have developed several intra-/intermolecular reactions, which employ substrates of 2-hydroxy- and 2-amino-substitued styrene derivatives and vinyl pyridines [69–71]. The transformation employs a combination of 2 equiv. of $PhI(OAc)_2$, overstoichiometric amounts of KI, and an additional nitrogen source, and although the reaction mechanism remains to be established fully, the prominent participation of the hypervalent iodine reagent is obvious.

Related diamination reactions of 1,3-butadienes and allenes were investigated by Muñiz (Scheme 23) [72]. For the former substrate class, it was observed that the regioselectivity could be predicted by the substitution pattern of the 1,3-butadiene core. For example, terminal aryl substitution in the substrate **105** resulted in selective 1,2-diamination with a remaining conjugated double bond in the products **106**. This regioselectivity could be inverted by ester substituents, which induce formation of vicinal diamination products upon concomitant formation of acrylates. Without such directing groups, the reaction of butadienes **107** follows diamination at the least hindered positions, which usually results in 1,4-diamination events giving products of the constitution **108**.

Allenes **109** provide propargyl amines upon treatment with preformed reagent **90** (Scheme 24) [73]. Depending on the exact reaction conditions, the regioselectivity can be influenced. Treatment with reagent **90** alone leads to clean formation of the propargylic amine **110** with the nitrogen group at the terminal position, whereas addition of triphenylphosphinoxide triggers the reaction to favor the formation of the propargylic amine **111** with the nitrogen group at the internal position.



Scheme 23 Diamination reactions of 1,3-butadienes

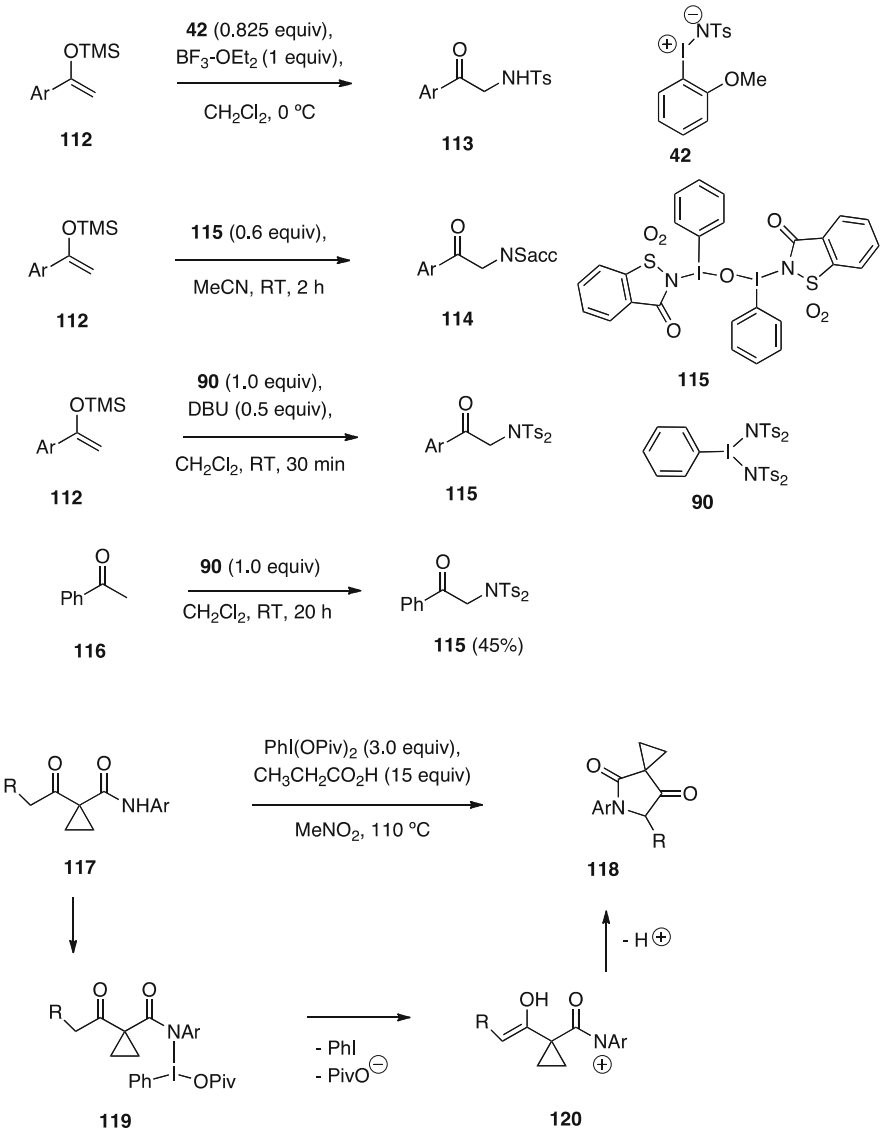


Scheme 24 Amination reactions of allenes

This switch was rationalized by an increased steric bulk in the transition state after the initial allene functionalization with the hypervalent iodine reagent.

4.4 α-Aminated Carbonyls from Amination of Silyl Enol Ethers

Progress in this field was accomplished through the development of new hypervalent iodine reagents. Because of the enhanced solubility of the reported 2-methoxyphenyliminoiodane motif **42** from Nemykin and Zhdankin [32], this reagent allowed for the development of various direct amination reactions of silyl enol ethers **112** to products **113** in good yields and within short reaction times (Scheme 25). The general reaction conditions call for the activation with a



Scheme 25 Amination reactions of enol ethers

stoichiometric amount of trifluoroborate additive, although, in some cases an alternative reaction protocol using only acetonitrile between room temperature and 81 °C could be employed.

Likewise, Zhdankin introduced the saccharin-based μ-oxo imidoiodane **115** [74]. This reagent provides suitable conditions for the transfer of the saccharin group within mild reaction conditions. This reagent readily converts preformed

silyl enol ether **112** into the corresponding α-aminated carbonyl derivatives **114** with excellent functional group tolerance and in good yields.

The isolated bistosylimido derivative **90** from Muñiz allowed for the same transformation [25]. In this case, it was found that an in situ formation of the reagent **90** from (diacetoxyiodo)benzene and free bistosylimide resulted in significantly lower yields of **115**. This observation was explained by the liberation of free acetic acid within the generation of **90** leading to cleavage of the silyl enol ether **112**. As a result, the preformed reagent **90** had to be employed for the present purpose.

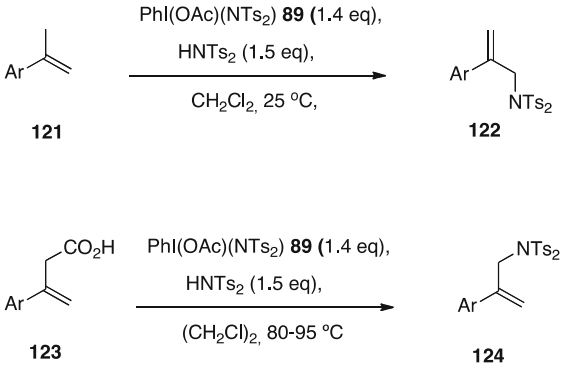
Importantly, compound **90** is capable of inducing direct α-amination of ketone **116** via in situ enolization; however, yields cannot compete with the pathway via preformed enol ethers.

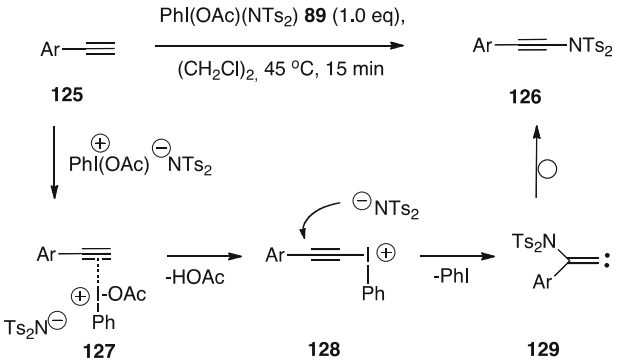
This theme was elaborated by Zhang who employed the 1,3-dicarbonyl substrate **117** [75]. Upon interaction of the amide part with the hypervalent iodine, as in **119**, the corresponding electrophilic nitrogen **120** can readily interact with the enol form of the other carbonyl. This C–N bond-forming event directly provides the final tetramic acid derivative **118**. Although the reaction was largely conducted for cyclopropyl derivatives such as that shown, larger cyclic dialkyl groups such as cyclopentane could also be used.

5 Allylic Amination

A new allylic amination was encountered using the $PhI(OAc)NTs_2$ reagent combination (Scheme 26) [76]. For several substrates **121**, the reaction to the corresponding allylic amines **122** was accomplished with complete chemoselectivity. For the present transformation, the preformed mixed reagent $PhI(OAc)NTs_2$ **89** turned out to provide the best performance. Mechanistic studies demonstrated that the reaction proceeds within an allylic transposition, i.e., with formation of the C–N

Scheme 26 Allylic amination reactions





Scheme 27 Acetylenic amination reactions

bond at the former alkene position. A single example on a related transformation within the $PhI(OAc)_2/HN(SO_2CF_3)_2$ system was also reported [67].

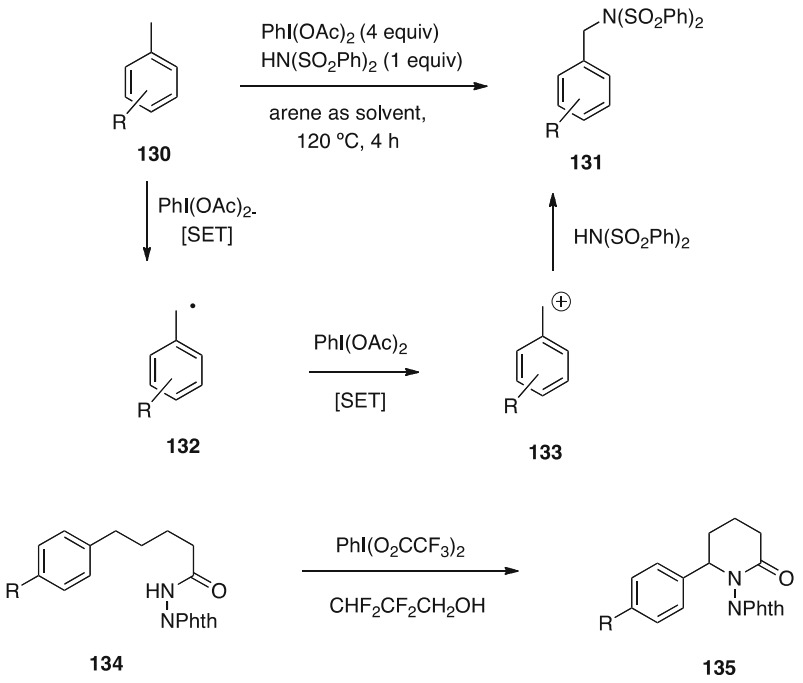
A complimentary approach was reported by Minakata, who used the same reagent combination within a sequential decarboxylation/amination strategy [77]. In this work, several allylic carboxylic acids **123** were submitted to decarboxylative amination to give the corresponding products **124** in very good yields.

6 Acetylenic Amination

The direct amination of terminal acetylenes was accomplished using the preformed $PhI(OAc)NTs_2$ reagent **89** (Scheme 27) [78]. Several alkynyl arenes **125** underwent the amination reaction with complete selectivity and in high yields. Short reaction times are required as the products start to degrade in the presence of acetic acid by-product. The overall transformation starts with coordination of the acetylene to the electrophilic iodine (**127**) center followed by C–H iodination. Subsequent Michael addition of the bistosylimide anion (**128**) leads to reductive deiodination and generates a vinylidene carbene **129**, which undergoes 1,2-aryl shift to form the aminated acetylene product **126**. Related aliphatic acetylenes form the same carbene intermediate, which engages in C–H bond insertion reactions to generate enimides as products.

7 Amination of Alkyl Groups

Regarding the amination of unfunctionalized alkyl groups, the reactivity of hypervalent bromine reagent **51** stands out [42]. However, there is some work on this type of transformation with iodine(III) reagents as well. Chang reported the direct intermolecular amination of toluene derivatives **130** (Scheme 28) [5]. The reaction



Scheme 28 Aliphatic C–H amination

employs a fourfold excess of $PhI(OAc)_2$ with respect to the nitrogen source, which in most cases was bis(phenylsulfonyl)imide. The arene substrate was used as solvent, which constitutes a certain synthetic disadvantage. Despite this fact, the reactions proceed with good yields. The authors rationalize the transformation to originate from two SET events mediated by the hypervalent iodine reagent via **132** to arrive at a benzylic cation **133**, which is trapped by the nitrogen source to provide the final benzylated product **131**.

An additional example comprises an intramolecular cyclization. The most notable is the transformation of the amide of *N*-amino phthalimide **134** which, upon treatment, with PIFA undergoes clean benzylic amination to the corresponding lactam derivatives **135** [79].

In addition, the reaction between hypervalent iodine reagents such as iodosylbenzene or its diacetate derivative with molecular iodine has been employed frequently in aliphatic amination reactions. These processes start from an initial formation of an alkyl hypoiodite derivative, which can promote subsequent radical amination pathways. An excellent use of this concept is the Suárez methodology for the generation of diversified aminated carbohydrate structures [80–86]. Although the hypervalent iodine reagent is not directly involved in the amination reaction, the efficiency of the method deserves mentioning within the present chapter. It was recently extended to catalytic transformations [87].

8 Conclusions

The application of hypervalent iodine(III) mediated and catalyzed amination of hydrocarbon substrates has developed into a useful tool for organic synthesis. Reactions comprise direct amination of sp-, sp^2-, and sp^3-hybridized C–H bonds and numerous oxidative transformations of alkenes, butadienes, and allenes. Some of these methods have been developed directly in the form of catalytic transformations, which adds to underline the synthetic potential of the field. Where applicable, the possibility for enantioselective transformations has been demonstrated for some cases. One can be optimistic that hypervalent iodine chemistry is able to complement existing methodology for oxidative amination reactions in a practical manner over the next few years.

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Arylation with Diaryliodonium Salts

Berit Olofsson

Abstract This chapter focuses on recent developments in metal-free and metal-catalyzed arylations with diaryliodonium salts (diaryl-λ^3-iodanes). Synthetic routes to diaryliodonium salts are briefly described, and chemoselectivity trends with unsymmetric iodonium salts are discussed.

Keywords Chemoselectivity • Diaryl-λ^3-iodanes • Hypervalent iodine • Iodine (III) compounds

Contents

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1 Introduction

The chemistry of diaryliodonium salts (Ar_2IX) has developed tremendously in the last decade. Diaryliodonium salts are air and moisture stable solid compounds which are easily available and applicable in a wide variety of transformations under both metal-free and metal-catalyzed conditions. Advantages of these electrophilic arylation reagents include their low toxicity, good selectivity, and high reactivity, making difficult transformations possible at ambient temperature without need for excess reagents. Their properties resemble those of aryl-substituted heavy metal reagents, which makes them green alternatives to stoichiometric reactions with, for example, lead, thallium, and tin derivatives. Metal-free reactions with Ar_2IX offer a solution to the problems with low threshold values for transition metals in the pharmaceutical industry.

The focus of this chapter is to provide an overview of the reactivity of diaryliodonium salts, discuss common synthetic routes to them, and describe the recent developments in applications of these reagents after a brief historical perspective in each section. The chemistry of hypervalent iodine compounds has been summarized in a number of books and reviews [1–3], and the topics of diaryliodonium salts [4, 5], cyclic diaryliodonium salts [6], and iodonium salts [7] have been reviewed. Literature summaries of mechanistic aspects and selected transformations with diaryliodonium salts are referenced in the appropriate sections below.

Diaryliodonium salts are industrially employed as photoinitiators in cationic polymerizations [8–10]. They have been employed as Lewis acids [11], as oxidants (via formation of phenyl radicals) [12, 13], and in the area of macromolecular chemistry [14, 15]. Furthermore, diaryliodonium salts show biological activity in various applications, usually because of their ability to act as radical initiators [3, 16]. Diphenyleneiodonium chloride (DPI) is a cyclic diaryliodonium salt which has found numerous biological applications, often as a NADPH oxidase inhibitor ([17]; see also [20–40] in [18]). The applications outlined above do not involve arylations and are hence not covered in this chapter.

2 Properties and Synthesis of Diaryliodonium Salts

2.1 Structure, Reactivity, and Chemoselectivity

X-Ray studies of diaryliodonium salts show the T-shaped structure typical for iodine(III) compounds, with the "counterion" X sharing a three-center four-electron (3c–4e) bond with the iodine and the apical aryl group (Fig. 1a) [19, 20]. Hence, the iodine has more than eight electrons in its valence shell, and fulfills the criteria for being hypervalent. The degree of dissociation to Ar_2I^+ and X^- in solution depends on both the solvent and the counterion [21]. The dissociated species is believed to retain the ~90° angle between the two aryl moieties and remain hypervalent as a solvent molecule (or another species) coordinates instead (Fig. 1b) [20, 22]. The term diaryliodonium salt and drawings with 109° bond angle (Fig. 1c) are thus somewhat misleading, but the IUPAC name diaryl-λ^3-iodanes has not become standardized yet. Unsymmetric diaryliodonium salts ($Ar^1 \neq Ar^2$) are best depicted according to Fig. 1d to avoid indication of which aryl group preferentially resides in the equatorial position. The structure and general reactivity of iodine(III) compounds has been described in detail by Ochiai [20].

The reactivity of iodine(III) compounds is based on the electrophilic nature of the iodine, which is derived from the electron distribution in the 3c–4e bond. In reactions with Ar_2IX, one aryl group is transferred to the nucleophile, and the other is reductively eliminated as ArI. The "hyperleaving group ability" of ArI as a neutral ligand is highly advantageous compared to anionic ligands which are expelled in nucleophilic aromatic substitutions or cross-coupling reactions [20, 23].

The general mechanism for metal-free reactions with Ar_2IX entails two steps, where the nucleophile first attacks the electrophilic iodine to give a T-shaped intermediate in a ligand exchange (Scheme 1a). This process occurs rapidly for iodine(III) species, and can be either associative or dissociative. In the subsequent step, the nucleophile and the equatorial aryl moiety are reductively eliminated in a ligand coupling [24]. The term ligand coupling is used to specify which type of reductive elimination takes place, as reactions with iodine(III) compounds offer several possibilities [20]. The ligand coupling is concerted, rate determining, and has rather high transition state energy, despite the highly exergonic nature. With certain nucleophiles, the ligand coupling can proceed via a five-membered transition state (TS) instead of the usual three-membered TS, as supported by calculations for α-arylations (Scheme 1b) [25–27].

Metal-free arylations can also proceed by a single electron transfer (SET) mechanism, by which an electron-rich arene forms a cationic radical upon treatment with Ar_2IX. A subsequent radical recombination gives the arylated product

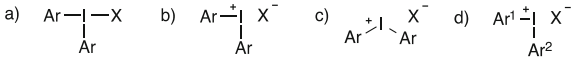
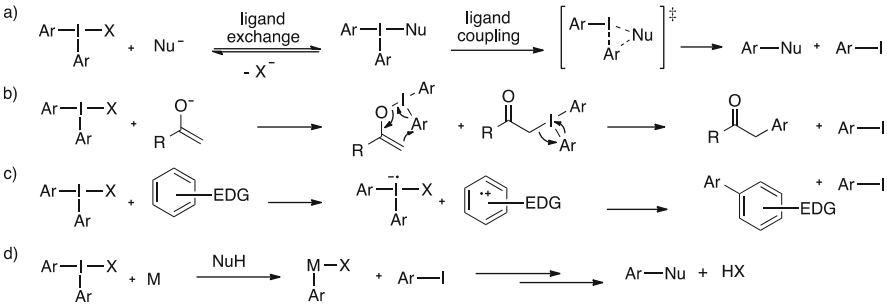


Fig. 1 Structure of $Ar^1(Ar^2)IX$: (**a**) T-shaped; (**b**) ionic T-shaped; (**c**) iodonium; (**d**) unsymmetric



Scheme 1 General mechanisms for: (**a**) metal-free arylation; (**b**) ligand coupling pathways in α-arylations; (**c**) SET reaction for biaryl formation; (**d**) metal-catalyzed reaction

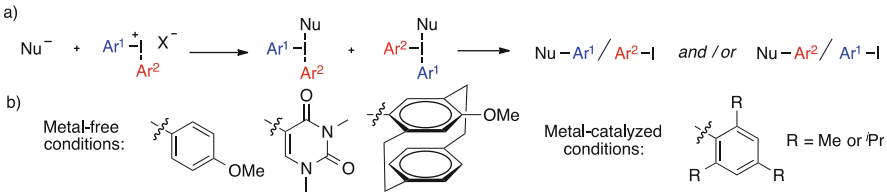
(Scheme 1c). This type of mechanism is common in the synthesis of biaryls by the coupling of two electron-rich aryl moieties (see Sect. 4.2.1) [28]. Kita and coworkers discovered that the fluorinated alcohols 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) are excellent solvents in many reactions with Ar_2IX and other hypervalent iodine reactions because of their ability to stabilize carbocation radicals in SET reactions [29, 30].

Many metal-free arylations with diaryliodonium salts were previously suggested to proceed by a radical mechanism [31], but investigations of both α-arylations and heteroatom arylations have recently disputed this, based on experiments with radical traps such as 1,1-diphenylethylene (DPE) and calculations, which favored a ligand coupling pathway [25–27, 32]. Mechanistic aspects of arylations with cyclic diaryliodonium salts have recently been investigated [33].

Diphenyliodonium 2-carboxylate [34] and (phenyl)[2-(trimethylsilyl)phenyl] iodonium triflate [35] form benzyne upon heating and treatment with a fluoride source, e.g., tetrabutylammonium fluoride (TBAF), respectively. The benzyne can be trapped with heteroatom and carbon nucleophiles. Benzyne formation has also been observed with other Ar_2IX [36].

Arylations under metal-catalyzed conditions are generally suggested to proceed by transfer of one aryl group to the metal to create a high oxidation state ArM complex, followed by reductive elimination with the nucleophile, which has either coordinated before (Pd) or after (Cu) the step with Ar_2IX (Scheme 1d). Catalytic cycles involving Pd^{II}/Pd^{IV} and Cu^{I}/Cu^{III} are often described, but the precise arylation mechanisms are still a matter of debate and are not covered here [37–43]. Copper-catalyzed reactions are often performed in dichloromethane (DCM) or 1,2-dichloroethane (DCE), using either a copper(I) or copper(II) source, whereas the Pd-catalyzed conditions vary more.

The drawback with diaryliodonium salts is the formation of a stoichiometric amount of iodoarene in the reaction. Arylations with unsymmetric diaryliodonium salts ($Ar^1 \neq Ar^2$) are often desired, both because these salts are more easily synthesized and because an inexpensive "dummy" aryl moiety is wasted as ArI. The chemoselectivity of the reaction, i.e., the preference to transfer Ar^1 over Ar^2, must be high to ascertain high yields and avoid purification problems (Scheme 2a).



Scheme 2 (**a**) Chemoselectivity in arylations with unsymmetric salts. (**b**) Common/advanced dummy groups

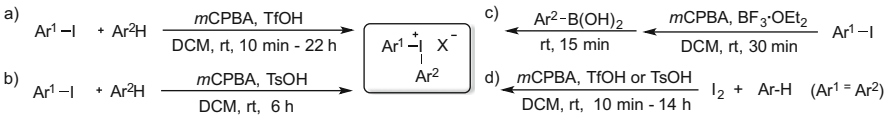
The general chemoselectivity trends are different in metal-free and metal-catalyzed reactions. In the former, transfer of the most electron-deficient aryl moiety is favored, but *ortho*-substituted aryl groups are often transferred despite being more electron-donating [27, 44, 45]. This trend is common for heteroatom nucleophiles, and is called the "*ortho*-effect" [46]. The electronic effects are easily explained by stabilization of the developing charges in the TS [25], whereas the *ortho*-effect is more difficult to explain and predict [27]. A complicating factor was recently observed in metathesis reactions of unsymmetric diaryliodonium salts $Ar^1(Ar^2)IX$ under certain conditions, where an aryl exchange resulted in formation of the corresponding symmetric iodonium salts $Ar^1{}_2IX$ and $Ar^2{}_2IX$ in situ, possibly altering the intrinsic chemoselectivity of the reaction [47, 48].

In metal-catalyzed reactions, steric factors usually control the selectivity, and hindered groups such as 2,4,6-trimethylphenyl (mesityl) and 2,4,6-triisopropylphenyl (TRIP) are very useful dummy groups [40, 49–51]. In the absence of steric effects, the most electron-donating aryl group is generally transferred with moderate selectivity. Common dummy groups, as well as more advanced alternatives such as cyclophane- and uracil-derived dummies [44, 52], are depicted in Scheme 2b.

Although the iodoarene can often be recovered and used in the synthesis of Ar_2IX [53], this process could be facilitated by the use of solid supported diaryliodonium salts. Polymer-bound reagents have, however, met with limited success in applications, possibly because of chemoselectivity problems resulting in the nucleophiles being transferred to the polymer backbone [42, 54]. Ionic liquid-supported Ar_2IX were recently synthesized and applied in chemoselective O-arylations without the need for chromatography [55].

2.2 Synthetic Routes

Since the first synthesis of diaryliodonium salts in 1894 [56], a large variety of synthetic routes to diaryliodonium salts have been reported. Although the majority of these are stepwise, efficient one-pot methods have recently been developed. The



Scheme 3 Olofsson's one-pot syntheses of diaryliodonium salts with *m*CPBA

topic has been reviewed in detail [1, 4, 5, 7], and the following text focuses on general strategies, commonly employed synthetic routes, and recent developments.

In one-pot routes to diaryliodonium salts, an iodoarene is generally mixed with an arene, an oxidant, and an acid to reach symmetric or unsymmetric Ar_2IX. When unsymmetric salts are desired, the more electron-deficient aryl group should originate from ArI, and the more electron-donating aryl group should come from the arene to avoid byproduct formation. One-pot reactions were for a long time very limited in scope and required harsh conditions [57].

Olofsson and coworkers recently developed several one-pot reactions which made a wide range of diaryliodonium salts available in short reaction times and high yields without need for excess reagents. The reactions employed *m*CPBA as oxidant in DCM, in combination with triflic acid (TfOH), tosic acid (TsOH), or $BF_3 \cdot OEt_2$, depending on the structure of the target Ar_2IX. The TfOH method is most versatile (Scheme 3a, X=OTf) [58, 59], whereas the TsOH method is more suitable for electron-rich salts (Scheme 3b, X=OTs) [60], and the $BF_3 \cdot OEt_2$ method is applied together with arylboronic acids in a regiospecific synthesis of salts with otherwise inaccessible substitution patterns (Scheme 3c, X=BF_4) [61]. The TfOH and TsOH reactions could be extended to the synthesis of symmetric diaryliodonium salts directly from iodine and arenes (Scheme 3d, X=OTf or OTs) [58–60, 62].

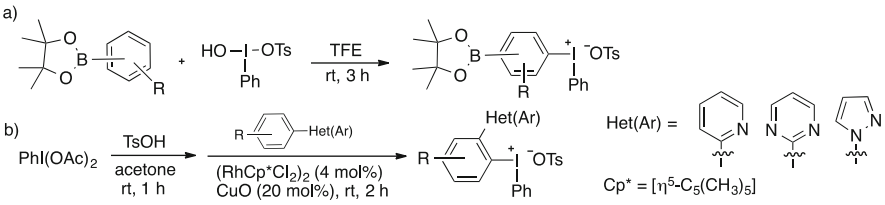
The organic oxidant *m*CPBA had not previously been used in synthesis of Ar_2IX (*m*CPBA had previously been employed to obtain other iodine(III) compounds [63, 64]) and proved very efficient because both the oxidant and its reduced derivative stayed in solution upon precipitation of the diaryliodonium salts, thus avoiding the purification problems observed in some methods employing inorganic oxidants. These synthetic routes have routinely been employed by many research groups during the last few years, and interesting applications include the synthesis of cyclic iodonium salts (see Sect. 3.4) [65, 66] and unsymmetric iodonium salts with F_5S-substituents [67], with N_3-substituents [68], or with a uracil dummy group [52, 69]. One-pot routes utilizing other oxidants, such as $K_2S_2O_8$/TFA [70, 71], H_2O_2/Tf_2O [72], AcOOH/TsOH [73], and Oxone/H_2SO_4 [18], have also been reported.

In stepwise reactions, an iodoarene is first oxidized to an iodine(III) compound under acidic conditions. After isolation, the iodine(III) compound is treated with an arene or an arylstannane, aryl boronic acid, or arylsilane to reach Ar_2IX [4]. A subsequent anion exchange is sometimes required to obtain a diaryliodonium salt that can be easily isolated and applied in arylations without interference from the

anion. A stepwise synthesis is convenient when commercially available iodine(III) reagents can be employed, e.g., reactions with (diacetoxyiodo)benzene (DIB, PIDA) [74, 75], [bis(trifluoroacetoxy)iodo]benzene (PIFA), and [hydroxy (tosyloxy)iodo]benzene (HTIB, Koser's reagent) [76–79]. HTIB is the most reactive of these reagents and does not require the acid activation generally needed for DIB and PIFA. (Diacetoxyiodo)mesitylene (also called iodomesitylene diacetate) has recently become commercially available and is often used in the synthesis of unsymmetric aryl(mesityl)iodonium salts [80], which are very useful in chemoselective metal-catalyzed arylations.

Kita and coworkers developed an efficient synthesis of aryl(phenyl)iodonium tosylates from HTIB and arenes in TFE at room temperature [29, 30]. This type of iodonium salt is chemoselectively employed in metal-free syntheses of biaryls (see Sect. 4.2.1). The synthetic strategy has been employed, for example, in the synthesis of polyfluorinated Ar_2IX [81] and acid-labile boron-substituted diaryliodonium salts from aryl boronates with HTIB or the reagent combination PIFA/AcOH (Scheme 4a) [82]. Suna and coworkers have recently described the synthesis of heteroaryl(aryl)iodonium salts from heteroarenes and [hydroxy(tosyloxy)iodo] mesitylene or DIB combined with TsOH or AcOH. The salts were either isolated or used in situ (see Sects. 3.1.2 and 3.2.2) because of their relative instability [83, 84]. (Diacetoxyiodo)arenes were recently combined with electron-donating arenes and trimethylsilyl triflate (TMSOTf) to provide unsymmetric iodonium triflates without the need for acid addition [85].

Although diaryliodonium salts are generally synthesized under transition metal-free conditions, an interesting rhodium- and copper-catalyzed synthesis was recently published. Arenes with N-containing directing groups were reacted with DIB/TsOH to provide aryl(phenyl) tosylates (Scheme 4b) which were chemoselectively applied in various metal-catalyzed transformations [86]. Salts with an oxime ether substituent could be obtained under rhodium- and silver-catalyzed conditions (see Sect. 3.1.2) [86].



Scheme 4 Synthesis of diaryliodonium salts from iodine(III) precursors

3 Arylation of Heteroatom Nucleophiles

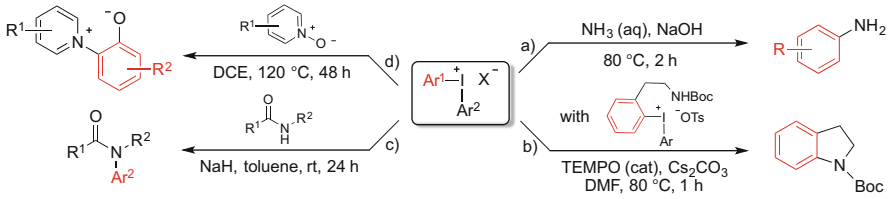
The arylation of heteroatom nucleophiles with diaryliodonium salts was investigated in the 1950s by Beringer, who screened the reactivity with hydroxide, alkoxides, phenoxides, benzoate, nitrite, sulfonamides, amines, sulfite, and sulfinate in refluxing protic solvents. The products were obtained in moderate to good yields, often using excess reagents [87]. McEwen and coworkers investigated arylations with a range of nucleophiles, including aliphatic alcohols, nitrite, azide, and thiocyanate in the 1970s, with the focus on kinetic and mechanistic studies [88, 89]. It is, however, only in the last 5–10 years that synthetically appealing protocols for the arylation of many heteroatom nucleophiles have been developed. Selected recent arylations are summarized below, and details on earlier heteroatom arylations can be found in the previous reviews on diaryliodonium salts [4–7].

3.1 Arylation of Nitrogen Nucleophiles

3.1.1 Metal-Free Reactions

Although Beringer's arylations of aniline and piperidine resulted in poor yields, reactions with sulfonamides delivered the N-arylated products in ~50% yield under basic conditions [87]. McEwen found that arylation of sodium azide was facile at 80 °C in dioxane/water, delivering arylazides in excellent yields [88]. The chemoselective arylation of azides has been demonstrated with an unsymmetric polyfluorinated salt [90], and a computational study supports the ligand coupling pathway [32, 33].

Carroll and coworkers developed a metal-free phenylation of anilines with diphenyliodonium trifluoroacetates in DMF at 130 °C [91]. A thorough chemoselectivity study with anilines and diaryliodonium triflates was later performed by the Olofsson group, revealing that electronics are more important than sterics in this transformation, and hence that both the mesityl and the trimethoxyphenyl groups are suitable dummy groups [27]. Carbazoles were efficiently arylated in toluene at 50 °C in the presence of ^{t}BuOK [92], and anilines could be obtained in aqueous ammonia at 80 °C (Scheme 5a) [93].



Scheme 5 N-Arylations under metal-free conditions

The arylation of aliphatic amines has been difficult under metal-free conditions, but intramolecular arylations using aminoalkyl-substituted iodonium salts to yield indolines were viable (Scheme 5b) [94]. The groups of Olofsson and Adolfsson recently accomplished a metal-free arylation of secondary amides at room temperature (Scheme 5c) [95]. A chemoselectivity study revealed a substantial *ortho*-effect, allowing selective transfer of a TRIP moiety and providing access to sterically hindered tertiary amides that are inaccessible by metal-catalyzed arylations.

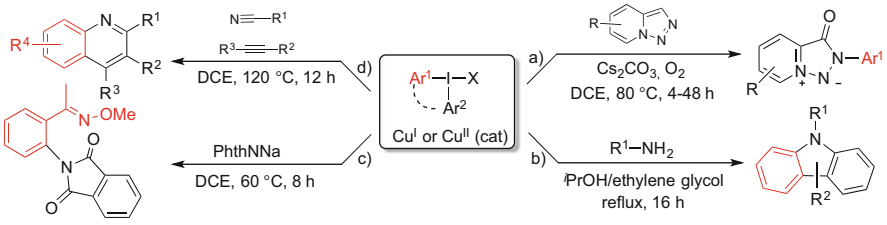
A sequential one-pot synthesis of unsymmetrical aryl urea derivatives was developed by arylation of N-substituted cyanamides under metal-free conditions, followed by a second N-arylation under copper-catalyzed conditions [96]. Chen and Chen devised the arylation of pyridine *N*-oxides with Ar_2IX via initial O-arylation followed by a 1,3-radical rearrangement to *o*-pyridinium phenolates, and arylation of pyridine *N*-amidates delivered *o*-pyridinium anilines (Scheme 5d) [97].

3.1.2 Metal-Catalyzed Reactions

Kang and coworkers developed a number of metal-catalyzed arylations with diaryliodonium salts under mild reaction conditions at the turn of the century, including the Pd-catalyzed arylation of secondary amines at room temperature and the Cu-catalyzed arylation of amines, anilines, amides, imidazoles, and triazoles at room temperature to 50 °C [98, 99]. The copper-catalyzed N-arylation of indoles, on the other hand, required heating to 150 °C in DMF [100], and makes an interesting comparison with the recently developed C-arylation of the same substrates (see Sect. 4.2.2).

N-Arylations of several other heterocycles have also been accomplished, including mono- and diarylation of imidazoles to form N-aryl imidazoles and imidazolium ions, respectively, which was extended to the synthesis of bis (*N*-heterocyclic) ligands [101, 102]. Pyridinium triazolinone ylides were obtained by a one-pot copper-catalyzed carboxygenation and chemoselective N-arylation of triazolopyridines with aryl(mesityl)iodonium salts (Scheme 6a) [103].

The groups of Wen and Nachtsheim developed one-pot syntheses of carbazoles from cyclic diaryliodonium salts and amines using copper- and palladium-catalyzed reaction conditions, respectively. This double arylation strategy made



Scheme 6 N-Arylations under copper-catalyzed conditions

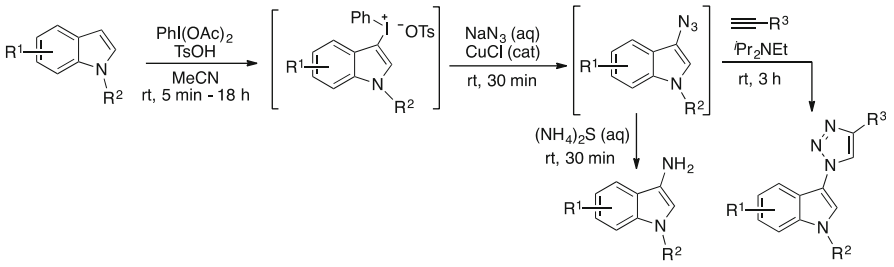
use of the stoichiometric amount of iodoarene formed in the reaction, which acted as the coupling partner in the cyclization. The products were obtained in moderate to good yields employing anilines, aliphatic amines, or tosylamides (Scheme 6b) [104, 105]. Cyclic iodonium salts were subsequently also reacted with sodium azide and alkynes in a copper-catalyzed synthesis of triazolophenanthridine derivatives by sequential N- and C-arylation [106].

Very recently, Li and coworkers utilized unsymmetric diaryliodonium tosylates with an *ortho*-directing oxime ether substituent (see synthesis in Sect. 2.2) in copper-catalyzed arylations of a variety of nucleophiles, including pyrrolidine, phthalimide (PhthNH), and nitrite (Scheme 6c) [86]. The observed chemoselectivity, with *ortho*-aryl transfer favored over phenyl transfer, has not been reported previously in metal-catalyzed reactions.

The copper-catalyzed cascade annulation of nitriles, diaryliodonium salts, and alkynes was recently described by Chen and coworkers. N-Arylation of the nitrile resulted in an *N*-arylnitrilium intermediate, which was trapped by the alkyne and subsequently underwent electrophilic annulation to yield substituted quinolines (Scheme 6d) [107]. The concept was later varied to reach polycyclic quinolines, quinazolines, quinazolinimine, and acridine scaffolds [108–110]. A similar cascade reaction delivered iminobenzoxazines by N-arylation of *ortho*-cyanoanilides followed by C–O cyclization [111], and the reaction of nitriles with [1,1-biphenyl]-derived iodonium salts resulted in phenanthridines [112]. The corresponding C-arylation cascade reactions are discussed in Sect. 4.3.

The copper-catalyzed N-arylation of sulfoximines was realized in aqueous polyethylene glycol at room temperature; acceleration in an ultrasound bath resulted in excellent yields within 10 min reaction time [113]. A one-pot synthesis of triazoles was accomplished under similar conditions by arylation of sodium azide followed by click coupling with terminal alkynes [114].

Suna and coworkers developed an elegant one-pot azidation of heterocycles by in situ formation of heteroaryl(phenyl)iodonium tosylates from heteroarenes, DIB, and tosic acid, with subsequent Cu-catalyzed azidation (Scheme 7) [115]. The unstable heteroaryl azides were converted in situ to triazoles by click reaction with alkynes, or reduced to the corresponding amines in high yields over the three-step/one-pot sequence. The heteroaryl moiety was chemoselectively transferred to the nucleophile, demonstrating the preference to transfer the more



Scheme 7 Suna's one-pot azidation of heteroaromatic compounds

electron-rich aryl moiety in metal-catalyzed reactions. The chemistry was later extended to the corresponding amination, now utilizing [hydroxy(mesyloxy)iodo] mesitylene, an HTIB derivative, as iodine(III) precursor for the synthesis of heteroaryl(mesityl)iodonium salts, as this resulted in improved chemoselectivity in the arylation [84]. A wide range of primary and secondary amines and anilines could be employed in this highly regioselective functionalization of indoles, pyrroles and other electron-rich N-containing heterocycles and arenes.

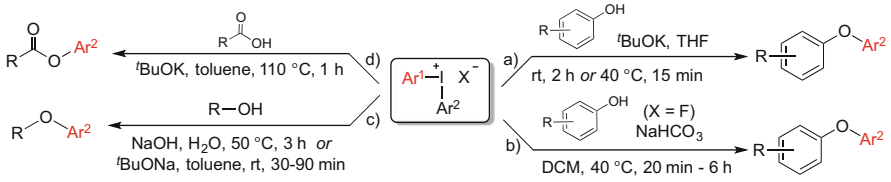
3.2 *Arylation of Oxygen Nucleophiles*

3.2.1 Metal-Free Reactions

Beringer's arylations of hydroxide, alkoxides, phenoxides, and benzoate in refluxing protic solvents [87] paved the way for several slightly modified protocols towards diaryl ethers [116]. The transformation was utilized in the synthesis of polyhalogenated diaryl ethers in the area of environmental chemistry [117, 118]. Still, the transformation remained quite untapped by the synthetic organic community for decades.

In 2011, Olofsson's group developed an efficient synthesis of diaryl ethers that was applicable to a large substrate scope (Scheme 8a). The reactions were performed in THF or toluene at room temperature or 40 °C, and the mild conditions proved compatible with racemization-prone α-amino acid derivatives, which could be arylated without erosion of the enantiomeric excess [119]. The chemoselectivity in phenoxide arylation with unsymmetric diaryliodonium salts was subsequently investigated, and the 4-methoxyphenyl moiety was found to be a suitable dummy group, resulting in completely chemoselective transfer of the other aryl group [27, 53]. A similar transformation was reported later, in which diaryliodonium salts with a 2,4-dimethoxyphenyl dummy group were utilized in acetonitrile with potassium carbonate as base [120].

Gaunt and coworkers recently reported that the synthesis of diaryl ethers could be performed under weakly basic conditions using diaryliodonium fluorides because hydrogen bonding between the fluoride and phenolic OH activated the nucleophile (Scheme 8b) [121]. Salts with other anions could be employed in the presence of TBAF [121]. Polymer-supported diaryliodonium salts have been



Scheme 8 Synthetic routes to aryl ethers and aryl esters

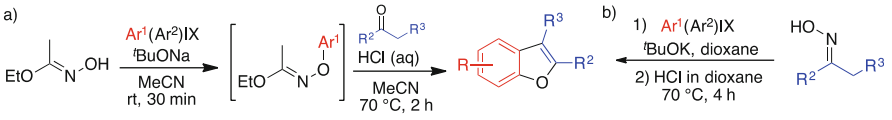
utilized in the synthesis of diaryl ethers with sodium phenoxides in DMF at 100 °C [54]. Yields were moderate, which might be because of poor chemoselectivity resulting in oxygenation of the polystyrene backbone. Ionic liquid-supported diaryliodonium salts were recently utilized in chemoselective O-arylations of phenols and carboxylic acids using literature conditions in good yields without need for chromatography [55].

In 1975, McEwen investigated the synthesis of simple alkyl aryl ethers by arylation of sodium alkoxides in protic solvents. Addition of the radical trap 1,1-diphenylethylene (DPE) was found to increase the yield of ethoxybenzene, as byproducts originating from radical formation were suppressed [89]. The arylation of aliphatic alcohols remained problematic until Olofsson and coworkers recently developed two synthetic routes to alkyl aryl ethers (Scheme 8c) [122, 123]. The first method was performed in water and proved applicable to allylic and benzylic alcohols, whereas the second method in toluene was suitable for non-activated aliphatic alcohols. In contrast to previously reported O-arylations from the group, these routes were sensitive to steric hindrance and electron-donating aryl groups could not be transferred. The use of excess alcohol and *tert*-butyl methyl ether (TBME) as solvent was later found to promote the arylation of secondary alcohols [124]. The reactions utilized unsymmetric salts with a mesityl dummy group, thus transferring electron-withdrawing aryl groups. This absence of an *ortho*-effect is unusual in metal-free O-arylations under metal-free conditions.

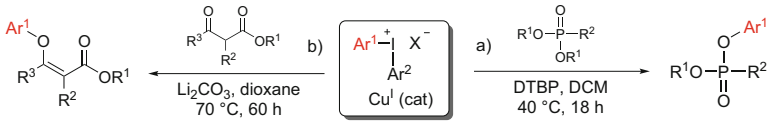
A high-yielding arylation of carboxylic acids was recently reported by the Olofsson group (Scheme 8d). Many functional groups were tolerated, and unsymmetric TRIP salts could be utilized to synthesize aryl esters chemoselectively with severe steric congestion on both the carboxylic acid and the aryl moiety [53, 125]. The same group later developed a synthesis of aryloxyamines by arylation of *N*-hydroxyimides and subsequent hydrolysis of the imide moiety [126].

The chemistry was extended to arylation of other N–O nucleophiles by arylation of ethyl acetohydroxamate, which allowed a more efficient access to aryloxyamines. A one-pot route to benzofurans was developed by arylation followed by addition of α-enolizable ketones under acidic conditions, resulting in [3,3]-rearrangement and cyclization (Scheme 9a) [127]. Kürti and coworkers simultaneously reported the arylation of oximes and other N–O nucleophiles in a strategy that was also extended to a one-pot synthesis of benzofurans (Scheme 9b) [128]. Similar transformations were subsequently reported by two other groups [129, 130].

O-Arylation of various P(O)–OH compounds has been achieved with diaryliodonium salts and Et_3N in toluene at 110 °C [131]. *Ortho*-formyl diaryl



Scheme 9 One-pot syntheses of benzofurans



Scheme 10 Copper-catalyzed O-arylations

ethers were obtained in a three-component reaction where arynes, generated from silyl aryl triflates, reacted with DMF in a [2+2]-fashion followed by O-arylation of the intermediate with diaryliodonium salts [132].

3.2.2 Metal-Catalyzed Reactions

Feringa and coworkers reported a copper-catalyzed O-arylation of dialkyl phosphonates and phosphoramidates with diaryliodonium triflates and 2,6-di-*tert*-butylpyridine (DTBP), giving easy access to mixed alkyl aryl phosphonates via elimination of one of the alkyl groups as the alkyl triflate prior to arylation (Scheme 10a) [133]. Aryl(mesityl)iodonium salts reacted in a chemoselective way. Copper-catalyzed arylations of hydroxamic acids [134] and carboxylic acids [135] have also been reported, the latter utilizing thiophosphoramides as cooperative catalysts to allow arylation at room temperature. Onomura's group discovered a Cu-catalyzed monoarylation of vicinal diols in toluene at 100 °C. Only traces of product were obtained with alcohols lacking the vicinal hydroxyl group [136].

A chemoselective O-arylation of β-keto esters was possible using copper-catalyzed reaction conditions with Li_2CO_3 at 70 °C for a long time (Scheme 10b) [137]. The products were obtained with excellent *Z*-stereoselectivity independent of the substitution pattern, and cyclic β-diketones could also be employed. The observed C/O-selectivity is opposite to that found in reactions under metal-free conditions (see Sect. 4.1). Heteroaryl(phenyl)iodonium acetates were discovered as intermediates in the Pd-catalyzed acetoxylation of pyrroles and indoles mediated by DIB [83]. This feature was also exploited in the amination of various heterocycles (see Sect. 3.1.2).

3.3 Arylation of Fluoride Nucleophiles

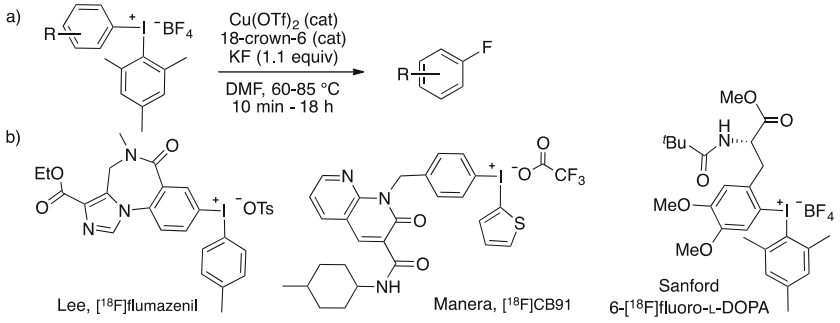
The arylation of fluoride with diaryliodonium salts has been extensively investigated because of the need for fluorine-18 labeled (hetero)aromatics in positron emission tomography (PET). [^{18}F]Fluoroarenes with a wide range of substitution patterns can be prepared from advanced diaryliodonium salts at high temperatures in short reaction times, which is important because of the short half-life of ^{18}F (110 min). Fluorination and radiofluorination of diaryliodonium salts have been reviewed several times in recent years [138–140], as have other strategies towards

^{18}F-(hetero)aromatics [141, 142]. Hence, only a narrow selection of fluorine arylations is outlined below. The elegant arylations utilizing iodonium ylides are outside the scope of this chapter [143, 144].

Diaryliodonium salts can be converted to fluoroarenes in moderate yields by heating with KF in the absence of solvent [145]. In 1995, Pike and Aigbirhio reported the first radiofluorination of diaryliodonium salts [146], and the group has continued in this area, for example, by employing microreactors to allow fast and efficient synthesis of radiofluorinated arenes useful as radiotracers [147, 148]. Several groups have investigated the chemoselectivity in fluoridation of diaryliodonium salts with (hetero)aromatic iodonium salts to avoid wasting an advanced aryl moiety as ArI in the arylation step [45, 149]. DiMagno and coworkers reported that the fluoridation of Ar_2IPF_6 was improved upon removal of inorganic salts after in situ formation of Ar_2IF, followed by heating to 140 °C in benzene [150]. Radical scavengers were found to increase the reproducibility in fluoridations with electron-rich salts [151].

The vast majority of fluoridations of diaryliodonium salts have been performed under metal-free conditions, but Sanford and coworkers recently developed copper-catalyzed conditions for efficient fluoridation with KF (Scheme 11a). The method has a wide scope, and unsymmetric mesityl salts could be chemoselectively employed, giving easy access to a range of fluoro(hetero)arenes. The methodology was subsequently modified to suit radiofluorination and applied to the synthesis of the radiotracers 4-[^{18}F]fluorophenylalanine and 6-[^{18}F]fluoroDOPA [152, 153].

Neumaier's group subsequently modified those conditions to allow radiofluorination with mesityl salts on a large scale in good yields using a "minimalist approach" with less base and no additives, including the synthesis of three clinically relevant PET-tracers [154, 155]. Scheme 11b illustrates the complexity of some unsymmetric diaryliodonium salts used in radiofluorination [153, 156, 157].



Scheme 11 (**a**) Cu-catalyzed fluoridation. (**b**) Diaryliodonium salts used in radiofluoridation

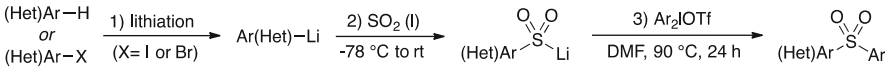
3.4 Arylation of Other Heteroatom Nucleophiles

This section describes selected arylations of phosphorus, sulfur, and halide nucleophiles under metal-free and metal-catalyzed conditions. Arylations of other nucleophiles, e.g., selenium and tellurium, have been reviewed previously [4]. Aryl phosphonates [$ArPO(OR)_2$] can be synthesized by arylation of phosphite anions with diaryliodonium salts and NaH in DMF at 70–80 °C [158]. A copper-catalyzed arylation of various phosphorous nucleophiles, e.g., diarylphosphine oxides and *H*-phosphonates, was recently reported to proceed at room temperature. The observed chemoselectivity with unsymmetric salts was opposite to the general trend in metal-catalyzed reactions (see Sect. 2.1), which was explained by a radical mechanism [159].

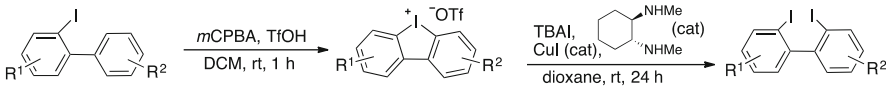
Sandin briefly screened the phenylation of thiophenol, cysteine, and thioglycolic acid in refluxing aqueous solutions in 1947 [160]. Several *S*-centered nucleophiles have since been arylated, including a metal-free phenylation of thiols and a Cu-catalyzed phenylation of thioethers to give sulfonium salts [161]. Sanford and coworkers described a metal-free arylation of thiols and alkyl aryl sulfides with diaryliodonium trifluoroacetate under acidic conditions in dioxane at 110 °C [162]. The thioether arylation was proposed to proceed via nucleophilic attack by the trifluoroacetate on the alkyl group in the intermediate sulfonium salt, yielding diaryl sulfides. Another metal-free arylation of diaryl sulfides gave triarylsulfonium salts in high yields at 120 °C in DCE [163].

In 2013, Manolikakes and Umierski developed the arylation of arylsulfinic acids to diaryl sulfones with a range of Ar_2IOTf reagents under metal-free conditions. A substantial *ortho*-effect was observed with unsymmetric salts, with selective transfer of mesityl and TRIP moieties over phenyl groups in good yields [164]. They subsequently reported a sequential one-pot route where the arylsulfinic acid lithium salts were formed from aryllithium reagents and sulfur dioxide prior to arylation as previously described (Scheme 12) [165, 166]. A few alkyl aryl sulfones were also prepared in the same fashion. A similar route to alkyl and aryl sulfones was reported using a DABCO-SO_2 complex (DABSO), which is a solid sulfur dioxide surrogate that avoids the handling of the toxic SO_2 gas [167]. A Cu-catalyzed arylation of sodium trifluoromethyl sulfinate (CF_3SO_2Na) could be performed on an 88-g scale, demonstrating that arylation with diaryliodonium salts is also viable on a large scale [168]. Arylthio-phenanthridines were synthesized by tandem Cu-catalyzed *S*-arylation of 2-biaryl isothiocyanates followed by Friedel–Crafts type cyclization in good yields [169].

The decomposition of diphenyliodonium chloride into chlorobenzene and iodobenzene at high temperature was reported by Meyer in 1894 [56], and since



Scheme 12 Manolikakes' one-pot synthesis of arylsulfones



Scheme 13 Synthesis of 2,2′-diiodobiaryls via cyclic iodonium salts

then several chemoselectivity and mechanism studies have been performed on the transformation of Ar_2IX into ArX and ArI [46, 170, 171], including calculations [32, 33]. DiMagno and coworkers recently developed a two-step synthesis of iodoarenes via the formation of unsymmetric diaryliodonium salts, which were treated with excess NaI to yield two different iodoarenes upon heating to 80–120 °C. High regioselectivities were obtained compared to direct iodination methods of substituted arenes [85].

Several copper-catalyzed versions of this reaction have been developed. Treatment of mesityl(aryl)iodonium salts with 1.5 equiv. CuCl or CuBr in MeCN at 80 °C resulted in the formation of aryl chlorides and bromides, respectively, in good yields [172]. Peters and Creutz recently utilized Olofsson's *m*CPBA/TfOH-mediated methodology (see Sect. 2.2) for the synthesis of cyclic diaryliodonium salts in a repeated sequence where formation of Ar_2IX was followed by copper-catalyzed opening with bromide or iodide upon heating. In this fashion, the synthesis of a tris(phosphino)alkyl ligand applicable in iron-catalyzed transformations was obtained [65]. Yoshikai used a similar strategy in the synthesis of 2,2′-diiodobiaryls, which were formed by Cu-catalyzed ring-opening with tetrabutylammonium iodide (TBAI) at room temperature (Scheme 13). The iodinated products were converted into ladder-type π-conjugated systems [66].

4 Arylation of Carbon Nucleophiles

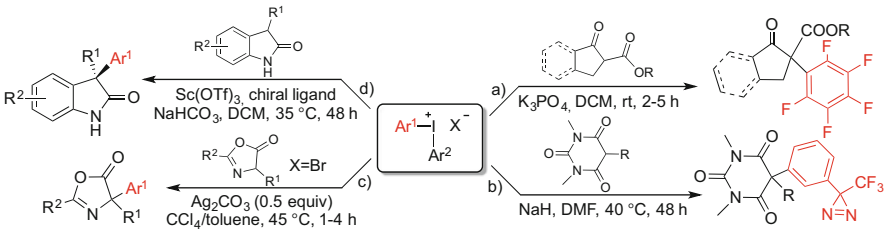
In the last decade, interest in metal-catalyzed C-arylations with diaryliodonium salts has flourished, with many important contributions, especially from the research groups of Sanford and Gaunt. In addition to developing numerous transformations in the area, they have demonstrated that unsymmetric diaryliodonium salts can generally be chemoselectively applied using mesityl or TRIP dummy groups, which facilitates the synthesis of the diaryliodonium salts. Synthesis of carbon–carbon bonds via metal-free strategies are important compliments to the area of transition metal-catalyzed couplings, as the use of expensive and toxic metals and noncommercial ligands is avoided. Several recent reviews cover C-arylations with diaryliodonium salts under metal-free [173] and metal-catalyzed [174–177] conditions. Asymmetric arylations [178], Suzuki reactions [179], and alkyne functionalization [180] with diaryliodonium salts have been reviewed separately.

4.1 α-Arylation of Carbonyl Compounds

In the 1960s, Beringer screened the capacity of diaryliodonium salts to achieve α-arylation with a wide range of carbonyl compounds, including ketones, β-diketones, β-ketoesters, malonates, and esters under basic conditions in protic solvents. Mixtures of mono- and diarylated products were sometimes obtained, and the C/O-selectivity was not always complete. Yields were generally moderate, and acyclic substrates were problematic – see [31, 181] and references therein. Several of the transformations were further investigated many years later, and Koser discovered that Ph_2IF could be utilized in the α-phenylation of silyl enol ethers using the fluoride to remove the silyl moiety [182]. The use of diaryliodonium fluorides in α-arylations was recently extended to other nucleophiles (see Sect. 3.2.1), including an α-cyano-α-phenyl ester, which could be arylated under mild basic conditions [121].

Oh and coworkers reported a room temperature arylation of α-substituted malonates with NaH in DMF in 1999 [183]. These conditions were recently applied in the chemoselective arylation of a cyclic β-ketoester with an unsymmetric, boron-substituted diaryliodonium salt, leading to a product with a suitable handle for further functionalizations [82]. Olofsson and coworkers performed a detailed chemoselectivity investigation with unsymmetric iodonium salts in the α-arylation of malonates, which resulted in the discovery of an "*anti ortho*-effect" and the conclusion that both mesityl and anisyl moieties are suitable dummy groups in these reactions [27]. This fact was utilized by the group of Shibata, who developed a pentafluorophenylation of cyclic β-ketoesters with unsymmetric TRIP salts under mild conditions (Scheme 14a) [81].

Ethyl acetoacetate was recently α-arylated with diaryliodonium salts in moderate to good yields in the presence of ^{t}BuOK in DMF at room temperature using excess amounts of reagents, and the products were subsequently transformed into quinolones [184]. Application of organic bases is uncommon in arylations under metal-free conditions, but DMAP could be employed in the α-arylation of 4-substituted pyrazolin-5-ones [185]. Trifluoromethyldiazirine-substituted iodonium salts containing an anisyl dummy group were utilized in the α-arylation of 5-alkylbarbiturates to obtain general anesthetic derivatives (Scheme 14b) [186].



Scheme 14 α-Arylation of carbonyl compounds

α-Arylations with diaryliodonium salts are rarely mediated by transition metals, but Chai's recent arylation of azalactones with Ar_2IBr utilized silver carbonate both as base and to complex the bromide anion. No reaction was observed with the corresponding triflate salts. The products were hydrolyzed to the corresponding α-aryl amino acids in excellent yields (Scheme 14c) [187].

Asymmetric α-functionalization of carbonyl compounds with iodine(III) reagents is discussed in Chap. 639 and in a recent review [178], and is only briefly covered here. Asymmetric α-arylations with chiral diaryliodonium salts have proven to be difficult to achieve, both because of complicated synthetic routes to chiral, unsymmetric salts with suitable dummy groups, and because of the modest enantioselectivities observed in the arylations [188, 189]. Ochiai and coworkers reported the only successful example to date, where 1,1′-binaphthyl-derived iodonium salts gave chemo- and enantioselective arylation of β-ketoesters in up to 53% *ee* (see Scheme 7 in Chap. X) [190].

Another strategy towards asymmetric α-arylation was demonstrated in a short total synthesis of (−)-epibatidine, which utilized a chiral base to desymmetrize cyclohexanones before arylation of the chiral enolate, yielding α-arylated ketones with high enantioselectivity [191]. The first general, asymmetric α-arylation with diaryliodonium salts was reported by MacMillan's group in 2011, employing a combination of copper- and organocatalysis in the α-arylation of aldehydes via formation of chiral enamines (see Scheme 8 in Chap. X) [192]. Shortly thereafter, the groups of MacMillan and Gaunt independently developed enantioselective arylations of *N*-acyloxazolidinone-derived silyl ketene imides using copper catalysis with chiral bisoxazoline ligands [193, 194].

Mechanistic studies by Olofsson and Norrby revealed that the reaction of enolates with diaryliodonium salts gave two T-shaped intermediates with C–I or O–I bonds. Product formation was favored from the O–I transition state, which explained why attempts using chiral anions or chiral phase transfer agents resulted in racemic arylation [26]. This observation was recently exploited by Feng and coworkers, who reported an elegant and highly enantioselective α-arylation of oxindoles. The reaction employed a chiral scandium(III) catalyst under basic conditions with the dual role of causing asymmetric induction by coordinating to the enolate oxygen, and at the same time preventing formation of the undesired O–I intermediate (Scheme 14d) [195].

4.2 Reactions with Arenes

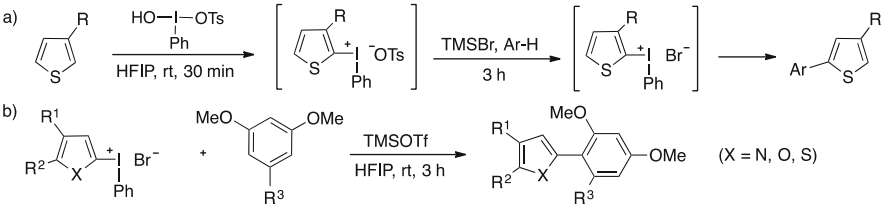
4.2.1 Metal-Free Arylations

The first synthesis of biaryls with diaryliodonium salts was reported by Yan and coworkers in 2006, who treated various Ar_2IX with excess sodium tetraphenylborate and tosic acid in water at 50 °C to obtain Ar–Ph in good yields [196]. Diaryliodonium bromides were more efficient than tetrafluoroborates, and

a selective transfer of the most electron-rich aryl group was observed with unsymmetrical diaryliodonium salts. This chemoselectivity is opposite to the general trend in metal-free reactions. The limited scope and poor atom efficiency of this protocol left room for improvements in the area, and several cross-couplings under more appealing conditions have since emerged.

In 2009, Kita's group made the breakthrough discovery that thiophenes could be cross-coupled with electron-rich arenes via in situ formation of unsymmetric diaryliodonium salts from HTIB and the thiophene (Scheme 15a) [197]. The reaction required activation by TMSBr and HFIP as solvent, and chemoselective transfer of the electron-rich heteroaryl group over the phenyl group was observed. The concept was applied in the regioselective synthesis of bithiophenes and of a regioregular oligothiophene useful as a photovoltaic dye molecule [198–200]. Biaryl couplings with 2-substituted heteroarenes were further explored, as these were unsuitable in the one-pot reaction described above. Successful cross-couplings could be achieved with isolated, unsymmetric heteroaryl(phenyl) iodonium salts by activation with TMSOTf in HFIP (Scheme 15b) [198]. Thiophenes, pyrroles, and furans could be converted to biaryls with electron-rich arenes in this two-step approach, proceeding via a SET mechanism [28, 198]. The methodology was also extended to the synthesis of biaryls lacking a heteroaryl moiety [200]. A detailed discussion of these cross-couplings, including mechanistic details, is given in Kita's recent account [28].

Ackermann and coworkers reported a C3-selective arylation of indoles using excess Ar_2IX in DMF at 100 °C. A minor amount of C2-arylation was observed with some substrates, and a mesityl dummy was superior to the anisyl group in arylations with unsymmetric salts [201]. The use of C3-functionalized indoles resulted in C2-arylation, which was utilized in the synthesis of indole-containing oligopeptides [202]. Interestingly, C3-substituted indoles had previously been selectively C3-arylated under basic conditions in DCE at room temperature, yielding aryl indolenines which were reduced to indolines [203]. Metal-free arylations of naphthalene and other arenes with diaryliodonium salts have been described, using the arene as solvent at elevated temperature [204, 205]. Phenols have been shown to undergo C-arylation in a dearomatization reaction, rather than O-arylation (see Sect. 3.2.1), under certain conditions [206].



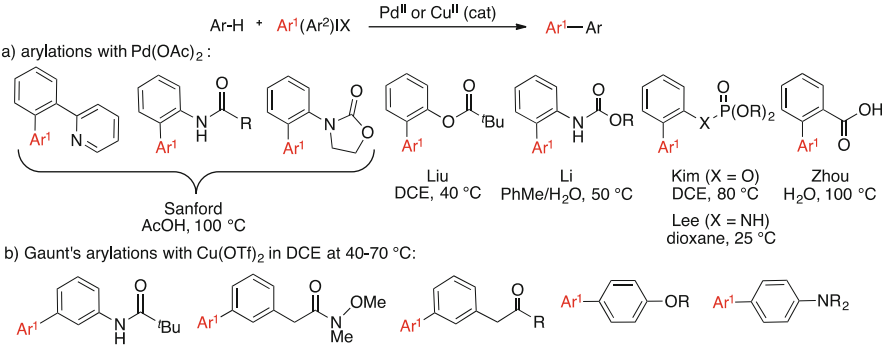
Scheme 15 Metal-free aryl–aryl couplings with electron-rich arenes and heteroarenes

4.2.2 Metal-Catalyzed Arylations

At the turn of the century, Kang's group reported several palladium- and copper-catalyzed cross-coupling reactions with organoboranes or organostannanes to give biaryls under mild conditions. The corresponding reactions under carbonylative conditions resulted in diarylketones [207, 208]. In 2005, Sanford and coworkers developed a Pd-catalyzed protocol for C–H arylation of N-functionalized arenes and heterocycles with diaryliodonium tetrafluoroborates. Pyridine-, oxazolidinone-, lactam-, and amide-derived directing groups could be employed, and unsymmetric and mesityl salts were applied for the first time in coupling reactions with Ar_2IX (Scheme 16a) [39–41]. Many Pd-catalyzed C–H arylations have since appeared with a variety of directing groups, including the *ortho*-arylation of pivaloyl aryl esters, carbamate-protected anilines and phenols, aryl phosphates, aryl phosphoramidates, and benzoic acids (Scheme 16a) (pivaloyl aryl esters [209]; aniline carbamates [210]; carbamate-protected phenols [211]; aryl phosphates [212]; aryl phosophoramidates [213]; benzoic acids [214]). A monoarylation of biphenyl derivatives with a $P(O)R_2$ directing group was developed to obtain polyaromatic monophosphorus ligands [215].

Diaryliodonium salts are frequently used as photoinitiators in cationic polymerization, and aryl radicals are generated with ruthenium- or iridium-based photocatalysts [10]. In 2012, Sanford exploited this feature in a combined Pd/Ir-catalyzed system for photoredox arylations of arenes with N-directing groups. The generation of aryl radicals allowed *ortho*-arylations at room temperature in MeOH, i.e., much milder conditions than previously described [216].

Gaunt and coworkers discovered that anilides were selectively *meta*-arylated in the presence of $Cu(OTf)_2$ in DCE at 70 °C (Scheme 16b) [80]. In a similar fashion, the group achieved the *para*-arylation of anilines and phenol ethers, and the *meta*-arylation of α-arylacetamides and α-arylketones [217, 218]. Unsymmetric salts with mesityl or TRIP dummy substituents could be chemoselectively employed, and the reactions also proceeded in the absence of copper at slightly higher temperature, which makes mechanistic interpretations difficult [43].

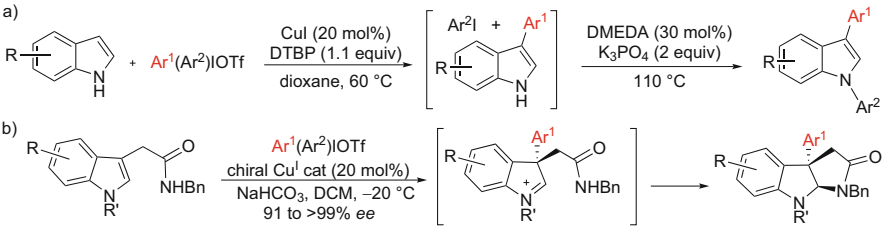


Scheme 16 Products in metal-catalyzed arylations of arenes with directing groups

The regioselective arylation of indoles has been thoroughly investigated by a number of groups. In 2006, Sanford and coworkers developed a Pd-catalyzed C2-arylation of indoles at room temperature in acetic acid. Mesityl salts could be chemoselectively applied, and no competing N-arylation was observed with N-unsubstituted indoles. Importantly, the diaryliodonium species could be generated in situ from the corresponding DIB-derivative and an arylboronic acid [219]. It was recently reported that the C2-arylation of indoles could be performed in water at room temperature or 40 °C using a heterogeneous nanopalladium catalyst [220], and similar conditions were employed in the C2-arylation of tryptophan-containing peptides [221]. The Pd-catalyzed arylation of 2,5-disubstituted pyrroles was achieved with symmetric Ar_2IBF_4 in DCE at 84 °C [222].

Gaunt's group reported a Cu-catalyzed regioselective arylation of indoles in 2008, in which the TRIP moiety was introduced as a better dummy substituent than the mesityl group [51]. N–H and N-alkyl indoles delivered the C3-arylated product with good to excellent regioselectivity, whereas *N*-acetylindoles afforded the C2-arylated product with moderate selectivity. The C3-arylation was applied on a 42-g scale as the first step in a total synthesis of dictyodendrin B [223]. Greaney and coworkers recently presented a way to avoid the atom economy problem arising from the formation of a stoichiometric amount of iodoarene in arylations with Ar_2IX [224], which had previously been addressed only in arylations with cyclic diaryliodonium salts (see also Sects. 3.1.2 and 4.3) [225]. Their approach combined two known copper-catalyzed transformations – the C3-arylation of indoles with Ar_2IX [51] and the N-arylation with iodoarenes [226], providing the diarylated product in a sequential one-pot reaction after careful optimization of the reaction conditions (Scheme 17a) [224].

The copper-catalyzed methodology for arylation of indoles was utilized in the C3-arylation of *N*-tosyl tryptamines and tryptophan derivatives to yield pyrroloindolines in a diastereoselective fashion [227, 228], and similar transformations were achieved with tryptophols [229, 230]. MacMillan's group developed an asymmetric copper bisoxazoline-catalyzed C3-arylation of indole-3-carboxamides, where the intermediate indole iminium ion was intramolecularly attacked by the amide substituent to form tricyclic pyrroloindolines with high enantioselectivities and good yields (Scheme 17b) [193].



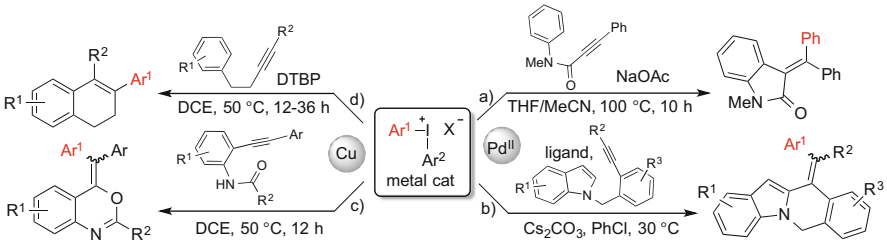
Scheme 17 Metal-catalyzed arylations of heteroaromatic compounds (DMEDA = *N*, *N*′-dimethylethylenediamine)

Glorius and coworkers recently developed a C3-selective arylation of thiophenes and benzothiophenes catalyzed by Pd/C in ethanol at 60 °C. (Benzo)furans and indole were selectively C2-arylated, and the heterogeneous reaction was insensitive to air and moisture [231]. The arylation of arenes lacking a directing group has been more difficult, and the Pd-catalyzed arylation of naphthalene required heating to 130 °C in nitrobenzene to proceed [232]. Interestingly, platinum catalysis allowed C–H arylation of a range of arenes with diaryliodonium trifluoroacetates with opposite regioselectivity to the Pd-catalyzed reaction [233]. Both systems required a large excess of arene, and only moderate yields were obtained. The use of a metal-organic framework improved the Pd-catalyzed phenylation of naphthalene, as the catalyst had a longer lifetime under the harsh conditions [234]. Polyaromatic hydrocarbons could be monoarylated in moderate yields with Pd/C in DME at 100 °C without excess reagents [235]. Biaryls could also be synthesized using a palladacycle catalyst in TFA at 100 °C, although product mixtures were obtained [236].

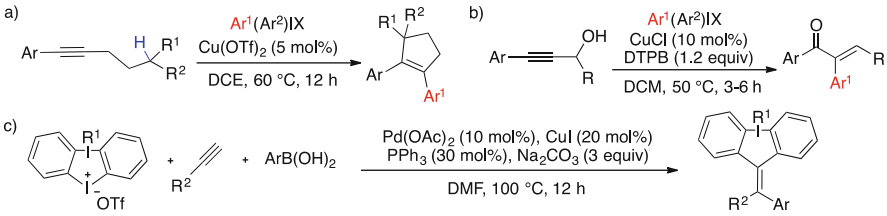
4.3 Reactions with Alkynes

The arylation of alkynes with diaryliodonium salts under metal-catalyzed conditions was thoroughly investigated by Kang and coworkers at the turn of the century. They developed Pd- and Cu-catalyzed conditions for cross-couplings and carbonylative cross-couplings with terminal alkynes at room temperature [237–239]. Other coupling partners, such as organoboranes or organostannanes, were also utilized. In the last 5 years, the area has attracted renewed interest as the arylation can be combined with subsequent reactions to obtain complex molecules in one pot.

In this vein, alkynyl-functionalized (hetero)arenes were utilized in Pd-catalyzed arylation and cyclization events to reach tetrasubstituted alkenes. This strategy proved successful with an *N*-phenylpropiolamide (Scheme 18a) [240] and *N*-(2-alkynylbenzyl)indoles (Scheme 18b) [241]. Copper catalysis was also viable, as demonstrated in reactions with 2-ethynyl anilides to yield benzoxazines (Scheme 18c) [242]. A copper-catalyzed carboarylation of electron-rich alkynes



Scheme 18 Metal-catalyzed tandem reactions involving arylation and cyclization



Scheme 19 Metal-catalyzed arylations involving rearrangements or cyclic iodonium salts

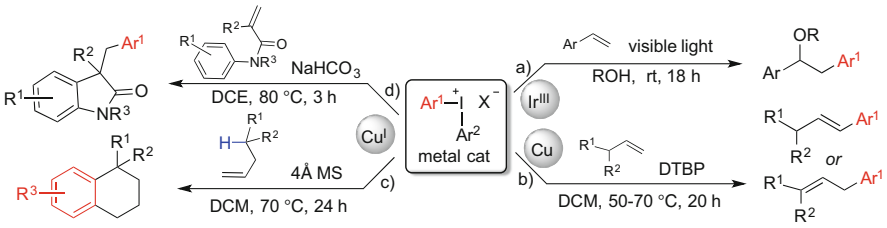
was proposed to proceed via a vinyl cation, which was trapped in an intramolecular Friedel–Crafts-type process (Scheme 18d) [243].

The groups of Chen and Gaunt simultaneously developed copper-catalyzed tandem reactions of aryl alkynes, where the arylation was followed by cyclization and elimination to provide diarylcyclopentenes (Scheme 19a) [244, 245]. This interesting transformation involves activation of an inert C(sp^3)-H bond and proceeds either via a 1,5-hydride shift or a concerted process, and proved applicable in the synthesis of spirocyclic compounds [244]. It was subsequently extended to alkoxy-substituted aryl alkynes in a tandem arylation and cycloetherification process to yield a variety of oxygen-containing heterocycles [246]. Scheme 19b depicts the synthesis of complex (*E*)-trisubstituted enones by Cu-catalyzed Meyer–Schuster rearrangement of propargylic alcohols to the corresponding allenols, which were trapped with Ar_2IX in the presence of 2,6-di-*tert*-butylpyridine (DTBP) [247]. Parallel to this work, Liu and coworkers developed a Cu-catalyzed arylation of propargylic alcohols to yield the corresponding β-hydroxy ketones. The reaction was proposed to proceed by a different mechanism, despite the similar reaction conditions, and could also be performed with alkynes lacking a hydroxyl group [243].

Several three-component Pd/Cu-catalyzed domino reactions with alkynes and diaryliodonium salts have been demonstrated. 2-(1-Alkynyl)-2-alken-1-ones were reacted with Ar_2IX and alcohols to yield tetrasubstituted furans under mild conditions [248]. Cyclic diaryliodonium salts, alkynes, and arylboronic acids could be combined to obtain exocyclic tetraaryl alkenes (Scheme 19c; see Sect. 3.1.2 for a similar N-arylation cascade) [249].

4.4 Reactions with Alkenes

Developments in this area parallel those in reactions with alkynes (Sect. 4.3) and Kang's group developed palladium-catalyzed cross-couplings of diaryliodonium salts and alkenes, and carbonylative couplings yielding vinyl aryl ketones, under mild conditions some 20 years ago [250, 251]. Heck-type couplings have received renewed interest, including the development of a coupling using a heterogeneous,



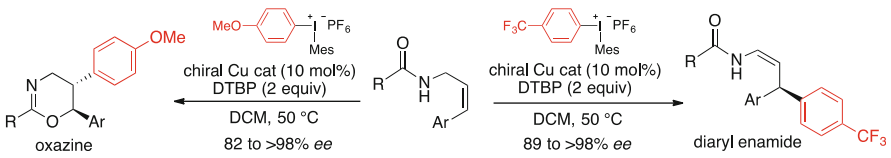
Scheme 20 Metal-catalyzed tandem reactions with alkenes

magnetically recoverable Pd catalyst in aqueous PEG [252]. The C3-arylation of cyclic enamides was reported in an approach towards 3-arylpiperidines [253].

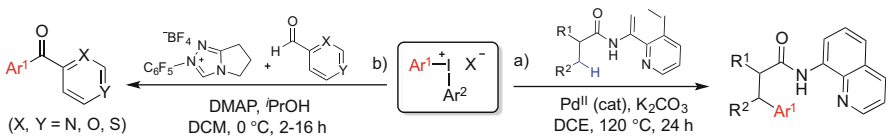
Since Sanford's discovery of C-arylations with diaryliodonium salts under photocatalytic conditions [216] (see Sect. 4.2.2), several groups have developed photocatalytic transformations with alkenes at room temperature. The copper-catalyzed arylation of allylic tosylamides (allylsulfones) provided allylic arenes via a radical mechanism in moderate to good yields [254]. A photoredox-catalyzed reaction of styrenes was performed with iridium catalysis and visible light, giving oxyarylation or aminoarylation products depending on the solvent used (Scheme 20a) [255]. The oxyarylation of alkenes under combined gold and photoredox catalysis required a large excess of Ar_2IX [256].

In 2012, Gaunt and coworkers published a copper-catalyzed arylation of simple alkenes which was proposed to proceed with a carbocation-type mechanism (Scheme 20b) [257]. This explained the formation of two regioisomeric products and allowed tandem rearrangements to take place with certain substrates. With continued focus on generation of carbocation intermediates, alkenes having homoallylic hydrogens could be arylated with a subsequent hydride shift and Friedel–Crafts-type cyclization to obtain tetrahydronaphthalenes in the same way as described for alkynes (Scheme 20c) [245]. Arylation of N-aryl acrylamides with concomitant cyclization delivered oxindoles in good yields (Scheme 20d) [258, 259]. The methodology was applied in the formal total synthesis of biologically active compounds.

Gaunt's group recently reported an intramolecular oxyarylation of allylic amides which probably proceeds via a stabilized carbocation, yielding oxazine heterocycles with *endo*-selectivity [260]. An enantioselective version was subsequently developed using a Cu/bisoxazoline catalyst. As usual, unsymmetric mesityl salts could be employed, and PF_6^- salts gave much higher enantioselectivity than ^-OTf. The reaction was regiodivergent, leading to oxazines with electron-rich salts, and to diaryl enamides with electron-poor salts (Scheme 21) [261].



Scheme 21 Enantioselective arylation of allylic amides



Scheme 22 (**a**) Activation of sp^3 C–H bonds. (**b**) Metal-free synthesis of diarylketones

4.5 Other C-Arylations

The arylation of sodium cyanide can be achieved in moderate yields with electron-withdrawing iodonium salts [87]. The synthesis of esters was achieved by palladium-catalyzed carbonylative reaction of alcohols with diaryliodonium salts under a CO atmosphere [262]. More recently, a base-mediated arylation of quinones with electron-donating iodonium salts in refluxing DCE was reported in moderate to good yields [263]. Quinoline anilides could be arylated at the β-carbon by a Pd- or Ni-catalyzed reaction proceeding via activation of sp^3 C–H bonds (Scheme 22a) [264, 265]. Vinyl isocyanides were arylated at room temperature in a photoredox-catalyzed system with an iridium catalyst and visible light, followed by cyclization to give isoquinoline derivatives [266].

Gaunt and coworkers discovered that heteroaromatic aldehydes could be converted to the corresponding ketones by arylation under metal-free conditions using a commercially available *N*-heterocyclic carbene catalyst (Scheme 22b) [52]. The reaction was proposed to proceed by formation of a Breslow intermediate from the aldehyde and the carbene, acting as a nucleophile in the subsequent arylation. Reactions with unsymmetric salts were rather unselective with common dummy groups, but salts with a uracil dummy substituent proved to be highly selective (see Sect. 2).

Kitamura and coworkers reported that treatment of (phenyl)[2-(trimethylsilyl) phenyl]iodonium triflate with TBAF results in the formation of benzyne, which can be trapped with furan and other dienes in cycloaddition reactions [35, 267, 268]. This feature was recently utilized with an iodonium salt containing an *ortho*-(pyridyldiisopropyl)silyl group [269]. Diaryliodonium salts are also useful in covalent grafting of carbon surfaces useful in materials chemistry [270–273].

5 Outlook

With the development of efficient synthetic routes to diaryliodonium salts, these hypervalent iodine compounds have become easily available and interesting alternatives to other arylation reagents. Their low toxicity, high stability, and high reactivity are attractive features which enable difficult transformations without the need for excess reagents or high temperatures. This chapter has summarized recent developments in metal-free and metal-catalyzed arylations of heteroatom nucleophiles and carbon-centered nucleophiles. The boundaries of the field have moved forward considerably in the last decade, and many more applications are foreseen based on the deepened mechanistic understanding of arylations under both metal-free and metal-catalyzed conditions.

Despite major achievements in this area, there are still several limitations to address. The formation of stoichiometric amounts of iodoarene make large-scale applications less appealing, and advancements in the area of solid-supported diaryliodonium salts would be of importance to simplify recovery of the iodoarene and avoid product purification problems. At present, such approaches are limited by time-consuming synthesis of the reagents, chemoselectivity problems, and/or moderate arylation yields. The development of reactions catalytic in diaryliodonium salt would be a major breakthrough with industrial relevance. Asymmetric arylations under metal-free conditions have proved to be very difficult to achieve, and further developments in this area are foreseen.

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Iodanes as Trifluoromethylation Reagents

Natalja Früh, Julie Charpentier, and Antonio Togni

Abstract This chapter describes synthesis, structural properties, activation modes, and applications of hypervalent iodine reagents for trifluoromethylation, thereby focusing on recent advances.

Keywords Benziodoxole · Benziodoxolone · Hypervalent iodine · Trifluoromethylation

Contents

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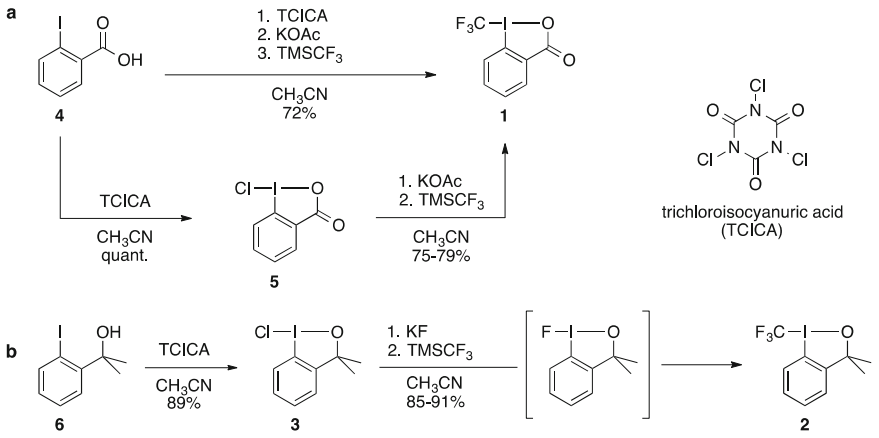
1 Introduction

Hypervalent iodine reagents for trifluoromethylation, in particular compounds **1** and **2** (Scheme 1) based on the benziodoxolone and benziodoxole scaffold, respectively, have been known since our original report in 2006 [1]. In more recent years these reagents have attracted the interest of the synthetic community in the area of organofluorine chemistry and quite a broad range of disparate applications have been disclosed, as documented in a recent comprehensive review article [2]. The success of compounds **1** and **2** is to be ascribed to their straightforward preparation also suited for large quantities, easy handling (for a discussion of possible safety issues see arguments in [2]), and, most importantly, to their adaptability to various reaction conditions and activation modes. We focus here on selected aspects mainly covering recent progress achieved in this area.

2 Synthesis

The idea to develop hypervalent iodine reagents for trifluoromethylation was inspired by earlier research on electrophilic chlorination using (dichloro-λ^3-iodo)-*para*-toluene carried out in our group [3]. We envisioned a hypervalent I-CF_3 unit to be accessed by an Umpolung of a nucleophilic CF_3 rather than a Friedel–Crafts-type electrophilic aromatic substitution as known for reagents derived from iodoperfluoroalkanes [4]. However, all attempts to install a trifluoromethyl group on different disubstituted (*para*-tolyl)-λ^3-iodanes failed, probably because of the instability of the corresponding product under the chosen reaction conditions (indicated by traces of CF_3I formed during the reaction). Therefore, a cyclic



Scheme 1 (**a**) Optimized reaction route to trifluoromethyl benziodoxolone **1**. (**b**) Optimized reaction route to trifluoromethyl benziodoxole **2** [6]

backbone was introduced to confer more stability to the product. Indeed, when 2-iodosylbenzoic acid was mixed with $TMSCF_3$ in the presence of catalytic amounts of fluoride, the formation of the desired product **1** was indicated by a new ^{19}F NMR signal at −35.7 ppm. Similarly, benziodoxoles are frequently used as stable λ^3-iodanes and thus reagent **2** was synthesized in a similar manner from known chloroiodane **3** [1, 5].

After thorough synthetic route optimization, reagents **1** and **2** can both be easily accessed from readily available starting materials in high overall yields of 72% and 80%, respectively (Scheme 1) [6].

The synthesis of reagent **1** starts with the oxidation of commercially available iodobenzoic acid (**4**) by trichloroisocyanuric acid (TCICA) as a cheap and safe formal Cl^+ source. Chloroiodane **5** can either be isolated in quantitative yields and further converted to the desired product **1** via exchange of chloride with acetate followed by the Umpolung step using Ruppert–Prakash reagent as CF_3^- source, or be directly used in a one-pot three-step procedure, again using KOAc and $TMSCF_3$ for the final two steps (Scheme 1a). Reagent **2** is synthesized in two steps from iodoalcohol **6**, which can be easily accessed from methyl anthranilate via Sandmeyer reaction followed by a Grignard addition. Compound **6** is first oxidized using TCICA to obtain chloroiodane **3**, which undergoes ligand exchange with KF and is subsequently converted to reagent **2** using $TMSCF_3$ (Scheme 1b). Both procedures can be carried out on a multigram scale, making access to these popular trifluoromethylating reagents easier than ever before.

3 Structure and Properties

The X-ray crystal structures of compounds **1** and **2** show a T-shaped geometry around the hypervalent iodine atom, as expected for a 10-I-3 compound [1, 7, 8]. The pseudo-trigonal bipyramidal geometry is confirmed by the corresponding bond angles, namely C8–I1–O1 being 170.43(12)° in **1** and 169.77(8)° in **2**, clearly deviating from the ideal 180°. Compound **1** is basically planar, as indicated by the torsion angles O1–I1–C2–C1 (0.3(2)°) and C8–I1–C2–C3 (0.7(3)°). In **2**, however, the replacement of the carbonyl oxygen atom of **1** by two methyl groups results in a significant twist of ca. 13° of the so-called 3c-4e bond (three-centers-four-electron bond) out of the plane of the phenyl core. The electronic properties of the carboxylate and alkoxide moieties in reagent **1** or **2**, respectively, show an effect on the corresponding I1–O1 and I1–C8 bond lengths. In the case of the electron-withdrawing carboxylate group in **1**, the I1–O1 bond is longer compared the bond in **2** with a more electron-donating alkoxy group (2.283(2) Å vs 2.118(1) Å). In comparison, the I1–C8 bond is shorter in **1** than in **2** (2.219(4) Å vs 2.267(3) Å) (Fig. 1).

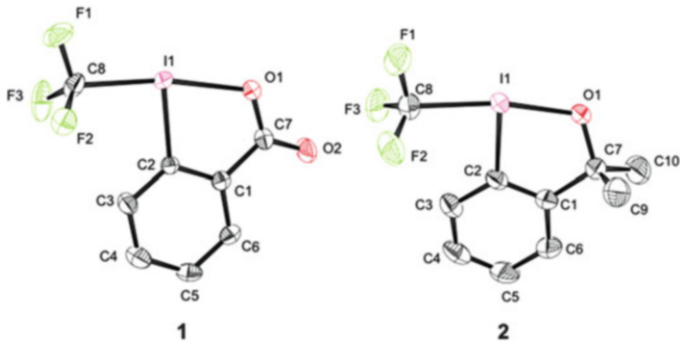
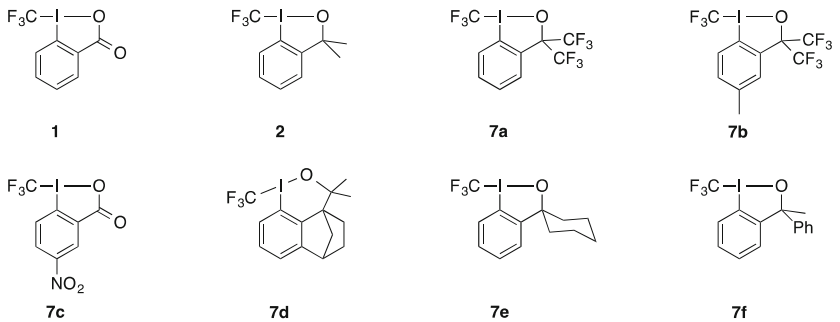


Fig. 1 ORTEP views of the X-ray crystal structures of **1** (CCDC-239458) and **2** (CCDC-618737) and adopted numbering (hydrogen atoms are omitted for clarity, thermal ellipsoids are set to 50% probability) [1, 5, 7]



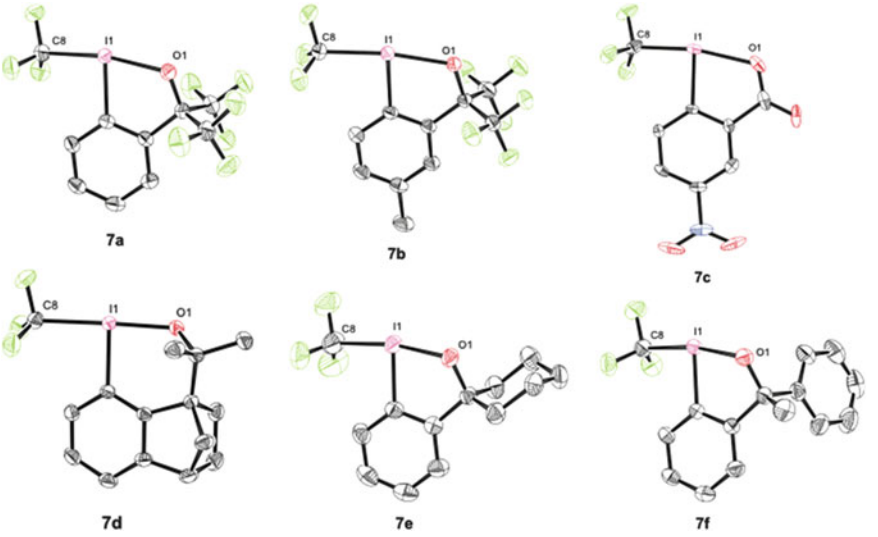
Scheme 2 Reagents **1** and **2** and their structural relatives **7a–f** [1, 5, 9–13]

In addition to the well-known reagents **1** and **2**, our group has prepared several structurally related derivatives **7a–f** with the aim of finding an inherent relationship between structure and reactivity [1, 5, 9–13] (Scheme 2).

In the solid state, all structures present a similar distorted T-shape, indicated by the C8–I1–O1 angle, which differs from the ideal 180° angle by ca. 10°. In the case of **7d**, a six-membered benziodoxine derivative, this angle is obviously closer to 180°. When comparing the bond lengths of the 3c-4e unit the only evident trend becoming apparent is that a shorter C8–I1 bond leads to a longer I1–O1 bond, and vice versa (Table 1).

The reactivities of compounds **7a–f** in the trifluoromethylation of *p*-toluenesulfonic acid were investigated and initial rates v_0 were determined. Although a vague trend suggests that lengthening of the I1–O1 bond concurs with a higher initial rate (see also Sect. 5), no clear structure-reactivity relationship can be formulated. Interestingly, for a set of reagents of type **2** the ^{13}C NMR chemical shift of the benzylic carbon correlates exponentially with v_0 [10]. Unfortunately, both types of correlations are based on relatively small data sets, such that firm QSAR-type conclusions cannot be drawn (Scheme 3).

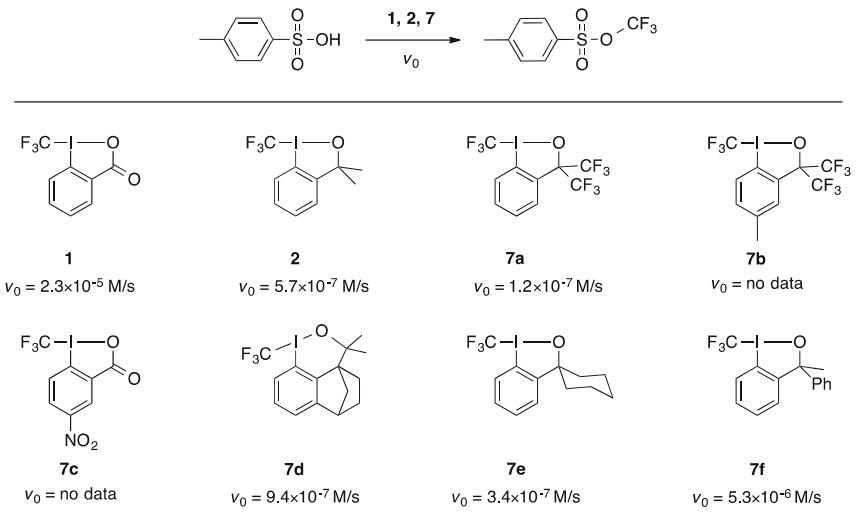
Table 1 ORTEP views of the X-ray crystal structures of **7a–f** (CCDC-281919, 281920, 958117, 771237, 771240, 771246) and selected bond lengths and angles [1, 5, 9–13]



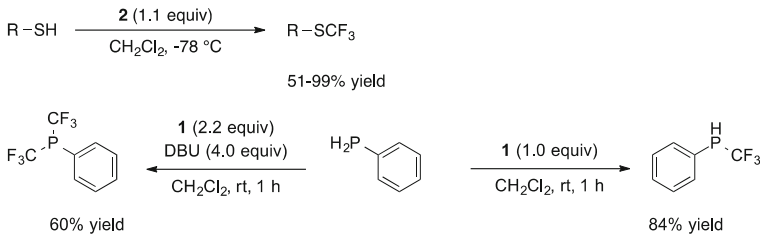
	1	**2**	**7a**	**7b**
C8–I1–O1	170.43(12)°	169.77(8)°	169.41(7)°	171.08(9)°
C8–I1	2.219(4) Å	2.267(3) Å	2.229(2) Å	2.236(3) Å
I1–O1	2.283(2) Å	2.118(1) Å	2.201(2) Å	2.198(2) Å
	7c	**7d**	**7e**	**7f**
C8–I1–O1	169.0(2)°	177.91(7)°	169.7(1)°	170.18(5)°
C8–I1	2.199(5) Å	2.304(2) Å	2.262(4) Å	2.258(2) Å
I1–O1	2.305(4) Å	2.098(1) Å	2.121(2) Å	2.135(1) Å

4 Trifluoromethylation of Organic Substrates by Use of Cyclic Iodanes

The design of this new class of trifluoromethylation reagents led to the development of a vast number of specific methodologies addressing a broad array of organic nucleophilic substrates. These cover heteroatom-centered nucleophiles such as thiols, phosphines, alcohols, and azoles, as well as carbon-centered nucleophiles in their virtually unlimited diversity. The formation of the new X–CF_3 or C–CF_3 bond relies on several different strategies as discussed below, in what is intended to be a brief overview. A more exhaustive account has recently appeared in the form of a comprehensive review article [2].



Scheme 3 Initial rates for reagents **1**, **2**, and **7** in the trifluoromethylation of *p*-toluenesulfonic acid [1, 9–12]

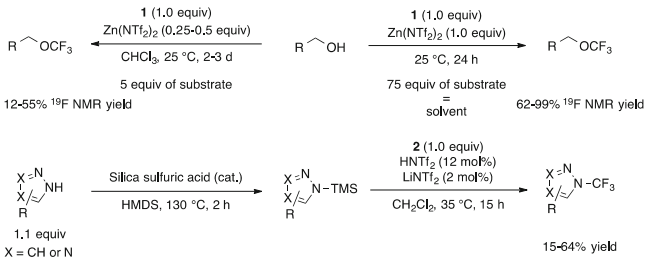


Scheme 4 Trifluoromethylation of thiols and phosphines [7, 14–16]

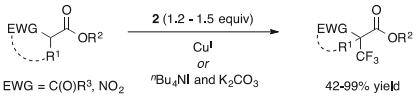
4.1 Heteroatom-Centered Nucleophiles

Phosphines and thiols undergo rapid trifluoromethylation, without the need of any additives as exemplified in Scheme 4 [7, 14–16]. Only in the case of primary phosphines leading to double trifluoromethylation is an excess of an organic base (1,8-diazabicycloundec-7-ene, DBU) needed to obtain the desired product.

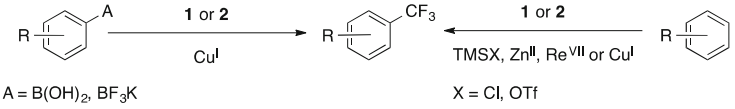
On the other hand, oxygen- and nitrogen-based nucleophiles mostly need the addition of a Brønsted or Lewis acid, often in stoichiometric amounts, even though some trifluoromethylation reactions allow the use of catalytic amounts of acid (Scheme 5) [17, 18]. The role of the acid is central and is discussed in more detail in Sect. 5.1. In several cases it has been observed that deprotonation or silylation of the substrate enhances reactivity, in parallel with the activation of the reagent by Brønsted or Lewis acids.



Scheme 5 Formation of trifluoromethyl ethers and trifluoromethyl *N*-heterocycles [17, 18]



Scheme 6 α-Trifluoromethylation of electron-poor esters [7, 21, 22]



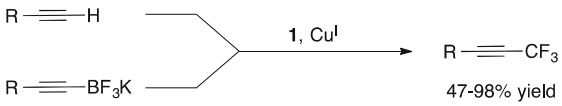
Scheme 7 Trifluoromethylation of arenes [23–31]

Obviously, the trifluoromethylation of highly acidic oxygen-based nucleophiles (sulfonic or phosphonic acids) occurs even without the addition of acid, as the substrate itself acts as activating agent in these cases (see Sect. 5.1) [19, 20].

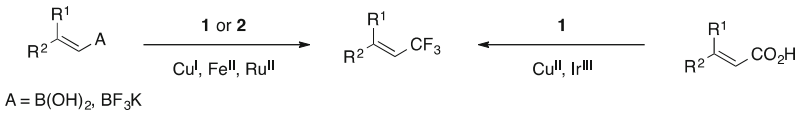
4.2 Carbon-Centered Nucleophiles

A first approach toward the trifluoromethylation of carbon-centered nucleophiles was to use the innate acidity of the substrate. Scheme 6 shows that esters bearing an electron-withdrawing group in the α-position are excellent substrates for carbon-trifluoromethylation, most often catalyzed by Cu^{I} salts [7, 21, 22].

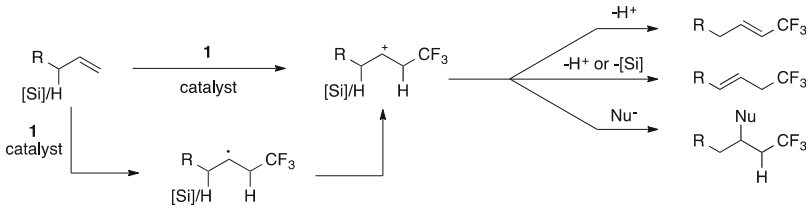
Electron-rich aromatic substrates undergo direct trifluoromethylation catalyzed by a variety of Lewis acids, such as Zn^{II} salts, silanes, rhenium, or copper complexes. In the absence of an appropriate directing group, this kind of trifluoromethylation displays very low or no regioselectivity. More electron-poor arenes have to be activated first and are able to undergo trifluoromethylation in the form of aryl boronic acids or trifluoroborates (Scheme 7) [23–31].



Scheme 8 Trifluoromethylation of alkynes [31, 32]



Scheme 9 Preparation of trifluoromethyl alkenes [30, 33–37]



Scheme 10 Trifluoromethylation and subsequent reactivity of unactivated alkenes [2]

A similar approach has been chosen for the trifluoromethylation of alkynes (Scheme 8). Under copper catalysis, the trifluoromethyl acetylenes are formed from either the free terminal alkyne or from the corresponding alkynyl trifluoroborate [31, 32].

Vinylboronic acids and vinyl tetrafluoroborates can be trifluoromethylated under conditions allowing for a one-electron reduction (see below for mechanistic details). Under similar conditions, unsaturated carboxylic acids undergo decarboxylative trifluoromethylation, leading to the formation of vinylic CF_3 derivatives (Scheme 9) [30, 33–37].

Extensive efforts have been devoted to the addition of a trifluoromethyl group to olefins. As summarized in Scheme 10, a crucial cationic (or radical) trifluoromethyl intermediate is formed upon exposing a terminal alkene to reagent **1** in the presence of a suited catalyst (the radical species may undergo oxidation generating the same cationic intermediate). This carbocation can then engage in different further transformations, depending on the reaction conditions and the neighboring groups: (1) loss of an α-proton or silyl group or (2) addition of a nucleophile. The nucleophile involved can be external such as the solvent (e.g., alcohols), the counter-ion of the metal catalyst (e.g., CuCl), the by-product derived from the trifluoromethylating reagent (i.e., 2-iodobenzoate), or a nucleophile originating from the corresponding silane (e.g., TMSCN or $TMSN_3$) or a boronic acid derivative. If the nucleophile is linked to the unsaturated moiety, a cyclic product is obtained. Additions across unsaturated bonds involving a trifluoromethyl group

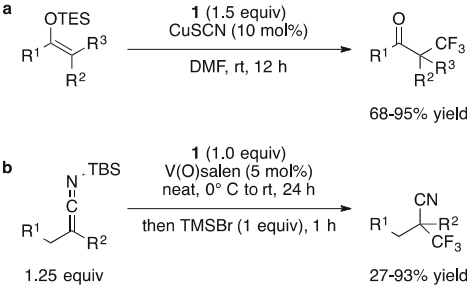
have been documented by a steadily increasing number of examples in recent years [2].

4.3 Recent Advances

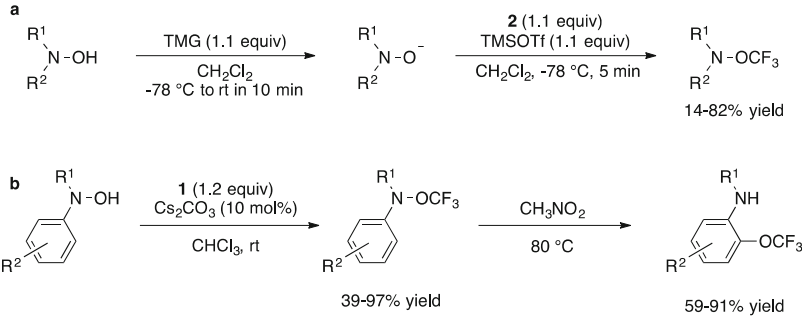
A number of reports documenting the extension of the general scope of trifluoromethylation reactions with **1** or **2** have appeared in the literature recently. Thus, the α-trifluoromethylation of ketones needs the generation (and isolation) of the corresponding enol derivatives, as exemplified in Scheme 11a [38]. In the presence of a Cu^{I} salt, α-trifluoromethylated ketones are subsequently formed in high yields from silyl enol ethers. Analogously, silyl ketene imines undergo smooth trifluoromethylation when using an oxovanadium(IV) catalyst. This simple transformation, which may be carried out under solvent-free conditions, leads to synthetically useful α-trifluoromethyl nitriles containing a quaternary center (Scheme 11b) [39]. In previous reports it has also been shown that slow trifluoromethylation of silyl ketene enol ethers and silyl ketene acetals takes place in the absence of any catalyst [40].

N,*N*-Dialkylhydroxylamines have been shown to be valuable substrates for trifluoromethylation using reagent **2** (Scheme 12a). After deprotonation of the substrate with tetramethylguanidine (TMG), rapid *O*-trifluoromethylation can occur when using the activated reagent **2** [41]. Ngai and co-workers developed a similar trifluoromethylation protocol for aromatic hydroxylamines, using Cs_2CO_3 as base in combination with reagent **1**, as shown in Scheme 12b [42]. It should be noted that the corresponding products are able to undergo a heat-induced rearrangement affording trifluoromethoxylated aniline derivatives. This sequence of transformations is also possible as a one-pot procedure, when using NaH as base.

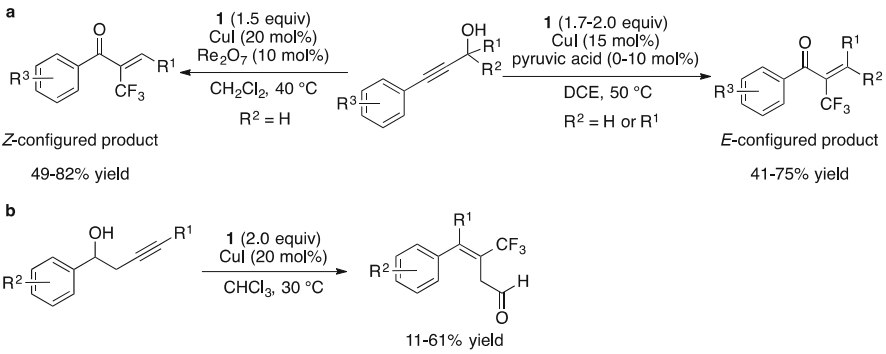
Both *E*- and *Z*-configured α-trifluoromethyl enones are accessible via a Meyer–Schuster-type rearrangement of propargylic alcohols (Scheme 13a) [43, 44]. Under copper catalysis, the *E*-configured enone is obtained. When adding a rhenium salt as co-catalyst, the *Z*-configured product forms preponderantly. A similar report shows



Scheme 11 α-Trifluoromethylation of silyl enol ethers (a) and silyl ketene acetals (b) [38, 39]

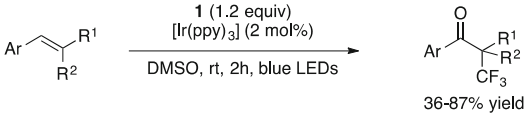


Scheme 12 Trifluoromethylation of hydroxylamines (a) with subsequent OCF_3 migration (b) [41, 42]



Scheme 13 Trifluoromethylation with subsequent aryl migration of (a) propargylic and (b) homopropargylic alcohols [43–45]

Scheme 14 Synthesis of α-trifluoromethyl ketones from olefins [46]

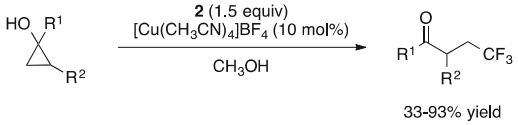


that even homopropargylic alcohols are able to undergo said transformation, forming β-trifluoromethylpentenal derivatives (Scheme 13b) [45].

In analogy to the addition of a trifluoromethyl group to a double bond, Akita and co-workers reported the formation of quaternary α-trifluoromethyl ketones by oxidation of the intermediate using DMSO under photoredox catalysis (Scheme 14) [46].

The formation of β-trifluoromethyl ketones has been achieved by exploiting the ring strains of three-membered rings [47]. As illustrated in Scheme 15, cyclopropyl alcohols react readily with a small excess of reagent **2** in the presence of a catalytic amount of Cu^I to furnish the desired β-trifluoromethyl ketones.

Scheme 15 Ring-opening and trifluoromethylation of cyclopropyl alcohols [47]



5 Activation Modes for Iodane-Based Trifluoromethylation Reagents

As mentioned above, the choice of an appropriate additive may be very crucial for trifluoromethylation reactions using hypervalent iodine compounds. Indeed, several different modes of activation of reagents **1** and **2** have been recognized. These empirical observations were supported further by kinetic and computational studies as well as by X-ray analysis of presumed intermediates isolated in crystalline form. Current knowledge shows that trifluoromethylation has mainly been achieved using (1) Brønsted acids and (2) Lewis acidic metal complexes. A few reports have also shown the successful application of Lewis bases for activation. In several cases, the innate acidity of the nucleophile or the solvent can also be exploited.

5.1 Activation by Protonation

The addition of strong Brønsted acids, such as $HNTf_2$, as shown in Scheme 5 for the trifluoromethylation of azoles, is one of the simplest ways to trigger trifluoromethylation by means of reagents **1** or **2**.

To investigate the role of Brønsted acid additives, a titration experiment has been carried out using $HNTf_2$ as proton source, in combination with benziodoxole-derived reagent **2** (Früh et al., unpublished results). Figure 2 shows a linear downfield shift of the ^{19}F NMR resonance from −41.6 to −23.3 ppm upon addition of the acid. Beyond 1 equiv. of $HNTf_2$, no further change in the ^{19}F NMR chemical shift of the trifluoromethyl group of reagent **2** is observed. This data led to the assumption that, in the presence of (strong) Brønsted acids, a monoprotonated form of reagent **2** (labeled $[H\mathbf{2}]^+$) is formed, acting as reactive intermediate in trifluoromethylation reactions.

A similar monoprotonation of benziodoxolone-based reagent **1** has been studied recently in our laboratory. Crystals obtained from an equimolar mixture of **1** and $NOSbF_6{\cdot}H_2O$ correspond to the protonated form of reagent **1** as hexafluoroantimonate salt incorporating a molecule of water ($[H\mathbf{1}][SbF_6]{\cdot}H_2O$), as depicted in Fig. 3 [48]. The crystallographic data indicate a lengthening of the I1–O1 bond (from 2.283(2) Å to 2.452(3) Å) accompanied by a shortening of the C8–I1 bond (2.125 (4) Å vs 2.219(4) Å) in non-protonated **1**). This lengthening of the I1–O1 bond indicates a weakening of the 3c-4e bond, and hence an increase of reactivity (see Sect. 3). The bond angles around iodine are altered only slightly, confirming that the hypervalent bond between oxygen, iodine, and the trifluoromethyl group is still

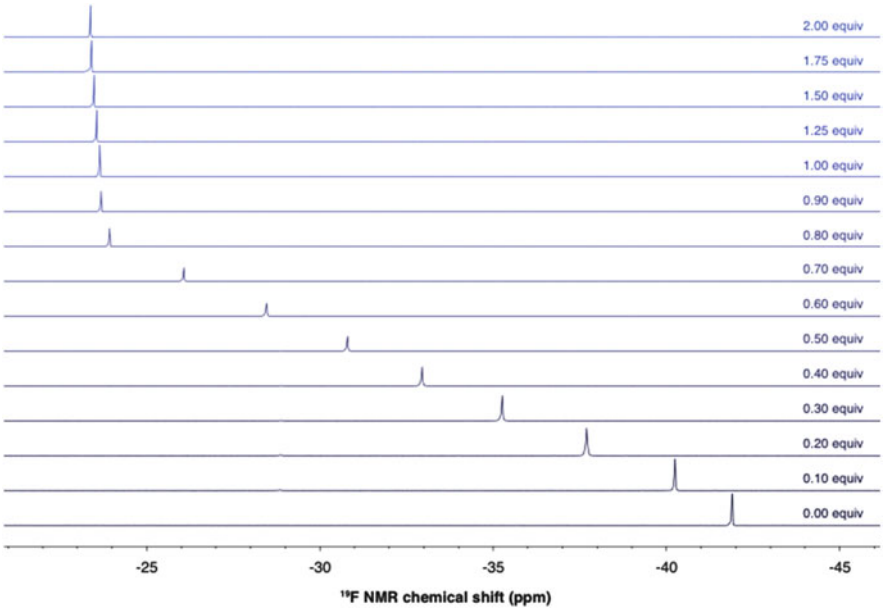


Fig. 2 ^{19}F NMR titration of reagent **2** with $HNTf_2$ (Früh et al., unpublished results)

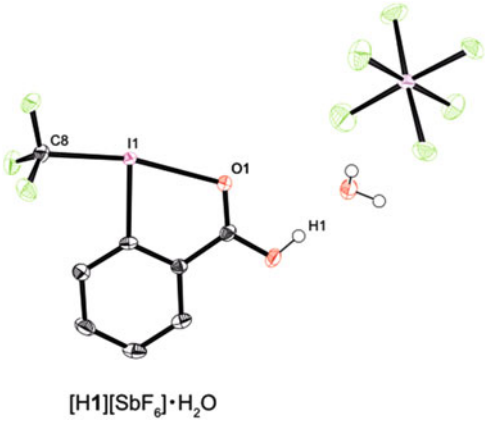
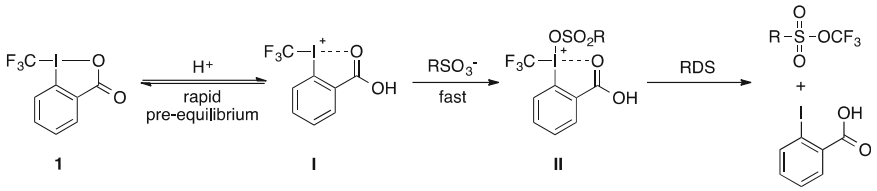


Fig. 3 ORTEP view of the X-ray crystal structure of [H**1**][SbF_6]·H_2O (thermal ellipsoids are set to 50% probability)

present in this structure. This disproves a common misconception that an activation of this kind of structures by Brønsted (or Lewis) acids via protonation (or coordination) to the oxygen would cleave completely the iodine–oxygen bond, thereby generating an extremely reactive cationic iodonium intermediate. Very similar observations have been made previously when analyzing the X-ray structures of protonated forms of reagent **2**.



Scheme 16 Mechanistic hypothesis for the trifluoromethylation of sulfonic acids (Welch et al., unpublished results)

Further insight into mechanistic details of trifluoromethylation reactions using reagents **1** or **2** could be gained when analyzing the kinetic profile of the trifluoromethylation of sulfonic acids (Scheme 16) (Welch et al., unpublished results). This clean reaction goes to completion overnight at room temperature and is hence very suitable for ^{19}F NMR monitoring.

Initial rate studies imply that the reaction is first order, both in reagent **1** and in substrate. Furthermore, a strong inverse kinetic isotope effect $k_H/k_D = 0.65$ was observed for this reaction.[1] Both these findings suggest that reagent **1** is being protonated by the sulfonic acid in a rapid pre-equilibrium reaction, forming intermediate **I** as represented in Scheme 16. Based on the observation that the sulfonate anion is not involved in the rate-determining step, it has been concluded that the protonated reagent ($[H\mathbf{1}]^+$) reacts rapidly with the sulfonate anion to form steady-state intermediate **II**. This step is only possible after protonation, because the I–O bond is already weakened, making the iodine center more prone to coordinating the additional anion. The rate-determining step (RDS) of this reaction is then the transfer of the trifluoromethyl group to the sulfonate anion, in a process reminiscent of a reductive elimination, leaving 2-iodobenzoic acid as by-product. It is conceivable that instead of this reductive-elimination-type reaction an S_N2-type process could take place.

The importance of protons as activating entities is further supported by computational studies. Indeed, frontier molecular orbital (FMO) calculations at the B3LYP/aug-cc-pVTZ level were performed for both reagents **1** and **2** and their protonated counterparts ($[H\mathbf{1}]^+$, $[H\mathbf{2}]^+$), and selected calculated molecular orbitals (MOs) are represented in Fig. 4 (Pinto de Magalhães et al., unpublished results). For both compounds **1** and **2** it has been demonstrated that protonation leads to the lowering of the antibonding combination of the hypervalent 3-center interaction (3cb*) to the level of the lowest unoccupied molecular orbital (LUMO). This is crucial for the reactivity of **1** and **2** as selective trifluoromethylation reagents, because the LUMO of the non-protonated species is localized along the C_{phenyl}–I bond (2cb*). Thus, protonation allows the homolytic cleavage of the CF_3–I bond, as

[1] Inverse kinetic isotope effects are often observed for reactions with a rapid pre-equilibrium for protonation/deprotonation because of the deuterated intermediate being a weaker acid and thus accumulating larger concentrations of the steady-state intermediate before the rate-determining step.

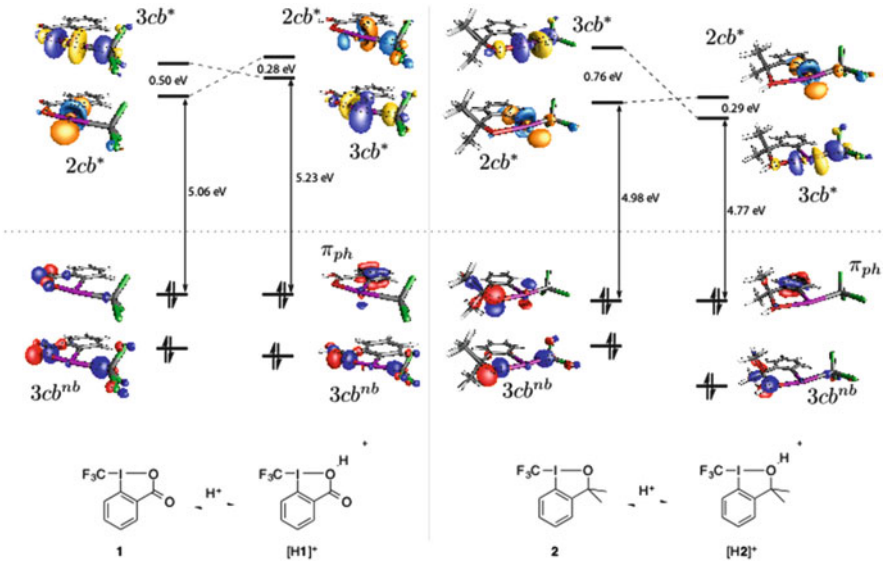


Fig. 4 Selected canonical molecular orbitals of **1**, $[H\mathbf{1}]^+$, **2**, and $[H\mathbf{2}]^+$ (Pinto de Magalhães et al., unpublished results)

opposed to the C_{phenyl}–I bond, in particular when single electron transfer (SET) processes become possible, e.g., in the case of reducing substrates. Interestingly, the energy difference between the highest occupied molecular orbital (HOMO) and the LUMO for reagent **2** is decreased upon protonation, whereas the opposite can be observed for compound **1**. It should also be noted that the antibonding 3cb* in $[H\mathbf{1}]^+$ and $[H\mathbf{2}]^+$ is more strongly polarized as compared to **1** and **2**, respectively, indicating a significantly weakened CF_3–I–O interaction.

5.2 Activation Using Lewis Acids

The *O*-trifluoromethylation of alcohols is carried out in the presence of $Zn(NTf_2)_2$ containing the extremely weak nucleophile triflimide (Scheme 5). However, it had been previously observed that $Zn(OTf)_2$ in the presence of reagent **1** leads to the formation of trifluoromethyl triflate (TFMT) [17]. Both these observations indicate that Zn^{2+} ions enhance the reactivity of the trifluoromethylation reagent. ^{19}F NMR spectroscopy reveals that the resonance of the trifluoromethyl group of **1** is shifted downfield from −33.0 to −26.9 ppm when an equimolar amount of $Zn(NTf_2)_2$ is added to the reaction mixture. This downfield shift is indeed similar to what is observed when Brønsted acids are added to reagent **2** (Fig. 2). Both high resolution electron-spray ionization mass spectrometry (HR ESI-MS) of a 2:1 mixture of **1** and $Zn(NTf_2)_2$, and pulsed-field gradient spin echo (PGSE) NMR of the reaction

mixture leading to trifluoromethyl ethers indicate the formation of a 2:1 adduct of reagent **1** with the zinc dication. X-Ray analysis of crystals obtained from a reaction mixture containing *p*-nitrophenol as substrate revealed further structural features of this 2:1 adduct, which was identified as $[Zn(\mathbf{1})_2(4\text{-}NO_2C_6H_4CH_2OH)_2(OH_2)_2][NTf_2]_2$ (Fig. 5). Thus, two molecules of compound **1** coordinate to the zinc dication via oxygen atom O2. Once again, a lengthening of the I1–O1 bond from 2.283(2) Å to 2.403(12) Å is observed in the solid state. This lengthening is slightly smaller than in the case of the protonated version of reagent **1** (see above). It is therefore possible to draw the analogous conclusion as previously, i.e., that the coordination to the Lewis acid weakens (but does not break) the I1–O1 bond, thereby rendering the iodine atom more electron-deficient and thus increasing its reactivity toward nucleophiles.

Sodeoka and co-workers recently conducted a thorough mechanistic study examining the copper-catalyzed aminotrifluoromethylation of alkenes [49]. They concluded that the copper(I) pre-catalyst is being oxidized by sacrificial **1** to form copper(II) complex **III**, which is the active catalytic species in the transformation. This complex, which also forms in the absence of substrate, was isolated and proven to be catalytically active. Furthermore, a ^{19}F NMR chemical shift change of the CF_3 group in **1** (from −34.6 to −32.1 ppm) is observed when adding a copper salt (CuI or **III** for instance) to reagent **1**, in agreement with what has been found when using zinc triflimide ($Zn(NTf_2)_2$) as Lewis acid (see above). It can therefore be envisaged that this copper(II) complex **III** acts as a Lewis acid, weakening the 3c-4e bond in adduct **IV**, thus enhancing its reactivity toward nucleophiles (Scheme 17). ESI-MS additionally reveals a mixture of copper(II) iodobenzoate complexes containing either one or two molecules of **1**, which are presumably involved in a rapid equilibrium and hence not distinguishable by ^{19}F NMR.

Another report concerning the trifluoromethylation of alkenes under copper catalysis based on gas-phase DFT calculations comes to a different conclusion [50]. This study points to a radical mechanism, with the copper(I) catalyst reducing reagent **1** by means of a single electron transfer (SET) as the key step in the catalytic cycle.

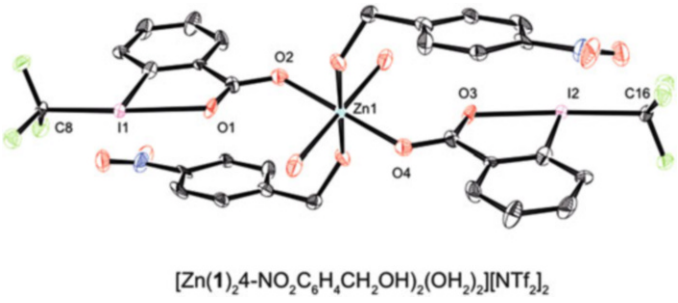
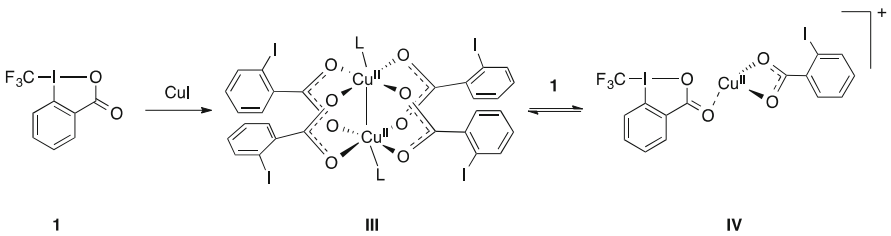


Fig. 5 ORTEP view of $[Zn(\mathbf{1})_2(4\text{-}NO_2C_6H_4CH_2OH)_2(OH_2)_2][NTf_2]_2$ (CCDC-720606; hydrogen atoms are omitted for clarity; thermal ellipsoids are set to 50% probability)



Scheme 17 Activation of **1** by a copper(II) iodobenzoate complex formed in situ [49]

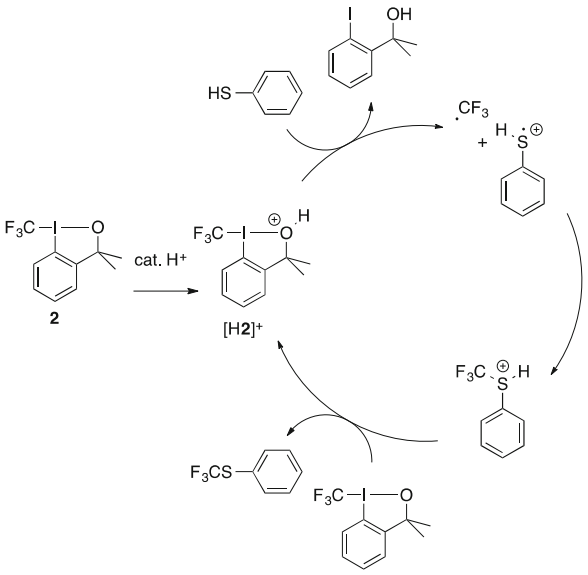
5.3 Activation by One-Electron Reduction and Radical Trifluoromethylations

The use of one-electron reductants as a third mode of activation of reagents **1** and **2** has been suggested recently by several authors. Indeed, it was often assumed that the catalytic activity of metals in the reaction could exclusively be attributed to their action as Lewis acids. However, currently there are several experimental and computational indications that many of these metal-induced reactions could also be radical processes. Indeed, the most successful metal salts – Cu^{I} and Fe^{II} – are known to undergo one-electron oxidations. This list of metal catalysts also includes photo-redox active complexes such as $[Ru(bpy)_3](PF_6)_2$ and $[Ir(ppy)_3]$, as well as oxovanadium (IV) species (see above) which are also known to react as one-electron reductants. Unfortunately, solid mechanistic findings are very scarce in this area, and only very loose hints exist toward the formation of a CF_3 radical by a one-electron reduction.[2] As described above, a single electron oxidation by hypervalent iodine reagent **1** or **2** might also be necessary to form the active catalyst, which then acts as a redox neutral Lewis acid in the catalytic cycle. Under this reaction mechanism, radicals are indeed involved in the steps leading to catalyst formation, and the catalytic cycle proceeds without one-electron transfer reactions. The current state of mechanistic knowledge about these reactions is insufficient to draw clear-cut conclusions.

It is indeed often difficult to discern unambiguously between radical pathways and acid-induced trifluoromethylations. Great care has to be invested into the analysis of the analytical data to avoid misleading pitfalls.[3] Indeed, as the example of the trifluoromethylation of thiols shows, both processes can, for instance, act in a synergistic fashion in a single catalytic cycle (Sala et al., unpublished results)

[2] The recent literature about trifluoromethylation reactions with compounds **1** and **2** often conveys "hypothetical" or "postulated" mechanistic schemes not backed up by experiments. While such mechanistic suggestions may be realistic, they still need to be examined in a very critical manner.

[3] It is often assumed that the formation of a TEMPO-CF_3 adduct demonstrates a radical pathway. However, it is often not clear whether the radical pathway is actually part of the trifluoromethylation reaction of the substrate or whether it is actually induced by the presence of TEMPO, because TEMPO is a trifluoromethylation substrate itself in the absence of a stronger nucleophile, under a series of conditions.



Scheme 18 Proposed mechanism for the trifluoromethylation of thiophenol (Sala et al., unpublished results) [12]

[12]. Experiments strongly suggest that protonated reagent **2** can accept one electron from the thiol, creating a CF_3 and a thiyl radical. Both radicals can then recombine to form a highly acidic sulfonium cation, which is able to protonate another molecule of **2** and release the trifluoromethyl thioether as product. This mechanism is supported by nitrone-spin trapping as well as EPR experiments. Additionally, metadynamic calculations, analyzing the stability of the intermediates, back up these mechanistic assumptions. This concept of protonation followed by a one-electron-reduction is further supported by the molecular orbital calculations mentioned previously, which indicate that protonation allows for the lowering of the 3c-4e bond, rendering it the LUMO. Only after this protonation does a one-electron reduction and homolytic cleavage of the I–CF_3 bond, resulting in the formation of a CF_3-radical species, become possible (Scheme 18).

6 Conclusion

The introduction of reagents **1** and **2** has contributed significantly to the development of trifluoromethylation chemistry in recent years and they are a prominent example of the utility of hypervalent iodine chemistry in synthesis. Although inherently limited to a single perfluoroalkyl group, they nevertheless serve as inspiration in view of inventing new and more versatile perfluoroalkylation reagents that should become accessible by similar synthetic routes. Along these lines, we are currently pursuing two main new research avenues. One of them is focusing on modifying the basic structure of the reagents, e.g., by investigating

benziodazolone derivatives, i.e., reagents containing a I–N bond as part of the 3c-4e hypervalent interaction. The second research avenue addresses reagents able to transfer functionalized perfluoroalkyl groups. Furthermore, we will still continue focusing on structural and mechanistic aspects of this chemistry.

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Alkynylation with Hypervalent Iodine Reagents

Jerome Waser

Abstract Alkynes are among the most versatile functional groups in organic synthesis. They are also frequently used in chemical biology and materials science. Whereas alkynes are traditionally added as nucleophiles into organic molecules, hypervalent iodine reagents offer a unique opportunity for the development of electrophilic alkyne synthons. Since 1985, alkynyliodonium salts have been intensively used for the alkynylation of nucleophiles, in particular soft carbon nucleophiles and heteroatoms. They have made an especially strong impact in the synthesis of highly useful ynamides. Nevertheless, their use has been limited by their instability. Since 2009, more stable ethynylbenziodoxol(on)e (EBX) reagents have been identified as superior electrophilic alkyne synthons in many transformations. They can be used for the alkynylation of acidic C–H bonds with bases or aromatic C–H bonds using transition metal catalysts. They were also highly successful for the functionalization of radicals or transition metal-catalyzed domino processes. Finally, they allowed the alkynylation of a further range of heteroatom nucleophiles, especially thiols, under exceptionally mild conditions. With these recent developments, hypervalent iodine reagents have definitively demonstrated their utility for the efficient synthesis of alkynes based on non-classical disconnections.

Keywords Alkynes • Alkynyliodonium salts • Ethynylbenziodoxol(on)e (EBX) reagents

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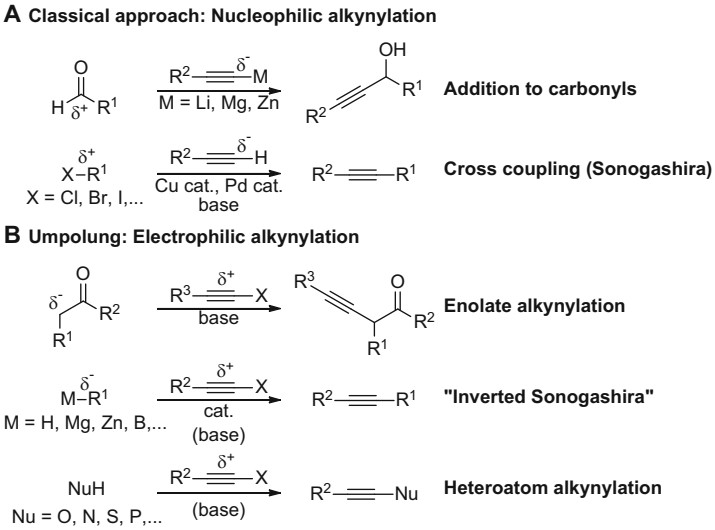
Contents

1 Introduction: The Umpolung of Alkynes

Alkynes are among the most versatile functional groups in organic chemistry [1]. This is because the triple bond is stable under many conditions, yet can be easily transformed to produce a broad range of useful functional groups. In the last few decades, alkynes have also found numerous applications in neighboring fields, such as chemical biology and materials science. For example, the [3+2] cycloaddition between alkynes and azides is now widely applied in these fields, as it is bio-orthogonal, easy to perform, and does not generate any waste (the paramount of a "Click" reaction) [2, 3]. As linear π-systems, alkynes have also found broad applications in organic electronics or dyes for photovoltaics. To allow continued progress in synthetic and applied fields, new flexible and efficient methods to synthesize alkynes are urgently needed.

Most of the methods to access alkynes by transfer of a triple bond are based on nucleophilic alkynylation (Scheme 1, **A**). This is not surprising, as the terminal C–H bond of alkynes is highly acidic because of the sp-hybridization, and the formation of acetylide anions is consequently facile. Methods such as addition of acetylides to carbonyl compounds [4] or the Sonogashira cross coupling [5, 6] are now routinely used for the synthesis of alkynes and are highly reliable. In stark contrast, the addition of alkynes onto nucleophiles requires an inversion of their inherent reactivity (an Umpolung, Scheme 1, **B**). This approach is more challenging and consequently has been less developed [7–9]. When considering the omnipresence of nucleophiles not only in synthetic organic chemistry but also in chemical biology and materials science, this is an important shortcoming. Indeed, reactions such as the alkynylation of enolates, the "inverted Sonogashira" coupling of C–H or C–metal bonds, or the direct alkynylation of heteroatoms are highly useful processes, which give access to molecular structures outside the reach of classical methods.

Because of the high reactivity of the hypervalent bond, hypervalent iodine reagents have been intensively used in organic chemistry [10–15]. They occupy a central place among electrophilic alkynylation reagents as they are ideally suited



Scheme 1 Nucleophilic and electrophilic alkynylation

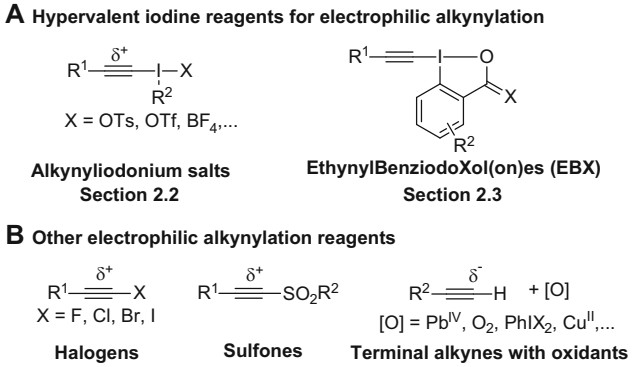


Fig. 1 Electrophilic alkynylation reagents

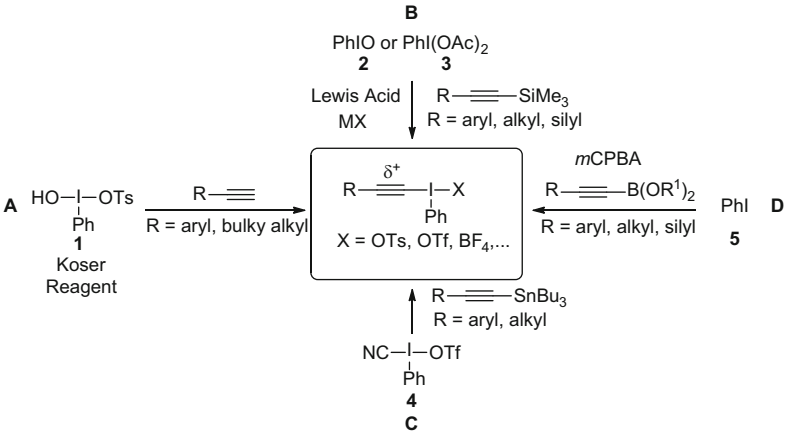
for allowing the inherent nucleophilicity of alkynes to be overcome (Fig. 1). Initial successes were encountered by the use of arylalkynyliodonium salts [16], for which selective transfer of the alkyne group to nucleophiles was observed. More recently, the stability and selectivity issues often present with alkynyliodonium salts have been overcome by the introduction of more stable cyclic reagents, especially ethynylbenziodoxol(on)es (EBX) [17, 18]. Because of their exceptional reactivity, hypervalent iodine reagents are often superior to less reactive reagents such as alkynyl halides [19] or sulfones [20–23]. On the other hand, they are more stable and less toxic than organometallic reagents such as organolead compounds [24, 25].

In this chapter, the use of hypervalent iodine reagents for alkynylation reactions is covered. The most important results up to the last review in the field [9] are

summarized, followed by a more detailed presentation of the most recent works up to June 2015. The use of alkynyliodonium salts is described first (Sect. 2), followed by the use of EBX reagents (Sect. 3). Each section is divided according to the class of alkynylated nucleophile (carbon or heteroatom). The focus is on reactions using well-defined hypervalent iodine alkynylation reagents.

2 Alkynylation Using Alkynyliodonium Salts

Alkynyliodonium salts are versatile reagents in organic chemistry, and their use goes far beyond alkynylation. For example, they can also be used in the synthesis of vinyliodonium salts, in cyclization reactions via carbene insertion, or in cycloaddition reactions [16]. Several methods have been developed for their synthesis from different iodine precursors (Scheme 2). Early methods focused on the reaction of terminal alkynes with Koser reagent **1** [26], but this approach had a limited scope, as it worked only with aryl or bulky alkyl group on the alkyne (Scheme 2, **A**). More general methods were then developed by the reaction of iodosobenzene **2** with alkynylsilanes in the presence of Lewis acids and metal salts (Scheme 2, **B**) [27–29]. As the purity of iodosobenzene **2** can be highly batch dependent, an alternative protocol starting from (diacetoxyiodo)benzene **3** was developed by Kitamura and co-workers [30]. The broadest substrate scope was achieved by Stang and co-workers starting from cyano(phenyl)iodonium triflate **4**, but this approach required the use of more toxic alkynyl stannanes (Scheme 2, **C**) [31, 32]. Finally, Olofsson and co-workers reported in 2012 a very practical one-pot oxidation-alkynylation protocol starting from iodobenzene **5** and using alkynyl boronic acid esters (Scheme 2, **D**) [33]. A limitation of this method is the use of the sometimes unstable and difficult to access boronic acid esters.

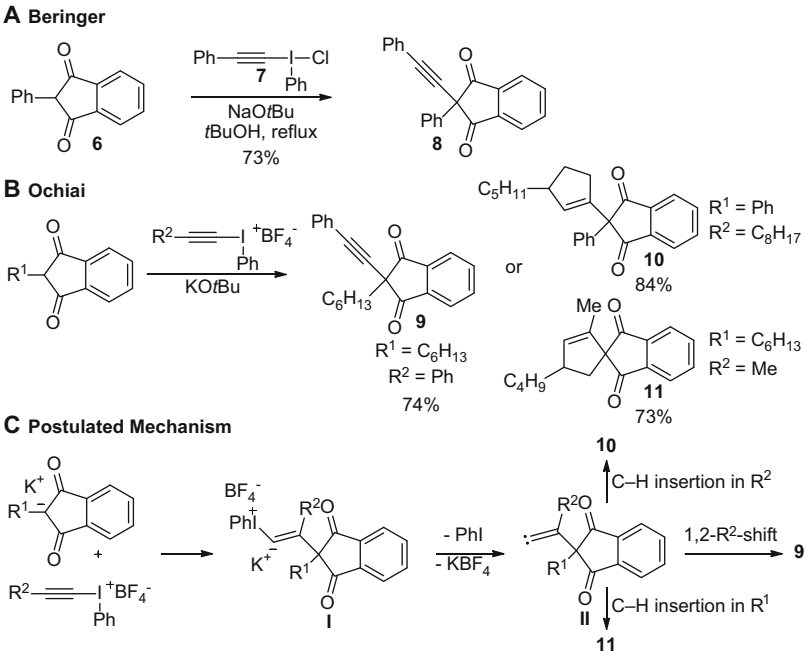


Scheme 2 Synthesis of alkynyliodonium salts

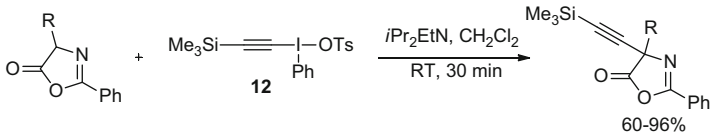
2.1 Alkynylation of C-Nucleophiles

2.1.1 Alkynylation of Acidic C–H Bonds

The reactivity of alkynyliodonium salts was first discovered in the alkynylation of diketones (Scheme 3). In 1965, Beringer and Galton reported the alkynylation of diketone **6** with alkynyl iodonium chloride **7** in 73% yield (Scheme 3, **A**) [34]. However, alkynyliodonium chloride **7** is unstable and decomposes to form the corresponding chloroalkyne, which probably precluded more extensive synthetic use of this transformation. In 1986, Ochiai and co-workers reinvestigated this reaction with more stable alkynyliodonium tetrafluoroborate reagents (Scheme 3, **B**) [35]. They found that the result was highly dependent on the substituent of the reagent: with a phenyl group, alkyne products such as **9** were obtained, but with aliphatic groups the formation of cyclopentenes such as **10** or **11** was observed. This result led Ochiai and co-workers to make a first mechanistic proposal for this transformation (Scheme 3, **C**). In contrast to many reactions with hypervalent iodine reagents, the initial attack of the nucleophile would not be on the iodine atom but on the conjugate position of the triple bond. The resulting vinyl anion **I**, which can indeed be trapped by acids to form vinyliodonium salts, would then undergo α-elimination of iodobenzene to give carbene intermediate **II**. At this point, if the adjacent substituent has a strong migrating aptitude, as is the case for



Scheme 3 Pioneering examples for the alkynylation of diketones and proposed mechanism



Scheme 4 Alkynylation of azlactones

a phenyl moiety, a 1,2-shift occurs to give alkyne product **9**. With aliphatic groups, the migration is slow, and C–H insertion in either the substrate or the alkyne substituent is observed to give **10** or **11**. In the case of the alkynylation, the use of fast migrating silyl or hydrogen substituents is especially relevant, as it gives access to versatile terminal acetylenes as products [36].

After this seminal work, the alkynylation reaction with alkynyliodonium salts was applied to several classes of substrates, including diketones [36–38], ketoesters [36], malonates [36, 39], and aminomalonates [40, 41]. The latter class of compounds is especially interesting, as it was also successful in the case of alkyl substituted alkynes. This was probably made possible by an efficient 1,2-shift of the nitrogen heteroatom.

In 2014, Nachtsheim and co-workers reported the alkynylation of azlactones with trimethylsilyl alkynyliodonium salt **12** (Scheme 4) [42]. The products obtained were easily transformed into various amino acid derivatives. The reaction was also successful in the case of aliphatic substituted alkynes, although C–H insertion was observed as a minor pathway. Interestingly, the use of EBX reagents led to exclusive formation of C–H insertion products, indicating that the same intermediate was not formed in both reactions.

2.1.2 Alkynylation of Organometallic Nucleophiles

As alkynyliodonium salts decompose in the presence of strong bases, the alkynylation of organolithium or organomagnesium reagents is not possible. On the other hand, organocopper reagents react smoothly with alkynyliodonium tosylates. Through the right choice of the organometallic reagent (organocopper or cuprate), the reaction was successful on sp [43], sp^2 [44], and sp^3 [43, 45] centers to give diynes, enynes, and aliphatic alkynes as products. Because of their high reactivity, alkynyliodonium salts have also found applications in palladium- or copper-catalyzed alkynylation reactions such as carbonylation [46], Heck coupling [47, 48], reactions with alkynes [49], and cross-coupling with organoboron/tin compounds [50]. However, their use in these transformations remains scarce, probably because of their somewhat low stability in the presence of transition metals and the availability of more convenient alkyne sources.

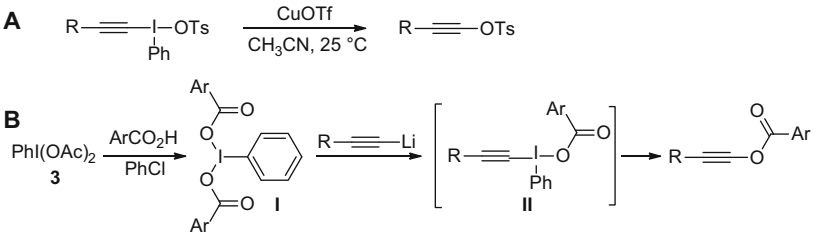
2.2 *Alkynylation of Heteroatoms*

The alkynylation of heteroatoms is interesting, as it gives access to highly reactive and useful acetylene derivatives. Because of the nucleophilicity of heteroatoms, the Umpolung approach represented by alkynyliodonium salts is especially attractive. In several cases, evidence has been gathered that these reactions also proceed via a conjugated addition/α-elimination/1,2-shift mechanism.

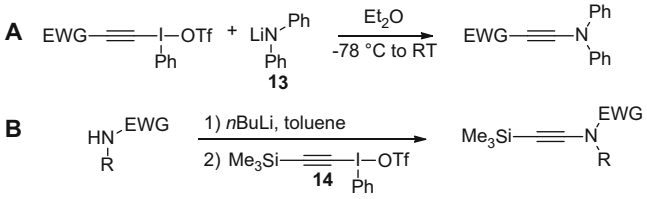
2.2.1 Alkynylation of Oxygen and Nitrogen Nucleophiles

As oxygen and nitrogen are hard nucleophiles, their reaction with alkynyl iodonium salts is often difficult and can lead to decomposition. In 1987, Stang and co-workers reported that alkynyliodonium tosylates can be converted to the corresponding ynol tosylates in the presence of copper triflate (Scheme 5, **A**) [51, 52]. The rearrangement of alkynyliodonium carboxylates is even easier and occurs spontaneously in the absence of any catalyst (Scheme 5, **B**) [53, 54]. In this case, the iodonium is best generated in situ by ligand exchange on (diacetoxyiodo)benzene **3** followed by addition of an alkynyl lithium reagent. The same approach could also be extended to ynol phosphates [53, 55].

The synthesis of ynamines was investigated later. The first example was reported by Stang and co-workers in 1994, but this transformation was limited to the synthesis of push-pull ynamines (Scheme 6, **A**) [56]. An important breakthrough was reported by Feldman and co-workers [57] and Witulski and co-workers [58], who demonstrated that alkynyliodonium triflates could be used for the synthesis of



Scheme 5 Alkynylation of oxygen nucleophiles



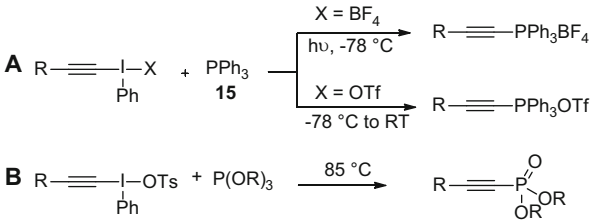
Scheme 6 Alkynylation of nitrogen nucleophiles

more stable ynamides (Scheme 6, **B**). The first efficient synthesis of this fascinating class of compounds allowed their widespread use in organic synthesis, especially in metal-catalyzed cycloisomerization and cycloaddition reactions [59]. The use of hypervalent iodine reagents is nowadays a classical method to access ynamides [60–68]. The method works especially well for the alkynylation of nitrogen bearing an electron-withdrawing group such as tosyl, acyl or carbamoyl [58, 60–65]. It works also for the alkynylation of heterocycles such as imidazole [66] or benzotriazole [67]. In 2012, Banert and co-workers also reported the first synthesis of azidoacetylene based on the reaction between an azide phosphonium salt and an alkynyliodonium tetrafluoroborate [68]. This highly unstable compounds decomposed with a half-life of 17 h at −30°C.

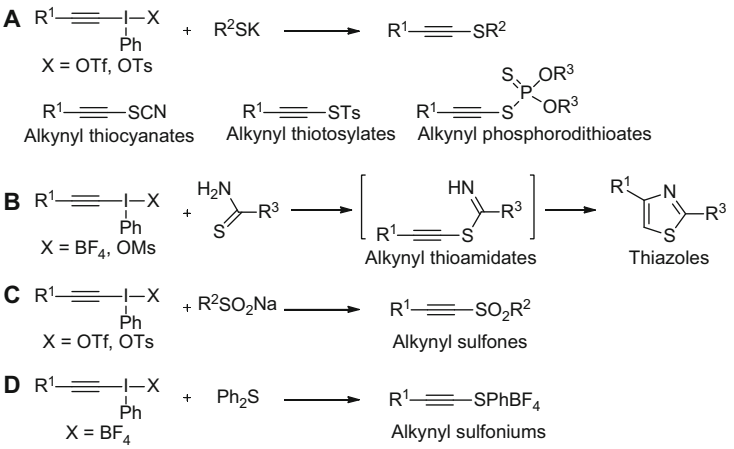
2.2.2 Alkynylation of Phosphorus, Sulfur, and Other Nucleophiles

The alkynylation of phosphorus nucleophiles has been less investigated (Scheme 7). Ochiai and co-workers first demonstrated in 1987 that the alkynylation of triphenylphosphine was possible with alkynyliodonium tetrafluoroborate salts under light irradiation (Scheme 7, **A**) [69]. The reaction most probably involves radical intermediates. In 1992, Stang and Critell showed that light irradiation was not needed if alkynyliodonium triflates were used [70]. Later, this methodology could be extended to other triaryl- or alkyl phosphines [71, 72]. In 1990, Koser and Lodaya also reported the synthesis of alkynylphosphonates by the Arbusov reaction of alkynyliodonium tosylates with trialkyl phosphites (Scheme 7, **B**) [73]. Alternatively, the same compounds can be obtained by the reaction of alkynyliodonium tosylates with sodium phosphonate salts [74].

The alkynylation of sulfur nucleophiles works well with alkynyliodonium tosylates and triflates as long as the sulfur atom is not too electron-rich, else oxidation reactions dominate. For example, alkynyl thiocyanates [38, 39, 75], thiotosylates [76], and phosphorodithioates [77] can be accessed in good yields (Scheme 8, **A**). The alkynylation of thioamides is also possible, but in this case the product obtained is unstable and spontaneously cyclizes to give a thiazole (Scheme 8, **B**) [78, 79]. The alkynylation of sulfinates with alkynyliodonium triflates or tosylates gives an efficient access towards alkynyl sulfones (Scheme 8, **C**) [80, 81]. If C–H bonds are easily accessible, carbene C–H insertion products can



Scheme 7 Alkynylation of phosphorus nucleophiles



Scheme 8 Alkynylation of sulfur nucleophiles

also be observed in these transformations [82]. In 2014, Hamnett and Moran reported that the efficiency of alkynyl transfer can be increased by using 2-iodoanisole instead of 2-iodobenzoic acid as core of the hypervalent iodine reagent [83]. Finally, alkynyliodonium salts can also be used to generate alkynyl sulfonium salts from diarylthioethers (Scheme 8, **D**) [84].

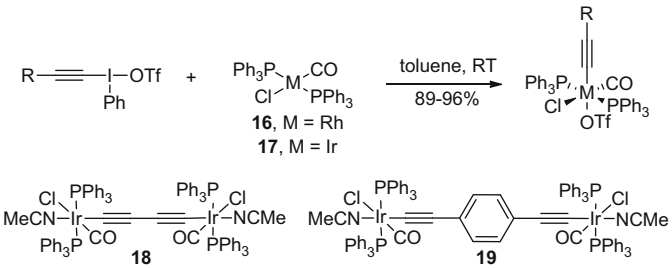
In addition to the alkynylation of second and third row main group heteroatoms, there are a few examples of alkynylation of heavier elements including arsenic [85], selenium, and tellurium [84, 86, 87].

2.3 Alkynylation of Metals

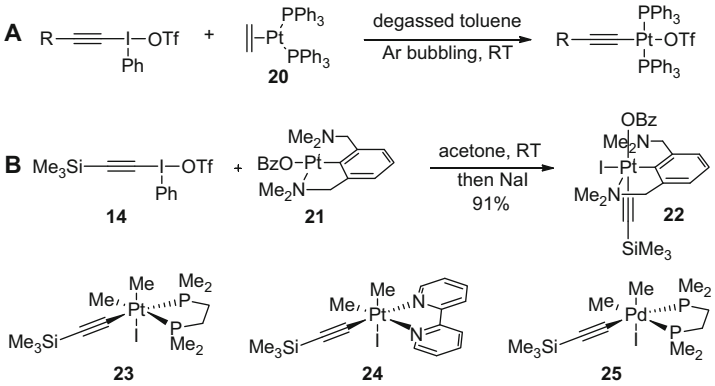
The reaction of alkynyliodonium salts with electron-rich transition metals usually results in an oxidative addition under formation of a metal–acetylide complex. Although this type of intermediates has been postulated in many catalytic reactions, this section is limited to the cases in which the metal complexes could be isolated and characterized.

As a first interesting example, Stang and Critell reported in 1990 the alkynylation of Vaska complexes **16** and **17** with alkynyliodonium triflates at room temperature in excellent yield (Scheme 9) [88]. Using bis-alkynyliodonium salts, the method could be extended to the formation of binuclear complexes such as **18** and **19**, or even trinuclear systems [89–91]. These conjugated polymetallic complexes have great potential for applications in nonlinear optics, organic conductors, or liquid crystals.

Stang and co-workers also demonstrated that reaction of platinum(0) complex **20** with alkynyliodonium triflate yielded alkynyl–platinum(II) complexes after careful optimization of the reaction conditions (Scheme 10, **A**) [92]. Canty and co-workers

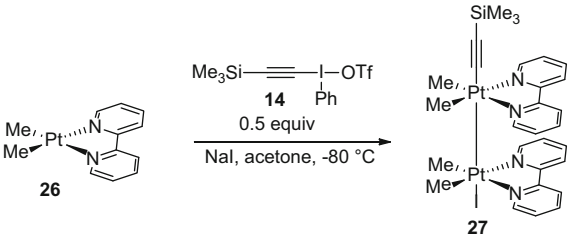


Scheme 9 Alkynylation of rhodium and iridium complexes



Scheme 10 Alkynylation of platinum and palladium complexes

then used the strong oxidizing properties of alkynyliodonium salts to access alkynyl–metal complexes in high oxidation states [93–98]. They first demonstrated that platinum(II) pincer complex **21** could be oxidized to platinum(IV)–alkynyl complex **22** in 91% yield using alkynyliodonium triflate **14** as reagent (Scheme 10, **B**) [93]. They showed that the method could also be used to access platinum complexes **23** and **24** bearing a diphosphine and a bipyridine ligand, respectively [94]. The availability of these highly oxidized metal complexes allowed them to study elemental steps of catalytic cycles, in particular reductive elimination [95–97]. They were also able to synthesize the corresponding palladium(IV) complex **25** and characterize it at low temperature, as it decomposed readily at room temperature [94]. In 2009, Canty and co-workers were also able to characterize a rare Pt dimer complex **27** at −80°C, obtained by reacting Pt(II)–bipyridine complex **26** with 0.5 equiv. of alkynyliodonium triflate **14** (Scheme 11) [98]. In principle, **27** can be considered as either a Pt(III)–Pt(III) or a Pt(II)–Pt(IV) dimer. The characterization of intermediate **27** is an important step on the way to understand better the mechanism of oxidation leading to high oxidation state metal complexes.



Scheme 11 Synthesis of platinum dimer complex **27**

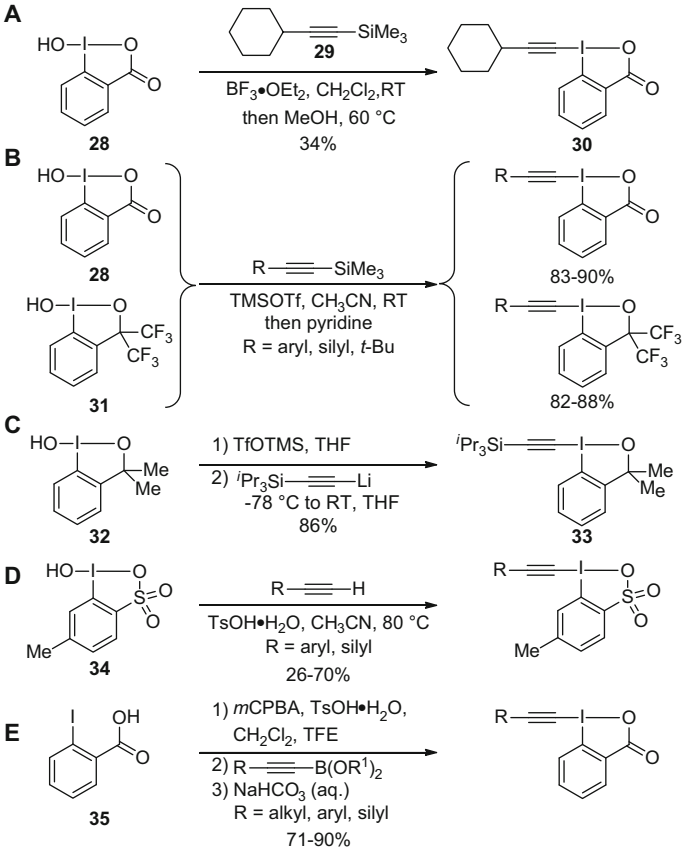
2.4 Conclusion on the Use of Alkynyliodonium Salts

With the discovery and use of alkynyliodonium salts, a new class of electrophilic alkynylation reagents has emerged. Because of their impressive reactivity, they could be broadly used to introduce acetylenes on carbon nucleophiles, heteroatoms, or metals. Nevertheless, with the exceptions of the alkynylation of nitrogen and new applications in the synthesis of alkynyl–metal complexes, most research on alkynyliodonium salts has been concentrated in the years 1985–1995, with rare more recent breakthroughs. In particular, very few applications using modern catalytic methods have appeared, in stark contrast to the use of aryliodonium salts in arylation reactions [99]. One of the possible reasons for this "drying out" of the field is the relatively low stability of alkynyliodonium salts, which often makes their use challenging.

3 Alkynylation Using Ethynylbenziodoxol(on)e (EBX) Reagents

One classical approach to enhance the stability of hypervalent iodine reagents is to incorporate the iodine atom into a cyclic structure fused to an aromatic ring (usually benzene) [17, 18]. Through the more rigid structure, the overlap of orbitals between the iodine atom and the benzene ring is further improved, which leads to increased stabilization. Furthermore, as the nucleophilic ligand of iodine (most often oxygen) is now part of the ring, reductive elimination and – in the case of alkynyl reagents – conjugate addition are slowed down significantly. This has the advantage of further extending the range of substituents tolerated on the iodine atom. When considering the strong *trans*-effect in the hypervalent iodine bond [100], this can be very important to modulate further the reactivity of the reagents.

The first synthesis of a cyclic hypervalent iodine reagent was reported by Ochiai and co-workers in 1991 by the reaction of 2-hydroxy-benziodoxolone **28** with alkynyl trimethylsilane **29** in the presence of boron trifluoride etherate (Scheme 12,



Scheme 12 Synthesis of cyclic alkynyl hypervalent iodine reagents

A) [101]. 1-[(Cyclohexyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one **30** (cyclohexyl-EBX) was obtained in 34% yield. In 1996, Zhdankin and co-workers significantly improved the synthesis of EBX reagents by the use of trimethylsilyl triflate as activator (Scheme 12, **B**) [102]. This protocol was especially efficient in the case of aryl or silyl substituted alkynes, and could also be used to access bistrifluoromethyl-substituted benziodoxole derivatives. Waser and co-workers showed later that the protocol was very useful for the synthesis of both benzene-ring modified analogues and silyl-substituted EBX reagents on larger scales (up to 40 g) [103, 104]. The synthesis of dimethyl-substituted ethynylbenziodoxole reagents was reported by Waser and co-workers in 2012 where the use of a more reactive lithium acetylide as alkynylation reagent was required in the synthesis (Scheme 12, **C**) [103]. Koser and co-workers already reported in 1993 that cyclic hypervalent iodine reagents bearing a more electron-withdrawing sulfonate group could also be easily accessed from the hydroxy derivative **34** using terminal acetylenes and toluene sulfonic acid as activator (Scheme 12, **D**) [105]. Finally, in 2012 Bouma and Olofsson developed

the first one-pot synthesis of EBX reagents starting directly from 2-iodobenzoic acid **35** (Scheme 12, **E**) [33]. *m*-Chloroperbenzoic acid was used as oxidant and alkynyl boronic acid esters as alkyne source. This protocol was general, allowing the synthesis of alkyl-, aryl-, and silyl-substituted EBX reagents in 71–90% yield.

Surprisingly, the synthetic potential of cyclic hypervalent iodine reagents has been overlooked for a long time. Prior to 2009, only Kitamura and co-workers reported the use of an iodobenzoic acid-based reagent, but in this case the protonated "open" form was used [38]. Since 2009, however, EBX reagents have been broadly applied in alkynylation reactions and have proven in many instances to be superior to the previously used alkynyliodonium salts.

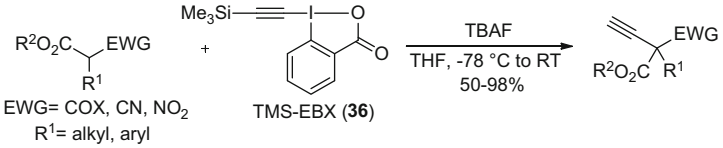
3.1 Alkynylation of C-Nucleophiles

3.1.1 Alkynylation of Acidic C–H Bonds

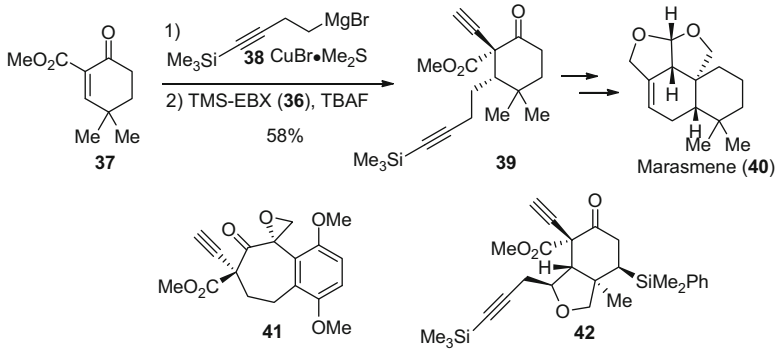
In 2010, Waser and co-workers reported the first study of the alkynylation of soft carbon nucleophiles using EBX reagents [106]. The alkynylation of ketoesters proceeded in nearly quantitative yields using TMS-EBX (**36**) and TBAF at low temperature to give directly the free acetylenes as products (Scheme 13). This method gave good yields not only for cyclic ketoesters but also for non-cyclic keto, cyano, and nitro esters. In situ ^{1}H NMR experiments showed that the silyl group was first removed under these reaction conditions to give the very reactive unsubstituted EBX reagent, which could be characterized at low temperature but decomposed at temperatures higher than −20°C. If the synthesis of aryl- or silyl-substituted alkynes is desired, good results were obtained using simply DBU as a base at room temperature [107].

The robustness of the method was further demonstrated by Yang and co-workers, who used it first in the synthesis of drimane-type sesquiterpenoids such as marasmene (**40**, Scheme 14) [108]. In this case, the required ketoester was obtained via conjugate addition of an organocuprate onto Michael acceptor **37**. Later, Yang and co-workers also used the methodology for the synthesis of compounds **41** and **42** used in the total syntheses of (−)-lingzhiol and a fragment of azadirachtin, respectively [109, 110].

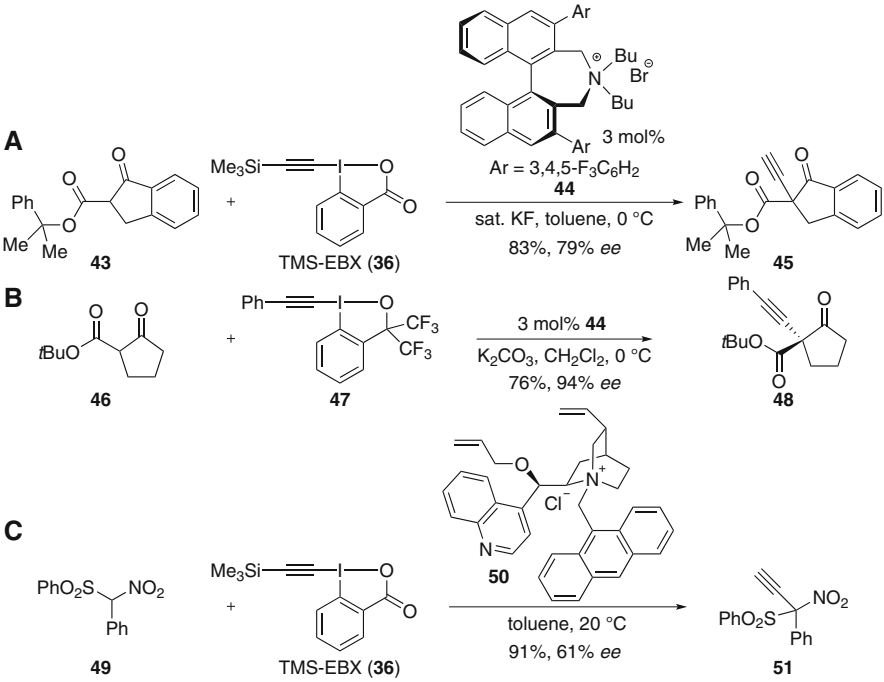
The enantioselective synthesis of compounds containing an all-carbon quaternary propargylic center would be highly desirable. In their first work, Waser and



Scheme 13 Alkynylation of activated ester derivatives with TMS-EBX (**36**)



Scheme 14 Applications of the alkynylation reaction in the total synthesis of natural products



Scheme 15 Asymmetric alkynylation of ketoesters and nitrosulfones

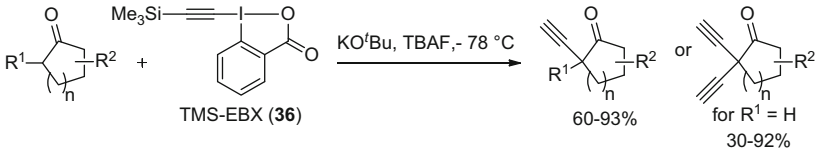
co-workers reported that a low enantioinduction was possible using cinchona-derived phase-transfer catalysts [106]. In 2013, they were further able to improve the enantiomeric excess by using the binaphthyl-based Maruoka phase transfer catalyst **44** (Scheme 15, **A**) [111]. Although alkyne **45** could be obtained in 83% yield and 79% *ee*, the enantioinduction was lower for other substrates. In 2014, Maruoka and co-workers finally reported the first highly enantioselective asymmetric alkynylation using a hypervalent iodine reagent (Scheme 15, **B**) [112]. Key

to obtaining high enantioinduction with ketoester **46** was the use of benziodoxole **47** instead of benziodoxolone reagents. The products obtained could be easily cyclized to the corresponding spiro compounds by iodination or selenenylation. Finally, Vesely and co-workers showed in 2013 that the asymmetric alkynylation of α-nitro sulfone derivatives was also possible using cinchona-derived phase-transfer catalyst **50** (Scheme 15, **C**) [113]. For example, alkyne **51** was obtained in 91% yield and 61% *ee*.

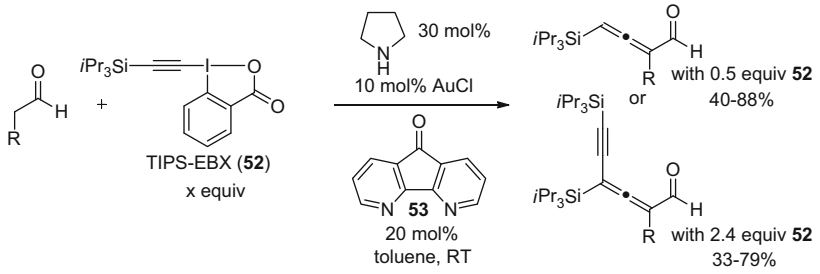
The scope of the alkynylation protocol has also recently been extended to other nucleophiles. Silva Jr. and co-workers reported the first alkynylation of simple aromatic ketones using TMS-EBX **36**, TBAF, and potassium *tert*-butoxide as a base (Scheme 16) [114]. It is noteworthy that the alkynylation reaction is still highly efficient under these strongly basic conditions. Cyclic products could be obtained in 60–93% yield. In the case of an unsubstituted α-position, diynes products were formed in 30–92% yield. Interestingly, the alkynylation was also successful with an aldehyde, which needed to be reduced immediately prior to isolation because of its instability.

In 2015, Vesely and co-workers further extended the scope of the alkynylation for C–H acidic heterocycles [115]. Alkynylated pyrazolone, oxindole, rhodanine, and azlactone could be obtained in good yields using TMS-EBX **36** and triethylamine as base in different solvents.

To extend the scope of the alkynylation of carbonyl compounds, the functionalization of aldehydes using enamine catalysis would appear as a logical choice. However, this transformation is still unknown. Nevertheless, Huang and co-workers reported in 2013 an important breakthrough in the area. The α-functionalization of aldehydes using pyrrolidine and a gold complex as co-catalyst became possible using TIPS-EBX **52** as reagent (Scheme 17)



Scheme 16 (Bis-)alkynylation of ketones and aldehydes



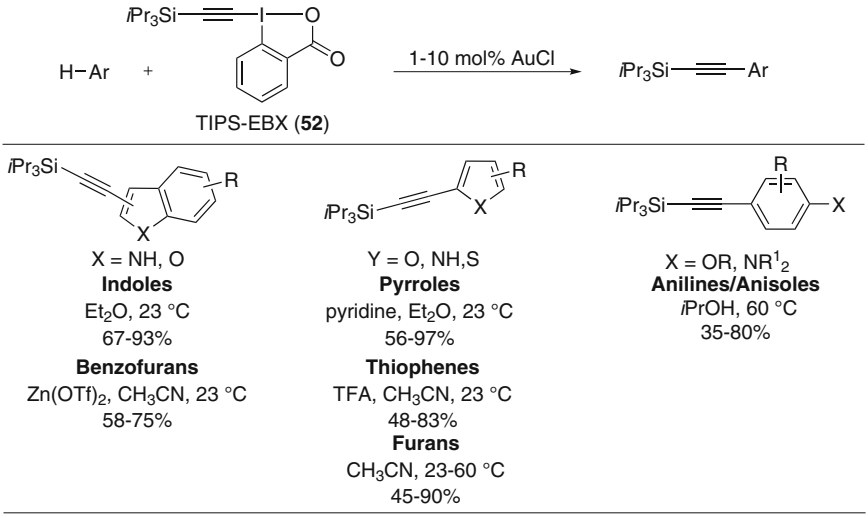
Scheme 17 Vinylidenation of aldehydes and cascade alkynylation

[116]. Although α-alkynylation was observed as a minor pathway, the main products were the corresponding allenes. Increasing amounts of alkynes were obtained with increasing steric bulk in the α-position of the aldehyde. Interestingly, the allenes obtained were still highly reactive under the reaction conditions and, if an excess of TIPS-EBX **52** was used, a second alkynylation event took place to give enynes in 33–79% yield.

3.1.2 Alkynylation of Aromatic and Vinylic C–H Bonds

In contrast to the alkynylation of acidic C–H bonds which can also be achieved using alkynyliodonium salts, the direct C–H functionalization of aromatic compounds or olefins has never been realized with this class of reagents so far. However, after several unsuccessful attempts using palladium or copper catalysts and alkynyliodonium salts for the alkynylation of heterocycles, Waser and Brand reported in 2009 the first efficient alkynylation of indoles using TIPS-EBX **52** and AuCl as catalyst (Scheme 18) [117]. With indole, selective C3-alkynylation was obtained. The reaction was tolerant to many functional groups such as bromides, acids, or alcohols. The method was already used in the synthesis of starting materials for Friedel–Crafts reactions of aminocyclopropanes [118] and for hydroamidation to access indole *cis*-enamides [119]. In 2010, Nevado and de Haro demonstrated that alkynylation was also possible using directly terminal propiolic ester derivatives and (diacetoxyiodo)benzene as co-oxidant [120].

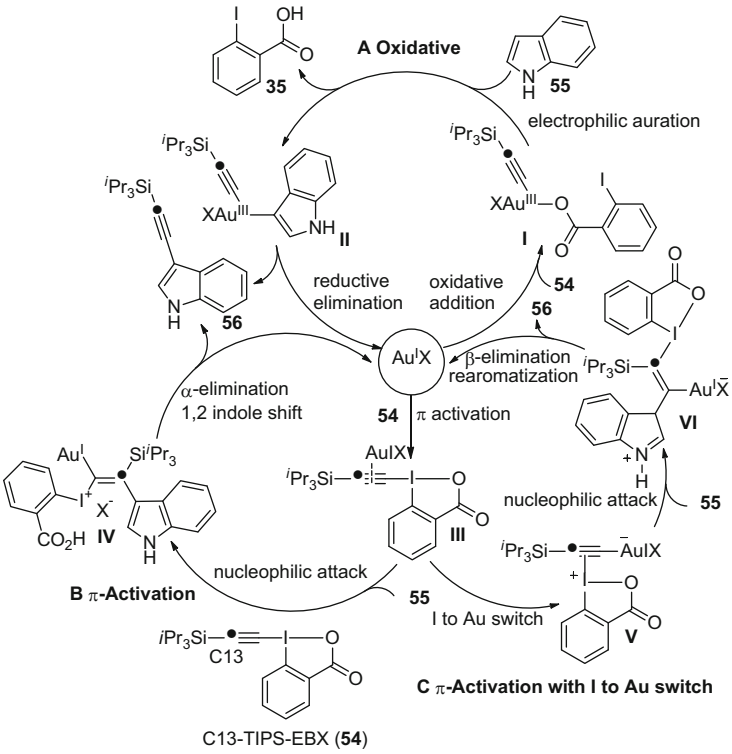
Because of the high stability of TIPS-EBX **52**, many reaction conditions are tolerated, which is important to optimize the alkynylation of other classes of aromatic compounds. For example, pyrroles were best functionalized in the



Scheme 18 Gold-catalyzed alkynylation of aromatic compounds

presence of pyridine to avoid decomposition [103]. In this case, selective functionalization of the more electron-rich position was observed, unless it was blocked. In contrast, less reactive thiophenes required co-activation with a Brønsted acid catalyst, trifluoroacetic acid [121]. The alkynyl thiophenes obtained are interesting building blocks for the synthesis of organic materials. Furans could also be alkynylated in acetonitrile, sometimes at slightly higher temperature [122]. The C2-alkynylation of less reactive benzofurans, on the other hand, required zinc triflate as co-activator [123]. Finally, the reaction was not limited to heterocycles. Electron-rich anilines or poly-methoxylated benzene rings could also be alkynylated at 60°C in isopropanol [124]. Nevertheless, only highly electron-rich benzene rings could be functionalized with this method.

Mechanistically, this new transformation is highly intriguing. Unfortunately, gold catalysts bearing phosphine or carbene ligands were not active for the reaction, which made the isolation of well-defined gold complexes highly challenging. Furthermore, the formation of gold particles was also observed during the reaction. Initially, two mechanisms were proposed as shown in Scheme 19 [103, 117]: (1) an oxidative mechanism involving oxidative addition of the reagent on the gold (I) catalyst to give a gold(III) intermediate **I**, followed by electrophilic auration to



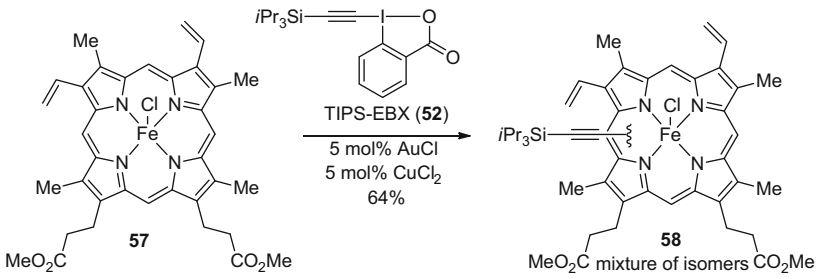
Scheme 19 Speculative mechanisms for the gold-catalyzed alkynylation

give **II** and final reductive elimination (Scheme 19, **A**) or (2) a π-activation mechanism proceeding via coordination of the gold catalyst to give intermediate **III** followed by nucleophilic addition leading to **IV** (Scheme 19, **B**). Finally, α-elimination and 1,2-shift would lead to the product. When the reaction was performed with C13-labeled reagent **54**, no shift of the silicium group was observed. For these reasons, the oxidative mechanism appeared more probable at this time, as a less favorable indole 1,2-shift would have to be proposed in the case of the π-activation mechanism. In 2014, Ariafard studied the mechanism in more detail by computational investigations [125]. Interestingly, it was found that both mechanisms **A** and **B** were too high in energy for a room temperature reaction. They proposed a novel pathway involving iodine to gold shift on the alkyne to give iodine-activated gold acetylide intermediate **V** (Scheme 19, **C**). Addition of indole **55** followed by β-elimination and rearomatization would also lead to product **56** without silicium shift. It would be interesting in the future to design experiments to investigate this unprecedented mechanism.

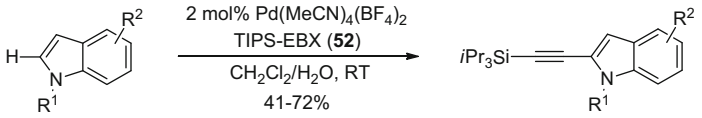
An impressive extension of the gold-catalyzed method was reported by Marletta and Nierth in 2014. They developed the direct alkynylation of protoporphyrin IX **57** using TIPS-EBX **52** and AuCl as catalyst (Scheme 20) [126]. Protoporphyrin IX **57** is one of the most important heme cofactors and the availability of alkyne-tagged derivatives would be very useful for studying biological processes. Interestingly, the use of $CuCl_2$ as co-catalyst was important to prevent the formation of gold nanoparticles which led to decomposition. The product **58** was obtained as a mixture of four isomers, but this was not an issue for studying biological processes.

The gold-catalyzed alkynylation of heterocycles allowed the functionalization of the most electron-rich position. Nevertheless, this is a limitation if the synthesis of other alkyne regioisomers is desired. In 2013, Waser and co-workers reported that the C2-selective alkynylation of indoles was possible using a palladium catalyst (Scheme 21) [127]. A current limitation of this approach is the requirement for an alkyl substituent on the nitrogen atom.

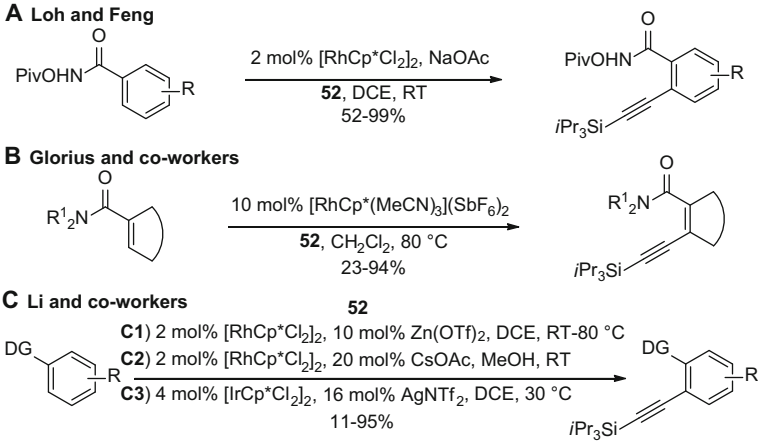
Until 2014, the alkynylation via C–H functionalization of non-activated aromatic rings using hypervalent iodine reagents was unknown. In 2014, the groups of Li, Loh, and Glorius reported nearly simultaneously a directing group strategy for the alkynylation of arenes using rhodium catalysis (Scheme 22). The work of Loh



Scheme 20 Alkynylation of protoporphyrin IX **57**

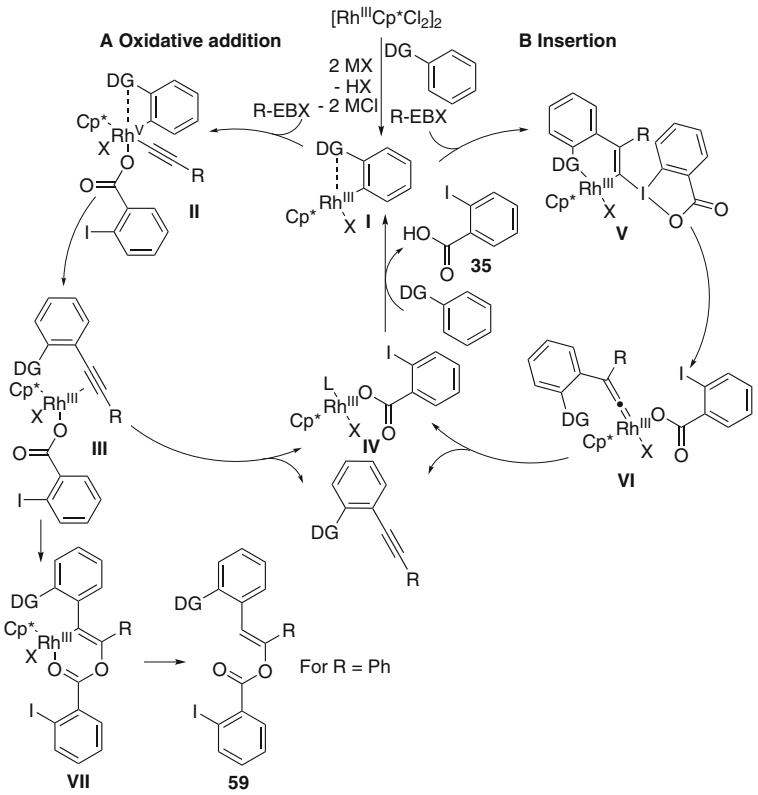


Scheme 21 Palladium-catalyzed C2-alkynylation of indoles



Scheme 22 Rhodium-catalyzed directed C–H alkynylation of arenes and olefins

and Fang involved a pivaloyl benzamide protecting group together with a rhodium (III)-Cp* catalyst and TIPS-EBX **52** as reagent (Scheme 22, **A**) [128]. A major advantage in comparison to previously reported C–H alkynylation methods is that the reaction could be performed at room temperature, giving excellent yields of products and tolerating many functional groups. Glorius and co-workers reported the alkynylation of benzamides using a cationic rhodium(III) complex (Scheme 22, **B**) [129]. In this case, the transformation could also be extended to olefins, giving β-disubstituted products containing either a benzene ring, a heterocycle, or an alkene. Li and co-workers reported a very complete study on the C–H alkynylation of arenes using TIPS-EBX **52** and either rhodium or iridium catalysts (Scheme 22, **C**) [130]. Using a rhodium(III)-Cp* catalyst activated by zinc triflate, a broad range of heterocycles such as pyridine, pyrimidine, or pyrazole could be used as directing groups (**C1**). The pyrimidine ring was not only successful in the case of benzene, but also for the functionalization of indole. This methodology has also been used by Zhou and co-workers to alkynylate a more functionalized indole substrate [131]. Non-aromatic directing groups such as oximes, nitrones, nitrosoanilines, azo- or azoxy-groups, and simple amides could also be used. For pivaloyl benzamides, they used conditions very similar to those reported by Loh and Fang (**C2**). They also reported the first example of C–H alkynylation catalyzed by an iridium(III)–Cp* complex activated by silver bistriflimide (**C3**). Methoyl benzamides were the best



Scheme 23 Speculative mechanisms for the rhodium-catalyzed alkynylation

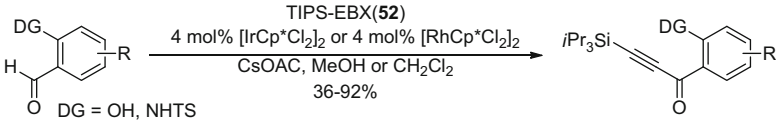
substrates in this case and the products were obtained in yields similar to those with the rhodium catalyst.

Preliminary mechanistic investigations were made my both Loh and Fang and Li and co-workers, leading to two speculative mechanisms, either via initial oxidative addition or via insertion (Scheme 23, **A** and **B**). Both mechanisms start with activation of the rhodium(III) chloride complex with different metal salts followed by formation of a rhodium(III) metalacycle **I** with the substrate including the directing group (most probably with a concerted metalation-deprotonation mechanism). Intermediate **I** could then reacts with the EBX reagent either via oxidative addition to give rhodium(V) intermediate **II** (**A**), or via insertion to give rhodium (III) intermediate **V** (**B**). For the latter, high regioselectivity is expected for the insertion because of the high polarization of the triple bond in EBX reagents. From **II**, reductive elimination gives rhodium(III) intermediate **III**. Decomplexation of the product and re-formation of the rhodium(III) metalacycle **I** with probably the benzoate acting as a base then closes the catalytic cycle. From **V**, α-elimination of the iodonium reagent leads to rhodium(III)–allenylidene complex **VI**. 1,2-Aryl shift

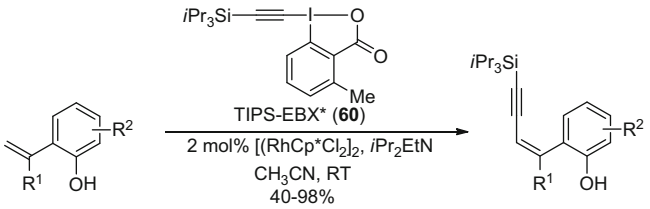
and product decomplexation then gives intermediate **IV**. Interestingly, Li and co-workers also observed the formation of product **59** if Ph-EBX was used as reagent. They proposed that **59** was formed from intermediate **III** via insertion into the alkyne to give **VII**, followed by protodemetalation. In support of this mechanism, Li and co-workers were indeed able to isolate rhodium(III) complexes corresponding to intermediates **I** and **VII** (but with a *tert*-butyl instead of the phenyl group for the latter). Furthermore, they argued that the insertion mechanism was less probable because of the high reactivity of rhodium(III) allenylidene intermediate **VI**, for which side reactions would have been expected, especially with nucleophilic directing groups.

With these three reports, the basis was set for a wider use of EBX reagents in rhodium catalysis. Loh and co-workers continued their work and reported the alkynylation of acryl tosyl imides and enamides [132, 133]. The reaction with acryl imides also proceeded with disubstituted alkenes and allowed the scope of this transformation to be extended. The alkynylation of enamides led to very useful enynamides as products, but was limited to α-substituted alkenes. Loh and co-workers also demonstrated that the methodology could be extended to the C7-alkynylation of indolines using a pyridine directing group on the nitrogen [134]. Interestingly, this reaction was also possible with Ph-EBX as reagent. The products can be easily oxidized to the corresponding indole derivatives. Zhu and co-workers reported the use of acetyl as directing groups and Zhou and Li and co-workers a pyrimidyl directing group with an iridium catalyst to achieve the same transformation [135, 136]. In 2014, Chang and co-workers developed the first C8-alkynylation of quinolone *N*-oxide using a rhodium catalyst [137]. The oxygen atom could easily be removed by reduction. The same year, Li and co-workers reported that azomethine ylides were also excellent directing groups for the alkynylation of benzene rings [138]. Finally, in 2015 Hong and Kang described the selective C–H alkynylation of quinolones [139]. In the absence of a directing group on the nitrogen and using a rhodium catalyst, C5-alkynylation was achieved selectively. Using a pyrimidyl directing group and, for the first time, a ruthenium catalyst, the C2-alkynylated products could be obtained.

Attempts have recently been made to extend the scope of rhodium-catalyzed C–H alkynylation beyond olefins and arenes functionalization via a classical five-membered metalacycle. Li and co-workers developed the directed C–H alkynylation of benzaldehydes (Scheme 24) [140]. Both alcohols and sulfonyl amines could be used as directing groups. With alcohols, an iridium catalyst in methanol was used, giving ynones in good yields. With sulfonyl amines the best results were obtained with a rhodium catalyst in dichloromethane.



Scheme 24 Directed C–H alkynylation of benzaldehydes



Scheme 25 Directed C–H alkynylation of *ortho*-vinyl phenols

In 2015, Nachtsheim and co-workers investigated the directed alkynylation of *ortho*-vinyl phenols with EBX reagents (Scheme 25) [141]. As only moderate yields were obtained using TIPS-EBX **52**, the more reactive TIPS-EBX* **60**, introduced by Waser and co-workers [103], was used. Apart from its enhanced reactivity, the *ortho*-methyl group in **60** also blocked pathways leading to C–H activation side products. Exclusive formation of the *Z*-enyne was observed, without alkynylation of the benzene ring. The best yields were obtained for α-alkyl or aryl substituted vinyl phenols. Unsubstituted products could be isolated in moderate yields, but no products were obtained for *β*-substituted vinyl phenols. Mechanistically, this reaction is interesting because it proceeds via the formation of a less frequent six-membered rhodium metalacycle. From this intermediate, the insertion-elimination-shift mechanism was proposed, although the oxidative addition pathway could also be operative.

For the synthesis of ynones, an alternative approach to metal catalysis was recently reported by Wei and Zhu and co-workers [142]. Instead of the generation of an acyl–metal bond, they speculated that an acyl radical generated by C–H abstraction under oxidative conditions could also react with EBX reagents. Indeed, this was the case using either *tert*-butyl hydroperoxide (TBHP) or di-*tert*-butyl peroxide (DTBP) as oxidant at 80–130°C. Although the reaction required a stoichiometric oxidant and elevated temperature, it has the advantage to be highly general, allowing reactions of aromatic, heteroaromatic, and aliphatic aldehydes. Yields were generally higher with aromatic aldehydes, but the reaction worked only with silyl EBX reagents. Aliphatic aldehydes were obtained in moderate yields, but the transformation could also be used for aryl EBX reagents.

3.1.3 Alkynylation of Aliphatic C–H Bonds

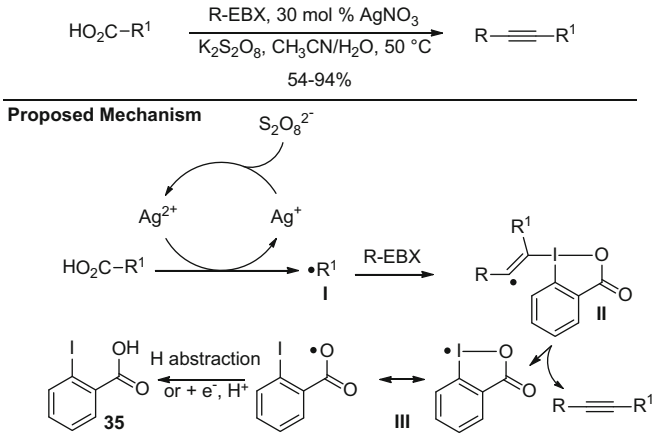
The alkynylation of sp^3-C–H bonds has in general been much less developed than that of sp^2-C–H bonds. Metal-mediated methods have been limited to the use of alkynyl bromides [143], whereas radical approaches have been dominated by alkynyl sulfones [21, 22]. Nevertheless, Yu and Chen and co-workers recently reported that aromatic EBX reagents were highly efficient for the interception of radicals generated in *α*-position to heteroatoms [144]. Silyl EBX could also be used. The inherent limitations of this radical-mediated approach are the requirement for a

large excess of substrate and the formation of mixtures of products when several C–H bonds are of similar strength.

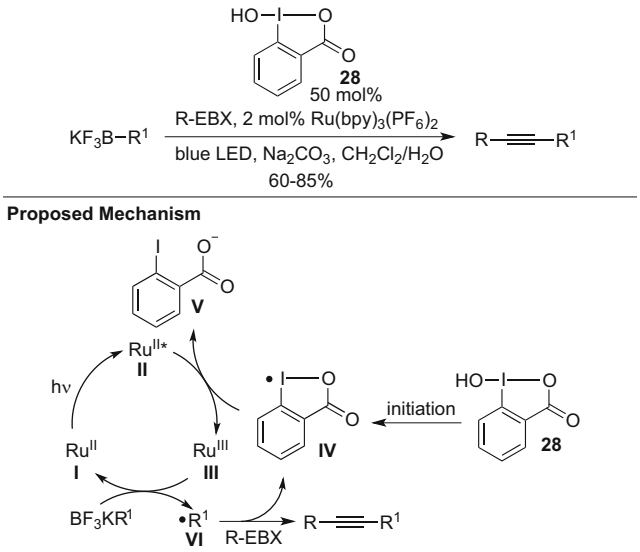
3.1.4 Alkynylation of C–C and C–B Bonds

The alkynylation of C–H bonds is a very attractive method from the point of view of synthetic efficiency, but it presents a serious issue of selectivity if no directing groups or polarizing heteroatoms are present. The use of pre-installed functional groups can be advantageous, provided that the starting materials are commercially available or easily accessible. In this context, Li and co-workers reported in 2012 the oxidative decarboxylative alkynylation of carboxylic acids as shown in Scheme 26 [145]. Starting from broadly available carboxylic acids, aliphatic, aromatic and silyl alkynes could be obtained in good yields. Impressively, the reaction was successful for the functionalization of tertiary, secondary, and primary acids. It also tolerated numerous functional groups such as bromine, esters, or imides. The reaction was proposed to proceed via the silver mediated oxidation of the carboxylate to form a carboxyl radical, which immediately loses carbon dioxide to give an alkyl radical **I**. The active silver(II) oxidant would be generated by oxidation of silver(I) by persulfate, allowing silver nitrate to be used as a catalyst. The alkyl radical would then add to the triple bond of the EBX reagent to give intermediate **II**. β-Elimination of iodo radical **III** then gives the product. Radical **III** is then most probably further reduced to the carboxylate and protonated to give **35**, or, alternatively, **35** is directly formed via C–H abstraction. Addition of the radical on the EBX reagent with reversed regioselectivity followed by an α elimination-1,2-shift sequence could also be considered.

In 2014, Chen and co-workers reported an alternative method based on the oxidative alkynylation of trifluoroboronate salts using a photoredox catalyst,



Scheme 26 Oxidative decarboxylative alkynylation of aliphatic carboxylic acids

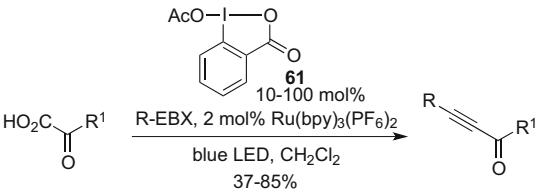


Scheme 27 Alkynylation of aliphatic trifluoroborate salts

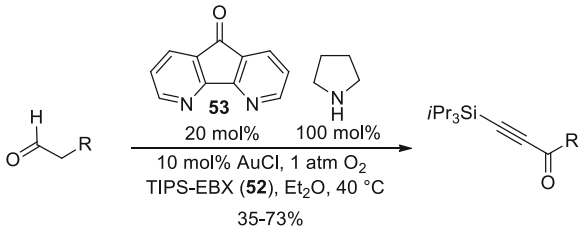
sub-stoichiometric amounts of hydroxybenziodoxolone **28**, and EBX reagents (Scheme 27) [146]. The reaction worked well for the transfer of aryl, silyl, and alkyl alkynes. Primary, secondary, and tertiary boronate salts were all successfully alkynylated. The reaction tolerated functional groups such as ketones, bromides, alcohols, and azides. Interestingly, the authors were also able to perform the alkynylation in buffered water solutions in the presence of several amino acids, demonstrating its potential for the functionalization of biomolecules. Concerning the reaction mechanism, the author proposed that light activation of the ruthenium (II) catalyst **I** generates a strongly reductive complex **II**, which is able to reduce radical **IV** (or hydroxybenziodoxole **28**). The ruthenium(III) complex **III** obtained is now a strong oxidant able to generate an alkyl radical **VI** from the boronate salt. As shown by Li and co-workers, radical **VI** then reacts with the EBX reagent to give the product and a further molecule of radical **IV**. In principle, a small amount of initiator would be enough to start a catalytic cycle. Nevertheless, in practice a relatively large amount (50 mol%) of hydroxybenziodoxole **28** is needed for an efficient transformation. The possibility of a reaction proceeding via a catalyst-independent radical chain reaction was excluded by a light on/off experiment, showing that light was always needed to observe conversion.

In 2015, Chen and co-workers reported an extension of the photoredox strategy for the synthesis of enones based on the decarboxylation of α-keto acids using EBX reagents and acetoxy benziodoxolone **61** as additive (Scheme 28) [147]. The reaction again worked best with aryl EBX reagents, but silyl- or alkyl-substituted alkynes could still be obtained in moderate yields. Aromatic, heteroaromatic, and aliphatic ynones were obtained in good yields. Interestingly, the methodology was

Scheme 28 Decarboxylative alkynylation of α-carbonyl-substituted carboxylic acids



Scheme 29 Ynones synthesis from aldehydes via C–C bond cleavage

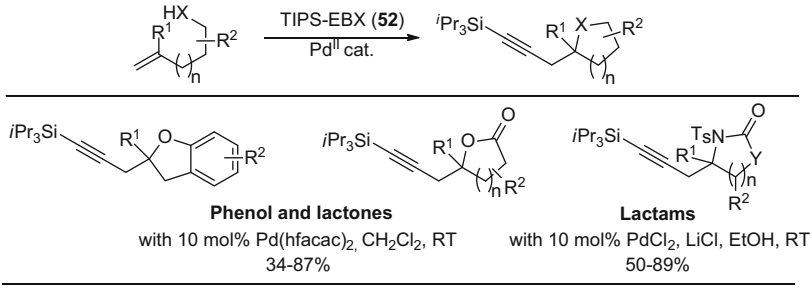


not limited to the synthesis of ketones, but could also be applied to access amides and esters. A similar catalytic cycle as for the alkynylation of boronates salts was proposed with oxidative generation of an acyl radical. The key difference is in the way the radical is formed. The authors proposed the formation of a covalent adduct between the carboxylate and benziodoxolone **61**, which would facilitate oxidation by ruthenium(III) to give the radical. In this process, **61** is not reduced and could be therefore used in catalytic amounts. Indeed, with only 10 mol% of **61**, the alkynylation product was still isolated in 56% yield.

Finally, in 2014 Huang and co-workers reported a fundamentally different approach to access ynones using EBX reagents [148]. During their work on the α-vinylidenation of aldehydes, using cooperative catalysis between an amine and a gold catalyst [116], they observed the formation of one carbon atom shorter ynones when oxygen was not carefully excluded. By performing the reaction under 1 atm of oxygen and optimizing the reaction conditions, they were able to obtain the ynones as major products (Scheme 29). The reaction worked well for the synthesis of primary and secondary aliphatic ynones. Interestingly, the formation of one ynamide was also reported. The authors proposed that the first step of this reaction is similar to α-vinylidenation with the formation of an enynamide. However, under an oxygen atmosphere this highly nucleophilic intermediate is oxidatively cleaved via the formation of a dioxetane ring. Indeed, pyrroldine-2-carboxaldehyde was observed as a side product.

3.1.5 Alkynylation as Part of Domino Processes

In domino processes, several new bonds are formed in a single transformation, leading to a more efficient synthesis [149]. The introduction of an alkyne group during domino processes would be highly desirable when considering the versatile

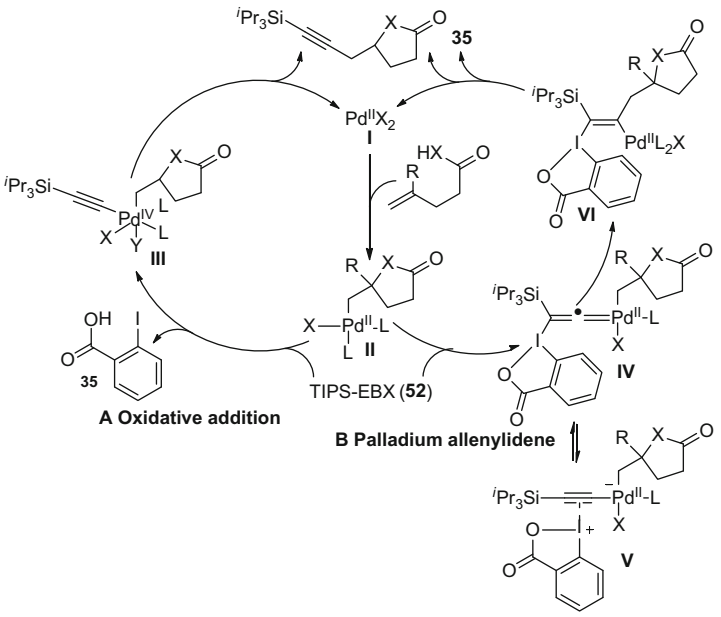


Scheme 30 Oxy- and amino-alkynylation of alkenes

reactivity of the triple bond. Nevertheless, alkynyliodonium salts were not used in such transformations, probably because they are often unstable in the presence of transition metal catalysts.

In 2010, Waser and co-workers reported the first example of intramolecular palladium-catalyzed oxyalkynylation of alkenes leading to the successive formation of a C–O and a C–alkyne bond (Scheme 30) [150]. Whereas the use of alkynyl iodonium salts led to the formation of the desired product in trace amounts only, good yields could be obtained using TIPS-EBX **52** with phenols as nucleophiles and palladium(II) bishexafluoroacetylacetonate as catalyst. Only electron-neutral or poor phenols could be used in this process, as electron-rich substrates decomposed. Aliphatic alcohols could not be used. On the other hand, acids gave lactones with wider applications. In this case, both aromatic and aliphatic acids could be used. In 2011, Waser and co-workers were able to extend the method to the synthesis of lactams using tosylimides as nucleophiles [151]. In this case, the best results were obtained with palladium(II) chloride as catalyst in ethanol. The reaction worked well for the synthesis of γ-lactams, oxazolidinones, and imidazolidinones. It was also easily scalable to the gram scale and was used in the total synthesis of the pyrrolizidine alkaloid trachelanthamidine. Finally, the method could also be applied to the synthesis of δ-lactams in moderate to high yields depending on the rigidity of the substrates.

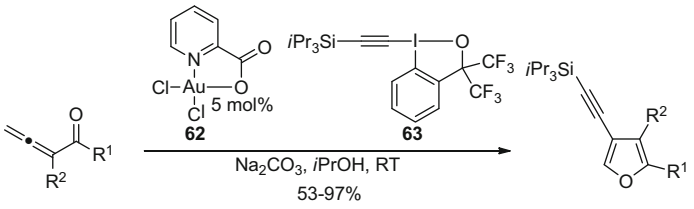
Originally, Waser and co-workers proposed a mechanism involving a palladium (IV) intermediate **III** (Scheme 31, **A**) [150]. Complex **III** would be accessed by either *syn*- or *anti*-oxy/aminopalladation of the olefin to give **II**, followed by oxidative addition of TIPS-EBX **52**. Reductive elimination would then give the observed product and regenerate the palladium(**II**) catalyst. This proposal was based on the work of Canty and co-workers, who were able to characterize palladium(IV)–alkynyl complexes [94]. However, Ariafard reported calculations in 2014 that gave a very high energy for this reaction mechanism [152]. They found a lower energy pathway leading to palladium allenylidene intermediate **IV**, which was in equilibrium with an iodine-bound alkynyl–palladium complex **V**, with **IV** being the major species. From **IV**, a facile α-insertion of the alkyl group give palladium(II) vinyl intermediate **V**. Finally, β-elimination of 2-iodobenzoic acid **35** would lead to the observed product.



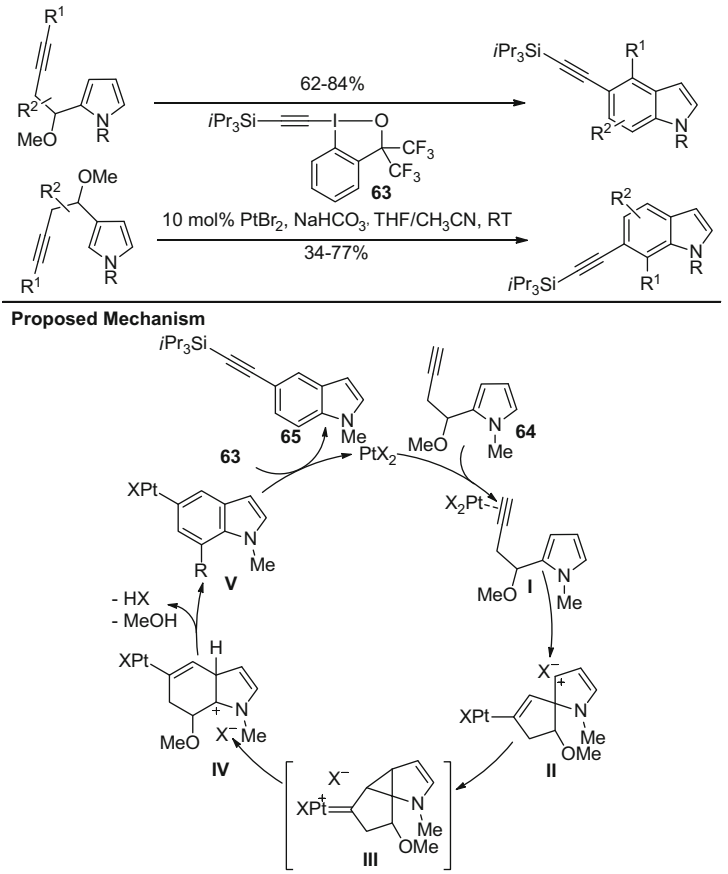
Scheme 31 Speculative mechanisms for the oxy- and aminoalkynylation reactions

After having successfully developed a domino process involving C(sp^3)–C (sp) bond formation as terminating event, Waser and co-workers investigated whether domino processes could also be used to make a C(sp^2)–C(sp) bond. Preliminary studies focused on the synthesis of indoles directly from *ortho*-alkynyl anilines [153]. A one-pot process could indeed be developed, but not a true domino transformation, as a gold(III) catalyst was required for cyclization and a gold (I) catalyst for alkynylation. A further limitation of this early work is that it gave access to products which are easily synthesized via direct C–H alkynylation. To overcome these limitations, Waser and co-workers decided to develop a domino reaction based on the gold-catalyzed cyclization of allene ketones to form furans reported by Hashmi and co-workers [154]. In this transformation, a C3-metallated furan is formed, which could be then alkynylated to give the electronically unfavored regioisomer. In 2013, they reported the first example of such a true domino reaction using gold(III) picolinate catalyst **62** and ethynylbenziodoxole **63** as reagent (Scheme 32) [122]. The reaction was efficient with electron-neutral and rich aromatic rings on the allene, but could not be used in the case of electron-poor substituents because of decomposition. It was particularly efficient with alkyl substituents.

After this work, the more challenging synthesis of arene-alkynylated indoles was investigated. Because of the enhanced reactivity of the pyrrole ring, the direct functionalization of indoles on the benzene ring is highly challenging. A domino process to access these compounds would therefore be very useful. They were able



Scheme 32 Domino cyclization-alkynylation of allene ketones



Scheme 33 Domino cyclization-alkynylation for the synthesis of arene-alkynylated indoles

to develop a platinum-catalyzed method starting from homopropargylic pyrrole derivatives and benziodoxole reagent **63** (Scheme 33) [155]. Gold catalysts could not be used in this process. Starting from C2-substituted pyrroles, C5-alkynylated indoles were obtained, whereas C3-substituted pyrroles gave C6-functionalized products. Mechanistically, this reaction most probably proceeds via activation of

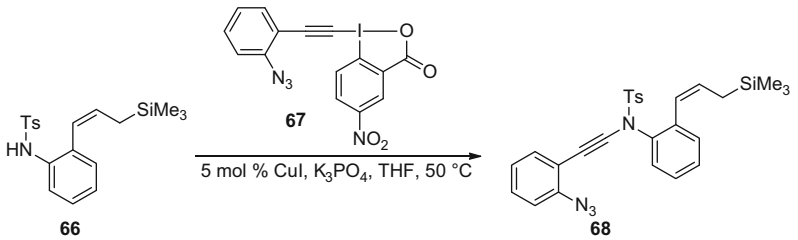
the triple bond in pyrrole **64** by the platinum catalyst (intermediate **I**), followed by intramolecular attack of the most nucleophilic pyrrole C2 position to give key intermediate **II**. 1,2-Shift of the vinyl-platinum substituent via a possible platinum carbene intermediate **III** then gives complex **IV**. Interestingly, shift of the ether substituent had been observed with gold catalysts for the simple cyclization process [156]. At this point, elimination of methanol and re-aromatization would give a platinum–aryl complex **V**, which would then react with benziodoxole **63** to give the observed product **65**. The mechanism of this last step is not clear at this stage. In the case of C3 substituted pyrroles, C2 attack would give the desired six-membered ring directly without the need for 1,2-shift.

3.2 Alkynylation of Heteroatoms

3.2.1 Alkynylation of Oxygen and Nitrogen Nucleophiles

Up to now, no efficient alkynylation of oxygen nucleophiles with EBX reagents has been reported. Also, in the case of nitrogen nucleophiles, alkynyliodonium salts remain the reagents of choice. Nevertheless, Cossy and co-workers reported in 2013 that the alkynylation of sulfonamides was possible with TMS-EBX **36** [157]. Interestingly, no alkynylation was observed in the case of carbamates, although these substrates are readily alkynylated with alkynyliodonium salts. Selective alkynylation of the tosyl amide in the presence of a carbamate was possible. This selectivity was exploited for the synthesis of tetrahydropyrazine heterocycles.

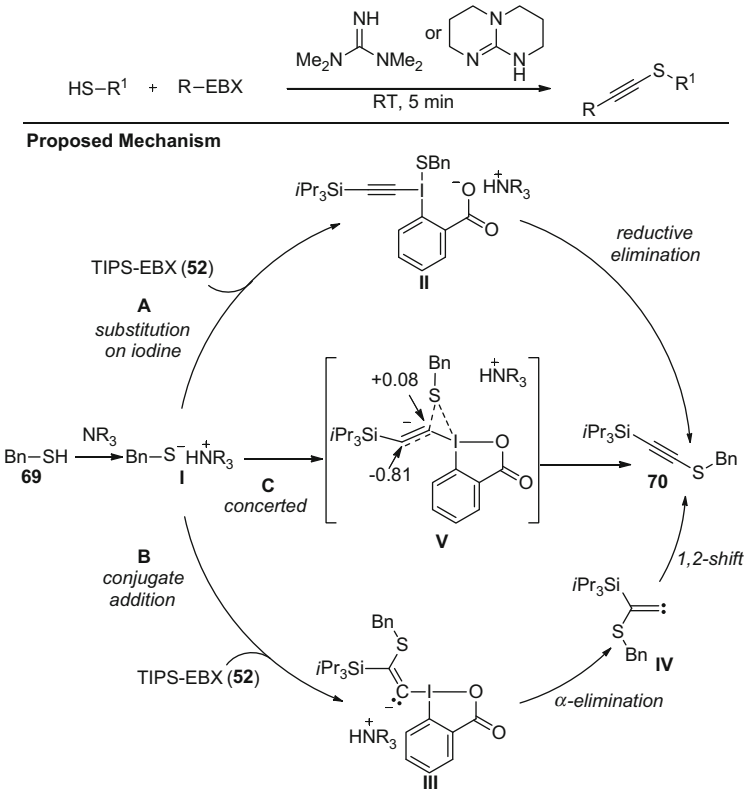
In 2014, Ohno and co-workers reported the synthesis of the more complex ynamides **68** based on the copper-catalyzed alkynylation of tosyl amide **66** using aryl EBX reagent **67** (Scheme 34) [158]. Interestingly, this constituted the first example of a copper-catalyzed reaction with an EBX reagent in which the alkyne group is kept in the product. Although alkynyl bromides have traditionally been used in copper catalysis for the synthesis of ynamides, they were not successful in this case.



Scheme 34 Copper-catalyzed alkynylation of tosyl amide **66** with EBX reagent **67**

3.2.2 Alkynylation of Phosphorus, Sulfur, and Other Nucleophiles

The alkynylation of numerous heteroatom nucleophiles has been highly successful with alkynyliodonium salts. Nevertheless, the alkynylation of omnipresent simple thiols had never been reported, probably because the oxidation of thiols to disulfides is readily promoted by alkynyliodonium salts. In 2013, Waser and co-workers demonstrated that the alkynylation of thiols was possible with TIPS-EBX **52** in high yields in less than 1 min reaction time at room temperature (Scheme 35) [159]. Key for success was the use of tetramethylguanidine (TMG) as a base. The scope of the reaction was very broad, as it included aliphatic thiols, thiophenols, heteroaromatic thiols, cysteines, and peptides. The transformation was tolerant to many functional groups, such as halogens, alcohols, acids, amides, anilines, and even the free amino group of cysteine. The thioalkynes obtained could easily be deprotected and reacted in a [3 + 2] cycloaddition with azides. In 2014, they further reported extension to glycosides, thioacids, and sulfide salts [160]. Furthermore, the use of non-silyl-substituted alkynes was also highly successful for all substrates classes. In some cases, the use of triazabicyclodecene



Scheme 35 Alkynylation of thiols with EBX reagents

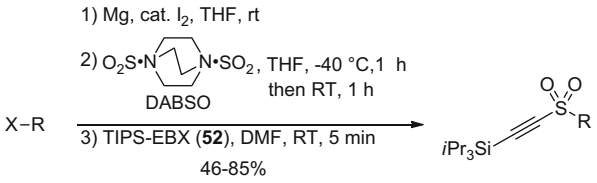
(TBD) as base gave superior results. The exception was thioacids, as the products were too unstable to be isolated in this case. Importantly, functional groups such as chloride, alcohol, or azide incorporated on the EBX reagent were also tolerated.

The fact that the reaction was successful for a wide range of EBX reagents was surprising, as side reactions dominated in the case of alkyl substituted alkynyliodonium salts (see Sect. 2.1.1). Waser and co-workers turned to calculations to gain a better understanding of the reaction mechanism [160]. Deprotonation of the thiol was proposed as the required step as no reaction occurred in the absence of base. A first possibility would then be attack of the thiolate **I** on TIPS-EBX **52** to give intermediate **II**, followed by reductive elimination (**A**). However, intermediate **II** was not observed in the calculations. A more probable mechanism involves conjugate addition to give **III**, followed by α-elimination and 1,2-shift to give **70** (**B**). This pathway was indeed found by calculations with a relatively low transition state of 23 kcal/mol leading to **III**, followed by a barrierless elimination/1,2-silyl shift to give product **70**. However, a third unprecedented pathway was also found by calculations: a concerted three-atom transition state mechanism leading directly to **70**, with an energy as low as 10.8 kcal/mol. The transition state **V** itself was distorted and showed a strong polarization, with the negative charge in the α-position and the positive charge in the β-position to silicium. The difference between the two pathways was much smaller for an alkyl substituent, probably because of the silyl effect.

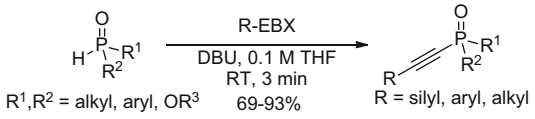
The reaction of sulfinates with alkynyl iodonium salts was successful, as these substrates are less easy to oxidize. Nevertheless, Waser and Chen demonstrated that EBX reagents can also be useful to synthesize alkynyl sulfones, as they allow a new one-pot procedure starting directly from Grignard reagents (Scheme 36) [161]. In this protocol, DABSO (DABCO·SO_2) is added after formation of the Grignard reagent. Addition of DMF and TIPS-EBX **52** gives aryl alkynyl sulfones in 46–85% yield. For base sensitive substrates, it was also possible to start from aryl iodides and use a palladium catalyst.

In 2014, Waser and Chen also reported that EBX reagents could be used in the alkynylation of phosphites (Scheme 37) [162]. The reaction also worked well for the alkynylation of phosphinates and secondary phosphine oxides.

Scheme 36 One-pot synthesis of alkynyl sulfones



Scheme 37 Alkynylation of phosphorus nucleophiles with EBX reagents



3.3 Conclusion on the Use of EBX Reagents

In contrast to alkynyliodonium salts, which have been used in organic synthesis for decades, EBX reagents have been used intensively only in the last 5 years. However, they have already made a strong impact in the synthesis of alkynes, as they allowed new transformations which were not accessible before. They were especially successful in transition metal catalysis, where they allowed the development of new C–H functionalization and domino reactions. They also demonstrated important advantages for the functionalization of acidic C–H bonds or carbon centered radicals. EBX reagents allowed new transformations with heteroatoms, such as the alkynylation of thiols, or presented distinct highly useful properties, for example in the alkynylation of tosyl amides, sulfinates, or phosphorus nucleophiles.

4 Conclusions

The importance of alkynes in organic chemistry cannot be overstated. They are now also increasingly useful in chemical biology and materials science. The introduction of alkynes as nucleophiles into molecules is currently the method of choice, but it limits the range of possible disconnections. As one of the best electrophilic alkyne synthons, alkynyliodonium salts have attracted strong interest since the mid-1980s. Even if very successful, their utility has been limited by their lower stability, especially in the presence of transition metals. Nowadays, their main routine use resides in the synthesis of ynamides. The introduction of more stable ethynylbenziodoxolone (EBX) reagents, first synthesized by Ochiai and Zhdankin, has initiated a renaissance of the use of hypervalent iodine reagents for alkynylation reactions. A wide range of mild reactions has now become available to introduce alkynes onto both carbon nucleophiles and heteroatoms, with the potential to revolutionize the way to disconnect this versatile functional group. As research is increasing apace in this area, many more exciting transformations can be expected to be discovered in the future.

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Rearrangements Induced by Hypervalent Iodine

Gaëtan Maertens and Sylvain Canesi

Abstract This chapter describes advances in hypervalent iodine(III)-induced rearrangements reported between 2004 and 2015, beginning with Hofmann-type rearrangements and aliphatic aryl transpositions. In both reactions the iodine(III) reagent may be off-the-shelf or catalytically generated in situ. A number of stereoselective transformations are discussed, followed by transpositions triggered through phenol dearomatization, including Wagner–Meerwein-type rearrangements, Prins-pinacol transpositions, and a tandem polycylization-pinacol process. Other rearrangements such as an iodonio-Claisen rearrangement, an *ipso*-rearrangement, and rearrangements performed using iodine(V) are also described.

Keywords Alkyl-shift · Hoffman rearrangement · Polycyclization and iodonio-Claisen · Prins-Pinacol · Ring expansions and contractions · Transposition

Contents

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1 Introduction

Hypervalent iodine reagents promote a host of useful rearrangements in the synthesis of highly functionalized compounds. Their ability to react first as an electrophile and then be transformed into an excellent leaving group readily initiates the migration of various substituents. In addition, cationic species may be generated during the dearomatization process under conditions favoring a dissociative mechanism. The latter can also trigger the migration of various chemical groups. Those characteristics have enabled the development of new Hofmann-type rearrangements as well as 1,2- and 1,3-allyl, alkyne, and alkyl shifts, Prins-pinacol-like transpositions, and iodonio-Claisen rearrangements. Some of these pioneering transformations were described in the last edition of Topics in Current Chemistry: Hypervalent Iodine Chemistry [1]. The reactions described below were reported between 2004 and 2015.

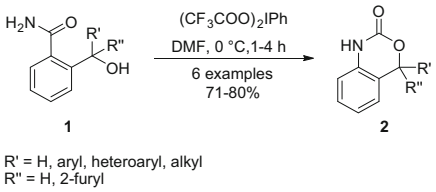
2 Hofmann-Type Rearrangements

Iodine(III) reagents have been shown to be effective in promoting Hofmann-type rearrangements. Although the transformations often involve a commercial reagent, catalytic versions have also been developed in which the active iodine(III) is generated in situ through reaction between iodobenzene and a co-oxidant such as *m*CPBA.

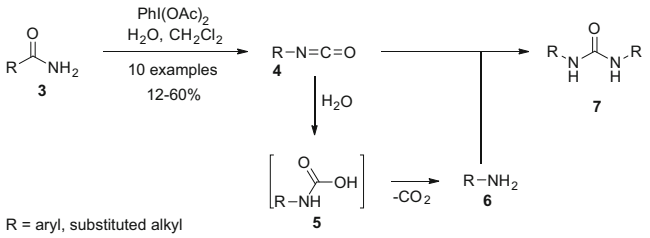
2.1 Reactions Using Commercial Reagents

As an example, 2-hydroxymethylbenzamide **1** may be converted into a benzoxazinone **2** using [bis(trifluoroacetoxy)iodo]benzene as shown in Scheme 1 [2].

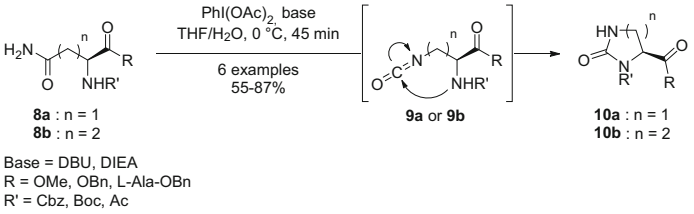
Symmetrical ureas may be generated in a reaction between an amide **3** and (diacetoxyiodo)benzene in the presence of water (Scheme 2) [3]. The transformation proceeds through an isocyanate **4**, some of which reacts with water to produce amine **6** via intermediate **5**. Amine **6** attacks unreacted **4** to deliver the desired symmetric urea **7**. A variety of aromatic and aliphatic substituents (including *tert*-butyl) have been successfully employed in this reaction.



Scheme 1 Formation of benzoxazinones **2** via Hofmann-type rearrangement



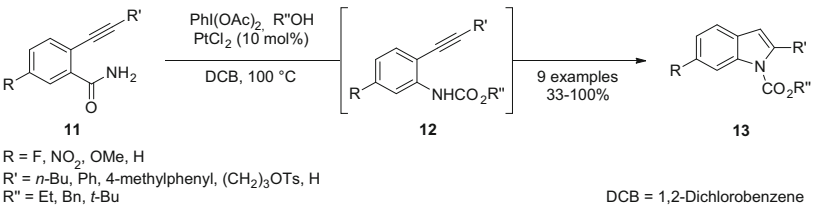
Scheme 2 Formation of urea **7** via Hofmann-type rearrangement



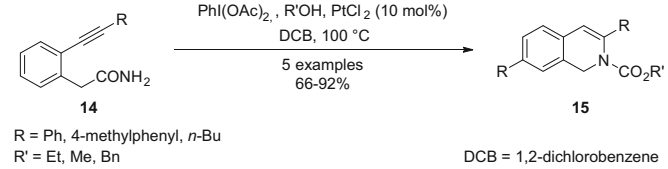
Scheme 3 Imidazolidinones and tetrahydropyrimidinones via Hofmann-type rearrangement

The reagent (diacetoxyiodo)benzene serves to transform protected asparagines and glutamines into imidazolidinones and tetrahydropyrimidinones as shown in Scheme 3 [4]. When reacted with $PhI(OAc)_2$ in the presence of a base, an asparagine **8a** undergoes Hofmann-type rearrangement to form an isocyanate **9a**, which is then trapped intramolecularly by the protected amine to deliver the desired imidazolidin-2-one-4-carboxylate **10a**. The same process occurs with glutamines **8b**, producing tetrahydropyrimidin-2-one-5-carboxylates **10b**.

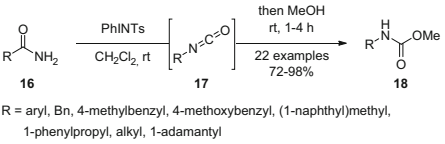
Treatment of 2-alkynylbenzamides **11** with (diacetoxyiodo)benzene in the presence of an alcohol such as ethanol or *tert*-butanol and a catalytic amount of platinum dichloride leads to indoles **13** as shown in Scheme 4 [5]. The transformation occurs through the formation of the corresponding isocyanate, which then reacts with the alcohol to produce a carbamate **12**. The carbamate undergoes an intramolecular nucleophilic addition to the alkyne moiety to deliver the indole **13**. Electron-withdrawing and electron-donating substituents on the aromatic subunit and aliphatic and aromatic substituents on the alkyne moiety are well tolerated. When a terminal alkyne is engaged in the reaction, the desired indole is obtained in lower yields.



Scheme 4 Formation of indoles **13** via Hofmann-type rearrangement



Scheme 5 Dihydroisoquinoline **15** formation via Hofmann-type rearrangement



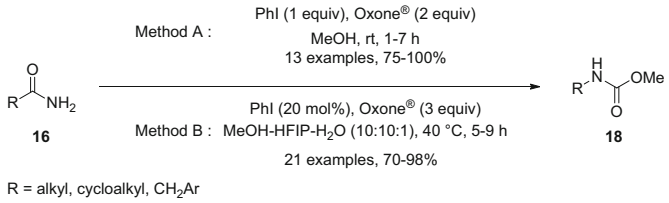
Scheme 6 General carbamate **18** formation via Hofmann-type rearrangement

The same conditions may be applied to the synthesis of dihydroisoquinolines **15** from 2-alkynylbenzylamides **14** (Scheme 5).

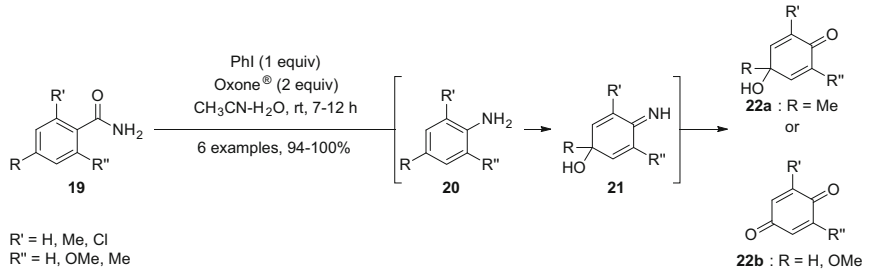
(Tosylimino)phenyl-λ^3-iodane, another iodine(III)-based reagent, also facilitates the conversion of a large variety of amides such as **16** into the corresponding isocyanates **17**, which are suitable precursors for the synthesis of methyl carbamates **18** as shown in Scheme 6 [6]. The reaction proceeds in very good yields with a variety of electron-rich and electron-poor aryl-substituted amides as well as bulky alkyl-substituted amides. Although no conversion was observed when a 2,4,6-trimethylphenyl substituent was present, the authors successfully synthesized isopropyl *N*-(4-methylphenyl)carbamate and *tert*-butyl *N*-(4-methylphenyl)carbamate by treatment of the corresponding isocyanates with suitable alcohols.

2.2 Reactions with Iodine Species Generated In Situ

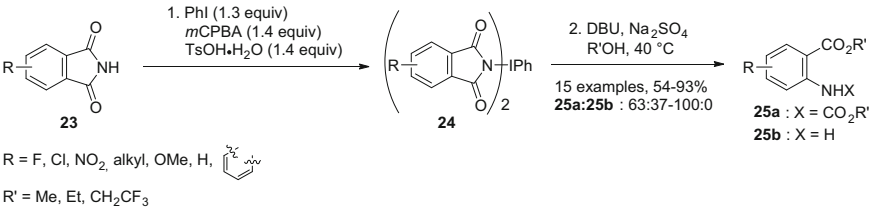
All of the reactions described above use a readily available hypervalent iodine reagent. The Zhdankin group has also reported Hofmann-type rearrangements employing an iodine(III) species generated in situ through reaction of iodobenzene and a co-oxidant. It is sometimes possible to employ a sub-stoichiometric amount of iodobenzene to catalyze the transformation. As an example, carbamates such as



Scheme 7 Carbamate **18** formation via a stoichiometric or catalytic Hofmann-type process



Scheme 8 Quinones and cyclohexa-2,5-dienimines via Hofmann-type rearrangements



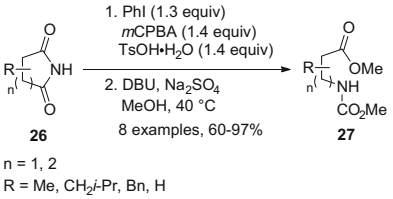
Scheme 9 Carbamates **25a** and arylamines **25b** via Hofmann-type rearrangement

18 may be obtained by treatment of amides **16** with 1 equiv. of iodobenzene in the presence of Oxone® as shown in Scheme 7 (Method A) [7] or with 20 mol% of iodobenzene and Oxone® (Method B) [8].

The same conditions as Method A (Scheme 7) may be applied to the synthesis of quinone derivatives **22** from benzamides **19** (Scheme 8) [7]. The reaction first produces arylamines **20** that are subsequently oxidized to the corresponding cyclohexa-2,5-dienimines **21** and finally hydrolyzed to **22**. This noteworthy tandem process developed by Zhdankin and coworkers extends the scope of oxidative dearomatization to arylamides.

Phthalimides **23** are transformed into a mixture of carbamates **25a** and arylamines **25b** by reaction with iodobenzene in the presence of *m*CPBA and TsOH•H_2O (Scheme 9) [9]. The suggested mechanism implies the formation of imide-λ^3-iodane intermediates **24** which undergo alcoholysis followed by Hofmann-type rearrangement to yield **25**.

Scheme 10 Amino acid **27** formation via Hofmann-type rearrangement



Under similar reaction conditions, amino acid derivatives such as **27** can be produced from **26** as shown in Scheme 10.

3 Aryl Transpositions

Hypervalent iodine compounds are also superior reagents for promoting aryl migrations. The electrophilic species generated during the activation may be trapped by an aryl via a Friedel–Crafts-like process, thus leading to rearranged compounds. The activation is generally performed on conjugated double bonds. Some stereoselective methods using chiral iodine(III) have been developed. In some cases, the rearrangements result in a ring contraction or a ring expansion.

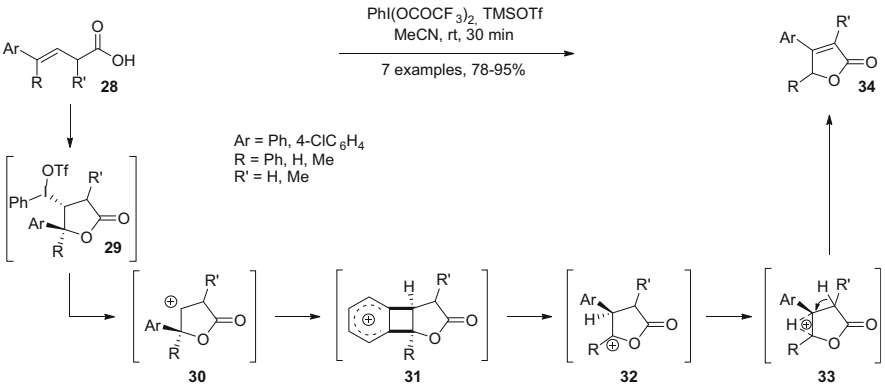
3.1 Racemic Pathway

Wirth and coworkers have demonstrated that an unsaturated acid **28** reacts with [bis (trifluoroacetoxy)iodo]benzene in the presence of TMSOTf to produce a furanone **34** (Scheme 11) [10]. The combination of the two reagents generates the highly active iodine(III) species $PhI(OTf)_2$ in situ. One proposed mechanism for this remarkable transformation involves the formation of a cationic intermediate **30**, which interacts with the aryl moiety represented by the intermediate **31**. This aryl substituent then migrates to produce the tertiary cation **32**, which in turn interacts with the vicinal hydrogen to furnish the observed furanone **34**.

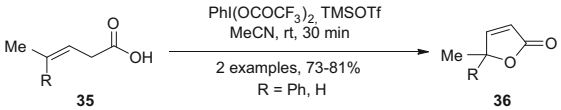
When a (*Z*)-alkene or a non-conjugated alkene **35** are employed, no transpositions are observed, and the furanone **36** is obtained instead (Scheme 12).

The same conditions developed by Wirth and coworkers have been applied to acids such as **37** and lead either to a pyranone **38a** or a ketone **39b** depending on the substituents present on the alkene moiety as indicated in Scheme 13. Finally, an enone **41** may be generated from an acid **40** using the same methodology through a Friedel–Crafts-type transformation.

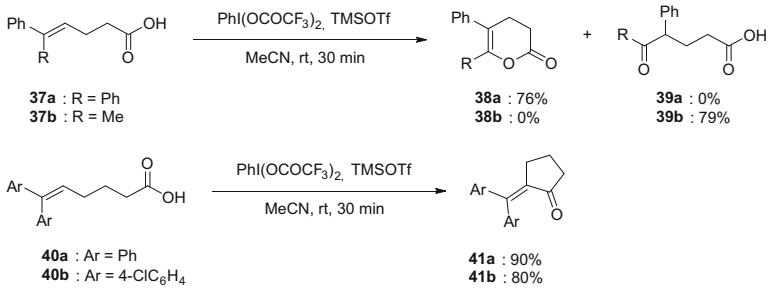
N-Arylcinnamamides **42** may be transformed into 3-arylquinolin-2-ones **43** by reaction with [bis(trifluoroacetoxy)iodo]benzene in the presence of $BF_3{\cdot}OEt_2$ (Scheme 14) [11]. This transformation appears to be compatible with several aryl groups and may also be performed in the presence of different *N*-aryl substituents.



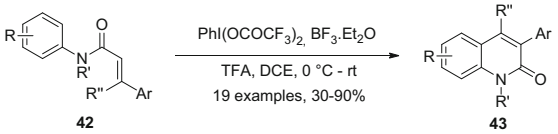
Scheme 11 Furanone **34** formation via aryl transposition



Scheme 12 Absence of transposition with acid **35**



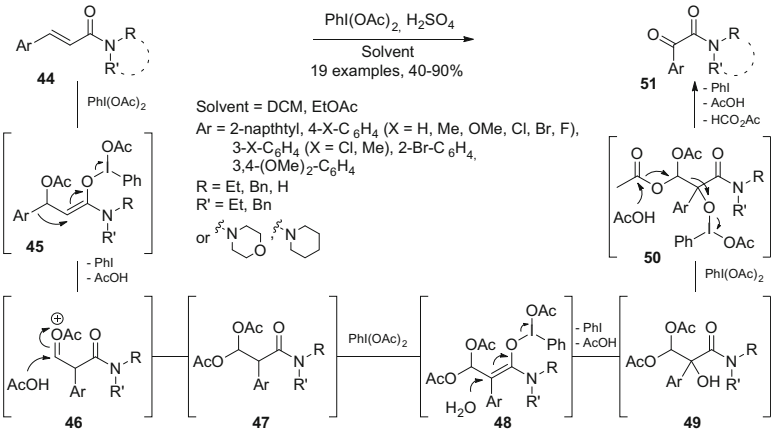
Scheme 13 Formation of pyranones **38** and ketones **39** and **41** via a 1,2-aryl shift process



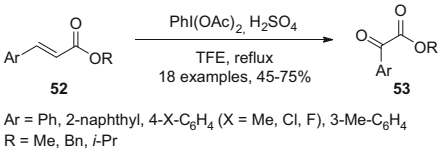
R = H, Me, OMe, F, Cl, Br, CF_3, CO_2Me
R' = Me, Bn, *i*-Pr, cyclopropylmethyl
R'' = H, Ar
Ar = Ph, 4-X-Ph (X = Br, Cl, OMe), 2-X-Ph (X = Cl, Br), 2-thiophenyl

Scheme 14 3-Arylquinolin-2-one **43** formation via a 1,2-aryl shift

The same group has demonstrated that treatment with (diacetoxyiodo)benzene in the presence of sulfuric acid transforms acrylic amides **44** into α-ketoamides **51** as shown in Scheme 15 [12]. The process is an example of a tandem aryl migration/C–C



Scheme 15 Synthesis of α-ketoamides **51** via a tandem aryl migration/C–C bond cleavage sequence

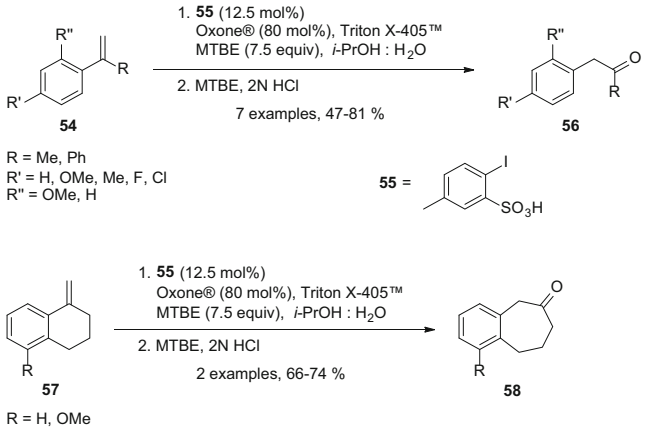


Scheme 16 α-Ketoesters **53** via a tandem aryl migration/C–C bond cleavage sequence

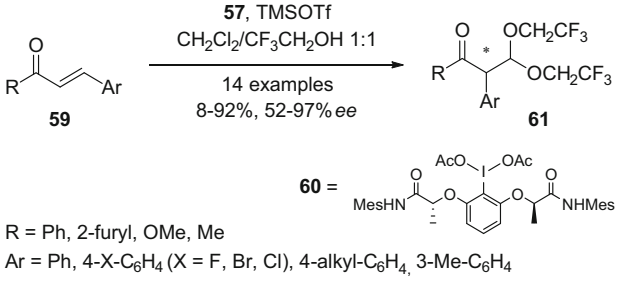
bond cleavage beginning with the formation of **45** through the generation of an iminium ion and departure of a hydrogen atom. The aryl moiety then migrates to produce intermediate **46**, which in turn reacts with a molecule of acetic acid to produce ketal **47**. A second attack of the amide (via the iminium ion) on the hypervalent iodine(III) with departure of a hydrogen atom generates **48**, which is hydrolyzed to **49**. Finally, the alcohol moiety reacts with (diacetoxyiodo)benzene to produce **50** and the C–C bond cleavage is induced by the hydrolysis of an acetate group, leading to α-ketoamides **51**.

The same method may be applied to the conversion of acrylates **52** into the corresponding α-ketoesters **53** (Scheme 16).

When treated with a sub-stoichiometric amount of 2-iodo-5-methylbenzenesulfonic acid **55** as a pre-catalyst and in the presence of Oxone® as a co-oxidant, olefin **54** is transformed into the corresponding ketone **56** as shown in Scheme 17 [13]. It should be stressed that those conditions imply only 80 mol% of Oxone®, in order to generate a reactive iodine species(III) and not to overoxidize the reagent into an iodine(V), which would probably be unable to promote the desired transformation. The authors also demonstrated that, under certain reaction conditions, olefin **57** can undergo a ring expansion to produce bicyclic ketone **58**.



Scheme 17 Formation of ketones **56** and **58** via a catalytic 1,2-aryl rearrangement

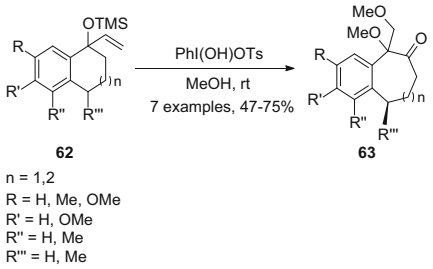


Scheme 18 α-Aryl ketone **61** formation via a stereoselective 1,2-aryl shift process

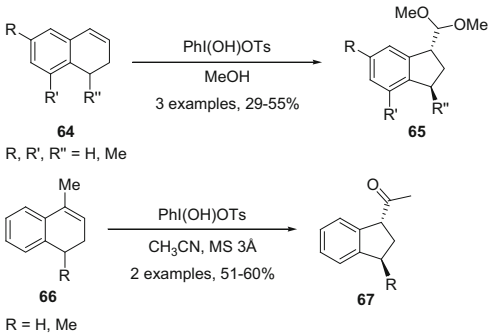
3.2 Stereoselective Pathway

Wirth and coworkers also demonstrated that the transpositions might be performed in a stereoselective fashion. Reaction of enones such as **59** with the modified Fujita reagent **60** developed by Ishihara and coworkers [14] transforms them into α-substituted ketones **61** as shown in Scheme 18 [15]. Although yields are higher when chalcones are employed, the reaction also proceeds with aliphatic ketones (R = Me, 10%) and esters (R = OMe, 12%, 96% *ee*). Many substituents on the migrating aromatic moiety, including fluorine, are well tolerated. However, no reaction is observed when a nitro or methoxy group is present.

Scheme 19 Synthesis of cycloheptanones and cyclooctanones **63** via ring expansions



Scheme 20 Ketal **65** and ketone **67** formation via ring contractions



3.3 *Ring Expansions and Contractions*

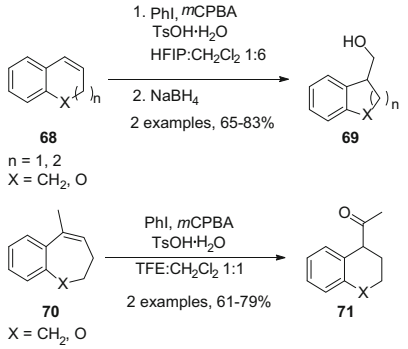
Another method enables conversion of silyl ethers **62** into the corresponding cycloheptanones **63** (Scheme 19) [16, 17]. In this case, a tandem oxidative ring expansion and addition promoted by HTIB (PhI(OH)OTs) occurs through the formation of a cycloheptenone intermediate. The authors also describe the formation of a bicyclic cyclooctanone ($n = 2$) in this process.

Conversely, hypervalent iodine reagents can also promote ring contractions. For example, a ketal **65** can be generated by reaction between a 1,2-dihydronaphthalene **64** and HTIB (PhI(OH)OTs) in methanol as shown in Scheme 20 [18]. If the reaction is performed in anhydrous acetonitrile, ketones such as **67** are obtained.

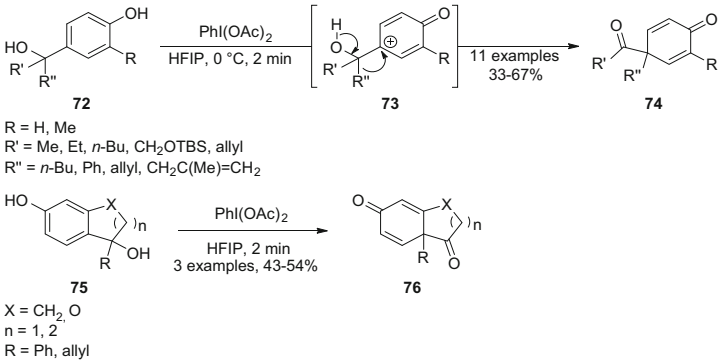
The same transformation can be performed with an in situ-generated PhI(OH)OTs, as shown in Scheme 21 [19]. The generation of the active species is carried out by reaction between iodobenzene and *m*CPBA in the presence of *p*-toluenesulfonic acid.

4 Transpositions via Phenol Dearomatization

Iodine(III) reagents are effective in the dearomatization of electron-rich aromatics such as phenols or anilines, generating highly electrophilic intermediates in these reactions. In addition to reaction with external nucleophiles, such intermediates can also be trapped in an intramolecular fashion to provoke a rearrangement. The



Scheme 21 Formation of **69** and **71** via catalytic ring contraction



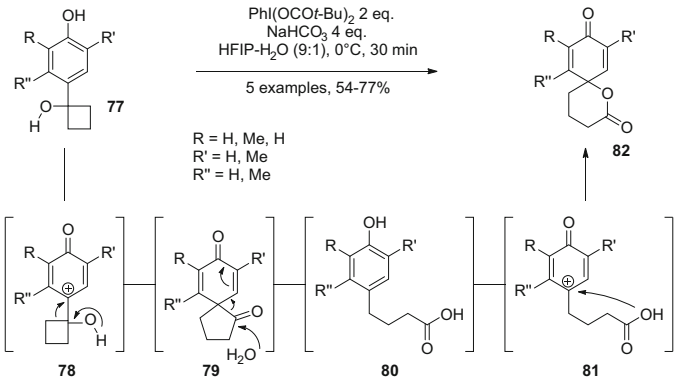
Scheme 22 Formation of dienones **74** and **76** via Wagner–Meerwein-type rearrangements

migrating substituent can be an alkyl, an allyl, or an alkyne moiety. Prins-pinacol and tandem polycyclization-pinacol processes have been developed using a similar strategy.

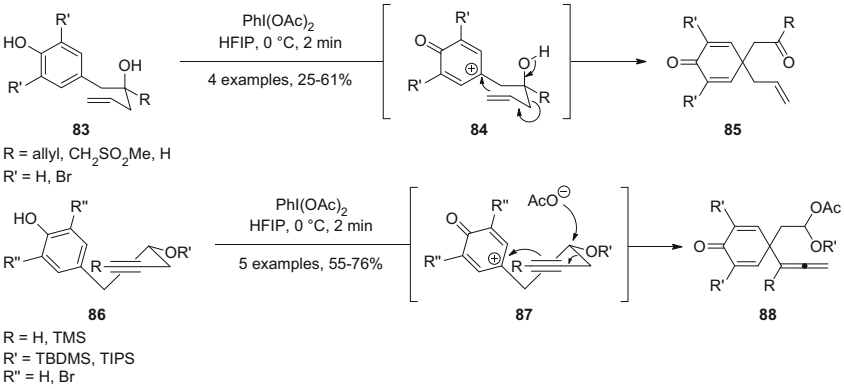
4.1 Alkyl, Allyl, and Alkyne Shifts

When phenols such as **72** are treated with (diacetoxyiodo)benzene in hexafluoroisopropanol, phenoxenium ions **73** are produced. A subsequent 1,2-shift involving the migration of the more electron-rich substituent produces a dienone **74** (Scheme 22) [20, 21]. Although the allyl group appears to be the best substituent for the 1,2-shift, the reaction can also be performed with an alkyl or aryl group as the migrating substituent. The process also extends to bicyclic phenols **75**, yielding dienones of type **76** as reaction products.

A similar strategy has been developed by Kita and coworkers, using a domino process to transform phenols **77** into spirolactones **82** as shown in Scheme 23



Scheme 23 Spirolactones **82** via a tandem Wagner–Meerwein-type/lactonization process

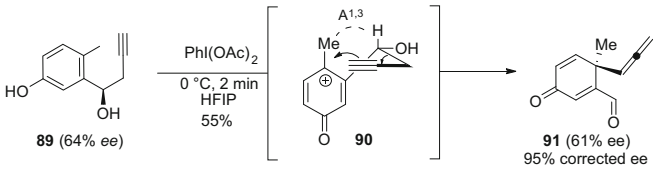


Scheme 24 Ketone **85** and allene **88** formation via 1,3-allyl or -alkyne shift

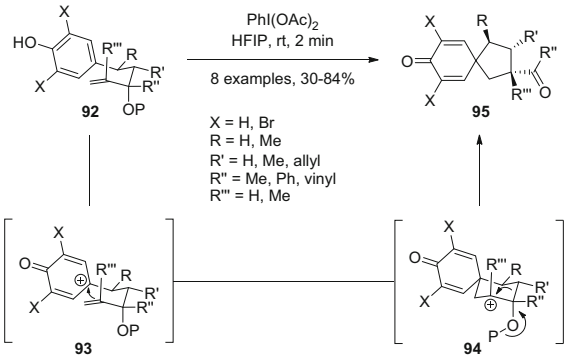
[22]. In this tandem approach, spiroketones **79** are produced as intermediates. The latter then re-aromatize by addition of water to produce carboxylic acids **80** through a retro-Claisen-like process, which undergoes another oxidation and spirolactonization to yield **82**.

This approach was extended to homoallylic alcohols **83** which produce ketones **85** (Scheme 24) [20]. If a propargyl substituent is employed as shown in **86**, the transformation leads to allenes of type **88**. In this case, the intermediate cationic species is trapped in situ by acetate originating from the iodane, thus producing an acetal functionality.

A stereoselective approach has been developed to enable chirality transfer from a chiral alcohol to a quaternary carbon center through a half-chair transition state as shown in Scheme 25 [21]. In that case, a mixture of alcohol **89** (64% *ee*) is converted into the dienone **91** (61% *ee*) with very good chemical yield as well as very good enantioselectivity (95% *ee* after correction).



Scheme 25 Stereoselective 1,3-alkyne shift process



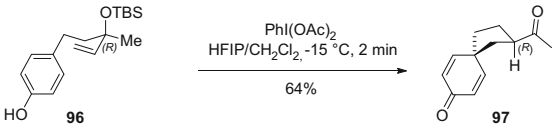
Scheme 26 Formation of dienones **95** via Prins-pinacol transposition

4.2 Prins-Pinacol Transpositions

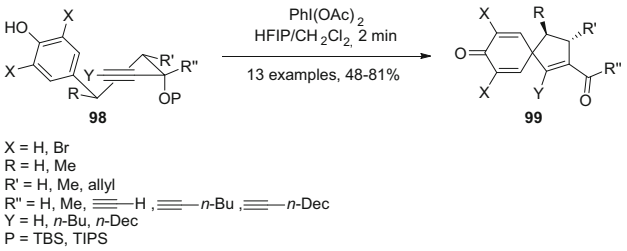
Dearomatization of phenols can also trigger a tandem Prins-pinacol process. When treated with (diacetoxyiodo)benzene, phenols **92** are converted into spiro-dienones **95** as shown in Scheme 26 [23, 24]. The process occurs through the formation of a phenoxenium ion **93**, which is intramolecularly trapped by the olefinic moiety to form the intermediate **94**. Ring contraction through migration of the *anti*-periplanar C–C bond followed by loss of the alcohol protecting group leads to **95**. All of the $A^{1,3}$, $A^{1,2}$, and 1,3-diaxial interactions and the stereoelectronic interactions of the chair-like transition state must be considered.

An enantioselective alternative exists in which the chirality of the substrate is transferred with an excellent enantiomeric excess to the emerging stereocenter of the final product with retention of configuration, as illustrated by the conversion of **96** into **97** (Scheme 27).

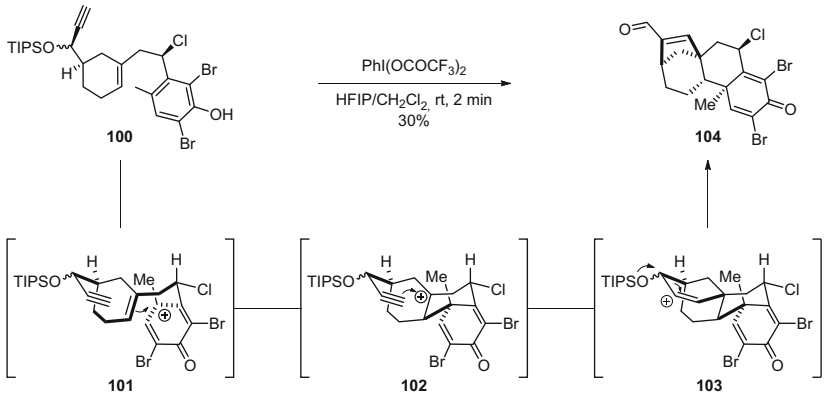
The process was extended to acetylenic compounds **98**, producing polyfunctionalized spiro-cyclopentenes **99** (Scheme 28) [23]. The absence of $A^{1,3}$ interactions allows the presence of substituents in position 2. As previously observed, the presence of a bromine atom in the *ortho*-position considerably increases the yield of the transformation.



Scheme 27 Formation of a quaternary carbon center with retention of configuration



Scheme 28 Synthesis of dienones **99** via Prins-pinacol transposition



Scheme 29 Tandem polycyclization-pinacol process

4.3 Tandem Polycyclization-Pinacol Process

A tandem polycyclization-Pinacol process has been developed using a similar strategy as described above. As shown in Scheme 29, the polyfunctionalized phenol **100** is transformed into the compound **104** when treated with [bis(trifluoroacetoxy) iodo]benzene in a mixture of hexafluoroisopropanol and dichloromethane [25]. The reaction occurs through a succession of chair-like transition states, in which the phenoxenium ion **101** is first trapped by the endocyclic alkene to deliver the intermediate **102**, which then reacts with the alkyne to produce cation **103**. The process concludes with a pinacol-like ring contraction. The presence of a chlorine

atom at the benzylic position appears to be important in controlling the stereoselectivity of this process. Indeed, by assuming an equatorial position, the chlorine atom forces the lateral chain to react on the top face as depicted in Scheme 29 and thus guides the entire cascade. It should be stressed that all of the asymmetric centers generated are stereocontrolled and the overall polycyclization occurs in a stereoselective fashion to produce enantiopure **104**. The resulting compact polyfunctionalized tetracyclic scaffold represents the main core of the kaurane family of alkaloids.

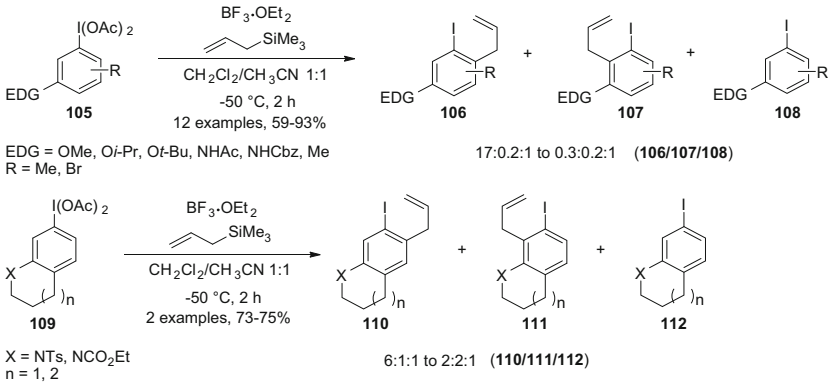
5 Other Rearrangements

The reaction of (diacetoxy)aryl-λ^3-iodanes **105** with (trimethyl)allylsilane in the presence of $BF_3{\cdot}Et_2O$ results in an iodonio-Claisen rearrangement yielding *ortho*-allyliodoarenes **106** as the major product and **107** and **108** as byproducts (Scheme 30) [26]. Two heterocyclic examples have also been reported. The presence of an electron-donating group in the *meta*-position appears to be necessary for this transformation.

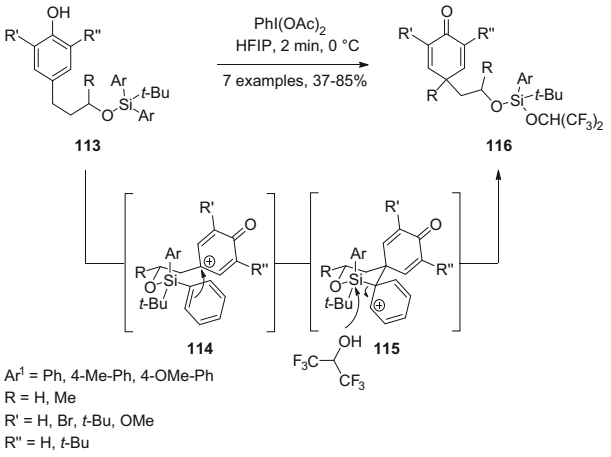
The *ipso*-rearrangement of arylsilanes can be triggered by dearomatization. When treated with (diacetoxyiodo)benzene, phenols such as **113** are transformed into dienones **116** as shown in Scheme 31 [27]. During this process, the phenoxenium ion **114** is produced. This is then trapped by the aryl moiety to produce intermediate **115**, and an attack of trifluoro-isopropanol on the silicon atom induces the rearomatization.

The process may be extended to *N*-sulfonyl anilines, as illustrated by the conversion of the substrate **117** into the bicyclic enone **119** as shown in Scheme 32 [27].

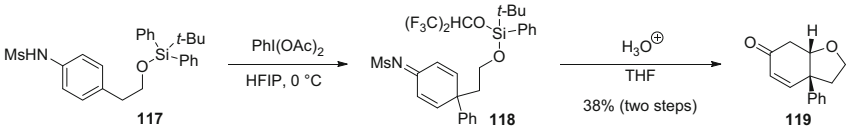
2-Substituted *N*-phenylbenzamides **120** are converted into ureas **124** by reaction with (diacetoxyiodo)benzene as shown in Scheme 33 [28]. The first step is the activation of the secondary amide, leading to the iodane compound **121**.



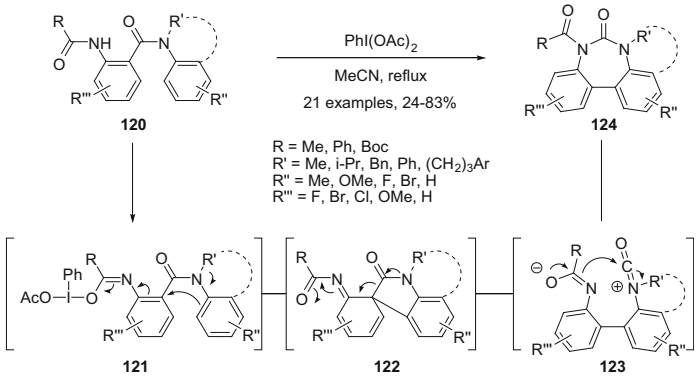
Scheme 30 Formation of iodoarenes via iodonio-Claisen rearrangement



Scheme 31 Dienone **116** formation via *ipso*-rearrangement



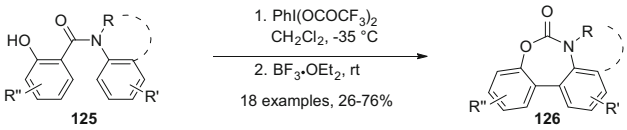
Scheme 32 Enone **119** formation via *ipso*-rearrangement



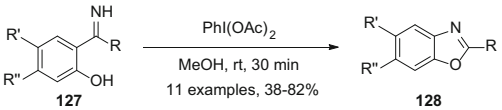
Scheme 33 Urea derivatives **124** via an oxidative tandem aryl-aryl coupling/rearrangement process

A Friedel–Crafts-like process yielding indolinone **122** then occurs. The latter subsequently rearomatizes to produce intermediate **123**, which finally undergoes an intramolecular lactamization to produce urea **124**.

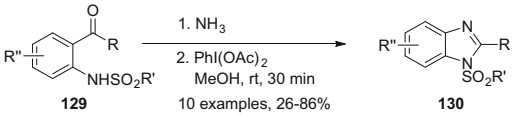
This noteworthy strategy applied to phenols **125** and followed by treatment with BF_3•OEt_2 leads to carbamates **126** (Scheme 34).



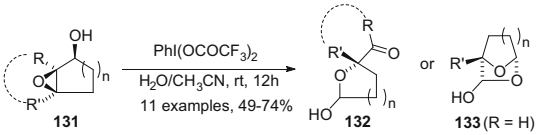
Scheme 34 Carbamates **126** via an oxidative tandem aryl-aryl coupling/rearrangement process



Scheme 35 Formation of benzoxazoles **128** via Beckmann-type rearrangements



Scheme 36 Benzimidazole **130** formation via Beckmann-type rearrangement



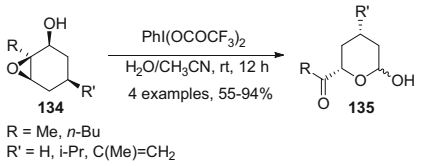
Scheme 37 Formation of lactols **132** and **133** via domino reaction

It has also been demonstrated that *o*-hydroxyaryl-ketimines **127** undergo an iodine(III)-mediated Beckmann-type rearrangement to produce benzoxazoles **128** as outlined in Scheme 35 [29].

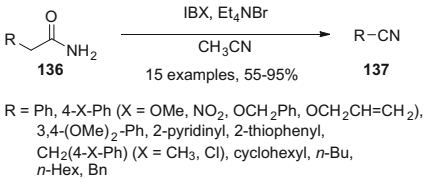
The same strategy was used in the synthesis of *o*-aminoaryl-ketimines **129** leading to *N*-sulfonyl-benzimidazoles **130** (Scheme 36).

[Bis(trifluoroacetoxy)iodo]benzene can initiate the rearrangement of a 2,3-epoxy-1-alcohols of type **131** into lactols **132** as shown in Scheme 37 [30, 31]. With R = H, the reaction leads to lactol **133**.

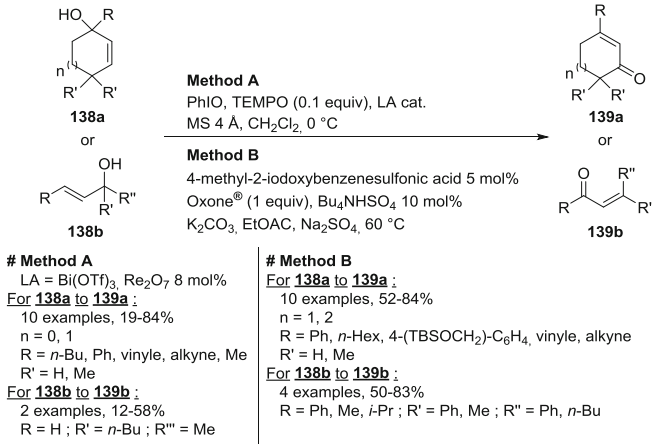
The same strategy also served to transform 2-substituted-2,3-epoxy-1-alcohols **134** into lactols **135** (Scheme 38) [31].



Scheme 38 Lactol **135** formation via domino reaction



Scheme 39 Cyanide **137** via Hofmann-type rearrangement with IBX



Scheme 40 Rearrangements of tertiary alcohols **138a** and **139b**

6 Rearrangements Using Iodine(V) Reagents

The rearrangements described in parts 2–5 involve iodine(III) reagents which can be obtained commercially or prepared in situ in a catalytic fashion. However, some authors have described rearrangements promoted by an iodine(V) oxidant. For example, when reacted with IBX in the presence of Et_4NBr, amides **136** undergo a Hofmann-type rearrangement to produce cyanides **137** (Scheme 39) [32].

Tertiary alcohols **138a** and **138b** can be rearranged to form enones **139a** and **139b** (Scheme 40). The transformations are performed either by IBX in the presence of a catalytic amount of TEMPO and a Lewis acid (Method A) [33] or

by 4-methyl-2-iodoxybenzenesulfonic acid in the presence of Oxone® and Bu_4NHSO_4 (Method B) [34].

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Asymmetric Synthesis with Hypervalent Iodine Reagents

Ravi Kumar and Thomas Wirth

Abstract This chapter describes recent developments in stereoselective synthesis using hypervalent iodine reagents.

Keywords Hypervalent iodine · Stereoselective reactions

Contents

1 Introduction

Hypervalent iodine compounds have attracted much attention in recent years because of their unique characteristic properties to promote unprecedented and versatile reactions under mild reaction conditions. Their potential as reagents in asymmetric and even catalytic oxidative protocols has been established over the last decade. This area has been reviewed from different points of view (for recent

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reviews, see [1–11]). The astounding progress and developments made in asymmetric synthesis with hypervalent iodine compounds are discussed in this review.

2 Asymmetric Synthesis with Hypervalent Iodine Compounds

The first ever chiral hypervalent iodine compound, diphenyliodonium tartrate, was reported in 1907 by Pribram [12]. However, the use of hypervalent iodine compounds in asymmetric synthesis has only been explored over the last decade. Access to asymmetric reactions can be obtained either through the use of chiral hypervalent iodine reagents or by using achiral hypervalent iodine compounds in combination with chiral ligands. Hypervalent iodine compounds are utilized in these reactions either in stoichiometric amounts or as catalysts. Various asymmetric transformations are achieved with moderate to excellent enantioselectivity with these reagents. This review is divided into different sections based on the type of transformations involved:

1. α-Functionalization of carbonyl compounds
2. Alkene functionalization
3. Phenolic oxidation
4. Oxidation of sulfides to sulfoxides
5. Rearrangement reactions
6. Heterocyclization reactions

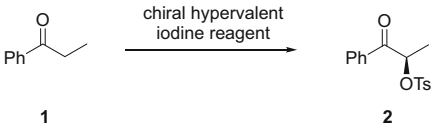
2.1 α-Functionalization of Carbonyl Compounds

Carbonyl oxidation with hypervalent iodine reagents involves the functionalization of the α-position of carbonyl compounds through the intermediacy of a hypervalent iodine enolate species. This electrophilic intermediate may be attacked by a variety of nucleophiles or undergo rearrangement or elimination [13]. Enantiomerically pure, α-substituted carbonyl compounds represent a family of derivatives important in nearly all fields of organic chemistry [14].

2.1.1 Carbon–Heteroatom Bond Formation

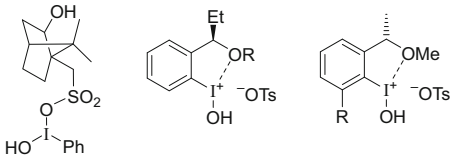
The functionalization of carbonyl compounds at the α-position represents one of the typical reactions of [hydroxy(organosulfonyloxy)iodo]arenes. As shown in Scheme 1, these reagents can be used for the α-oxytosylation of ketones such as propiophenone **1** and obtain product **2**. Encouraged by Koser's model [15, 16], Varvoglis et al. investigated the attachment of a chiral moiety to the hypervalent iodine reagent **3** (Fig. 1) [17]. This reagent **3** reacts with ketones to afford the oxysulfonylation products with good regioselectivity using non-symmetrical ketones, albeit with low stereoselectivity for all the cases investigated.

Scheme 1 Asymmetric α-oxytosylation reaction



1 **2**

Fig. 1 Chiral hypervalent iodine reagents **3–5**



3 **4** **5a** (R = OMe)
5b (R = Et)

A major development in this area was achieved by the introduction of new chiral hypervalent iodine reagents **4** and **5** (Fig. 1) [18–20]. High stereoselectivity in chiral selenium-mediated alkene oxidations, in which the selenium cation is coordinated to the oxygen atom, turned out to be the guiding concept for the development of these reagents [21, 22]. With chiral iodine(III) reagent **4** (Fig. 1), the enantioselectivity of the oxytosylation of propiophenone as shown in Scheme 1 could be improved [19]. A series of *ortho*-substituted chiral iodine(III) derivatives **5** were evaluated as stereoselective electrophilic reagents in the α-oxytosylation reaction. After optimizing the substituents in the chiral moiety and the stereoelectronic properties of the reagents **5**, as well as the reaction conditions, the product **2** was obtained with up to 40% *ee* (using **5b**) [20].

Enantioselective α-oxytosylation reactions are not limited only to the stoichiometric use of chiral iodine(III) reagents. Catalytic amounts of enantiomerically pure iodoarenes in the presence of *m*CPBA as stoichiometric oxidant with *para*-toluene sulfonic acid also gave promising results [23]. Enantiopure iodoarenes with very different structural features were optimized to afford the desired α-oxytosylated products in moderate to good enantioselectivity. A series of chiral ethers and esters were evaluated as a new class of chiral iodine catalysts [24, 25]. Promising enantioselectivities were observed using catalysts **6** (**2**: 27% *ee*), **7** (**2**: 39% *ee*) and **8** (**2**: 26% *ee*) in the α-oxytosylation of propiophenone (Fig. 2). A further enhancement of the enantiomeric excess in such reactions was highlighted by the use of 3,3′-diiodo-BINOL-fused maleimides **9**. These compounds were found to be the most efficient catalysts, leading to the formation of oxytosylated product **2** in up to 46% *ee* when used together with 1.5 equiv. of *m*CPBA and *para*-toluene sulfonic acid [26].

Chiral aryl iodides containing norephedrine or pseudo-ephedrine moieties such as **10** [27], chiral iodooxazoline catalyst **11** [28] and the spirobiindane scaffold **12** [29] were also proven to have potential towards catalytic asymmetric α-oxytosylation reactions. The best results obtained in terms of enantioselectivity of product **2** using these chiral iodine catalysts are 18% *ee* (with **10**), 48% *ee* (with **11**) and 53% *ee* (with **12**) (Fig. 3).

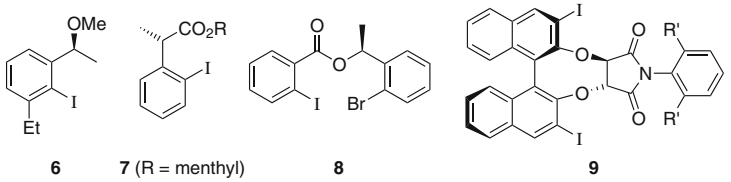


Fig. 2 Pre-catalysts **6–9** used for α-oxytosylation reactions

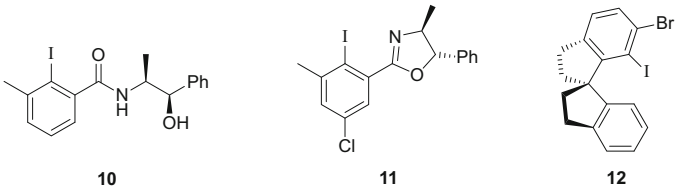
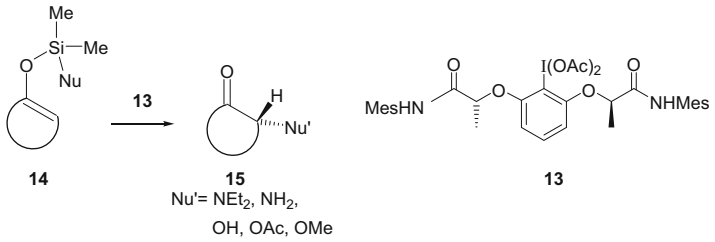


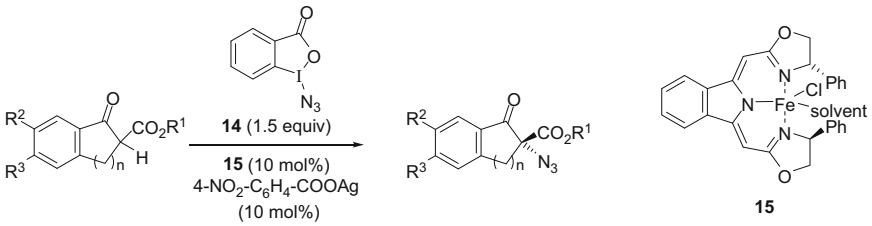
Fig. 3 Chiral aryl iodides **10–12**



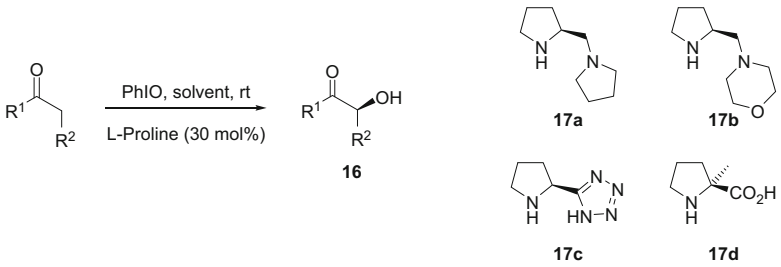
Scheme 2 Asymmetric O- and N-substitution of ketones developed by Wirth et al

Asymmetric carbon–heteroatom bond formation involving different oxygen and nitrogen nucleophiles was further rationalized using chiral hypervalent iodine reagent **13**. This asymmetric α-functionalization of carbonyl derivatives includes the concept of 'silyl temporary tethers'. The strategy developed herein allows rapid access to nitrogen- and oxygen-substituted ketones of type **15** from enol ethers **14** in a simple operation with up to 94% *ee* (Scheme 2). These findings allow novel retrosynthetic planning and a rapid assembly of structures previously accessible only by multistep sequences [30].

Hypervalent iodine reagents show excellent compatibility with organocatalysts which is demonstrated in different examples. A productive merger of iodine reagents in combination with metal catalysts and organocatalysts allowed excellent results for α-functionalizations. Gade et al. exploited this multicatalysis approach for the asymmetric azidation of β-ketoesters and 3-aryloxindoles using iodine(III) compound **14** (Scheme 3) [31]. The azidation of β-ketoesters was performed using catalytic amounts of the iron(II) chloride complex **15** and silver carboxylate as shown in Scheme 3, yielding the products in up to 93% *ee*.



Scheme 3 Enantioselective α-azidation via productive merger of iodine(III) reagents with iron catalysts

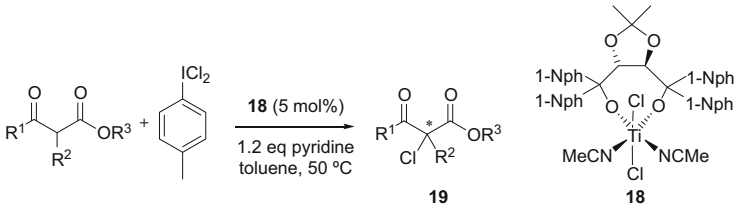


Scheme 4 Proline-catalyzed α-hydroxylation reaction

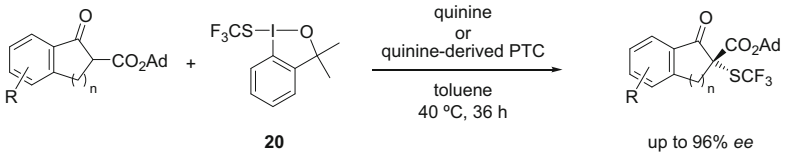
Amino acids can catalyze the biomimetic asymmetric α-oxidation of aldehydes and ketones [32, 33]. The direct proline-catalyzed asymmetric α-oxidation of ketones with iodosobenzene as stoichiometric oxidant yielded the corresponding α-hydroxylated products **16** with up to 77% *ee* [34]. Diamines **17a–d** can also be used to catalyze this transformation, albeit with moderate yields and enantioselectivities up to 63% (Scheme 4).

Catalytic asymmetric halogenation reactions are still rarely studied. Togni et al. developed the efficiency of [Ti(TADDOLato)] complexes **18** in combination with the fluorinating agent Selectfluor^{TM} in the catalytic fluorination of β-ketoesters. In 2004, this group executed the asymmetric chlorination of β-ketoesters using titanium complexes **18** with (dichloroiodo)toluene to generate enantiomerically enriched α-chlorinated products **19** (Scheme 5) [35].

The incorporation of a thiotrifluoromethyl (SCF_3) group into small molecules is of great interest to the pharmaceutical and agrochemical industries. The preparation of the electrophilic thiotrifluoromethylated hypervalent iodine reagent **20**, which was found to be quite stable in many solvents, even at elevated temperatures, was achieved by the Shen group. The authors reported the use of reagent **20** in combination with quinine or quinine-based phase transfer catalysts (PTC) in the enantioselective thiotrifluoromethylation of β-ketoesters as shown in Scheme 6 [36].



Scheme 5 Catalytic asymmetric chlorination of β-ketoesters

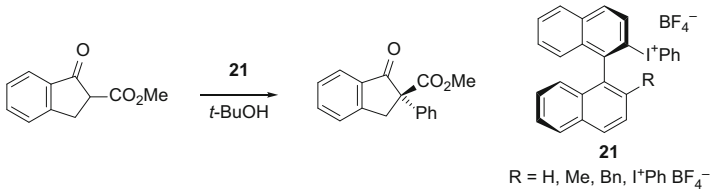


Scheme 6 Thiotrifluoromethylation reaction reported by Shen et al

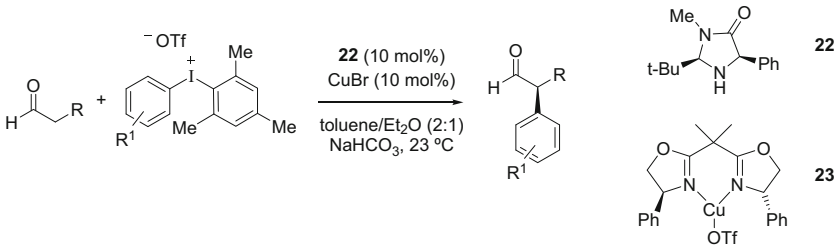
2.1.2 Carbon–Carbon Bond Formation

Stereoselective carbon–carbon bond formations with hypervalent iodine reagents are also prominently described in the literature. Direct asymmetric α-arylation reactions are not easy to perform. Ochiai et al. synthesized chiral diaryliodonium salts such as [1,1′-binaphthalen]-2-yl(phenyl)iodonium tetrafluoroborate derivatives **21** via a BF_3-catalyzed tin-λ^3-iodane exchange reaction and developed the direct asymmetric α-phenylation of enolate anions derived from cyclic β-ketoesters (Scheme 7) [37]. A beautiful example of direct asymmetric α-arylation of cyclohexanones in the course of a natural product synthesis was presented through the desymmetrization of 4-substituted cyclohexanones using Simpkin's base, followed by coupling with diaryliodonium salts [38]. Other binaphthyl iodonium salts related to **21** have also been reported [39].

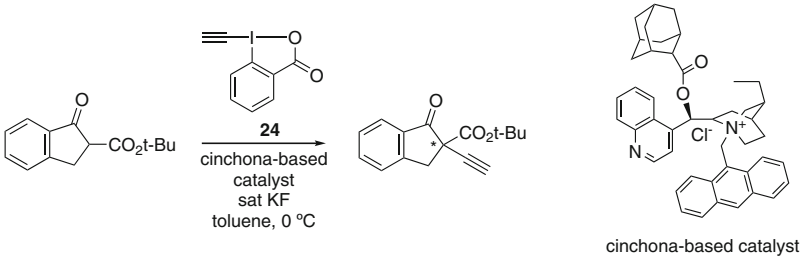
As already discussed, a productive merger of hypervalent iodine reagents with metal catalysts and organocatalysts gave interesting results in enantioselective transformations. Diaryliodonium salts in combination with copper catalysts and organocatalysts such as **22** were utilized to arylate enantioselectively a wide range of aldehyde derivatives (Scheme 8) [40]. Excellent enantioselectivity was also realized by using chiral copper catalyst **23** containing a bisoxazoline ligand in α-arylation reactions of *N*-acyloxazolidinones [41, 42]. Furthermore, scandium (III) complexes of chiral *N*,*N*′-dioxides bearing tetrahydroisoquinoline backbones were found appropriate for N-unprotected 3-substituted oxindoles (up to 99% *ee* and 99% chemical yield) [43]. The synergistic combination of iodine reagents with organocatalysts and metal catalysts is not restricted to arylation reactions and was found useful in the enantioselective α-trifluoromethylation of aldehydes [44], β-ketoesters [45] and in α-vinylation reactions [46].



Scheme 7 Direct asymmetric α-arylation using chiral diaryliodonium salts **21**



Scheme 8 α-Arylation of aldehydes using diaryliodonium salts with copper catalysts

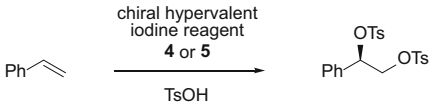


Scheme 9 Cinchona-based catalysis for enantioselective α-ethynylations

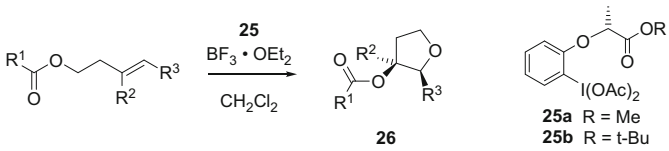
Enantioselective organocatalytic α-ethynylation reaction of β-ketoesters was investigated by Waser et al. through benziodoxolone-mediated cinchona-based catalysis using reagent **24** (Scheme 9) [47]. The products were obtained in up to 40% *ee*. The Vesely group explored a similar cinchona-based catalytic approach towards the asymmetric α-alkynylation of nucleophilic fluorocarbons [48].

2.2 *Alkene Functionalization*

Alkene substrates on oxidation with hypervalent iodine reagents allow various transformations depending on their structure and on the reaction conditions. Some of these reactions using chiral hypervalent iodine reagent are reported to be stereoselective. As described earlier, the Wirth group developed new chiral



Scheme 10 Dioxytosylation reactions of styrene



Scheme 11 Intramolecular oxygenation of but-3-enyl carboxylates developed by Fujita et al

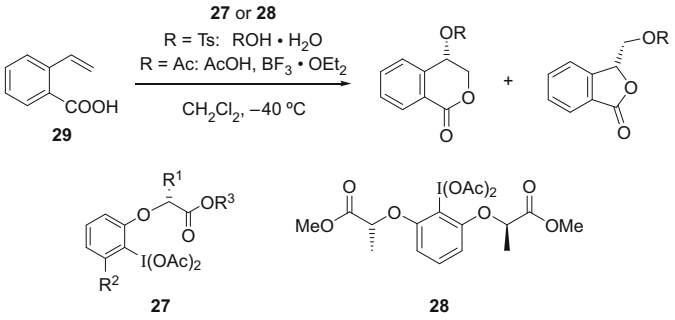
hypervalent iodine(III) reagents **4** and **5** for α-oxytosylations [18, 20–22]. Reaction of these reagents with styrene also gave promising results, leading to the formation of dioxytosylated products with enantioselectivities up to 65% (Scheme 10).

The stereoselective construction of substituted tetrahydrofurans as enantiomerically pure form is of great interest because many biologically active compounds have such oxygen heterocycles. Fujita et al. developed the synthesis of tetrahydrofuran-3-yl carboxylates **26** via intramolecular oxygenation of but-3-enyl carboxylates using lactic acid-derived chiral λ^3-iodanes **25** (Scheme 11) [49, 50]. The *endo*-selectivity achieved in this case contrasts with the *exo*-selectivity observed in the reaction with conventional oxidizing reagents. The products **26** are obtained in up to 64% *ee*.

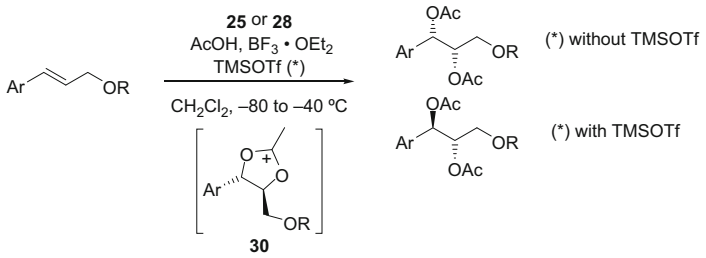
Further elaboration of this reaction principle using substrates such as 2-ethenylbenzoic acid **29** and methyl *ortho*-alkenylbenzoates provided enantiodifferentiating *endo*-selective oxylactonizations after oxidation with chiral iodine reagents **27** and **28** (Scheme 12) [51, 52]. The protocol developed here was found quite useful in the synthesis of several polyketide metabolites [53, 54]. In addition to the stoichiometric use of iodine(III) reagents, these oxylactonization reactions can also be performed using only a catalytic amount of chiral iodoarenes in presence of *m*CPBA as terminal oxidant [51]. Furthermore, changing the substrates to *ortho*-alkenylbenzamides, the intramolecular oxygenation reaction gave isochroman-1-imines via a sequence of oxidation reactions [55].

An interesting example with a switchover of the stereochemical course was observed during the enantioselective diacetoxylation of alkenes using chiral iodine (III) reagents (Scheme 13) [56]. Enantioselective Prevost and Woodward reaction products were formed through the optically active 1,3-dioxolan-2-yl cation intermediates **30**.

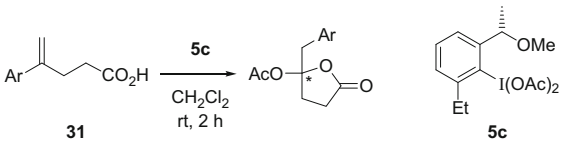
Intramolecular oxygenation reactions were also used in the asymmetric synthesis of different substituted lactone derivatives. Using chiral λ^3-iodane **5c**, lactonization of 4-aryl-4-pentenoic acids **31** gave rearranged lactones through phenonium ion participation in 56% yield, albeit in only 4% *ee* (Scheme 14) [57]. Another example of lactonization involving enantioselective



Scheme 12 *Endo*-selective oxylactonization of 2-ethenylbenzoic acid **29**



Scheme 13 Enantioselective Prevost and Woodward reactions

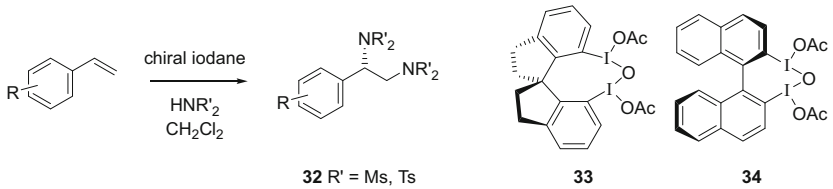


Scheme 14 Lactonization of 4-aryl-4-pentenoic acids **31**

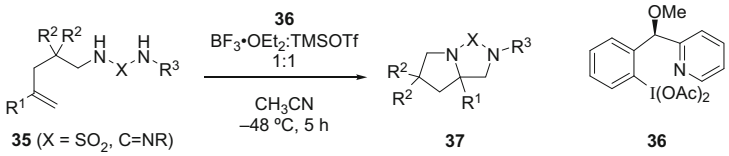
oxytrifluoromethylation of olefinic acids catalysed by copper salts gave moderate enantiomeric ratios [58].

In addition to oxygen nucleophiles, inter- as well as intramolecular asymmetric alkene oxidations using nitrogen nucleophiles were also studied. Direct asymmetric intermolecular diamination reactions using spirocyclic (**33**) [59], lactate-based (**28**) [57] or binaphthyl (**34**) [60] chiral λ^3-iodanes were investigated using different alkene substrates (Scheme 15). The intermolecular diamination reaction works well with a series of alkenes; however, styrenes represent a privileged substrate class with respect to enantioselective induction and reagent **28** was identified as the most suitable for this transformation. The products **32** are obtained in up to 95% *ee* and they can be recrystallized to >99% *ee*.

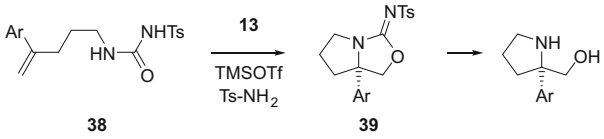
For intramolecular diaminations, a novel chiral hypervalent iodine reagent **36** was successfully synthesized and used in the enantioselective cyclization of guanidine and sulfodiamine derivatives **35** to give cyclized products **37**, which can be



Scheme 15 Intramolecular diaminations reported by Muñiz et al



Scheme 16 Intramolecular diamination of guanidine and sulfodiamines **35**

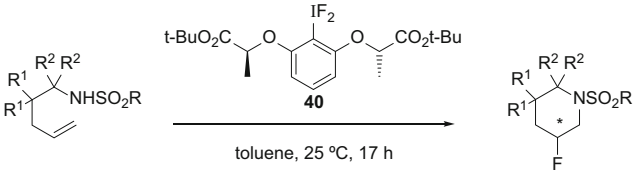


Scheme 17 Enantioselective synthesis of isourea derivatives **39**

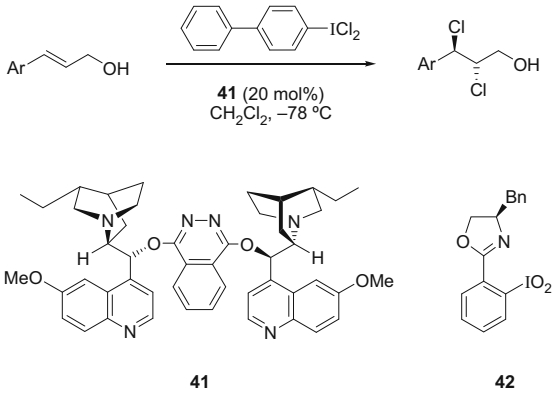
easily reduced to the corresponding diamines (Scheme 16) [61]. This reaction was initially performed using chiral lactate-based iodine(III) reagents, but the cyclized product was only obtained with up to 52% *ee*. The novel hypervalent iodine reagent **36** with an efficient coordination of the pyridine nitrogen to the iodine atom is responsible for selectivities up to 96% *ee*. Cyclizations of *N*-tosylated urea derivatives **38** using chiral λ^3-iodane **13** were also successfully studied for the synthesis of aminoalcohols (up to 96% *ee*) via isourea derivatives **39** (Scheme 17) [62].

A similar approach was used for intramolecular aminofluorination of unactivated olefins mediated by the chiral hypervalent iodine(III) reagent **40** leading to the enantioselective formation of fluorinated piperidine ring derivatives (Scheme 18) [63]. Reagent **40** performs the aminofluorination of pentenamines showing total regioselective control for the 6-*endo* cyclization products in favour of piperidine formation in excellent enantiomeric excesses (up to 81% *ee*, 99% *ee* after recrystallization).

Despite tremendous advances in the development of chiral methods, asymmetric alkene dichlorination remains one of the challenges. This reaction was successfully achieved for *trans*-cinnamyl alcohols as substrates using (dichloroiodo)arenes in combination with dimeric cinchona alkaloid derivatives **41** leading to products with up to 85% *ee* (Scheme 19) [64]. Chiral iodine(V) reagent **42** in combination with pyridine hydrobromide led to the dibromination of β-methylstyrene in only 3% *ee* [65].



Scheme 18 Regioselective 6-*endo* fluorinated cyclisation of pentenamines

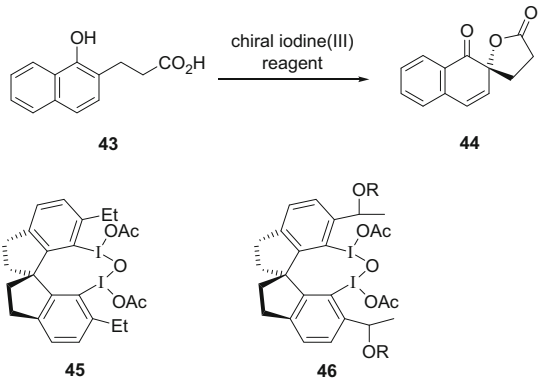


Scheme 19 Asymmetric dichlorination of *trans*-cinnamyl alcohols

2.3 Phenolic Oxidation

Phenolic oxidations are pivotal steps frequently involved in the biosynthesis of natural products, which possess a variety of important biological activities. Therefore, a continuing interest exists in such transformations, in particular in asymmetric oxidative protocols. Kita et al. performed asymmetric dearomatization of naphthols **43** mediated by chiral hypervalent iodine(III) reagents, **33** and **45** having a rigid spirobiindane backbone (Scheme 20) [66, 67]. A series of other *ortho*-functionalized spirobiindane reagents of type **46** were synthesized. Intramolecular oxidative substitution of **43** afforded five-membered spirolactone **44** with good levels of enantioselectivity (up to 92% *ee*). Conformationally flexible iodoarenes employed in this study produced almost racemic products. Catalytic use of these chiral catalysts with *m*CPBA as cooxidant afforded the chiral spirolactones without detrimental effects on the *ee* values.

Further advancements in the Kita oxidative spirolactonization of naphthols were explored by Ishihara et al. using catalytic amounts of rationally-designed conformationally flexible C_2-symmetric iodoarenes **47** and **48** (Fig. 4) [68–70]. The iodine (III) reagents, generated in situ, were expected to exhibit intramolecular either n to σ* interactions between the electron-deficient iodine(III) center and the Lewis-basic group or intramolecular hydrogen bonding interaction between the acidic hydrogen and the ligand which should allow a suitable chiral environment to give selectivity in the reaction.



Scheme 20 Enantioselective oxidative dearomatisation of naphthols **43** developed by Kita et al

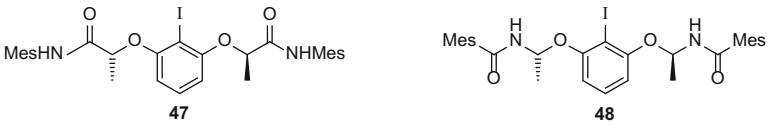
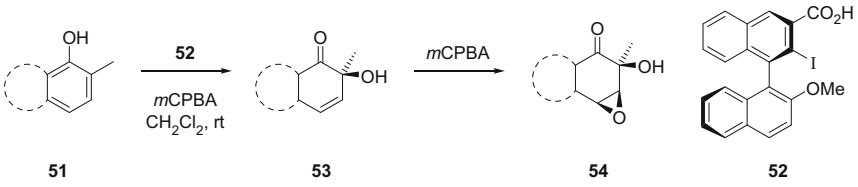


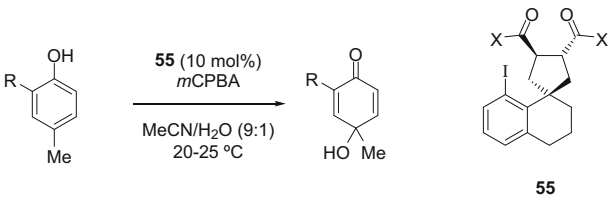
Fig. 4 C_2-symmetric iodoarenes **47** and **48**

Scheme 21 Diels–Alder dimerisations of alkylphenols **49**



Scheme 22 Asymmetric hydroxylative phenol dearomatization

The oxidation of *ortho*-alkylphenols **49** with iodine(V) derivatives of type **42** containing chiral oxazoline moieties led to asymmetric [4+2] Diels–Alder dimerizations. The *ortho*-alkylphenols **49** were transformed into *ortho*-quinol dimers **50** with significant levels of asymmetric induction (up to 77% *ee*) (Scheme 21) [71]. Similar substrates **51** were subjected to hydroxylative phenol dearomatization to give *ortho*-quinol products **53** (Scheme 22) [72]. The protocol was devised making use of the chiral iodoarene **52** in combination with *m*CPBA; however, an



Scheme 23 Stereoselective phenolic dearomatization using chiral aryl iodide catalysts **55**

excessive use of the cooxidant in this reaction afforded directly the epoxide product **54** in up to 91% yield.

New chiral aryl iodide catalysts **55** were prepared by Harnerd et al. for assessing the stereoselective phenolic dearomatization. Catalysts **55** derived from 8-iodotetralone and tartaric acid could be used to synthesize enantioenriched *para*-quinols (up to 60% *ee*) from phenols as shown in Scheme 23 [73].

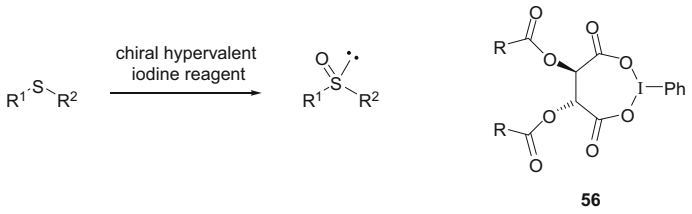
2.4 Oxidation of Sulfides to Sulfoxides

Chiral sulfoxides find immense use, reflecting a wide interest in both convenient auxiliaries in asymmetric synthesis and products with biological properties containing a chiral sulfinyl group. Since the pivotal report of Imamoto and Koto [74], who discovered that chiral hypervalent iodine reagents of the suggested structure **56** are capable of asymmetrically oxidizing prochiral sulfides to sulfoxides, other research groups have also emphasized the utilization of chiral iodine reagents towards these transformations. Imamoto and coworkers generated chiral iodine(III) reagents **56** in situ by the reaction of iodosylbenzene and different L-tartaric anhydrides and realized the asymmetric oxidation of sulfides (Scheme 24).

Despite the potential of chiral iodinanes, asymmetric synthesis using these reagents was rarely explored until 1990. Preparation of chiral iodinanes **57** (Fig. 5) by ligand exchange reaction between menthol and Koser's reagent [PhI(OH)OTs] was found quite useful for achieving asymmetric sulfide oxidation [75]. Chiral λ^3-iodane **1**, used by Varvoglis et al. to assess asymmetric α-oxysulfonylation of carbonyl compounds, also gave good results in the sulfide oxidation.

Reactions of chiral λ^5-iodanes, amino acid-derived benziodazole oxides **58** [76], (*S*)-proline based reagents **59** [77], and iodylarenes **60** bearing ester motives [78] with non-symmetric sulfides to give asymmetric sulfoxide formation further recognized the importance of such transformations.

Not only do chiral hypervalent iodine reagents have the potential for such conversions, achiral iodanes in combination with chiral auxiliaries can also be used in asymmetric oxidative protocols. The Kita group performed the controlled oxidation of sulfides to sulfoxides using iodoxybenzene ($PhIO_2$) in a cationic reversed micellar system. High chemical yields and good stereoselectivities



Scheme 24 Asymmetric oxidation of sulfides to sulfoxides

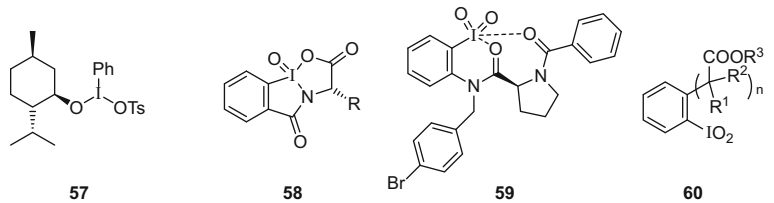


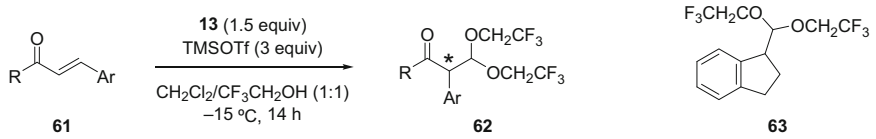
Fig. 5 Structures of chiral iodine reagents **57–60**

(up to 72% *ee*) were achieved by employing a catalytic amount of cetyltrimethylammonium bromide (CTAB) and a tartaric acid-based chiral source [79]. The solubilization and activation of $PhIO_2$ was achieved by adding catalytic amounts of CTAB and the tartaric acid derivative. In a similar approach, the use of water and catalytic amounts of magnesium bromide for sulfoxide formation was investigated, although with only moderate enantioselectivities [80].

SIBX is a non-explosive formulation of the λ^5-iodane 2-iodoxybenzoic acid (IBX) stabilized by benzoic acid. This reagent combination can be used as a suspension in various organic solvents to oxidize sulfides to sulfoxides. Most yields were comparable to those obtained using IBX or other iodanes such as PhIO and $PhIO_2$. The use of a chiral tartaric acid-based source in addition to SIBX gave asymmetric sulfoxide formation with moderate enantioselectivities [81].

2.5 Rearrangement Reactions

The nature of hypervalent iodine(III) compounds to react as electrophiles and then act as excellent leaving groups makes them highly suitable reagents for generating cationic intermediates, which can either react directly with nucleophiles or lead to rearranged products under ring expansion, ring contraction, or aryl migration. The Wirth group published a seminal report on the stereoselective rearrangements of chalcones **61** with high enantioselectivities mediated by chiral hypervalent iodine reagents **13** (Scheme 25) [82]. The enantioselectivity of this transformation was closely related to the choice of the solvent and Lewis acid employed. Under optimal reaction conditions, the stereoselective rearrangement to **62** was observed in



Scheme 25 Stereoselective rearrangement of chalcones **61**

enantioselectivities of up to 97%. A first enantioselective ring contraction of dihydronaphthalene was also performed using this method to afford indene acetal **63** with up to 70% enantiomeric excess.

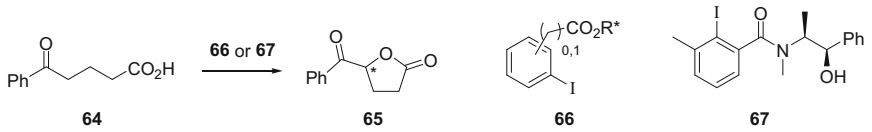
2.6 Heterocyclization Reactions

The enantioselective lactonization of 5-oxo-5-phenylpentanoic acids **64** was studied using chiral λ^3-iodanes **66** to yield 5-benzoyldihydrofuran-2(3*H*)-ones **65**, albeit with low *ee* values (Scheme 26) [83]. Scope of this asymmetric lactonization process was further studied by employing other chiral aryl iodides such as **67** [84].

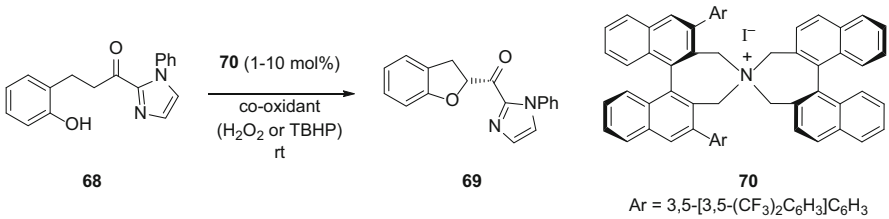
The optically active 2-acyl-2,3-dihydrobenzofuran skeleton is a key structure in several biologically active compounds. The asymmetric oxidation of ketophenols **68**, catalyzed by in situ generated chiral quaternary ammonium (hypo)iodite salts **70**, with hydrogen peroxide as cooxidant, opened up a new enantioselective, metal-free route to 2-acyl-2,3-dihydrobenzofurans **69** (Scheme 27) [85]. The substituents at the 3,3′-positions of the binaphthyl moiety of the salt **70** played an important role in the enantioselectivity as well as in the chemical yield of the reaction. The products are formed in up to 96% *ee*.

Aziridines are key structural motifs present in natural products such as mitomycins and azinomycins and versatile building blocks which can undergo various useful transformations. Hypervalent iodine-mediated intramolecular aziridinations of allylic carbamates and reaction of *N*-tosyliminophenyliodinane (PhI = NTs) with double bonds have been reported to be efficient and practical routes to access these three-membered rings. Allylic carbamates **71** undergo enantioselective aziridine formation on oxidation with chiral binaphthyl hypervalent iodine compound **72** (Scheme 28) [86].

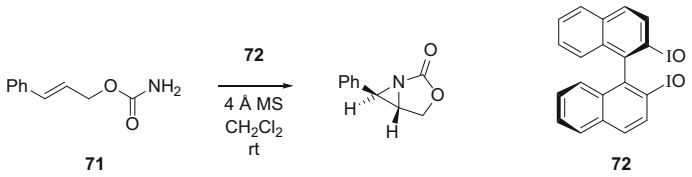
Reactions of *N*-tosyliminophenyliodinanes (PhI=NTs) as nitrene source with alkenes in the presence of chiral ligands also present a valuable method to achieve asymmetric aziridination reactions. Cinnamate esters **73** yield enantiomeric aziridinate products in good selectivities on reaction with chiral bisoxazolines **23** and *N*-tosyliminophenyliodinanes in the presence of copper salts (Scheme 29) [87]. Biaryl Schiff bases **74** can also be used as ligands in the enantioselective aziridination of cinnamate esters, chromenes and styrenes [88]. Chiral C_2-symmetric salen-type ligands **75** were also found to be highly effective for the



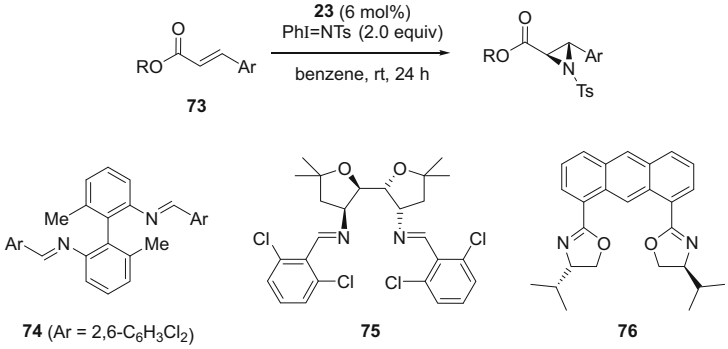
Scheme 26 Enantioselective lactonization of 5-oxo-5-phenylpentanoic acid **64**



Scheme 27 Chiral quaternary ammonium (hypo)iodite salt-mediated asymmetric oxidation of ketophenols **68**



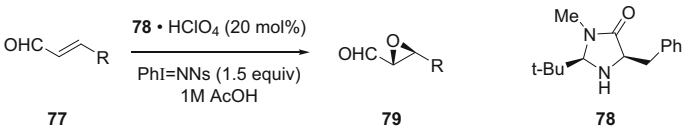
Scheme 28 Intramolecular aziridination of allylic carbamates **71**



Scheme 29 Stereoselective aziridination of cinnamate esters **73**

enantioselective control of the copper-catalyzed asymmetric aziridination of cinnamate esters [89].

Copper complexes of bisoxazoline ligands [90] such as **76** with a more rigid structure and other optimized bisoxazoline ligands [91] can asymmetrically aziridinate chalcone substrates with high enantioselectivities.



Scheme 30 Organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes **77**

Epoxides can also be accessed asymmetrically using hypervalent iodine reagents in combination with imidazolidinone catalysts **78** (Scheme 30). The methodology developed by MacMillan et al. includes participation of hypervalent iodine reagent in a 1,4-heteroconjugate addition reaction for the organocatalytic, asymmetric epoxidation of α,β-unsaturated aldehydes **77**. This organocatalytic reaction allows for the enantioselective formation of epoxides **78** from a wide array of electronically and sterically diverse α,β-unsaturated aldehydes [92].

3 Outlook

This review summarizes important aspects of hypervalent iodine compounds in asymmetric synthesis. Some of the transformations have been achieved with excellent enantioselectivities, thus opening up a new era in this field. Several oxidation reactions such as the functionalization of carbonyls, phenolic oxidation, sulfide oxidation and alkene functionalization have been achieved with good enantiocontrol. Seminal contributions have inspired remarkable subsequent studies, but considerable effort is still needed to enfold new reactivities, develop efficient catalytic asymmetric protocols and further improve the enantiocontrol of these processes. The generation of new families of chiral compounds containing polyvalent iodine atoms can tackle important challenges and their application to other disciplines, such as total synthesis or pharmaceutical chemistry. Furthermore, the search for new chiral ligands which can be utilized in combination with achiral hypervalent iodine reagents can also make significant contributions in this area in the future.

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Organoiodine(III) Reagents as Active Participants and Ligands in Transition Metal-Catalyzed Reactions: Iodosylarenes and (Imino)iodoarenes

John D. Protasiewicz

Abstract This chapter overviews the roles of transition metal complexes having the organoiodine(III) reagents iodosylarenes (ArIO) and (imino)iodoarenes (ArINR) as ligands in catalysis. Mechanistic implications are discussed.

Keywords Atom and group transfer • Catalysis • Hypervalent iodine • Structure • Transition metal complexes

Contents

1 Introduction

1.1 General

Hypervalent organoiodine reagents are diverse and have a rich history [1–7]. As many of these reagents are easily prepared, they are heavily utilized for a variety

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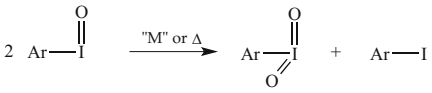
of reactions. In particular, the atoms and groups attached to the hypervalent iodine center can undergo interesting and productive coupling reactions with a large range of substrates. The scope and speed of these reactions can often be greatly expanded when used in conjunction with transition metal catalysts. These catalysts can also afford access to entirely new types of reactivity unavailable to uncatalyzed reactions of hypervalent reagents. For example, impressive advances in palladium- and copper-catalyzed processes for selective oxidation reactions and transfer reactions of phenyl, CF_3, azide, and other groups have recently been made [8–15].

This chapter presents an overview of recent discoveries involving unusual interactions of organoiodine(III) reagents of the form ArI=O and ArI=NTs (Ts=*para*-toluenesulfonyl) with transition metal complexes. These two classes of reagents have drawn considerable attention for their ability to hand off NR and O groups to metals for addition and insertion reactions to organic substrates such as olefins and CH bonds. In a number of cases, metal complexes having appropriate chiral ligands can effect the enantioselective formation of products, and in so doing increase the value of these reactions. During the delivery process and activation of the metal complex, high oxidation state [M=X] (X=NR or O) species are usually implicated as the active oxidizing species. The electronic nature of the M=X functionality has come into question as well. However, over the years, complexes of hypervalent iodine compounds have been suggested on the basis of various spectroscopic techniques, challenging the notion that discrete M=X species are the only viable species capable of selective hydrocarbon oxidations. Although this review is focused on catalytic reactions involving ArI=O and ArI=NTs compounds, hypervalent compounds of the form $ArI{=}CR_2$ (iodonium ylids) are also useful and significant in their own right [16], but are excluded to keep this chapter a reasonable length.

1.2 Organoiodine(III) Chemistry Background

Organoiodine(III) reagents are the most widely used hypervalent organoiodine reagents for transition metal-catalyzed reactions. Organoiodine(III) compounds are usually more reactive and less stable than analogous organoiodine (V) reagents. For example, heat or metal complexes can effect the disproportionation of iodosylbenzenes (1) [17–19]:



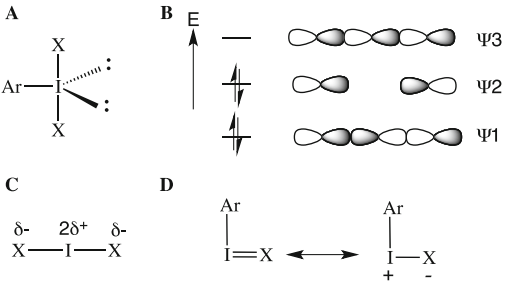
(1)

Readers new to hypervalent iodine chemistry can see that most reagents feature aryl

groups as an "ancillary" ligand (usually Ar=phenyl). Iodobenzene-based iodine (III) reagents keep reagent cost economical, and such reactions generate iodobenzene as a co-product which is easily removed (which can be recovered and recycled if need be). Organoiodine(III) reagents based on simple alkyl groups are usually unstable because they can undergo very facile nucleophilic attack at the carbon atom bearing the electropositive iodine atom.

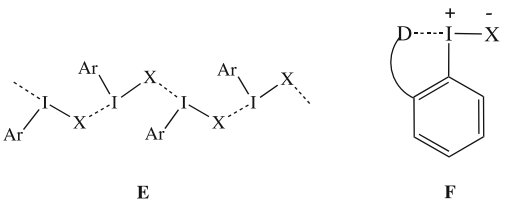
The idealized geometry for hypervalent iodine compounds of the form $ArIX_2$ is based on a T-shape (Scheme 1, **A**). In some compounds, such as diaryliodinium salts, the X group has more ionic character and is thus associated weakly. The bonding along the axial axis, the hypervalent bond, is weaker owing to a 3-center 2-electron bond that results in formal 0.5 bond order for each I–X bond (Scheme 1, **B**). The non-bonding electrons (Ψ2) in this model by necessity are distributed over the two X positions (Scheme 1, **C**). Strongly electron-withdrawing or electron-delocalizing atoms and groups can best accept this added charge and maximize the stability of hypervalent iodine compounds. For compounds of the form ArI=X (X=NR or O), one can draw a double bond (which is often done for convenience), but the more appropriate resonance structure lies more on the side of a single bond with large charge buildup on the I and X atoms (Scheme 1, **D**). For this reason, most of the compounds of the form PhINR have electron-withdrawing groups $R=SO_2R'$ (R'=aryl or CF_3).

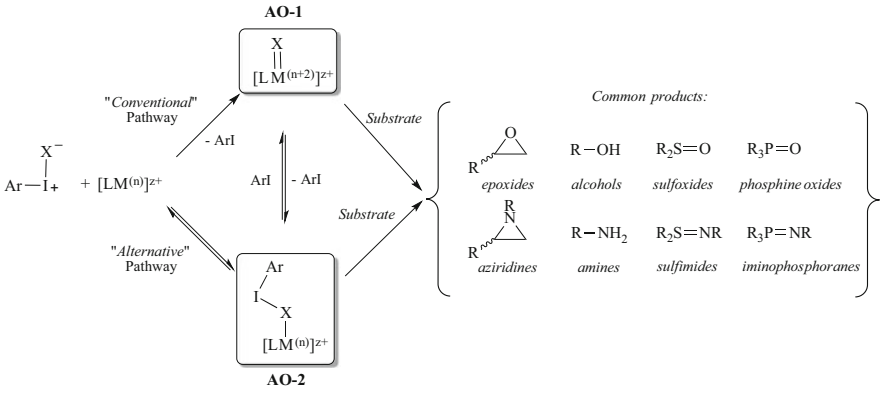
The structures of PhINTs and PhIO are polymeric (Scheme 2, **E**) because of the aggregation of the positive iodine and negative X atoms (I···X secondary bonding). Although no single crystal X-ray structure of PhIO is available, the average I–O/I–C and I···O bonds were estimated at 2.04 and 2.38 Å, respectively [20]. The single crystal structure of PhINTs confirms a related zig-zag polymeric structure with I–N and I···N distances of 2.039(2) and 2.482(2) Å, respectively [21]. The polymers are insoluble in non-reactive organic solvents and, hence, make mechanistic studies of transition metal-catalyzed reactions a challenge. The polymerization of ArIX units can be disrupted by integration of units *ortho* to the iodine atom that can position another electronegative donor atom (**D**) in the *pseudo*-trans position (Scheme 2, **F**) [22]. This strategy has been used successfully to introduce chiral donor ligands around hypervalent iodine centers for generating effective enantioselective reagents for organic synthesis [23, 24].



Scheme 1 Hypervalent bonding and structures

Scheme 2 Secondary bonding and structures



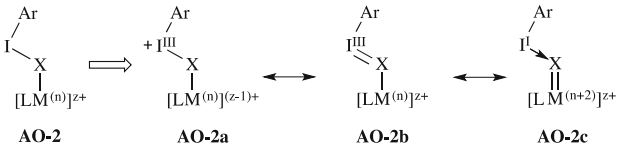


Scheme 3 Possible mechanisms for reactions of ArIX with transition metals

Hypervalent iodine compounds are excellent oxidants, and have been used in a wide range of transition metal-catalyzed processes. The PhIO and PhINTs reagents have enjoyed particular popularity for functionalizing CH bonds and for addition to olefins. Scheme 3 depicts two pathways by which ArI=X might react with a transition metal complex. The exact nature of the metal intermediates has been the subject of much discussion and speculation. It is believed that in the vast majority of these reactions the hypervalent iodine reagent follows a "conventional" pathway whereby the metal complex accepts the O or NTs group to form the active higher oxidation state metal species (active oxidant **AO-1**, Scheme 3). This review does not inventory or discuss "conventional" catalyzed oxidations using PhIO or PhINTs. Early on in the history of iodosylbenzene, however, this conventional view was questioned and "alternative" pathways were considered, involving active oxidants having coordinated hypervalent iodine species (**AO-2**, Scheme 3). This discussion is actually part of a much broader discussion on the nature of transition metal catalysts and active species involving primary oxidants such as hydrogen peroxide, *tert*-butylhydroperoxide, *meta*-chloroperbenzoic acid, etc., where similar intermediates of the form $[L_nM\text{-}O\text{-}Y]$ could be envisioned (Y = OH, O^{t}Bu, etc.). These other oxidants are not covered in this chapter in order to chronicle many of the specific cases where involvement of hypervalent iodine–metal complexes has been proposed and evidence detected. In this chapter we also do not discuss the nature of the multiple bonds between metal and X atoms.

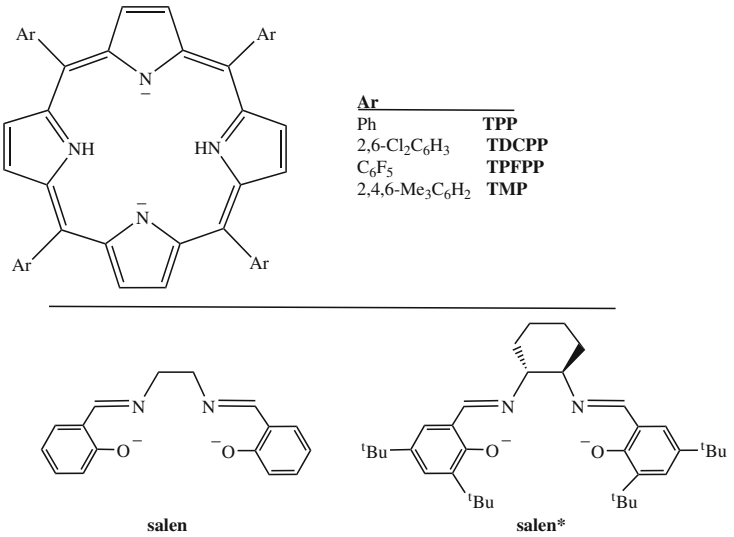
In this survey, the alternative active oxidants are often drawn as shown in Scheme 3 (**AO-2**). However, it is important to recognize that this generic depiction may leave some ambiguity as to the nature of the oxidation state of the iodine atom. Scheme 4 displays a range of possible resonance structures. It should be noted that many catalysts are cationic (or have labile anionic ligands), and that binding of ArIX to cationic metal centers may increase the formal positive charge at iodine (**AO-2a**). Thus, in a number of proposed and determined structures the iodine(III) center has increased its coordination number by the binding of anions such as halides or acetate.

Many of the complexes to be covered have *meso*-tetraarylporphinato and salen-type ligands. For convenience, some of the more common abbreviations and structures are shown in Scheme 5.



AO-2 **AO-2a** **AO-2b** **AO-2c**

Scheme 4 Resonance structures of ArIX adducts with metal complex



salen **salen***

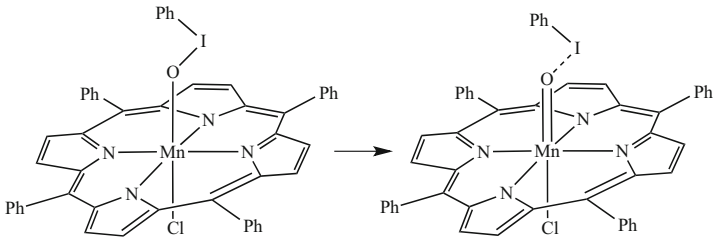
Scheme 5 Ligand structures

2 Intermediates Involving Iodosylarenes as Ligands in Transition Metal-Catalyzed Reactions

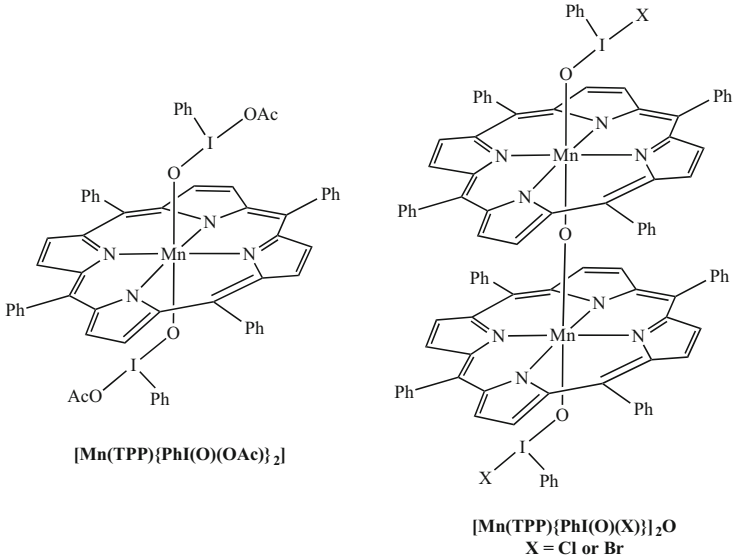
In 1976, two reports appeared describing the use of iodosylbenzene (PhIO) for cytochrome P450-catalyzed oxidations. This discovery quickly caught the attention of the biomimetic community, as researchers sought to understand the mechanisms of oxidations for transition metal containing biological systems. These discoveries also drew the attention of the inorganic community, which sought to model and develop new catalysts, especially those based upon metal porphyrin complexes that could emulate the active site of cytochrome P-450, for the selective oxidation of hydrocarbons [25]. Iodosylbenzene, which is easy to prepare and use, often gave cleaner results than catalytic reactions using other primary oxidants. It thus became one of the preferred reagents and a veritable oxygen atom warehouse in these oxidation reactions. One drawback to this reagent, however, is that its insolubility made careful studies of the reactions difficult under heterogeneous conditions, which in turn hampered identification of the active oxidizing species.

It did not take long after 1976 for suggestions that iodosylbenzene might play a special role in transition metal-catalyzed oxygenation reactions to appear. In 1979, Groves first suggested iodosylbenzene could bind to an iron center, and that such a complex could be considered as an active oxygen atom transfer species [26]. In 1980, Groves also proposed an iodosylbenzene ligand for the black microcrystalline complex isolated from the reaction of iodosylbenzene and [(TPP)MnCl] (TPP=*meso*-tetraphenylporphinato dianion) [27]. Two possible structures (Mn (III) iodosylbenzene and an Mn(V) oxo complex) were considered, as shown in Scheme 6. It was recognized that the structure on the right could be on the pathway to a metal oxo species. This material reacted cleanly with norbornene to produce norbornene oxide, iodobenzene, and [(TPP)MnCl]. Its use as a catalyst for hydrocarbon oxidations with iodosylbenzene was also demonstrated. In the same issue as the above article, Hill reports on the formation and UV–visible spectra of a compound formed by reaction of [(TPP)MnCl] and excess iodosylbenzene also capable of hydrocarbon oxidation [28].

In 1983, a pair of papers from the Hill group reported the isolation of two different types of iodosylbenzene adducts of manganese porphyrin complexes [29, 30]. Reaction of [(TPP)Mn(OAc)$_2$] with 3 equiv. of PhI=O and 6 equiv. of



Scheme 6 Structures of proposed iodosylbenzene complex



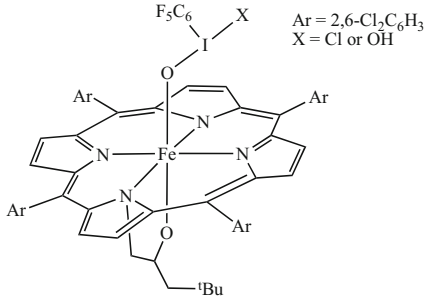
Scheme 7 Structures of proposed iodosylbenzene complexes

glacial acetic acid in chlorobenzene led to a purple paramagnetic microcrystalline compound proposed as [(TPP)Mn{PhI(O)(OAc)}$_2$] (Scheme 7, left). The compound reacted with olefins and hydrocarbons to produce epoxides and alcohols. Reaction of [(TPP)Mn(X)$_2$] (X=Cl or Br) with iodosylbenzene in chlorobenzene also yielded purple complexes, which were formulated as dimeric μ-oxo dimanganese structures, [(TPP)Mn{PhI(O)(X)}]$_2$O (Scheme 7, right). These structures were consistent with the results of UV–vis, IR, NMR spectroscopy and magnetic susceptibility. Subsequent I-127 Mössbauer studies of [(TPP)Mn{PhI(O)(X)}]$_2$O were also consistent with this proposed structure [31].

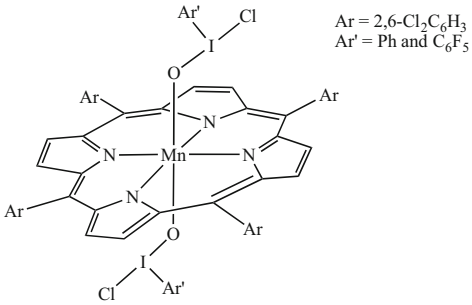
In 1984, Valentine reported that an iodosylbenzene might be capable of bridging two Cu(II) ions via its oxygen atom, and that such a complex might lose PhI to generate an active [Cu^{III}–O–Cu^{III}]$^{4+}$ species [32]. A dicopper complex was later found to react with PhIO to produce a new complex that slowly releases PhI [33]. This adduct, in the presence of excess cyclohexene, yielded significant amounts of the corresponding epoxide.

Following these initial reports, there has been a continuous flow of articles reporting spectroscopically characterized or detected iodosylbenzene complexes. In 1985, Dolphin and Traylor proposed that iodosylpentafluorobenzene (C_6F_5IO) had a possible role in binding to *N*-alkylated iron porphyrins (Scheme 8) [34]. Such species were generated by the action of C_6F_5IO on a mixture of 4,4-dimethyl-1-pentene and [(TDCPP)FeCl] (TDCPP=*meso*-tetrakis(2,6-dichlorophenyl) porphinato dianion). The unstable materials showed ESR spectra that were consistent with ferric complexes.

Scheme 8 Structures of proposed iodosylbenzene complexes



Scheme 9 Structures of proposed iodosylbenzene complexes



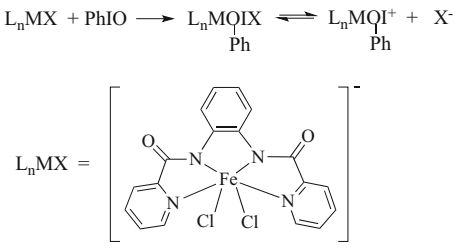
In 1989, Volz reported the isolation of an iodosylbenzene complex of [(TDCPP)MnCl] from the reaction of the components at −78°C (Scheme 9) [35]. The crystalline compound could epoxidize olefins, oxygenate cyclohexane, and oxidize triphenylphosphine. Interestingly, reaction of this material with ammonia led to the formation of the manganese(V) nitrido complex [(TDCPP)Mn≡N]. In 1992, Volz reported details for related C_6F_5IO complexes [36].

In 1990, Valentine reported that redox inactive complexes of zinc, as well as aluminum–porphyrin complex [(TPP)AlCl], could catalyze the epoxidation of olefins by PhIO [37]. The results for [(TPP)AlCl] were later revised when it was discovered that use of ultrapure aluminum yielded no epoxide, and that contamination by traces of iron in the original aluminum complex was likely responsible for catalytic epoxidation [38].

In 1991, Valentine reported the use of an iron complex of the bis(2-pyridinecarboxamido)benzene ligand for epoxidation reactions of olefins using iodosylbenzene [39]. Interestingly, the reaction products were similar to those produced with either $Fe(OTf)_3$ or $Al(OTf)_3$ as catalysts. With this and other data, a mechanism involving electrophilic attack of the olefin by soluble iodine(III)–metal complexes was proposed (Scheme 10) [40].

Later Valentine also reported that olefin epoxidation and hydrocarbon oxidations by iodosylbenzene catalyzed by metal porphyrin and cyclam complexes (metal=Fe, Mn, or Ni) in the presence of excess $H_2{}^{18}O$ showed full incorporation of the ^{18}O label into the product [41]. This finding was in contrast to similar

Scheme 10 Formation of proposed iodosylbenzene adduct



reactions that used other oxygen atom donors, such as hydrogen peroxide, *tert*-butyl hydroperoxide, and *meta*-chloroperbenzoic acid. Solid iodosylbenzene (polymeric) was shown not to exchange ^{18}O in the presence or absence of catalysts, suggesting that the facile exchange of label occurs after iodosylbenzene has dissociated from the insoluble polymer and is coordinated to the metal center.

In 1995, Watanabe and Morishima reported studies on the mechanism of the iron porphyrin epoxidation reactions of norbornylene and α-methylstyrene using peracids [42]. During this work they also noted that competitive epoxidations of these olefins using PhIO and C_6F_5IO gave different results, and it was suggested that the PhIO–Fe complex was an active oxidant.

In 1997, Shim reported that, by switching the X ligand from Cl to ArO (Ar=4-$MeOC_6H_4$ or 4-$^tBuC_6H_4$) in [(TPP)MnX], reactions with iodosylbenzene yielded mononuclear iodosylbenzene complexes, as opposed to the bridging μ-oxo species detailed earlier by Hill [43]. These materials could oxidize cyclohexane and epoxidize styrene. The complexes were characterized by elemental analysis, UV–visible, IR, and ESR spectroscopy.

In 1997, Plattner reported direct evidence for a manganese salen oxo complex [44]. In this work, an acetonitrile solution of [(salen)Mn(MeCN)]ClO_4 was added to a suspension of PhIO in acetonitrile. The electrospray MS results of the mixture showed peaks consistent with oxo complexes of the form $[(salen)Mn(O)]^+$ and $[(salen)Mn(MeCN)(O)]^+$. Peaks corresponding to $[(salen)Mn(O)]^+ \cdot PhIO$ were also seen in low intensity. MS data for the μ-oxo dimer of the form $[(salen)MnOMn(salen)]^{2+} \cdot 2PhIO$ were also obtained. Using in situ ^1H NMR techniques, in 2000, Talsi reported studies of the action of PhIO on [(salen)MnCl] in $CDCl_3$ at reduced temperatures [45]. One of the observed species was assigned as the oxo complex $[(salen)Mn(O)]^+$, and two other species were formulated as related μ-oxo dimers $[L(salen)MnOMn(salen)L']^{n+}$ (L, L′ are PhIO or Cl^-).

In 2000, Collman and Brauman reported on a series of competitive oxidation studies using the P-450 model complex [(TPFPP)FeCl] (TPFPP=*meso*-tetrakis (pentafluorophenyl)porphinato dianion) and iodosylarenes PhIO and C_6F_5IO, as well as (diacetoxyiodo)benzene $PhI(OAc)_2$ [46]. For example, in oxidations of 1:1 mixtures of cyclohexane/d_{12}-cyclohexane catalyzed by [(TPFPP)FeCl], ratios of k_1/k_2 are 5.8 for PhIO and 4.3 for C_6F_5IO as primary oxidants, respectively. This and other data suggest that the active species that transfer oxygen atoms involve metal complexes of the iodosylarenes, probably of the same type of structure as those presented above. In 2000, Nam presented evidence for two distinct reactive

intermediates in iron porphyrin-catalyzed epoxidations [47]. They also suggested that the reason for high selectivity for epoxidation of *cis*- over *trans*-stilbene (15:1) with iodosylbenzene catalyzed by [(TPP)FeCl] was the presence of steric interactions between a ligated PhIO and the incoming olefin.

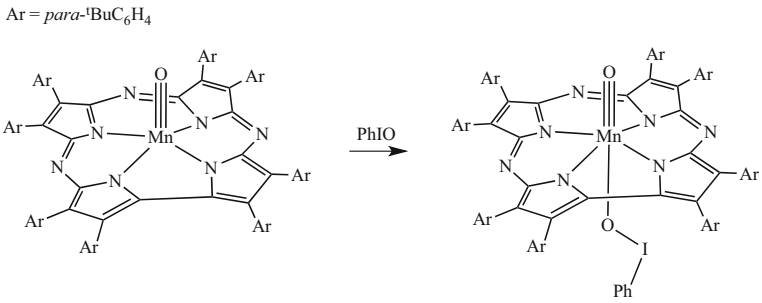
In 2002, Roschmann reported on detailed studies on the epoxidation of *cis*-stilbene by [(salen*)Mn]X complexes (X=Cl or PF_6) that yielded mixtures of *cis*- and *trans*-epoxides [48]. A range of oxygen atom donors were examined, including PhIO and C_6F_5IO. The *cis*:*trans* ratios depended on the identity of both the oxygen atom donor and counterion. They concluded for a range of primary oxidants there is competitive olefin oxidation by Mn oxo and Mn–(oxygen donor) complexes. For the iodosylarenes, the main oxidant appears to be the Mn oxo species. Small differences in *cis*:*trans* ratios between PhIO and C_6F_5IO were attributed to oxidation of Cl^- to OCl^-, as OCl^- can then serve as an oxo donor.

In 2003, Nam and Que reported a very important connecting link between iron oxo complexes and iron iodosylbenzene complexes [49]. Specifically, they were able to establish, by a combination of UV–vis, ESR, and EXAFS spectroscopy, that excess iodobenzene (PhI) can reduce certain oxo iron(IV) porphyrin π-cation radicals to iron(III) porphyrin iodosylbenzene complexes (2) (Porph=TDCPP or TDFPP=*meso*-tetrakis(2,6-difluorophenyl)porphinato dianion). Interestingly, addition of pentafluoroiodobenzene C_6F_5I does not reduce the oxo iron(IV) porphyrin complex, but addition of varying amounts of 1,2-difluoro-4-iodobenzene allows observation of all three species in (2). Also noteworthy is the fact that addition of excess PhI to the analogous oxo iron(IV) porphyrin $[(TMP)^{+\cdot}Fe^{IV}=O]^+$ complex (TMP=*meso*-tetramesitylporphinato dianion) does not result in formation of the iodosylbenzene complex. The TDCPP-iron and TDFPP-iron iodosylbenzene complexes readily epoxidize olefins and undergo rapid oxygen exchange with $H_2{}^{18}O$. This work was expanded upon in a detailed report in 2006 that provided further insights and details of the mechanism [50].

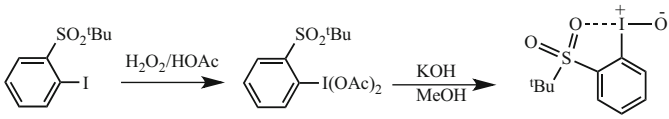
$$\left[(\text{Porph})^{+\cdot}\text{Fe}^{\text{IV}}=\text{O}\right]^+ + \text{ArI} \rightleftharpoons \left[(\text{Porph})\text{Fe}^{\text{III}}\text{-O-IAr}\right]^+ \qquad (2)$$

In 2004, Collman examined the impact of various donor ligands ($Ph_3P=O$, pyridine *N*-oxide and 1-methylimidazole) on the [(salen*)MnX] (X=Cl, BF_4, or OAc) catalyzed epoxidation of olefins [51]. In the presence of some of these donors, the particular iodosylarene (PhIO, C_6F_5IO, or MesIO) chosen made a significant impact on the enantioselectivities of styrene oxide produced. Unlike the previous related study by Roschmann [48], oxidation of Cl^- was judged not to be the key explanation for different results with different iodosylarenes. The results suggested that there are two active oxidants for styrene, one of which is a manganese iodosylbenzene complex.

In 2004, Goldberg provided evidence for another type of mechanism for PhIO in catalysis. The manganese corrolazine (Cz) complex (Scheme 11) can be oxidized to a stable [Mn(Cz)O] complex [52]. This complex can slowly oxidize thioethers, and is rather unreactive towards *cis*-stilbene. In the presence of PhIO it becomes an



Scheme 11 Structure of proposed iodosylbenzene complex



Scheme 12 Synthesis of soluble iodosylbenzene ^{s}ArIO

efficient catalyst for oxidation of PhSMe and for epoxidation of stilbene. Interestingly, ^{18}O labeling studies showed that the oxygen atom of the iodosylbenzene is preferentially transferred to PhSMe over the oxygen atom of the Mn oxo unit. The results suggested that the [(Cz)Mn≡O] complex merely serves as a Lewis acid catalyst for the oxygenation reactions of PhIO. Later work revealed a similar mechanism was probably operative for olefin epoxidation using a related manganese imido complex [(Cz)Mn≡N] [53].

In 2004, Bryliakov reported on the [(salen*)FeCl]-catalyzed oxidation of sulfides with iodosylbenzene [54]. Enantioselectivities up to 99% were achieved for oxidation of thioanisole. Importantly, use of other oxidants such as H_2O_2, ^{t}BuOOH, or *m*-CPBA gave good conversions to the sulfoxide but without enantioselectivity. This suggested that the latter reactions proceeded through a different pathway than when using iodosylbenzene. Analysis of ^{1}H NMR spectra at −40°C of mixtures of [(salen*)FeCl] and PhIO allowed detection of a new species formulated as [(salen*)Fe(OIPh)Cl], and no free PhI. Addition of excess *p*-BrC_6H_4SMe to this mixture and warming to 0°C resulted in liberation of free PhI, generation of *para*-$BrC_6H_4S(O)Me$, and loss of the signals for the proposed intermediate.

Up until this point, one reason for uncertainty of the role of these isolated iodosylarene complexes in actual catalytic oxidation reactions was a lack of detailed kinetic analysis for operating systems. Studies of catalytic systems were somewhat veiled by the heterogeneous nature of reaction mixtures because of the insolubility of iodosylbenzene. In 1999, Protasiewicz reported the synthesis of an iodosylarene ^{s}ArIO (^{s}Ar=*ortho*-$^{t}BuSO_2C_6H_4$) that was both soluble and a potent primary O-atom transfer reagent (Scheme 12) [55]. In addition, the structure of this monomeric iodosylbenzene was reported shortly thereafter in 2000 [56]. The

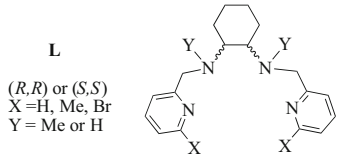
solubility arises from the fact that an intramolecular I···O bond (from an S=O oxygen atom) fill a coordination site *trans* to the I–O bond so that it cannot undergo the polymerization reaction (Scheme 2, E). This material, as well as its imino cousin ^{s}ArINTs, has been used in a number of mechanistic studies to gain further insights into the role of iodosylarenes in catalytic oxygenation reactions [22]. The increased solubility also opened up possibilities for low temperature studies. In $CDCl_3$ solution, and in the presence of [Mn(salen)OAc], ^{s}ArIO undergoes rapid catalytic disproportionation to ^{s}ArI and the iodoxyarene $^{s}ArIO_2$ [55].

In 2006, Collman and Brauman employed ^{s}ArIO in investigations of kinetics of the [(TPFPP)MnCl]-catalyzed epoxidation of *cis*-cyclooctene, styrene, and 1-decene [57]. Their results established that the iodosylarene and metal complex rapidly react to form an active oxidant, which then reversibly forms an adduct with the substrate and then produces the epoxide product. The overall reaction follows saturation kinetics and can be fitted with a Michaelis–Menten model. The identity of the active oxidant, however, could not be unambiguously established.

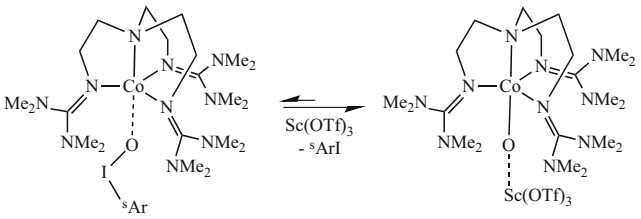
In 2009, Nam and de Visser presented experimental and theoretical (DFT) results on the ability of PhIO to activate weak hydrocarbon CH bonds with and without assistance from iron complexes [58]. Interestingly, PhIO was found to be able to dehydrogenate 1,4-cyclohexadiene to produce benzene at room temperature. Computations suggested that the reaction of ethylbenzene with PhIO occurs by a concerted H-atom abstraction transition state. Surprisingly, it was calculated that hydroxylation of ethylbenzene by PhIO should be even faster than by [(porphyrin)FeCl].

In 2010, Bryliakov reported on the use of a series of $[(L)Mn(O_3SCF_3)_2]$ complexes (Scheme 13) for the epoxidation of olefins using peracetic acid, *m*-chlorobenzoic acid, *tert*-butyl hydroperoxide, cumyl hydroperoxide, PhIO, and MesIO [59]. The enantioselectivities of the epoxidations varied depending on oxidant. Based on this finding, as well as other observations, iodosylarene $[(L)Mn{=}O(OIAr)]^{2+}$ complexes were proposed to be the active oxidizing species, similar to the intermediates proposed earlier by Goldberg [52].

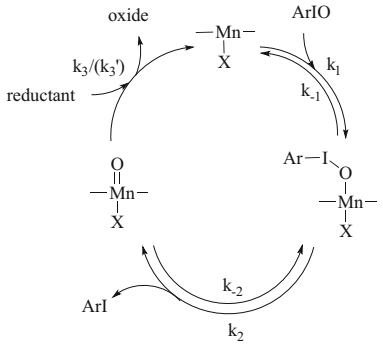
In 2011, Ray reported on the use of the soluble iodosylarene ^{s}ArIO to prepare a $Sc(OTf)_3$ capped cobalt(IV) oxo complex (Scheme 14) [60]. This material was prepared by the addition of 3 equiv. of ^{s}ArIO to [Co(TMG_3tren) (OTf)]OTf (TMG_3tren=tris[2-(*N*-tetramethylguanidyl)ethyl]amine) in the presence of Sc $(OTf)_3$ at −60°C. Interestingly, when the reaction is performed in the absence of $Sc(OTf)_3$, an orange product is generated which was formulated as the ^{s}ArIO complex [Co(TMG_3tren)OI^{s}Ar)]. The spin 3/2 material was characterized by



Scheme 13 Ligand structure



Scheme 14 Reactivity of iodosylbenzene complex



Scheme 15 Catalytic cycle

UV–vis, EPR, and X-ray absorption spectroscopy. The ^{s}ArIO complex was more efficient at H-atom abstraction from dihydroanthracene than the $Sc(OTf)_3$-stabilized oxo complex.

In 2012, Lei reported a detailed kinetic analysis of the catalytic reaction of manganese porphyrins [(Porph)MnCl] (Porph=TPP, T(*p*-OMe)PP, T(*p*-Cl)PP, and T(*o*-Cl)PP, TDCPP) with the soluble iodosylarene ^{s}ArIO for two types of reactions [61]. The first was the reaction with 2 equiv. of TBPH (TBPH=2,4,6-$^{t}Bu_3C_6H_2OH$) that generates water and 2 equiv. of the radical 2,4,6-$^{t}Bu_3C_6H_2O\cdot$. The second reaction involved conversion of *cis*-stilbene to the corresponding epoxide. Both reactions were studied by low temperature UV–visible spectroscopy (0°C), as well as by electrospray ionization mass spectrometry (ESI-MS). During these catalytic reactions of olefins, both Mn iodosylbenzene adducts and [(Porph)Mn^{V}=O] could be simultaneously observed. In the absence of substrate, ^{s}ArIO and [(TDCPP)MnCl] generates the intermediate [(TDCPP)Mn(OI^{s}Ar)Cl] which, upon addition of excess ^{s}ArI, returned [(TDCPP)MnCl]. [(TDCPP)Mn(OI^{s}Ar)Cl] completely converts to the corresponding Mn oxo complex. The proposed mechanism is shown in Scheme 15 for the overall process, showing that the active oxidant is not the iodosylbenzene complex.

The year 2012 was very important for the coordination chemistry of iodosylbenzene, with two important single crystal X-ray structures finally bringing

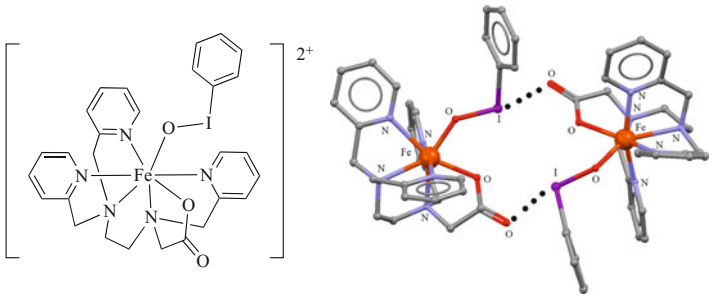


Fig. 1 Structure of iron iodosylbenzene complex

definitive structural proof and details for transition metal iodosylbenzene complexes. The first example was reported by McKenzie [62]. The reaction of PhIO with $[(tpena)Fe]^{2+}$ (generated by dissolving the dimer $[(tpenaH)Fe\text{-}O\text{-}Fe(tpenaH)]^{4+}$ in acetonitrile) led, after crystallization, to $[(tpena)FeOIPh](ClO_4)_2(MeCN)(H_2O)_{0.5}$ (tpena ligand shown in Fig. 1). This material has limited stability (days) even at −40°C in the solid state, and survives only for a few hours at RT in acetonitrile. The structure of $[(tpena)FeOIPh]^{2+}$ cation has two independent molecules in the lattice, and the average Fe-OIPh distance is 1.933(3) Å. The average I–O distance is 1.920(3) Å, the average Fe–O–I bond angle is 125.8(2)°, and the average O–I–C bond angle is 91.2(2)°. The single crystal structure of PhIO has not been determined, but corresponding values for the soluble iodosylarene ^{s}ArIO are d_{IO}=1.848(6) Å and $\angle_{O\text{-}I\text{-}C}$=94.8(3)°. The soluble iodosylarene also features a close I···O intramolecular secondary bond at 2.707(5) Å approximately *trans* to the I–O oxygen atom, and an intermolecular I···O secondary bond at 2.665(6) Å approximately *trans* to the I–C carbon atom. The structure presented shows the iodine as being two coordinate, which would be unusual. Examination of the structure shows suggests the existence of intermolecular I···O=C(ligand) bonding between cationic [(tpena)FeOIPh] units with I···O distances of 2.564 and 2.555 Å, located approximately *trans* to the I–O oxygen atoms (as depicted in Figure 1). ESR spectra of this compound were consistent with a high spin Fe(III) complex. The isolated iodosylbenzene complex is able to effect the oxidation of thioanisole both stoichiometrically and catalytically. It was proposed for this material that the iodosylbenzene complex served as a reservoir for an active iron oxo species $[(tpena)FeO]^{2+}$.

In 2012, Fujii announced two new di-iodosylbenzene complexes obtained by the reaction of a $[(salen^*)MnCl_2]$ with 2 equiv. of PhIO or MesIO (Mes=2,4,6-$Me_3C_6H_2$) [63]. The compounds were characterized by UV–vis, ^{1}H NMR, EPR, CD, IR, and ESI-MS spectroscopic techniques. Data were consistent with high spin Mn(IV) species and the proposed structure is $[(salen^*)Mn\{OI(Cl)Ar\}_2]$. The structure of the Mes derivative is shown in Figure 2, confirming that the iodosylmesitylene has "inserted" into the Mn–Cl bonds. The *trans* disposition of two $ArI(X)O^-$ groups is reminiscent of previously proposed structures. The geometry at iodine is T-shaped with an O–I–Cl average bond angle of 172.6°

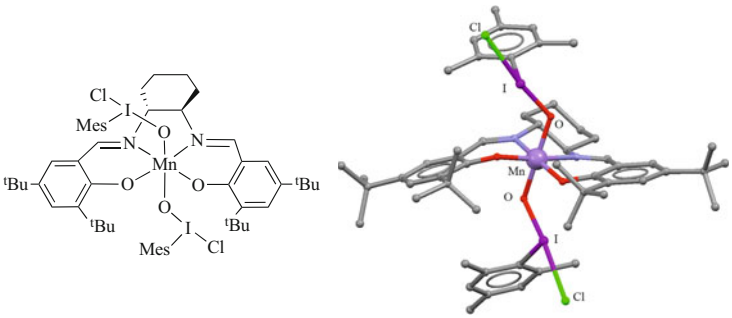
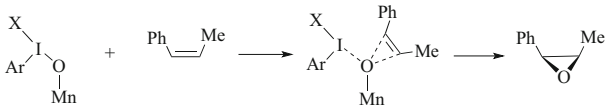


Fig. 2 Structure of manganese iodosylbenzene complex



Scheme 16 Mechanism for reaction of iodosylbenzene complex with olefin

(two molecules in asymmetric unit of cell). The average I–O bond length of 1.969 Å is considerably longer than that found in the monomeric iodosylarene ^{s}ArIO (1.848(6) Å) and resembles that found in Koser's reagent [PhI(OH)OTs] (1.940 Å). Paralleling previous studies, the oxygen atoms in [(salen*)Mn{OI(Cl)Ar}$_2$] undergo facile exchange with oxygen atoms of water in dichloromethane. These compounds can also effect the stoichiometric and catalytic oxidation of thioanisole and epoxidation of styrenes. Based on the enantioselectivities of the single turnover experiments (higher enantioselectivities for olefin epoxidations), it was suggested that different mechanisms may be operating for each type of oxygen transfer process. Also interesting was the finding that the MesIO complex gives higher enantioselectivities than the PhIO complex, which provided support that these complexes can directly transfer oxygen atoms to olefins.

In 2013, Fuji expanded their study of the iodosylarene adducts [(salen*)Mn{OI(Cl)Ar}$_2$] to include 2,4,6-$Et_3C_6H_2IO$ and other anions with synthesis of [(salen*)Mn{OI(X)Mes}$_2$] (X=BzO=$C_6H_5CO_2$, TsO=4-Me-$C_6H_4SO_3$) [64]. The complexes were characterized by ^{1}H NMR, EPR, UV–vis, CD, ESI MS, and IR spectroscopy. ^{18}O labeling studies allowed identification of ^{16}O/^{18}O sensitive bands between 577 and 634 cm^{-1}. Parallel DFT calculations supported the assignment of these bands as O–Mn–O antisymmetric stretching modes. Oxidation rates of thioanisole were fastest when the aryl group was C_6F_5 and when the X anion was *p*-toluenesulfonate in [(salen*)Mn{OI(X)Ar}$_2$]. DFT studies on the mechanism of the oxygen atom transfer from [(salen*)Mn{OI(Cl)Mes}$_2$] to *cis*-β-methylstyrene favored a three-center transition state as shown in Scheme 16.

In 2014, Templeton and Jones reported a very different type of iodosylarene complex with a completely different metal center [65]. During studies to generate

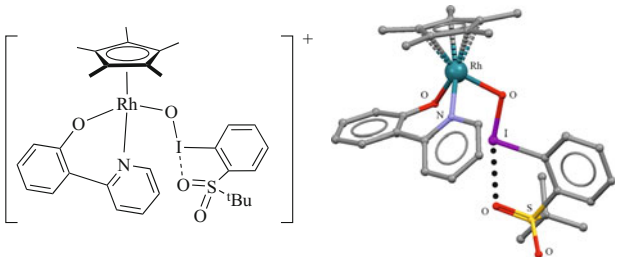
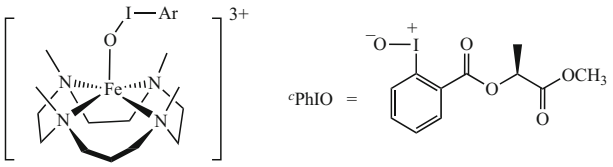


Fig. 3 Structures of ruthenium iodosylbenzene complex



Scheme 17 Iron cyclam iodosylarene complex (*left*) and chiral iodosylarene (*right*)

late metal oxo complexes it was discovered that an organometallic complex of ^{s}ArIO could be structurally characterized (Figure 3). This material could be prepared via two different routes. Each route required addition of 2 equiv. of ^{s}ArIO. The structure of [Cp*Rh{2-(2-pyridyl)phenoxide}(OI^{s}Ar)] (Fig. 3) reveals that the I–O bond length has increased to 1.909(4) Å from that of 1.848(6) Å in ^{s}ArIO. There is also a shortening of the intramolecular I···O=S bond distance in the ^{s}ArIO unit from 2.707(5) to 2.652(4) Å. Despite heating of [Cp*Rh{2-(2-pyridyl)phenoxide}(OI^{s}Ar)], no evidence for formation of a rhodium oxo was seen. No evidence of iridium iodosylarene complexes were observed in related iridium complexes; instead, oxidation of a coordinated isonitrile was observed [66].

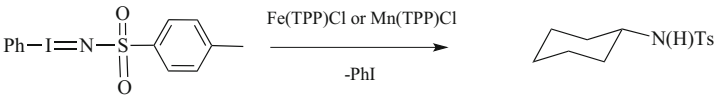
The year 2014 also saw an interesting report from Latour and Nam which describes the synthesis and reactivity of highly reactive non-heme iron(III) iodosylarene complexes $[(13\text{-TMC})\text{FeOIAr}]^{3+}$ (13-TMC=13-tetramethylcyclam, Ar=Ph or C_6F_5) [67]. These complexes, generated at −40°C, were very active in oxidation of CH bonds of hydrocarbons and for sulfoxidation reactions. Although these compounds could not be isolated, they were characterized by CSI-TOF MS, UV–vis, EPR, Mössbauer, and Raman spectroscopy. The data were consistent with iron(III) complexes having iodosylarene ligands (Scheme 17, left). Under the same conditions at which these compounds readily oxidize cumene, the corresponding iron(IV) oxo complex $[(13\text{-TMC})\text{Fe(O)}]^{2+}$ did not. The two complexes rapidly exchange their oxygen atoms with $H_2{}^{18}O$ within seconds. A plot of the log of the second-order rate constant for oxidation of hydrocarbons by the PhIO complex versus the CH bond strength of the hydrocarbon (ranging from Ph_3C-H to Cy-H) gave a linear correlation. A Hammett-type study of the oxidation of p-XC_6H_4SMe revealed a ρ value of −1.9, which indicated an electrophilic character for the

iodosylarene complexes. Another key argument against the involvement of iron oxo complexes as active oxidants in these reactions was the finding that addition of excess C_6F_5I to the reactions did not inhibit the oxidation of either cumene or thioanisole. If the reaction required liberation of ArIO from iodosylarene complex to form iron oxo species, then adding ArI should push any equilibrium back to iodosylarene complex.

In 2015, Nam reported studies of $[(13\text{-TMC})FeOIAr]^{3+}$ complexes for olefin epoxidation reactions [68]. The range of iodosylarenes was extended to add ^{s}ArIO, MesIO, and a novel iodosylarene having a chiral auxiliary ^{c}PhIO (Scheme 17, right). As in their 2014 study, the iodosylarenes were much more active than the corresponding iron(IV) oxo complex $[(13\text{-TMC})Fe(O)]^{2+}$. Impressively, the complex having the chiral iodosylarene provided good enantioselectivities for epoxidation of several olefins. For example, chalcone was epoxidized with 76% *ee*. Because the departure of the ^{c}PhI group should also render a potential iron-oxo species achiral, this was strong evidence for the active species having a coordinated iodosylarene.

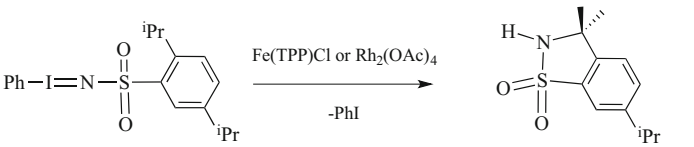
3 Intermediates Involving (Imino)iodoarenes as Ligands in Transition Metal-Catalyzed Reactions

(Tosylimino)iodobenzene (PhINTs) is a relatively "newer" tool for catalysis compared to iodosylbenzene, being first reported in 1975 [69]. Nevertheless, applications of this reagent in transition metal-catalyzed reactions have become an important class of reactions in their own right. In 1982, it was discovered that manganese or iron porphyrins could catalyze the insertion of the NTs from PhINTs into a CH bond of cyclohexane (3) [70]:



(3)

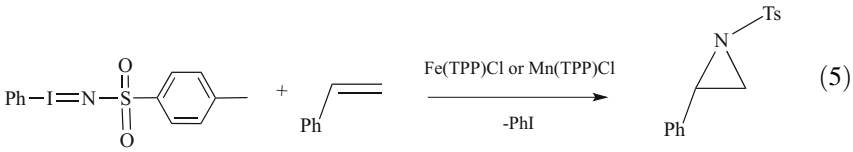
Soon afterwards, it was also discovered that the CH bonds of the hypervalent iodine reagent could be catalytically activated in the presence of iron porphyrin or rhodium catalysts (4) [71]:



(4)

The use of manganese and iron porphyrins to catalyze NTs transfer from PhINTs to olefins to form aziridines (catalytic aziridination) was first described in 1984 (5)

[72]. Owing to the great interest in aziridines, especially if they could be produced catalytically and enantioselectively (from pro-chiral olefins), these reactions developed rapidly [73, 74]:



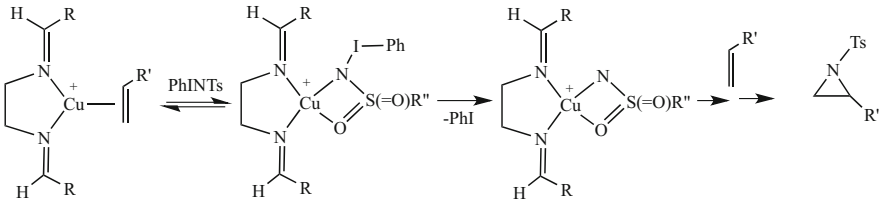
(5)

Because of the similarity between PhIO and PhINTs, it might be expected that PhINTs can also play a role besides that of a simple imino source during transition metal-catalyzed reactions. Some recent reports that either observe these species or consider their involvement in metal-catalyzed reactions are chronicled below. The general field of transition metal-catalyzed reactions of $ArINSO_2Ar'$ have been subject to several recent reviews [16, 75–77]. A newer development involves the in situ generation of reactive PhINR species (from $PhI(OAc)_2$ and RNH_2) that feed into catalytic cycles [78, 79].

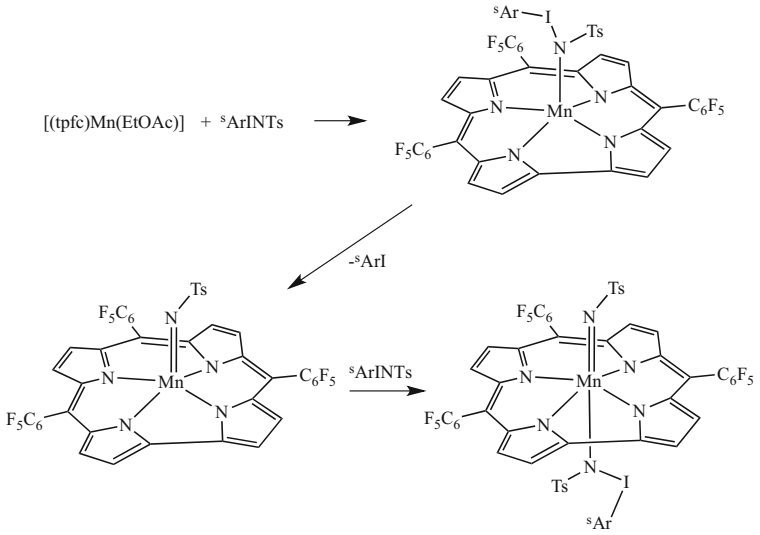
In 1999, Che reported on the catalytic asymmetric amidation of the CH bonds of hydrocarbons by [(Porph*)ML,L′] (M=Ru, L, L′=CO, EtOH; M=Mn, L=OH^-, MeOH; Porph*=1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethyanoanthracen-9-yl) porphinato dianion) with PhINTs. The electrospray mass spectrum of a mixture of [(Porph*)Mn(CO)(EtOH)] and PhINTs in dichloromethane displayed a significant signal for a PhINTs complex [(Porph*)Mn(PhINTs)]. A Hammett-type study of substituted ethylbenzenes suggested, however, the reaction proceeded via benzylic radicals arising from H-atom abstraction by a manganese tosylamido intermediate [80].

In 2000, Andersson and Norrby reported a detailed theoretical treatment (DFT) of the copper-catalyzed aziridination (Scheme 18), exploring how PhINTs bind to a model copper complex, and its role in the catalytic cycle for olefin aziridination [81]. Binding of copper(I) was stronger to PhINTs than binding of ethylene. The binding mode was κ^2 via both the N and O atoms of PhINTs, and the I–N bond is lengthened by 0.38 Å, suggesting a very weak bond (Scheme 17). This agrees with the calculated very low barrier (5 kcal/mol) to breaking the I–N bond. The PhINTs–copper complex was not believed to be reactive enough to react with an olefin, however. The overall reaction involved a Cu(I)/Cu(III) cycle.

In 2006, Abu-Omar reported on stop-flow studies of the reactions of the soluble ^{s}ArINTs reagent (^{s}Ar=*ortho*-^{t}Bu$SO_2C_6H_4$), an analogue of the soluble iodosylarene described above, with the manganese corrole complex [(tpfc)Mn(EtOAc)] (tpfc=5,10,15-tris(pentafluorophenyl)corrole (Scheme 19) [82]. [(tpfc)Mn(EtOAc)] can catalyze the reaction of PhINTs with styrene to form aziridines. In this study, an initial adduct of the ^{s}ArINTs with Mn corrole leads to a detectable mono-adduct [(tpfc)Mn{N(Ts)I^{s}Ar}] (Scheme 16). The initially formed adduct then loses ^{s}ArI to form an isolable Mn imino complex [(tpfc)Mn(=NTs)]. This imino complex, however, is not the active catalyst for imino transfer to olefins.



Scheme 18 Proposed mechanism for reaction of PhINTs with copper complex

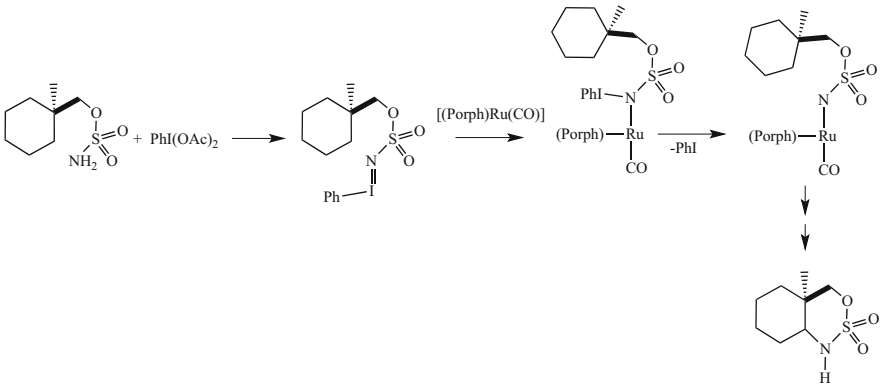


Scheme 19 Reaction of Mn complex with PhINTs

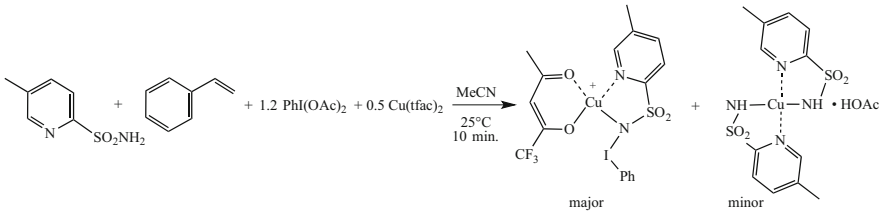
Labeling and kinetic studies indicate that imino transfer proceeds from a [(tpfc)Mn(=NTs){N(Ts)I^{s}Ar}] complex, and thus this catalyst operates in a fashion that is reminiscent of the manganese oxygenating system reported by Goldberg [52]. Hydrogen atom abstraction from hydroanthracene (to form anthracene), however, can occur upon reactions with an intermediate [(tpfc)Mn{N(Ts)I^{s}Ar}] species [83].

In 2007, Che reported on the use of DFT computational methods to probe the mechanism of $Rh_2^{II,II}$ carboxylate complex-catalyzed amidation of carbamates by $PhI(OAc)_2$ [84]. The calculations for a model complex $[Rh_2(O_2CH)_4]$ showed that binding of an in situ generated (carbonylimino)iodobenzene PhINC(O)OR (R=(*S*)-2-methylbutyl) was favorable. Loss of PhI was predicted by a large negative ΔG value and thus the metal-nitrene was proposed to be the active catalyst.

In 2008, Che and Phillips examined the mechanism of [(porphyrin)Ru(CO)]-catalyzed amidation of sulfamate ester (Scheme 20) using DFT computational methods [85]. The formation of a $PhINSO_2(OR)$ complex was favorable, but the energy barrier to release PhI from that species to form an Ru-$NSO_2(OR)$ nitrene



Scheme 20 Reaction of PhINTs with Ru complex

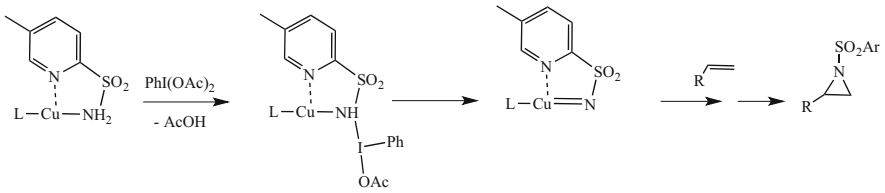


Scheme 21 Formation of Cu ArINTs complex

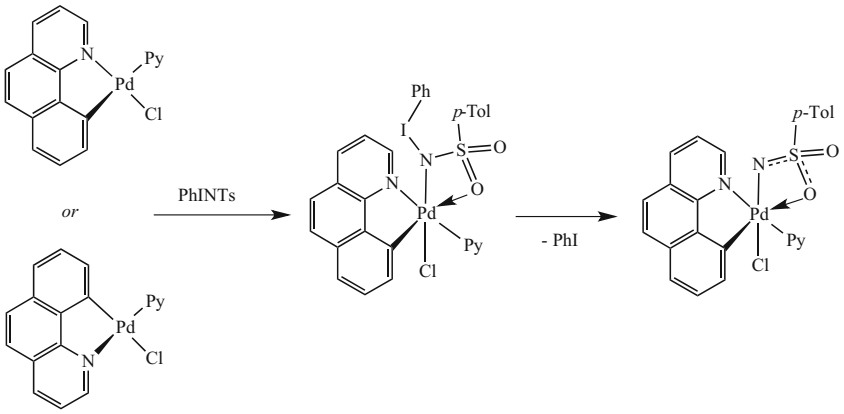
complex was only 0.3 kcal/mol. It was concluded that the [(porphyrin)Ru(CO) {NSO_2(OR)}] complex was the active species for the subsequent CH bond activation.

In 2008, Kim and Chang reported on the catalytic aziridination of styrenes and other olefins by 2-pyridylsulfonamide and $PhI(OAc)_2$ using copper complexes [86]. These reactions do not require preformed (arylsulfonylimino)iodobenzenes $PhINSO_2Ar'$. During investigations of the mechanism, a copper $PhINSO_2Ar'$ complex was detected by ESI-MS as a major species (Scheme 21). A chelated nitrenoid complex derived from an unusual hypervalent iodine intermediate (Scheme 22) was proposed, based on Hammett plot analysis, kinetics and computational studies.

In 2010, Cundari reported a detailed computational study (DFT) of the mechanism of palladium-catalyzed reactions of benzo[*h*]quinoline with PhINTs [87]. In these reactions the NTs group inserts into a palladacycle Pd–C bond. The study explored several intermediates that precede formation of the CN bond, one of which



Scheme 22 Formation of Cu nitrene complex

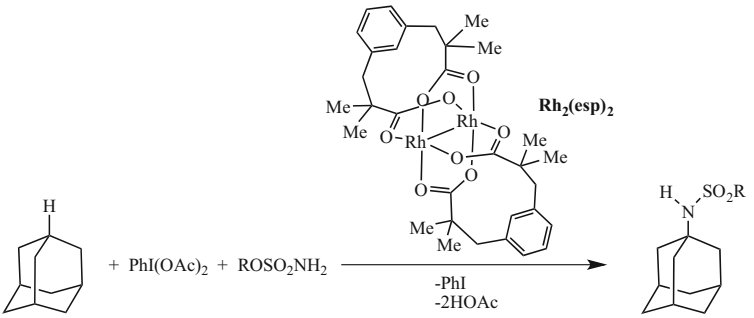


Scheme 23 Proposed Pd PhINTs complex

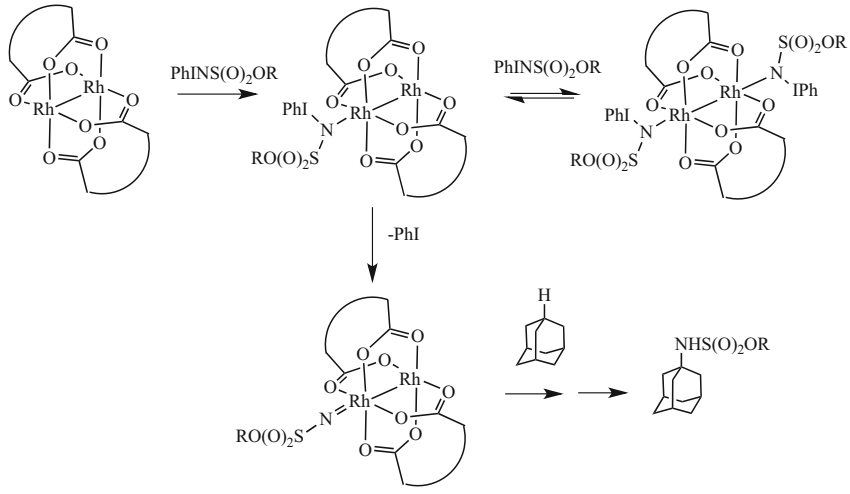
is a Pd–OIPh complex (Scheme 23). Reaction with either isomer of the cyclometalated benzoquinoline–Pd complex with PhINTs is exothermic (ca. 5–5.6 kcal/mol). As seen before, the adduct binds via both N and O atoms of the PhINTs. Loss of PhI was expected to occur without a real transition state, as the I···N interaction is very weak (3.06 Å). By contrast, previous DFT studies on Ru (II)·PhINTs and Rh_2(II,II)·PhINTs adducts predicted IN bond lengths of 2.08 and 2.10 Å [84, 85].

In 2012, Du Bois and Zare published details of a novel method to observe intermediates in the CH amination reactions catalyzed by dirhodium carboxylate complexes [88]. In this study, desorption electrospray ionization (DESI) was coupled to mass spectroscopy to capture transient intermediates from solution having very short lifetimes (ca. nanoseconds to microseconds). $Rh_2(esp)_2$ is a catalyst for the amination of alkanes, such as adamantane, as shown in Scheme 24.

This technique allowed detection of a number of intermediates from the mixing of CH_2Cl_2 solutions of $PhI(OAc)_2$ and $ROS(O)_2NH_2$ with solutions of adamantane and [$Rh_2(esp)_2$] in CH_2Cl_2. Amongst the species identified were the mono and bis adducts of [$Rh_2(esp)_2$] arising from the in situ formation of $PhINS(O)_2OR$ from $PhI(OAc)_2$ and $ROS(O)_2NH_2$. Although $PhINS(O)_2OR$ could be observed in these experiments, earlier attempts to observe an (imino)iodobenzene by ^{1}H NMR



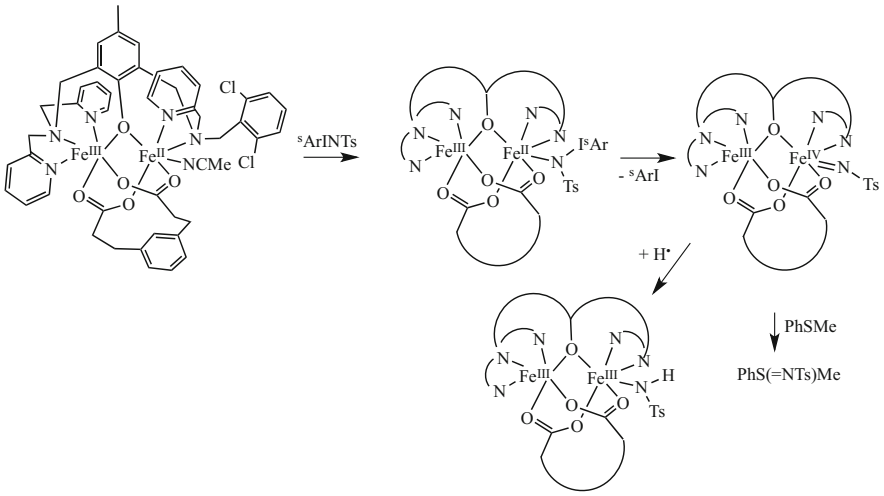
Scheme 24 Catalytic amidation of alkane by Rh_2 complex



Scheme 25 Formation of Rh_2 PhINR complex

spectroscopy from reaction of $PhI(OAc)_2$ and $ROS(O)_2NH_2$ in CD_2Cl_2 were unsuccessful [89]. The adducts of the hypervalent iodine reagents, however, are not the active oxidizing species. The mono adduct loses PhI to yield the proposed active nitrene species (Scheme 25).

In 2014, Maldivi and Latour used DESI-MS, optical, and Mössbauer experiments to identify an ^{s}ArINTs adduct of the di-iron species shown in Scheme 26 [90]. This compound loses ^{s}ArI to provide a fleeting intermediate iron nitrene complex that could only be detected by the sensitive DESI-MS technique. This intermediate rapidly reacts with thioethers or hydrogen atom donor (2,4-di-*tert*-butylphenol).



Scheme 26 Formation and reactivity of iron nitrene species

4 Conclusions and Outlook

This survey documents the history and development of iodosylarenes and (arylsulfonylimino)iodoarenes acting as ligands to transition metal complexes during catalytic oxo and nitrene transfer processes. In the case of iodosylarenes, single crystal X-ray structures have recently provided incontrovertible identification and structural information on such complexes. In most cases, however, such complexes have been identified by spectroscopic techniques as well as through their reactivity patterns since these complexes are often unstable or unisolable. Although iodosylarene and (arylsulfonylimino)iodoarene complexes are suggested in a minority of cases where PhIO and PhINTs reagents are utilized in catalytic applications, it can be safely concluded that such adducts can indeed be bona fide intermediates. The remaining question now, in such cases, lies as to the specific role these complexes play in oxidation processes. Are they simply precursors for generating active metal oxo or nitrene complexes, or can [M(XIAr)] (X=O or NR) complexes be the active oxidants themselves? For some of cases detailed here, the latter seems to be the case.

A number of other themes arise from this survey. Binding of PhIO to metal complexes can activate the PhIO oxygen atom towards facile O-atom exchange with water. Binding of PhIO to metal complexes (especially cationic complexes) can also increase the electrophilic character of the iodine center and draw in other anions and donors, especially chloride, to increase the coordination number at the iodine center. Thus, it is probable that many of the structures that have been formulated over the years as [M-O-I-Ph], are likely to have structures with [M-O-

I(X)Ph] or [M-O-I(···X)Ph] functionalities. Reactive metal-oxo complexes can also interact with added ArI to set up equilibria involving iodosylarene–metal complexes. The substituents on iodosylarenes can play a significant role in these equilibria, and in influencing enantioselectivities for oxidation reactions. Modern computational methods have provided significant understanding on the stability of these complexes and their conversion to metal oxo and nitrene species.

Although there are many parallels between ArIO and ArINTs reagents, for reasons that are unclear, there appears to be little or no evidence for (tosylimino) iodoarene–metal complexes as active oxidants. This, however, may be because fewer studies have appeared where this possibility has been examined. In addition, some of the reactivity reported for PhIO complexes has yet to be authenticated for corresponding PhINTs complexes. It is likely that structures of [M-N(SO_2R)IAr] are more complex because of the ability of the sulfone functionalities to coordinate to metals as well.

Even though great strides are being made in developing organocatalytic methods that obviate the need for expensive or sometimes toxic transition metal catalysts [91], there continues to be a need for transition metal catalysts to carry out many useful transformations with desired selectivity, yields, speed, and enantioselectivity. As the appreciation for hypervalent iodine atom and group transfer species as ligands in active oxidants grows, so too do new applications and complexes that can take advantage of synergistic [M]-[XIAr] interactions.

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Halogen Bonding in Hypervalent Iodine Compounds

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Abstract Halogen bonds occur when electrophilic halogens (Lewis acids) attractively interact with donors of electron density (Lewis bases). This term is commonly used for interactions undertaken by monovalent halogen derivatives. The aim of this chapter is to show that the geometric features of the bonding pattern around iodine in its hypervalent derivatives justify the understanding of some of the longer bonds as halogen bonds. We suggest that interactions directionality in ionic and neutral λ^3-iodane derivatives is evidence that the electron density distribution around iodine atoms is anisotropic, a region of most positive electrostatic potential exists on the extensions of the covalent bonds formed by iodine, and these positive caps affect, or even determine, the crystal packing of these derivatives. For instance, the short cation–anion contacts in ionic λ^3-iodane and λ^5-iodane derivatives fully match the halogen bond definition and geometrical prerequisites. The same holds for the short contacts the cation of ionic λ^3-iodanes forms with lone-pair donors or the short contacts given by neutral λ^3-iodanes with incoming nucleophiles. The longer and weaker bonds formed by iodine in hypervalent compounds are usually called secondary bondings and we propose that the term halogen bond can also be used. Compared to the term secondary bond, halogen bond may possibly be more descriptive of some bonding features, e.g., its directionality and the relationships between structure of interacting groups and interaction strength.

Keywords Crystal engineering • Halogen bond • Hypervalent iodine • Supramolecular chemistry

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Contents

1 Introduction

In this chapter we discuss the geometric features of the bonding pattern around iodine in some of its hypervalent derivatives [1–6] to support the interpretation of some of the bonds given by iodine as halogen bonds. Specifically, some of the bonds formed by iodine in hypervalent compounds are longer and weaker than regular covalent bonds and they are typically called secondary bondings [7–11]. We discuss the structural features of hypervalent iodine derivatives to show that these longer and weaker bondings can be considered as bona fide halogen bonds. According to the recent IUPAC recommendation [12], a halogen bond occurs when "there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity". It is common to use the term halogen bond to designate interactions given by monovalent and electrophilic iodine atoms [13–17] and this chapter aims at proving that the term can be equally used to designate some interactions given by iodine in its hypervalent derivatives. An anisotropic distribution of the electron density around the iodine atom is the very basis of its ability to form halogen bonds and the resulting directionality in attractive interaction with nucleophiles, a fingerprint of halogen bonds. The structural characteristics of hypervalent iodine compounds in the solid evidence how the directionality of observed secondary bonds is fully consistent with the anisotropic distribution of electron density expected for di-, tri-, and tetravalent iodine atoms. To designate these secondary bonds as halogen bonds is thus justified. The anisotropic distribution of the electron density in some mono-, di-, tri-, and tetravalent elements and its relevance to the attractive interactions they form with nucleophiles is discussed in the following section. Hypervalent iodine derivatives are considered in the successive sections.

2 Anisotropic Distribution of Electron Density: Generalities

Atoms in molecules are often considered as interpenetrated spheres with a uniform surface electrostatic potential. This approximation allows for a convenient understanding of many molecular properties, but the interactions formed by molecules are one example of when the above sketched model reveals its limits. Intermolecular interactions typically involve the outermost regions of molecules and an accurate description of these regions is instrumental to the in-depth comprehension of interactions. Indeed, when atoms are covalently bound to a molecular fragment, the electron density distribution around them becomes more and more anisotropic with an increased electron-withdrawing ability of the bound fragment. This results in the formation of a region of lower electron density, which is named σ-hole and frequently has a positive electrostatic potential, and another region where the electron density is higher and the electrostatic potential is typically negative [18, 19]. For instance, in monovalent halogens the σ-hole forms a cap on the covalent bond axis and opposite to it, and the region of higher electron density is a belt orthogonal to the covalent bond [20]. Halogens thus adopt an ellipsoidal shape with the minimum radius on the elongation of the covalent bond and the maximum radius orthogonal to it (Fig. 1). This phenomenon, known as polar flattening, has been proven through statistical analyses of data in the Cambridge Structure Database (CSD), direct study of electron density via X-ray, and theoretical calculations [21–24].

The anisotropic distribution of the electron density in halogen atoms of monovalent halogen derivatives accounts for their well-established amphoteric behavior and the different geometry of interactions formed with different entering groups.

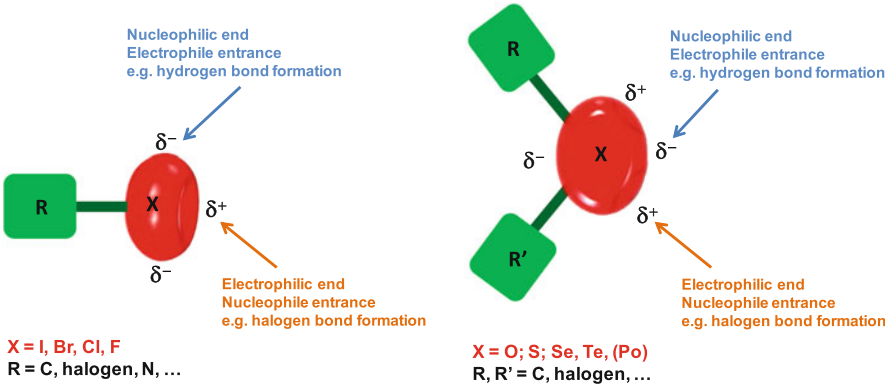

Fig. 1 *Left*: Schematic representation of the anisotropic distribution of the electron density in monovalent halogen derivatives. The polar flattening and the different geometry of interactions involving halogen atoms are reported. *Right*: Localization of regions of higher and lower electron density in divalent chalcogen derivatives and directionality of interactions involving the different regions

It is well known that halogen atoms can function as electron-donor sites and form attractive interactions with electrophiles. Their ability to work as hydrogen bond acceptors was recognized as early as the 1920s [25–27] and halogen atoms of halocarbons can also function as electron-donor sites to several other elements, e.g., when coordinating alkali or alkaline earth metal cations (a CSD search (CSD version 5.34, November 2012 plus one update, ConQuest version 1.15) for C–X···Y short contacts (Y=Li^+, Na^+. K^+, Rb^+, Cs^+ and X=Cl, Br, I) gave 140 hits and 296 counts, and revealed that the median value of the C–X···Y angle is 103.08° (only structures with C···Y > 3.0 Å were considered). Cations enter the most negative region of the halogen atom (i.e., the belt orthogonal to the C–X bond), thus confirming that the halogen atom is working as the nucleophile). All these interactions are in the direction orthogonal to the covalent bond formed by the halogen as any electrophile enters the halogen preferentially where the surface electrostatic potential is more negative [28]. On the other hand, monovalent halogens can also function as electrophiles and form attractive interactions with nucleophiles [13–17]. This behavior may not be very intuitive as it contrasts with the common understanding of halogens as sites where the electron density is high because of their high electronegativity. Nevertheless, this behavior becomes obvious if the anisotropic distribution of the electron density is taken into account. In analogy with the hydrogen bond, where the electrophile is a hydrogen, these interactions are named halogen bond [13]. The history of this interaction goes back to the beginning of the nineteenth century, when J. J. Colin reported the synthesis of the first halogen bond-based supramolecular adduct on reaction of dry iodine and gaseous ammonia [29], but it has only been since the late 1990s that a comprehensive model of the interaction has been developed and its general potential in self-assembly and recognition processes has been realized [13–17, 30]. Nucleophiles obviously enter in monovalent halogens along the extension of their covalent bond and linearity of the interaction is highest for iodine and decreases in the order moving to bromine, chlorine, and fluorine [31, 32]. The halogen bond strength follows the same trend of directionality, namely it increases in the order F < Cl < Br < I and, for a given nucleophile and a given halogen atom, it increases with the electron-withdrawing ability of the residue bound to the halogen atom [33]. In fact, the more electronegative the atom bound to the halogen, the larger the σ-hole and the more positive its electrostatic potential, both effects increasing the strength of formed halogen bonds [34]. For instance, iodobenzene and its pentafluoro analogue have σ-holes where the maximum electrostatic potential, calculated in vacuum, is +103 and +166 kJ/mol, respectively [35]. The relationship between the strength of the halogen bond given by a halogen atom and the electronegativity of the atom to which it is covalently bound accounts for the fact that, in different halocarbons where the halogen atom remains the same, the halogen bond strength depends on the hybridization of the halogen bound carbon and increases with the *s* character of the hybrid orbitals at carbon (the generally observed scale of decreasing strength is $Csp > Csp^2 > Csp^3$) [36].

The anisotropic distribution of the electron density in atoms and the resulting directionality of interactions with nucleophiles and electrophiles are not limited to monovalent halogens. On the contrary, they are quite common phenomena which have been evidenced in many elements through experimental studies and predicted via calculations. In general, any atom forming covalent bonds tends to have regions of depleted electron density on the extension of these bonds and regions where the electron density is higher orthogonal to the covalent bonds. Nucleophiles form attractive interactions with the former areas and electrophiles with the latter.

Since the 1970s it has been known that sulfur undergoes attractive interactions with nucleophiles, preferentially on the extension of the axis of the covalent bonds in which it is involved (Figs. 1 and 2), whereas electrophiles enter orthogonal to the covalent bonds [37–39]. The heavier Group 16 elements also show anisotropic

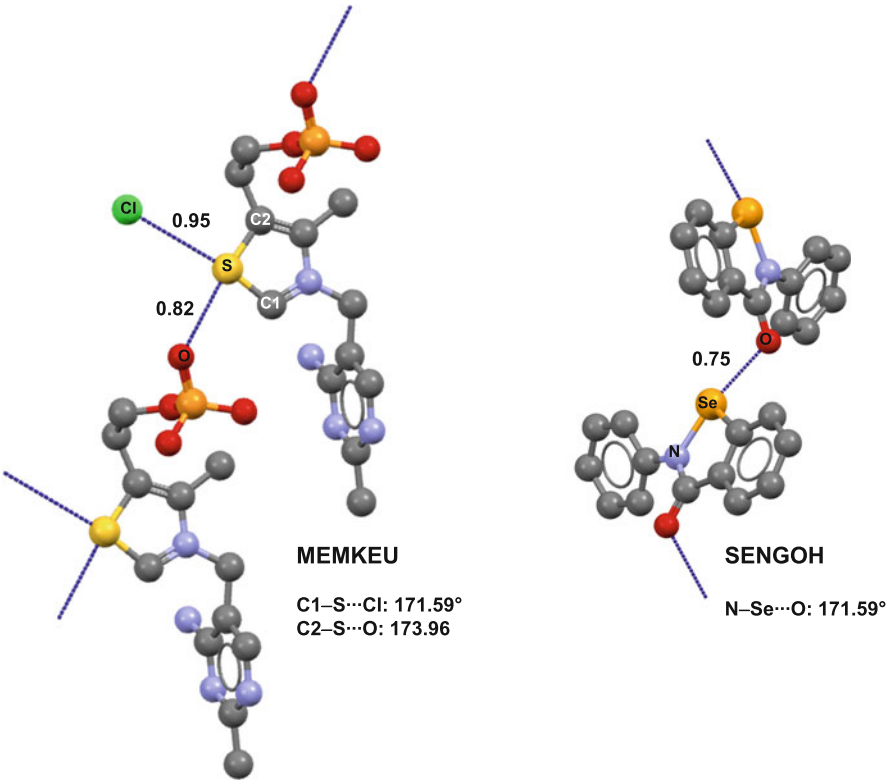

Fig. 2 Ball and stick representations (Mercury 3.5) of the crystal structure of: MEMKEU, the phosphate of thiamin, a vitamin of the B complex, wherein sulfur forms two chalcogen bonds (*dotted blue lines*) thanks to the entrance of chloride and phosphate anions on the extended covalent bonds at sulfur; SENGOH, 2-phenyl-1,2-2*H*-benzisoselenazole-3-one wherein selenium forms one directional chalcogen bond. CSD Refcodes and the Normalized contacts (*Nc*, see onwards) are given. Color code: *gray*, carbon; *sky-blue*, nitrogen; *red*, oxygen; *ocher*, phosphorus; *light yellow*, sulfur; *green*, chlorine; *dark yellow*, selenium

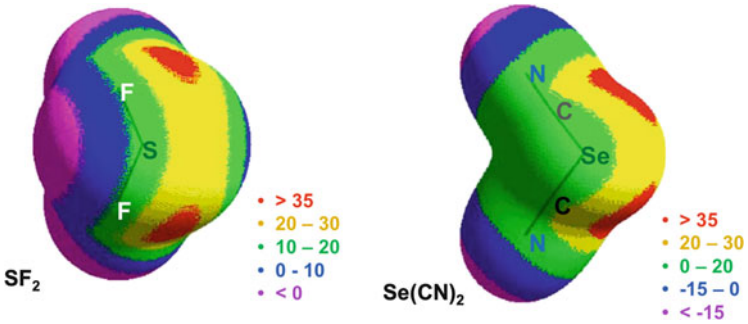

Fig. 3 Calculated electrostatic potential computed on the 0.001 electrons/Bohr^3 contour of the electron density in SF_2 and $Se(CN)_2$. Both molecules show two equivalent σ-holes (in *red*) approximately located on the extensions of the covalent bonds, F–S (*left*) and C–Se (*right*)

distribution of the electron density (Fig. 3) and directionality in the interaction with nucleophiles and electrophiles similar to sulfur [40–46]. The general features of interactions that chalcogens form with nucleophiles parallel those of analogous interactions given by halogens; distinctive characteristics are that chalcogens typically form two covalent bonds, two σ-holes can be present on their extensions, and two interactions with nucleophiles can be formed. This is particularly the case when both residues bound to the chalcogen have a strong electron-withdrawing ability, namely the two σ-holes have remarkably positive electrostatic potentials. The attractive interactions formed have been named chalcogen bonds, in analogy to the halogen and hydrogen bonds described above.

Recent experimental and theoretical studies have demonstrated that the electron distribution is anisotropic also around the Group 15 elements atoms [47–54]. Phosphorus, arsenic, antimony, and bismuth show areas of depleted electron density, namely σ-holes, along the extension of their covalent bonds and these areas can have a remarkably positive electrostatic potential if the atom/group bound to the pnictogen atom has a strong electron-withdrawing ability (Fig. 4). Pnictogens can display up to three positive σ-holes capable of forming directional short contacts with three incoming electron donors. The name pnictogen bond has been proposed for the resulting interactions.

Importantly, in Group 14 elements the anisotropic distribution of the electron density, the presence and localization of areas of depleted electron density, and the pattern of resulting interactions show features parallel to those described above for Groups 15, 16, and 17 elements [55–60]. Four covalent bonds being typically formed by Group 14 elements, up to four σ-holes, and four attractive interactions with entering nucleophiles, can develop. The name tetrel bond has been suggested for these interactions, once again referring to the name of the group of the electrophilic atom.

For instance, both theoretical and experimental evidence indicates that Si bound to electron-withdrawing groups displays an anisotropic distribution of electron density, and four regions of positive electrostatic potential are present on the

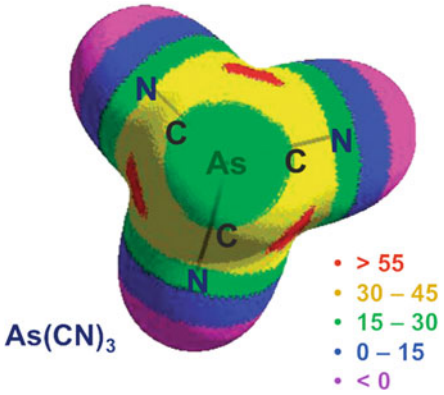

Fig. 4 Calculated electrostatic potential computed on the 0.001 electrons/bohr^3 contour of the electron density of $As(CN)_3$. The molecule shows three σ-holes (in *red*) on the extensions of the C–As covalent bonds

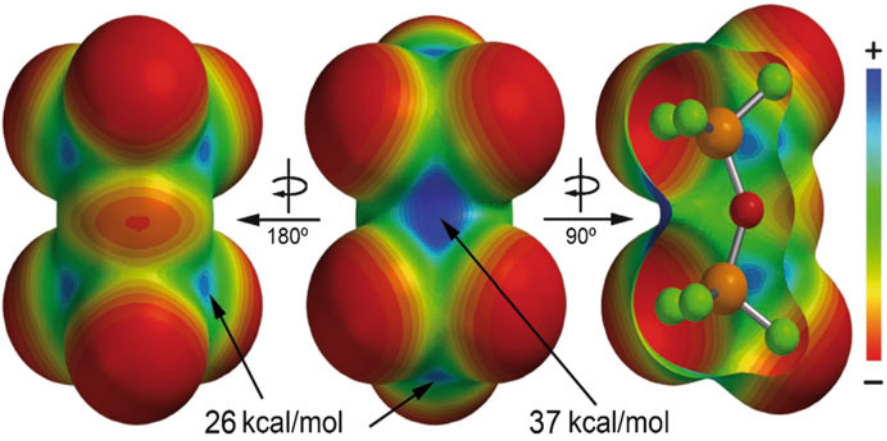

Fig. 5 Molecular electrostatic potential surface for $F_3Si–O–SiF_3$. The four regions of electron density depletion on the Si atom are depicted as *blue areas*

atom surface (Fig. 5). Even compounds as simple as methanol and fluoromethane present a σ-hole opposite to the C-heteroatom covalent bond. Importantly, the entrance of nucleophilic species in σ-holes at carbon has been suggested as the specific force that stabilizes S_N2 reaction pathways.

Clearly, atoms forming covalent bonds tend to have regions of depleted electron density (σ-holes) on the extensions of and opposite to the bonds and regions where the electron density is higher orthogonal to the covalent bonds. For a given atom, the maximum number of observable σ-holes is the number of the σ bonds in which it is involved. Nucleophiles enter the σ-holes and electrophiles enter regions of higher electron density. If this is the case for chalcogens, pnictogens, and tetrels,

which are typical di-, tri-, and tetravalent elements, respectively, it can also be the case for di-, tri-, and tetravalent iodine derivatives. We thus examined the geometric features of crystalline structures of hypervalent iodine derivatives (see following sections). As nucleophiles form short contacts with hypervalent iodine atoms preferentially along the extensions of the covalent bonds in which they are involved, one of the key features of the halogen bond is fulfilled and it is thus justified to use the term to designate these interactions. This term may possibly be more descriptive of some features of the bonding (e.g., its directionality and the relationships between structure of interacting groups and interaction strength) than the commonly used term secondary bond. The proposed use of the term halogen bond for some of the long bonds around iodine atoms in hypervalent iodine derivatives implies a conceptual frame for the bonding pattern around iodine that complements other models available in the literature for this pattern (e.g., the three-center, four-electron (3c-4e) bonding model for λ^3-iodanes).

3 Ionic λ^3-Iodane Derivatives

Diaryl-λ^3-iodanes are well-known iodine(III) compounds and can work as excellent electrophilic arylating agents because of the remarkable electron deficiency at iodine. Because of their relatively low cost and toxicity, they are promising substitutes for transition metal-based reagents [61].

In this section we discuss short and directional C–$I^+\cdots$Y interactions (Y=charged or neutral electron-rich species) in crystalline structures of ionic diaryl-λ^3-iodane derivatives Ar–I^+–Ar Y^- (Y^-=any anion) and congeners [62]. X-Ray structural data of iodonium salts show, in most cases, short and remarkably directional contacts between the positively charged iodine atom and anions. Electrostatic cation–anion attraction accounts for these short separations, but the preferential entrance of anions along the extension of the C–I bonds (Fig. 6) suggests that factors other than electrostatic attraction are also influential. As discussed above, linear directionality is a distinctive geometric feature of interactions between nucleophiles and monovalent halogens or several other di-, tri-, and tetravalent elements and is a consequence of the presence and localization of σ-hole (s). The electrostatic potential at the outer surface of iodine(III) compounds under discussion is entirely positive, but we suggest that it is most positive on the extension of C–I^+ bonds as, similar to other divalent elements, typically chalcogens, the two covalent bonds determine a depletion of electron density at their elongation. Calculations on the diphenylbromonium cation confirmed that this is the case on bromine [63]. We consider interactions directionality in ionic λ^3-iodane derivatives as evidence that the electron density distribution around iodine atoms is anisotropic, a region of most positive electrostatic potential exists on the extensions of the C–I bonds, and these positive caps affect or even determine the overall crystal packing of these solid hypervalent iodine derivatives. The short cation–anion contacts in ionic λ^3-iodane derivatives fully match the halogen bond definition and

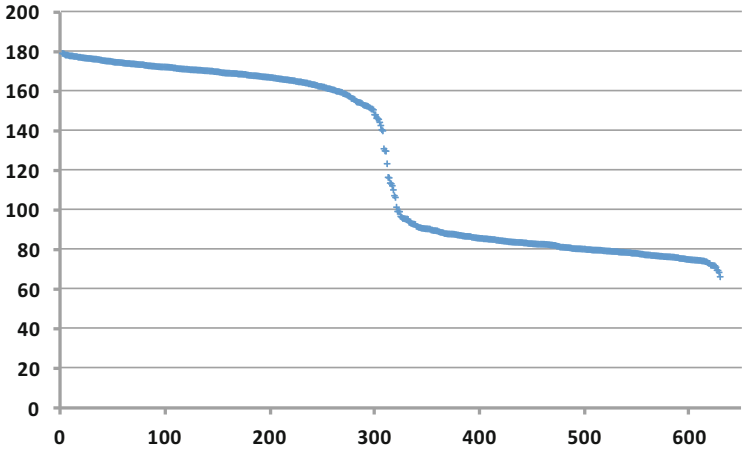

Fig. 6 Plot of the 629 different C–I^+···Y angles (Y=N, O, S, F, Cl, Br, I) present in the 114 structures of the CSD that contain the moiety C–I^+(···Y)–C. Any angle is a cross. Angles are clustered around 180° and 90°, namely on the elongation of the two C–I^+ covalent bonds (which are nearly orthogonal to each other)

prerequisites; as a consequence they can be named halogen bond, similar to the linear short contacts formed by monovalent iodine atoms with incoming nucleophiles.

The two residues bound to iodine in diaryliodonium salts and their analogues bearing alkenyl and alkynyl residues adopt a nearly orthogonal arrangement. A search (ConQuest 1.17) in the CSD for the moiety C–I^+–C affords 127 structures and a median value of 94.6° for the C–I^+–C angle. In these systems, iodine atoms typically behave as bidentate electrophiles and form two short contacts with two entering nucleophiles, in most cases the corresponding counterions. For instance, this is the case for the diphenyl iodonium chloride, bromide, iodide, and other systems which form tetrameric adducts (Figs. 7 and 8) [64–66]. In these tetramers, and in several other systems [67–70], anions work as bidentate sites and the observed square-shaped geometry is a consequence of the fact that the C–I^+–C angle is close to 90° and the iodine···halide bonds are on the elongation of C–I^+ bonds.

The observed iodine···halide halogen bonds are quite short as shown by the respective 'normalized contact' *Nc* defined as the ratio $D_{xy}/(rX + rY)$, where D_{xy} is the experimental distance between the halogen bond-donor atoms X (namely the hypervalent iodine) and the halogen bond-acceptor atoms Y (namely the halide anion in the examples mentioned above) and *r*X and *r*Y are the corresponding van der Waals radius for the halogen bond-donor and the Pauling ionic radius, or van der Waals radius, for the anionic, or neutral, halogen bond acceptor, respectively. *Nc* is a useful indicator of the interaction strength, more useful than the halogen bond distance itself, because it allows distances between different interacting sites to be compared. The infinite chain, either linear, zig-zag, or with an helicoidal

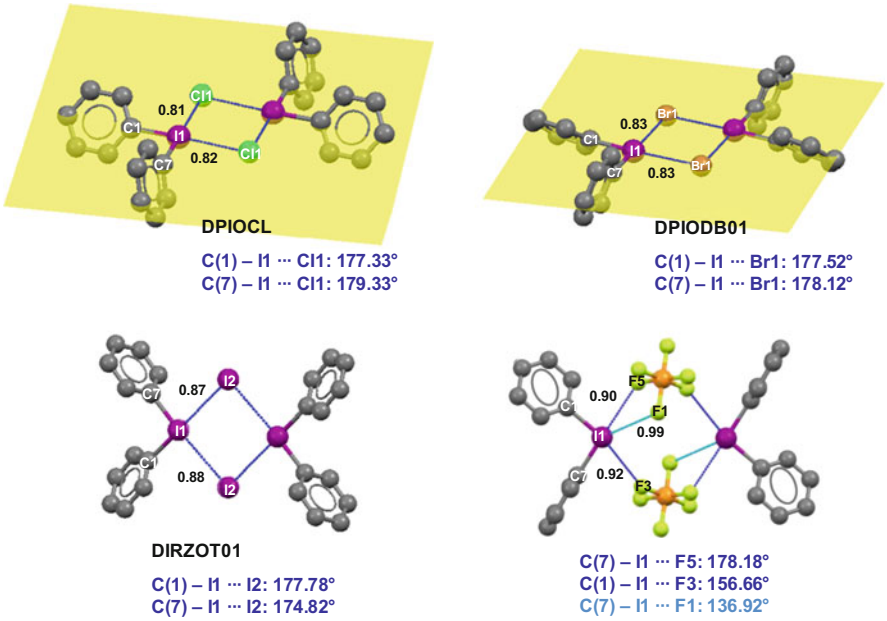

Fig. 7 Ball and stick representations (Mercury 3.5) of the crystal structure of square-shaped arrangements in adducts formed by $(C_6H_5)_2I^+ \cdot X^-$ (X=Cl, Br, I, PF_6^-). CSD Refcodes and Normalized contacts (*Nc*) are given. For DPIOCL and DPIODB01 the planar arrangement of the four halogen atoms has been evidenced by representing their least squares planes (in *yellow*). Color code: *gray*, carbon; *brown*, bromine; *violet*, iodine; *ocher*, phosphorus; *light-green*, fluorine. Halogen bonds are *blue dotted lines*; in the hexafluorophosphate salt, the longer and less directional I···F contact, formed as a "byproduct" of the halogen bonds, is in *sky blue*

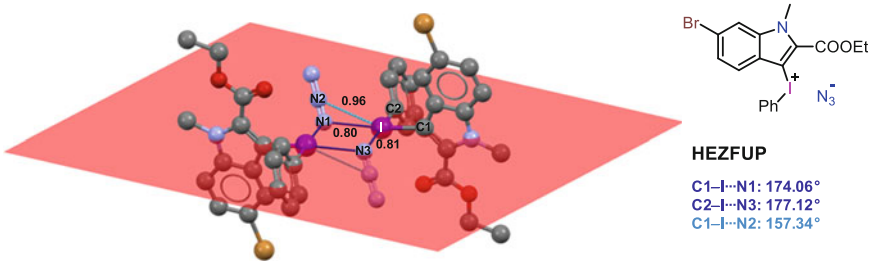

Fig. 8 Ball and stick representations (Mercury 3.5) of the crystal structure of the square-shaped arrangement in the iodonium azide HEZFUP. CSD Refcodes and Normalized contacts (*Nc*) are given. Halogen bonds are *blue dotted lines*; the longer and less directional I···N contact, formed as a "byproduct" of the halogen bonds, is in *sky blue*. The reported least squares plane (in *red*) through the halogen bonded atoms is evidence that the geometric features of shorter and more directional I···N contacts are those typical for halogen bonds. Color code: *gray*, carbon; *brown*, bromine; *violet*, iodine; *red*, oxygen; *blue*, nitrogen

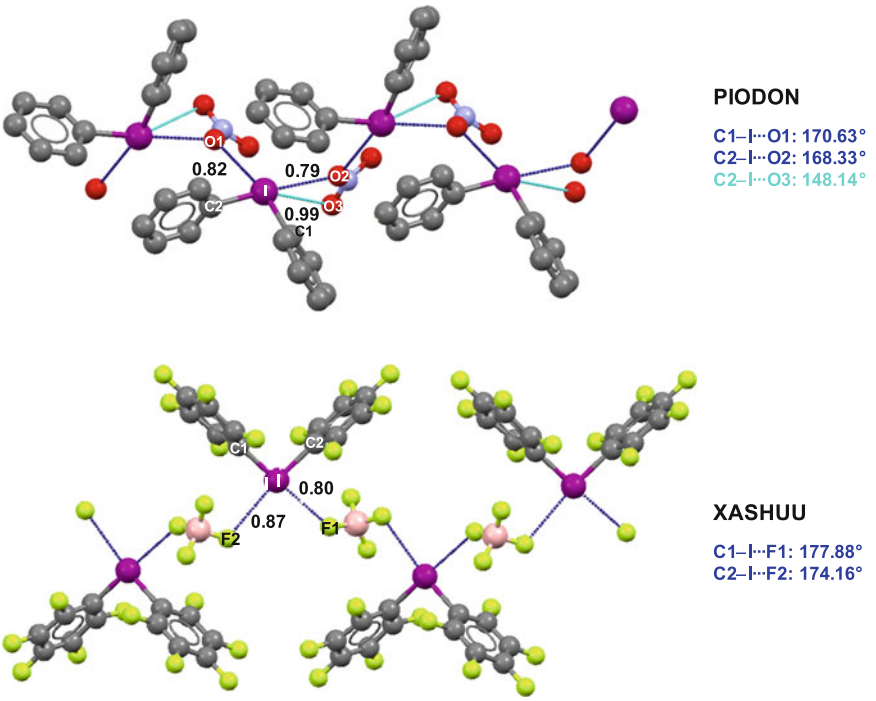

Fig. 9 Infinite chains formed by $(C_6H_5)_2I^+ \cdot NO_3^-$ (*top*) and $(C_6F_5)_2I^+ \cdot BF_4^-$ (*bottom*). Color code: *pink*, boron; other colors as in Fig. 2. Halogen bonds are *blue dotted lines*; in PIODON, the longest and least directional I···O contact, formed as a "byproduct" of the halogen bonds, is in *sky blue*

arrangement (Fig. 9), is another fairly common structural motif frequently present in the packing of crystalline iodonium salts wherein the iodine atom and the anion both behave as bidentate sites [71].

In most cases the linear directionality of the interaction is quite remarkable, but when polyatomic anions are used (e.g., NO_3^-, BF_4^-, PF_6^-, (Ar)R-SO_3^-, N_3^-), the entrance of one atom of the anion on iodine may deliver other atoms of the anion close to iodine which can form additional and poorly directional iodine···anion short contacts [72–74]. For instance, this is the case for fluorine, nitrogen, and oxygen atoms in diphenyliodonium hexafluorophosphate and nitrate (Figs. 7 and 9) and other systems (Fig. 8) [75]. It can be expected that, if the electrostatic potential on the iodine surface is uniformly positive, no correlation exists between the interaction length and the angle C–I···entering-atom. In contrast, in the systems mentioned above where iodine works as a tridentate halogen bond-donor, the least linear C–I···entering-atom interaction also tends to be the longest one. This relation is consistent with the fact that the electrostatic potential on the iodine surface is positive everywhere, but becomes most positive at the C–I extension (there is a σ-hole in that area) so the nucleophilic atom gets closer to iodine if it enters that extension.

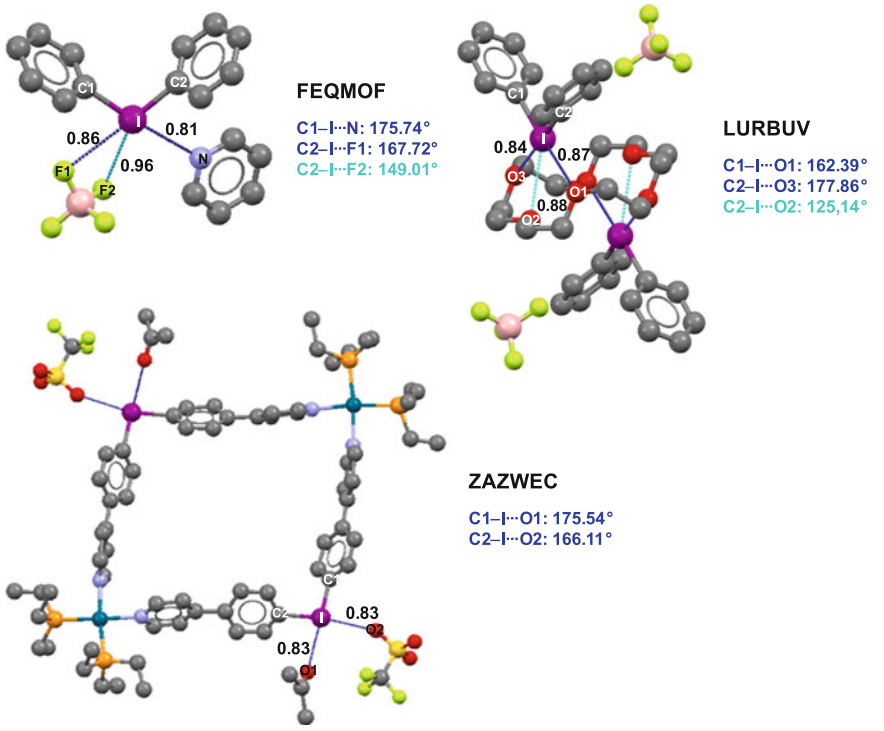

Fig. 10 Structure of diaryl iodonium derivatives where neutral lone pair donors substitute for the anion in forming halogen bonds with the iodine atom. Color code: *green-blue*, palladium, other colors as in Figs. 2 and 9. Halogen bonds are *blue dotted lines*; in LURBUV, the longest and least directional I···O contact, formed as a "byproduct" of the halogen bonds, is in *sky blue*

Mainly when the anion is a poor nucleophile (e.g., a BF_4^- or a CF_3–SO_3^- anion), neutral donors of electron density prevail over the anion in entering the iodine of iodonium salts (Fig. 10). This is the case, for instance, for the nitrogen atom of pyridine and the oxygen atom of acetone or dimethylsulfoxide [76–79]. The cation–anion attraction is absent in these contacts, but the directionality of these interactions is the same as when anions enter the iodine atom. This indicates that factors affecting I···anion contacts are the same as factors affecting I···lone-pair electron contacts. It is interesting to observe that 18-crown-6 can substitute for tetrafluoroborate in entering the iodine atom of diphenyliodonium cation: In the structure of LURBUV (Fig. 10) the shortest I···O and I···F distances are 2.949 and 7.170 Å, respectively [80]. When substituting for a fluoroborate anion as a nucleophile, the crown behaves similar to polyatomic anions: One oxygen atom enters the iodine on the extension of the C–I bond, but, because of the covalent connectivity in the crown, other oxygen atom(s) are delivered close to the iodine which forms more than two halogen bonds. Importantly, the shorter halogen bonds are once again the more linear ones. The interaction pattern around iodine in ionic λ^3-iodane

derivatives wherein the two covalently bound residues are different affords further evidence that the surface electrostatic potential at the iodine atoms is anisotropic and the observed interactions can be considered halogen bonds formed on nucleophile interactions with iodine σ-holes [67, 81–85]. In derivatives where the two pendants at iodine are the same, iodine atoms behave as bidentate sites and the two resultant contacts have different lengths. The shorter separation is typically the more linear one and is on the elongation of the more electron-withdrawing residue. This observation cannot be explained by a simple electrostatic model which would predict an isotropically decreased electron density at iodine when appended residues become more electron withdrawing. This decreased electron density would result in a shortening of both contacts at the halogen. In contrast, the σ-hole model anticipates that the depletion of the electron density on the elongation of a covalent bond is selectively dependent on the electronegativity of the bonded groups. In ionic λ^3-iodane derivatives with two different residues bound to iodine, two different σ-holes are expected on the halogen. The more positive and extended hole is on the elongation of the more electron-withdrawing pendant and a shorter and more linear halogen bond results. For example, this happens in the crystal structure of 4-methoxyphenyl-perfluorotoly-iodonium sulfonate (Fig. 11) wherein the halogen bond on the elongation of the perfluoroaromatic residue is ca. 10% shorter than that on the extension of the hydroaromatic residue and the two C–I···O angles are 174.24° and 164.08°, respectively. Other λ^3-iodane derivatives bearing two different aryl residues at iodine show the same behavior and the same holds for alkynyl-aryl-λ^3-iodane derivatives, the shorter and more linear halogen bond being on the elongation at the alkynyl pendant as a Csp is more electronegative than a Csp^2 [81–85].

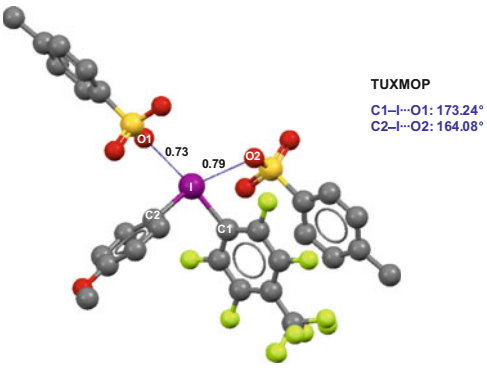

Fig. 11 Crystal structure of [(4-methoxyphenyl)-(2,3,5,6-tetrafluoro-4-trifluoromethylphenyl)]-iodonium toluene-4-sulfonate. Halogen bonds are *blue dotted lines* and colors codes are as in Fig. 10. The halogen bond on the elongation of the C–I bond formed by the 4-$CF_3C_6F_4$ moiety is shorter and more directional than the halogen bond on the elongation of the C–I bond formed by the 4-CH_3-C_6H_5 moiety

4 Neutral λ^3-Iodane Derivatives

The examples described above prove the general tendency of the iodine atom of diaryliodonium salts and congeners to form strong and linear interactions with anions. It is thus not surprising that, when a CO_2^- group is *ortho* to the iodine atom in Ph–I^+–Ph derivatives, one of the oxygen atoms of the carboxylate forms an oxygen–iodine bond which is nearly as short as a covalent O–I. A 1,2-benziodoxol-3(1*H*)-one moiety is formed, namely these λ^3-iodane derivatives assume a neutral rather than ionic structure. The pattern of covalent bonds around iodine atom has a T-shaped geometry with the O–I bond nearly collinear with one C–I bond and orthogonal to the other. Consistent with the anisotropic distribution of the electron density described in Sect. 2 for covalently bound atoms, it is expected that a σ-hole is present on the extension of the orthogonal C–I covalent bond of these neutral λ^3-iodane derivatives. It is also expected that the packing of these species in crystals is driven, or influenced, by the tendency to deliver nucleophilic sites as close as possible to these σ-holes. Indeed, this is the case in nearly all structures of neutral λ^3-iodane derivatives reported in the CSD. The incoming nucleophile is usually the carbonyl oxygen of the 1,2-benziodoxol-3(1*H*)-one moiety and the formed halogen bond affords infinite chains or discrete adducts (Fig. 12) [86–92]. Other neutral nucleophiles, e.g., water [93] or dimethylsulfoxide [94], can also enter the σ-hole on iodine of neutral λ^3-iodane derivatives (Fig. 13).

Alternatively, a chloride anion [88] can prevail over the carbonyl oxygen of the 1,2-benziodoxol-3(1*H*)-one moiety and enter preferentially the iodine atom. The formed I···O halogen bond is strong enough to drive the formation of heteromeric two component systems (Fig. 14) [89].

A T-shaped pattern of covalent bonds around the iodine similar to that in λ^3-iodane derivatives described above is also observed when the nucleophilic

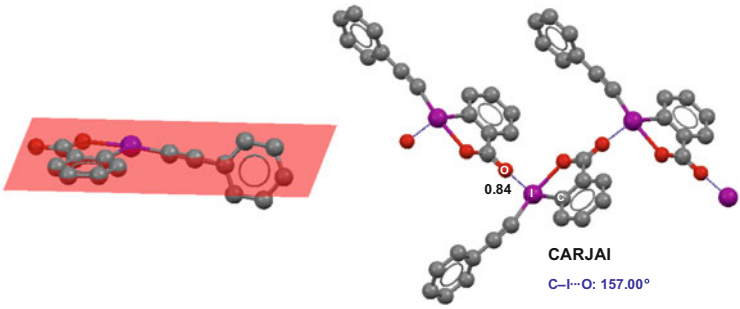

Fig. 12 Crystal structure of 1-(phenylethynyl)-1,2-benziodoxol-3(1*H*)-one where two different I–O bonds are present. One is 2.309 Å long (i.e., it is similar to a covalent I–O bond), is depicted as a *solid red-violet line*, and forms the planar 1-substituted-1,2-beniodoxolone moiety (*left*). The other I···O bond is 2.933 Å long (i.e., 0.84 the sum of oxygen and iodine van der Waals radii) and forms infinite and supramolecular chains (*right*). It can be considered as a halogen bond, is depicted as a *blue dotted line*, and is produced by the entrance of a lone pair of the carbonyl oxygen in the σ-hole of iodine. Color codes as in Fig. 2

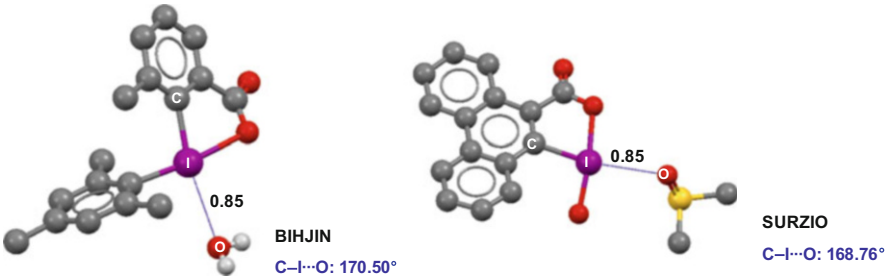

Fig. 13 Halogen bonds (*blue dotted lines*) formed by water (*left*) and dimethylsulfoxide (*right*) with the iodine atom of neutral λ^3-iodane derivatives having a T-shaped pattern of covalent bonds around iodine. Color codes as in Fig. 2

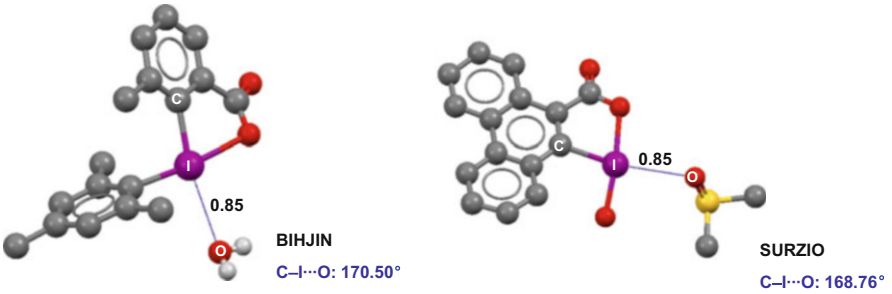

Fig. 14 Halogen bonds (*blue dotted lines*) formed by chloride anions with the iodine atom of neutral λ^3-iodane derivatives. Color codes as in Fig. 7

substituent *ortho* to the iodine atom in Ph-I^+-Ph derivatives is different from a carboxylate. T-shaped geometries were observed when the *ortho* substituent is an enolate carbon [81] or an alcoholate oxygen [95–100] and in the respective crystals a nucleophilic site (usually the oxygen atom of another benziodoxole unit) forms a short contact with iodine on the elongation of a C–I covalent bond (Fig. 15).

The nucleophilic atom entering the extension of the orthogonal C–I covalent bond can also be the oxygen of a sulfonate group [101] or the nitrogen of a cyano group [102] bound to the benziodoxole iodine atom (Fig. 16, left). T-shaped geometries giving quite linear halogen bonds are also observed in neutral λ^3-iodane derivatives where the trivalent iodine forms acyclic arrays rather than benziodoxole rings as is the case for cyano-fluoro-pentafluorophenyl-λ^3-iodane [103], where the halogen bond-acceptor atom is the iodine-bound fluorine (Fig. 16, right).

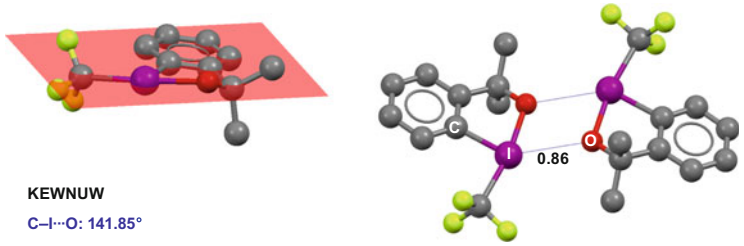

Fig. 15 Crystal structure of 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1λ^3,2-benziodoxole (Togni's reagent, a very popular trifluoromethylating agent). As in 1,2-benziodoxol-3(1*H*)-one analogues, two different I–O bonds are present: One is 2.118 Å long (i.e., it is similar to a covalent I–O bond), is depicted as a *solid red-violet line*, and forms the planar 1-substituted-1,2-beniodoxole moiety (*left*); the other I···O bond is 2.998 Å long (i.e., 0.86 the sum of oxygen and iodine van der Waals radii), is depicted as a *blue dotted line* (as it can be understood as a typical halogen bond), and forms dimers (*right*) via the entrance of an oxygen lone pair in the σ-hole of iodine

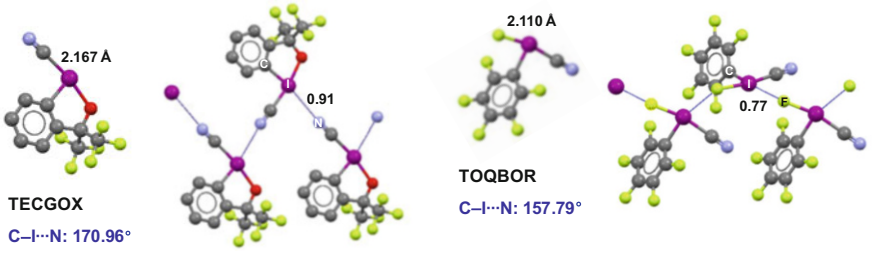

Fig. 16 TEGCOX: crystal structure of 1-cyano-3,3-bis(trifluoromethyl)-1,3-dihydro-λ^3-benzoiodoxole where the iodine is bound to two cyano Group. The I–CN bond is 2.167 Å long (i.e., it is quite similar to typical I–C covalent bonds), is depicted as a solid *grey-violet line*, and forms the T-shaped pattern of covalent bonds around iodine. The I···NC bond is 3.233 Å long (i.e., 0.91 the sum of nitrogen and iodine van der Waals radii), is depicted as a *blue dotted line*, and forms infinite chains via the entrance of the nitrogen lone pair in the σ-hole of iodine. TOQBOR: crystal structure of cyano(fluoro)(pentafluorophenyl)-λ^3-iodane wherein the fluorine atom interacts with iodine as the cyano group in TEGCOX

5 Other Hypervalent Iodine Derivatives

Some λ^5-iodane derivatives are very useful oxidizing reagents in organic synthesis, e.g., 2-iodoxy-benzoic acid (IBX) and the Dess–Martin reagent (DMP) effectively convert primary and secondary alcohols to aldehydes and ketones, respectively [104]. Also directional preferences of short contacts observed in the solid between electron rich sites and iodine of some λ^5-iodane derivatives are nicely consistent with an asymmetric electron density distribution on iodine resulting in the presence of most positive regions on the covalent bonds extensions, and the preferential entrance of nucleophiles in these regions [105]. For instance, the σ-hole model predicts that in the spirocyclic compound shown in Fig. 17, the electrostatic

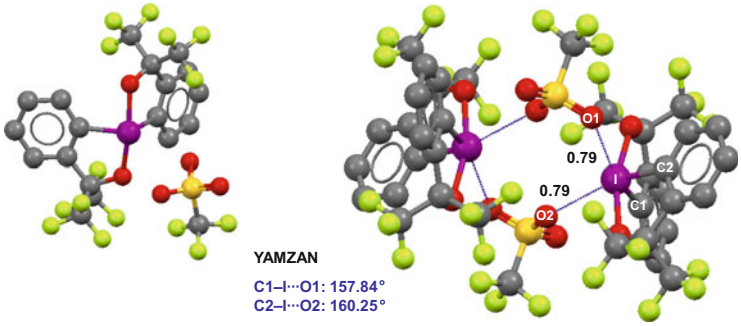

Fig. 17 Molecular structure of bis[αα-bis(trifluoromethyl)benzenemethanolato(2-)-C^2,O^α]iodine trifluoromethansulfonate (*left*) and its halogen bonded dimer (*right*) present in the solid. Halogen bonds are *blue dotted lines*

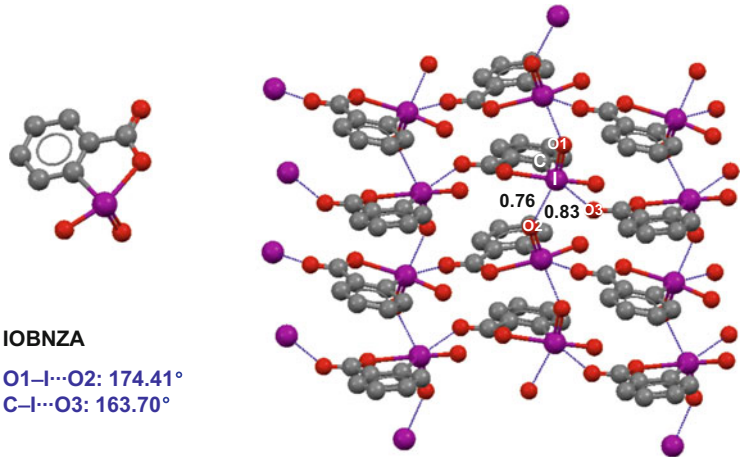

Fig. 18 Single molecule (*left*) and 2D net (*right*) formed by 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide. Halogen bonds are *blue dotted lines*; color code as in Fig. 2 [107]

potential at the outer surface of iodine is entirely positive, but it is most positive on the extension of C–I^+ bonds. In the crystal, iodine behaves as a bidentate electrophile and two oxygen atoms of two different trifluoromethanesulfonate anions enter the σ-holes at iodine, form short and directional halogen bonds, and assemble a tetrameric unit [106]. 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide self-assembles in the solid after a similar protocol and affords two-dimensional (2D) and infinite nets (Fig. 18) [107].

6 Conclusions

After the IUPAC definition, a halogen bond occurs when "there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity" [12]. Extensive experimental and computational results consistently prove that in monovalent halogens the electrophilic region is on the extension of and opposite to the covalent bond in which they are involved. Linear directionality is thus a fingerprint of halogen bonds. The ability of a covalent bond to give rise to a region of depleted electron density on its elongation is a general phenomenon and chalcogens, pnictogens, and tetrels, which typically form two, three, and four covalent bonds, can display up to two, three, and four regions of decreased electron density, respectively. These regions can be markedly positive if on the elongation of a covalent bond to an electron- withdrawing group, and they can form short, directional, and attractive contacts with nucleophiles. We surmised that if chalcogens, pnictogens, and tetrels can form attractive and directional interactions with nucleophiles as a consequence of an anisotropic distribution of the electron density on their surface, the same may also happen for di-, tri-, and tetravalent iodine derivatives. In this chapter we have discussed the geometric features of the bonding pattern around iodine in some of its hypervalent derivatives [1–6] as a strong indication that: (1) the distribution of the electron density around the hypervalent iodine atom is anisotropic; (2) this anisotropy affects the interactions the iodine atom is involved in, and (3) some of the longer and weaker bonds given by iodine can be considered halogen bonds. Specifically, interactions formed by neutral and ionic λ^3-iodane and λ^5-iodane derivatives fully match the geometrical prerequisites of halogen bonds. In the literature these longer and weaker bonds are typically named secondary bondings [7–11] but the use of the term halogen bond may offer the advantage to convey immediately some key features of the interaction, such as its directionality and the relationships between structure of interacting groups and interaction strength [108–110].

Polyvalent halogens show a particularly complex and manifold bonding pattern and many studies have analyzed the nature and properties of these bonds [111, 112]. This is particularly true for polyvalent iodine derivatives where the unique features of the bonds given by iodine enables the diversified and useful reactivity of these derivatives, e.g. in oxidation and carbon–carbon bond formation reactions. The mindset underlying the concept of the halogen bond may, when applied to hypervalent iodine compounds, offer new opportunities to design and to manipulate the bonding pattern around the iodine atom. Possible advantages may span numerous and different fields, for instance the control of the stereo- and enantioselectivity in reactions of hypervalent iodine derivatives.

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Index