Springer Theses
Recognizing Outstanding Ph.D. Research

Ana Escribano Cuesta

New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids

Springer

Springer Theses

Recognizing Outstanding Ph.D. Research

For further volumes:
http://www.springer.com/series/8790

Aims and Scope

The series "Springer Theses" brings together a selection of the very best Ph.D. theses from around the world and across the physical sciences. Nominated and endorsed by two recognized specialists, each published volume has been selected for its scientific excellence and the high impact of its contents for the pertinent field of research. For greater accessibility to non-specialists, the published versions include an extended introduction, as well as a foreword by the student's supervisor explaining the special relevance of the work for the field. As a whole, the series will provide a valuable resource both for newcomers to the research fields described, and for other scientists seeking detailed background information on special questions. Finally, it provides an accredited documentation of the valuable contributions made by today's younger generation of scientists.

Theses are accepted into the series by invited nomination only and must fulfill all of the following criteria

- They must be written in good English.
- The topic should fall within the confines of Chemistry, Physics, Earth Sciences, Engineering and related interdisciplinary fields such as Materials, Nanoscience, Chemical Engineering, Complex Systems, and Biophysics.
- The work reported in the thesis must represent a significant scientific advance.
- If the thesis includes previously published material, permission to reproduce this must be gained from the respective copyright holder.
- They must have been examined and passed during the 12 months prior to nomination.
- Each thesis should include a foreword by the supervisor outlining the significance of its content.
- The theses should have a clearly defined structure including an introduction accessible to scientists not expert in that particular field.

Ana Escribano Cuesta

New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids

Doctoral Thesis accepted by
the Institute of Chemical Research
of Catalonia (ICIQ), Spain

Springer

Author
Dr. Ana Escribano Cuesta
Lead Optimization Fungicides
BASF SE
Ludwigshafen
Germany

Supervisor
Prof. Dr. Antonio M. Echavarren
Institution of Chemical Research of Catalonia, ICIQ Avgda
Tarragona
Spain

ISSN 2190-5053 ISSN 2190-5061 (electronic)
ISBN 978-3-319-00701-4 ISBN 978-3-319-00702-1 (eBook)
DOI 10.1007/978-3-319-00702-1
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013941498

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Parts of this thesis have been published in the following journal articles:

Encapsulation Studies of Cationic Gold Complexes within a Self-Assembled Hexameric Resorcin[4]arene Capsule

Adriaenssens, L.; Escribano-Cuesta, A.; Homs, Anna.; Echavarren, A. M.; Ballester, P. *Eur. J. Org. Chem*. **2013**, DOI: 10.1002/ejoc.201201592

The Role of Cyclobutenes in Gold(I)-Catalyzed Skeletal Rearrangement of 1,6-Enynes

Escribano–Cuesta, A.; Perez–Galan, P.; Herrero-Gomez, E.; Sekine, M.; Braga, A. C.; Masseras, F.; Echavarren, A. M. *Org. Biomol. Chem*. **2012**, *10*, 6105–6111

Gold–Catalyzed Alkyne Cyclizations with Alkenes and Arenes

López–Carrillo, V.; Escribano–Cuesta, A.; Huguet, N.; Echavarren, A. M. Organic Reactions, *accepted*

Synthesis of the Tetracyclic Core Skeleton of the Lundurines by Gold–Catalyzed Cyclization

Ferrer, C.; Escribano–Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020

Gold-Catalyzed Reactions of 1,5- and 1,6-Enynes with Carbonyl Compounds: Cycloaddition vs. Metathesis

Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J*. **2009**, *15*, 5646–5650

To my family
The difference between persistence
and stubbornness is success

S. J. Danishefsky

Life is what happens to you
while you're busy
making other plans

John Lennon

Supervisor's Foreword

Gold chemistry has attracted increasing attention in recent years in the realm of homogeneous catalysis. In particular, gold complexes have been found to be the most powerful catalysts for electrophilic activation of alkynes toward a variety of nucleophiles under homogeneous conditions. Moreover, allenes and alkenes can also be effectively activated by gold complexes. Our group at the Institute of Chemical Research of Catalonia (ICIQ) has developed new gold-based methodologies for the formation of carbon–carbon bonds based on the attack of different nucleophiles like alkenes, arenes, and electron-rich heteroarenes to alkynes. It has been the purpose of this Ph.D. thesis to discover new gold-catalyzed transformations of alkynes and to develop new transformations for the ready build up of molecular diversity and complexity, in particular in the selective formation of tricyclic compounds, dihydropyrans, 1,3-dienes, and cyclobutenes. Furthermore, an approach for the synthesis of the tetracyclic core of the lundurines has been developed by using a gold-catalyzed cyclization reaction as the key step. The lundurines are a new type of indoles alkaloids, characterized by an unusually complex architecture with a cyclopropane fragment embedded within a hexacyclic ring system that includes a 1*H*–azocine[5,4–*b*]indole ring. Interestingly, lundurines B and D have shown significant in vitro cytotoxicity toward B16 melanoma cells.

This work is an important contribution in the development of new synthetic methodology using gold catalysts. The synthesis of the tetracyclic core of the lundurines is a major step toward the achievement of an efficient total synthesis of this class of antitumor compounds.

Tarragona, May 2013 Antonio M. Echavarren

Contents

Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations of "Guidelines for authors" of *J. Org. Chem.* **2007**, *70*, 13A–27A.

Boc	*tert*-Butyloxycarbonyl
BOP	Bis(2-oxo-3-oxazolidyl)phosphinic
cod	Cycloocta-1,5-diene
Cy	Cyclohexyl
dba	Dibenzylideneacetonato
DCC	*N,N′*-Dicyclohexylcarbodiimide
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMEDA	*N,N′*,-Dimethylethane-1,2-diamine
DNBS	2,4-Dinitrobenzenesulfonyl
dppm	1,1-Bis(diphenylphosphino)methane
Fmoc	9-Fluorenylmethyloxycarbonyl
hfacac	Hexafluoroacetylacetonato
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
methallyl	2-Methyl-allyl
Mes	Mesityl (2,4,6-$Me_3C_6H_2$)
NMP	*N*-Methylpyrrolidine
OTf	Trifluoromethanesulfonate
phen	1,10-Phenantroline
PMP	Pentamethyl piperidin
PNBn	*p*-Nitrobenzyl
Tos	*p*-Toluenesulfonyl
TSA	*p*-Toluensulfonic acid

Chapter 1
Introduction

Transition metal catalysis is one of the most important tools in organic synthesis, making the development of highly efficient and selective transformations possible. In this context, the electrophilic activation of alkynes by π-Lewis acids [1] has become a broadly used transformation for the synthesis of highly functionalized carbo- and heterocycles.

1.1 Metal-Catalyzed Alkyne Activation

In the field of homogeneous catalysis, electrophilic metals [palladium(II), platinum(II), rhodium(II), iridium (I), ruthenium(II), cobalt(I), titanium(II) and gold(I)] activate alkynes under mild conditions [2–8]. When an alkyne behaves as a ligand, there are four orbitals that can participate in the bonding (Fig. 1.1) [4]. The in-plane orbitals, $\pi_{\|}$ and $\pi^{*}_{\|}$, are responsible for a σ-donor interaction (M $\leftarrow$ L donation) and a π-acceptor interaction (M $\rightarrow$ L back-donation) respectively. The orthogonal, out-of-plane orbitals, $\pi_{\perp}$ and $\pi^{*}_{\perp}$, are engaged in the M $\leftarrow$ L π donation and the δ symmetry M $\rightarrow$ L back-donation respectively. This latter interaction can be neglected, due to the weak overlap of the orbitals.

In the case of $[Au(alkyne)]^{+}$ complexes, the contributions of the individual σ and π terms have been analyzed quantitatively by high level computational methods [9]. For the $[Au(acetylene)]^{+}$ complex, the σ interaction is the largest contribution to the orbital term (ca. 65 %), followed by the in-plane π back-donation (ca. 27 %) and the orthogonal π back-donation (ca. 7 %) (see Fig. 1.1). Thus, alkynes are strong-electron σ donors, but fairly weak π acceptors toward gold(I). Consequently, for $[Au(alkyne)]^{+}$ complexes the Dewar-Chatt-Duncanson model [10–12] predicts an elongation of the triple bond, due to the net shift of electron density from the bonding π into the antibonding π^{*} orbital. Furthermore, the coordination withdraws electron density from the alkyne. Thus, the alkyne is more electrophilic, and hence more susceptible to nucleophilic attack.

A. Escribano Cuesta, *New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids*, Springer Theses, DOI: 10.1007/978-3-319-00702-1_1,

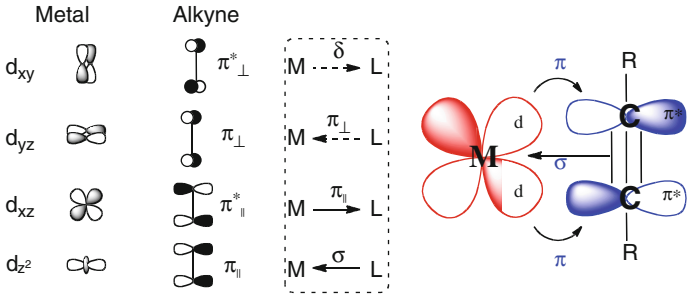


Fig. 1.1 Qualitative orbital diagram

The addition of water to alkynes catalyzed by Brønsted acids usually requires harsh conditions and leads to numerous side reactions. A classical solution is the replacement of a proton by the isolobal Hg^{2+}. The soft character [13, 14] of this large and polarizable cation has a much greater affinity to the substrate, leading to reactions that proceed under mild conditions [5]. However, the use of stoichiometric amounts of toxic mercury salts is inconvenient. This problem was solved by the use of gold, which shows a higher affinity to π systems. In addition, the $[AuL]^+$ fragment can be readily cleaved under the reaction conditions, thus ensuring an efficient turnover. Consequently, the $[AuL]^+$ fragment can be considered equivalent to H^+ and Hg^{+2}, but with an increased carbophilic character. However, this consideration is too simplistic. Thus, gold complexes can form carbene intermediates [15–18], in which the main contribution to the substantial shortening and strengthening of the $[Au{=}CH_2]^+$ bond is due to relativistic effects [19, 20]. These properties make gold an excellent soft Lewis acid for the activation of C–C multiple bonds [5] under mild reaction conditions. As a result, gold complexes have been successfully employed in nucleophilic additions (using heteroatom- or carbon nucleophiles), Friedel–Crafts reactions, C–H activations, hydrogenations, and oxidations [2–8].

1.2 Gold Properties

Gold is a metal characterized by its high electronegativity [21–24]. The high Lewis acidity of gold in comparison with other metal of group 11 can be explained by the contraction of the valence s or p orbitals due to the relativity. As a result, an expansion of the atomic d and f orbitals takes place, because of an increased shielding effect by the contracted core. The altered intrinsic energies and diffuse character of the d orbitals explain the chemically soft character of gold(I) complexes. These effects lead to a net contraction of the Au–L bond. However, this bond contraction is sensitive to the nature and the electronegativity of the ligand present in the coordination sphere of gold. This fact has a high impact in the

catalyst properties, because it allows the modulation of the reactivity of the gold complex depending of the ligand. The formal "pulling in" of a ligand results in more effective orbital overlap and increased bond strength.

1.3 Gold Complexes for Alkyne Activation

Simple AuCl, $AuCl_3$ or $NaAuCl_4$ are carbophilic enough to catalyze the addition of nucleophiles to alkynes. However, gold(III) can be reduced easily to gold(0) and AuCl by disproportionation. Therefore it is necessary to stabilize gold with donor ligands. The reactivity of the complexes can be modulated by changing the ligand in the coordination sphere of gold. For example, an increase in the electron-density of the metal is clearly observed by moving from electron-withdrawing to electron-donating ligands (Fig. 1.2).

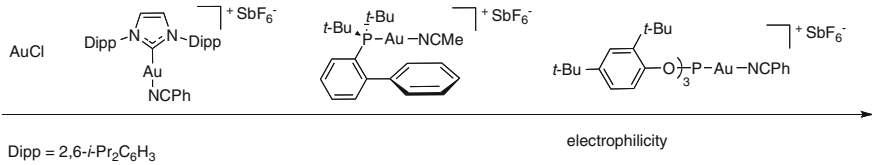


Fig. 1.2 Ligand modulation of the reactivity of gold(I) complexes

Gold(I) preferentially coordinates in a linear bi-coordinative geometry. This limited coordination requires the abstraction of one ligand from a neutral bi-coordinate gold(I) species to generate in situ $[AuL]^+$. In the case of $[AuMe(PPh_3)]$, the Au-alkyl bond is cleaved by a protic acid [25, 26]. Similarly, cationic gold(I) complexes can be formed in situ by chloride abstraction from [AuLCl] complexes using one equivalent of a silver(I) salt with a non-coordinating anion [27–29]. The cationic version of these complexes with a weakly coordinated ligand (acetonitrile or benzonitrile in most cases) instead of the chloride has been prepared.

In general, complexes with donating ligands that are sterically hindered are very robust catalysts, due to their higher stability. Complexes **1-4** bearing bulky biphenyl phosphines, which are excellent ligands for palladium-catalyzed reactions, lead to very active catalysts upon activation with silver(I) salts [30]. The analogous cationic version, complexes **5-8** are more convenient catalysts [15, 31, 32] since reactions can be carried out in the absence of silver(I) salts [28]. Related complexes **9** and **10** with a weakly coordinated bis(trifluoromethane-sulfonyl)amide NTf_2 have also been reported [33] (Fig. 1.3).

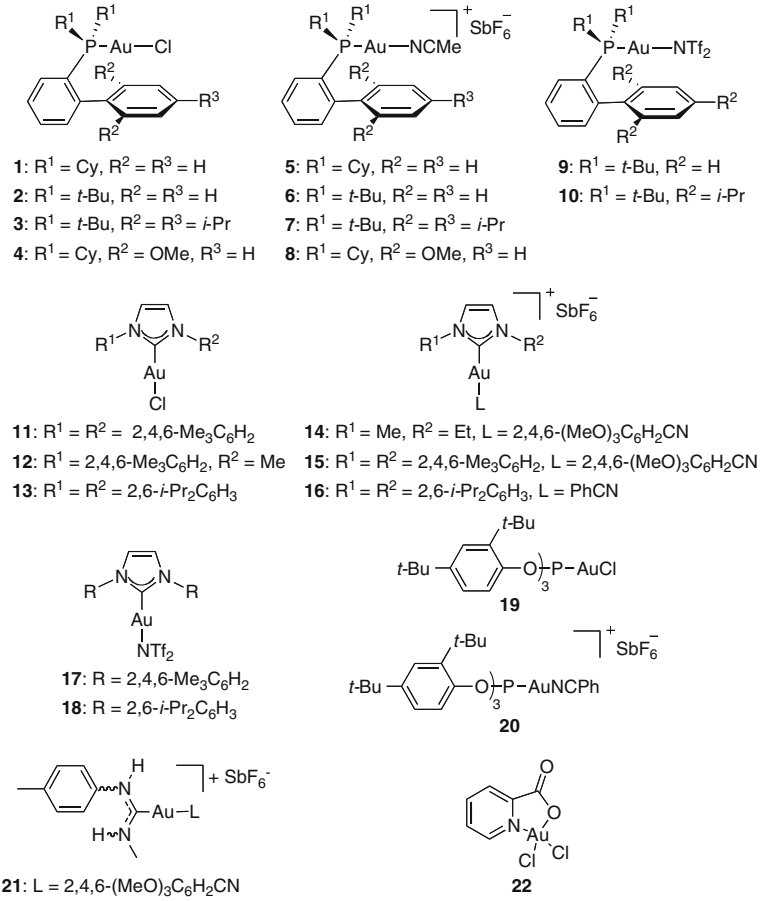


Fig. 1.3 Gold complexes

Gold complexes with *N*-heterocyclic carbenes (NHC) [34–37], such as **11-13** [16, 30, 38–42], cationic **14-16**[43, 44] as well as neutral **17** and **18** [45, 46], usually afford more selective catalysts, due to the more donating ability of the NHC in comparison with phosphine ligands. Gold hydroxo complex [Au(IPr)OH] can also be used as catalyst by activation with a Brønsted acid [47, 48]. Acyclic carbenes [49–53], such as **21**, and other related carbenes [54–58] also give rise to selective catalysts of moderate electrophilicity.

Gold(I) complexes with phosphites as ligands are more active catalysts, due to their more electron-withdrawing character. The complexes **19** [31] and its cationic derivative **20** [42, 59, 60], bearing tris(2,6-di-*tert*-butylphenyl)phosphite are among the most electrophilic cationic gold(I) catalysts reported to date.

In general, gold(III) complexes characterized by a square-planar geometry, are used less than gold(I) complexes. The use of pyridinecarboxylic acid as ligand, as

in complex **22** [61, 62], allows the stabilization of the catalyst. It is worth mentioning that higher oxidation states also increase the affinity to hard donor sites. Therefore, gold(III) complexes are more oxophilic, whereas gold(I) complexes are more carbophilic.

1.4 Gold-Catalyzed Nucleophilic Additions to Alkynes

Gold(I) complexes exhibit excellent chemoselectivity towards C–C π-systems. Although $[AuL]^+$ does not selectively coordinate alkynes over other π-systems, alkynes are activated selectively because the nucleophilc attack is thermodynamically more favored. In the context of 1,6-enynes, while the $[AuL]^+$ species indifferently coordinates to both π-systems, the addition occurs exclusively to the $[Au(alkyne)]^+$ complex, which has a lower LUMO than the analogous $[Au(alkene)]^+$ complex [63].

The coordination of the $[AuL]^+$ fragment to the alkyne moiety allows the *anti* attack of nucleophiles due to the formation of π-complex **I** and, consequently, the formation of *(E)*-alkenyl-gold complex **II** as intermediate (Fig. 1.4).

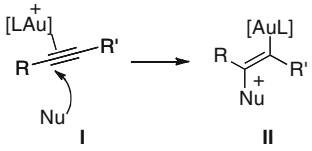


Fig. 1.4 Gold(I)-catalyzed addition of nucleophiles to alkynes

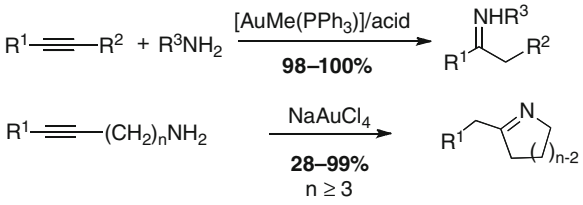
Gold-catalyzed nucleophilic addition to alkynes are operationally safe and simple to perform, and do not generally require rigorously inert reaction conditions.

1.4.1 Gold-Catalyzed Addition of Carbon-and Heteronucleophiles to Alkynes

The gold-catalyzed inter- and intramolecular addition of carbon- and heteronucleophiles to alkynes leads to a wide variety of products [6]. In the case of nitrogen nucleophiles, the addition of amines,[1] anilines [67, 68], imines [69], pyridines[2] and azides [72] is possible (Scheme 1.1).

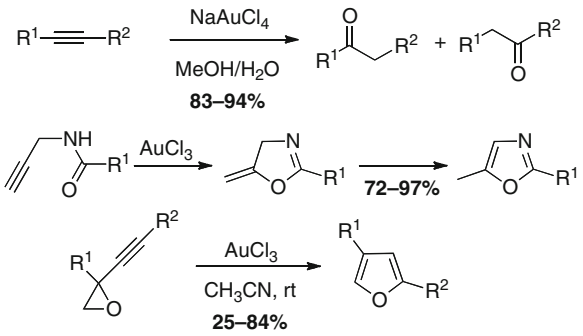
[1] Selected examples: [64–66].

[2] Selected examples: [70, 71].



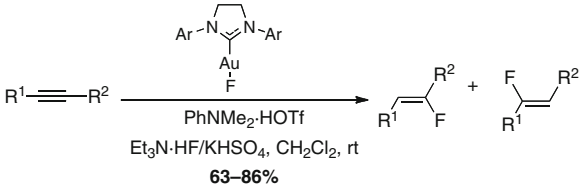
Scheme 1.1 Selected examples for the addition of nitrogen nucleophiles to alkynes

Alcohols,[3] carboxylic acids [79], carbonyl compounds,[4] carboxamides [84], epoxides,[5] sulfoxides[6] and thiols[7] can also participate as nucleophiles (Scheme 1.2).



Scheme 1.2 Selected examples for the addition of oxygen nucleophiles to alkynes

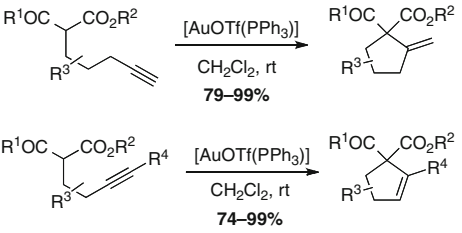
The hydrochlorination [92] and hydrofluorination [93] of alkynes catalyzed by gold complexes have also been reported (Scheme 1.3).



Scheme 1.3 Gold(I)-catalyzed hydrofluorination of alkynes

[3] Selected examples: [73–78].
[4] Selected examples: [80–83].
[5] Selected examples: [85–87].
[6] Selected examples: [88, 89].
[7] Selected examples: [90, 91].

Two types of carbon nucleophiles are commonly utilized in gold catalysis: electron-rich (hetero)arenes [3, 6] and 1,3-carbonyl compounds [94–104]. The first will be discussed later. The addition of 1,3-carbonyl compounds to alkynes, known as the Conia-ene cyclization [94–104], takes place via the corresponding enol tautomer or the corresponding silyl enol ether (Scheme 1.4).

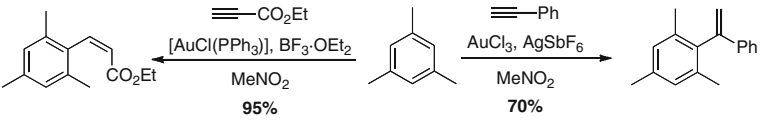


Scheme 1.4 Gold(I)-catalyzed intramolecular addition of 1,3-carbonyl compounds

1.4.2 Gold-Catalyzed Friedel-Crafts-Type Reactions

The gold-catalyzed reaction of alkynes with aromatic units has been extensively studied [105–107]. This reaction allows the synthesis of polycyclic aromatic and heteroaromatic systems via Friedel-Crafts-type processes. Although, the C–H activation of aryl compounds by gold(III) has been known for more than 70 years,[8] it is accepted that the Friedel-Crafts-type reaction proceeds via $[Au(alkyne)]^+$ complexes and subsequent electrophilic aromatic substitution with the arenes or heteroarene compounds.

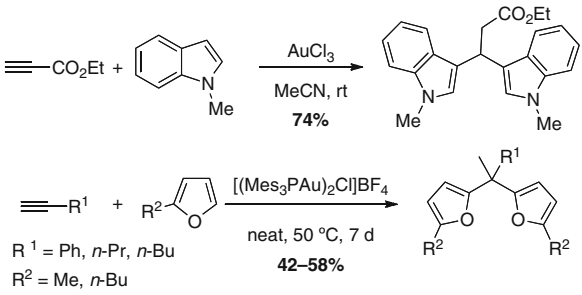
The gold-catalyzed intermolecular hydroarylation of electron-rich alkynes leads to 1,1-disubstituted alkenes [116]. The inverse regioselectivity in favor the 1,2-disubstituted alkenes is observed for alkynes with electron-withdrawing groups (Scheme 1.5) [117].



Scheme 1.5 Gold-catalyzed hydroarylation of alkynes

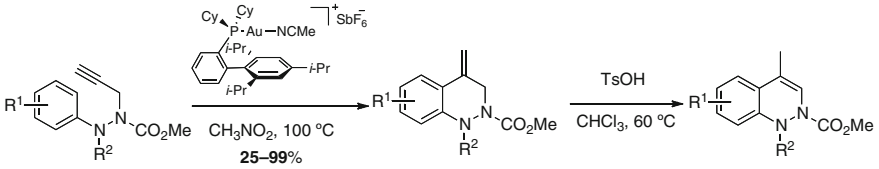
[8] Selected examples for the direct auration of arenes and heteroarenes: [47, 108–115].

In contrast, the intermolecular reaction of heteroarenes, such as indoles [118], 2,3-benzofurans [119], and furanes [120, 121],[9] generally results in a double addition to the alkyne (Scheme 1.6).



Scheme 1.6 Gold-catalyzed Friedel-Crafts-type addition of heteroarenes to alkynes

The intramolecular gold-catalyzed hydroarylation of alkynes is a well-established methodology, which allows the synthesis of a broad range of complex products. Some examples are the synthesis of *N*-tosyl-1,2-hydroquinolines [122], cinnoline derivatives [123], phenantrenes [124], coumarines [117], and pyrrolo[1,2-a]quinilines [125, 126] (Scheme 1.7).

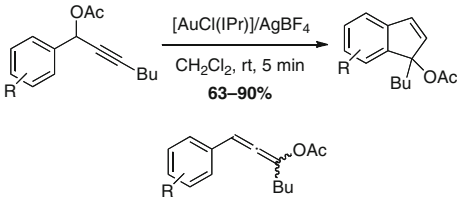


Scheme 1.7 Formation of cinnoline by gold(I)-catalyzed hydroarylation of *N*-propargyl-*N*′-arylhydrazines

Indenes can be synthesized via intramolecular hydroarylation of propargyl acetates catalyzed by NHC gold(I) complexes [127, 128]. The formation of the indenes proceeds via a 1,3-shift to form an allene, followed by the hydroarylation (Scheme 1.8). Notably, this reaction requires strictly anhydrous conditions, because conjugated enones and enals are isolated in the presence of water [129]. Related transformations include reaction with propagyl sulphides or dithioacetals,

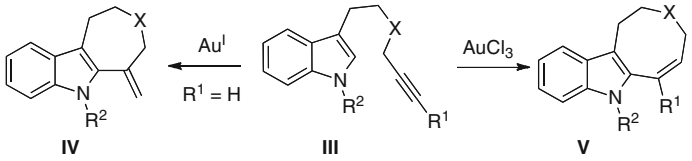
[9] In contrast, the gold(I)-catalyzed reaction of phenylacetylene and 2,5-disubstituted furane delivers the product of mono-addition and a phenol derivative.

to produce indenes [130], or the synthesis of naphthalenes via double migration cascade reactions [131, 132].



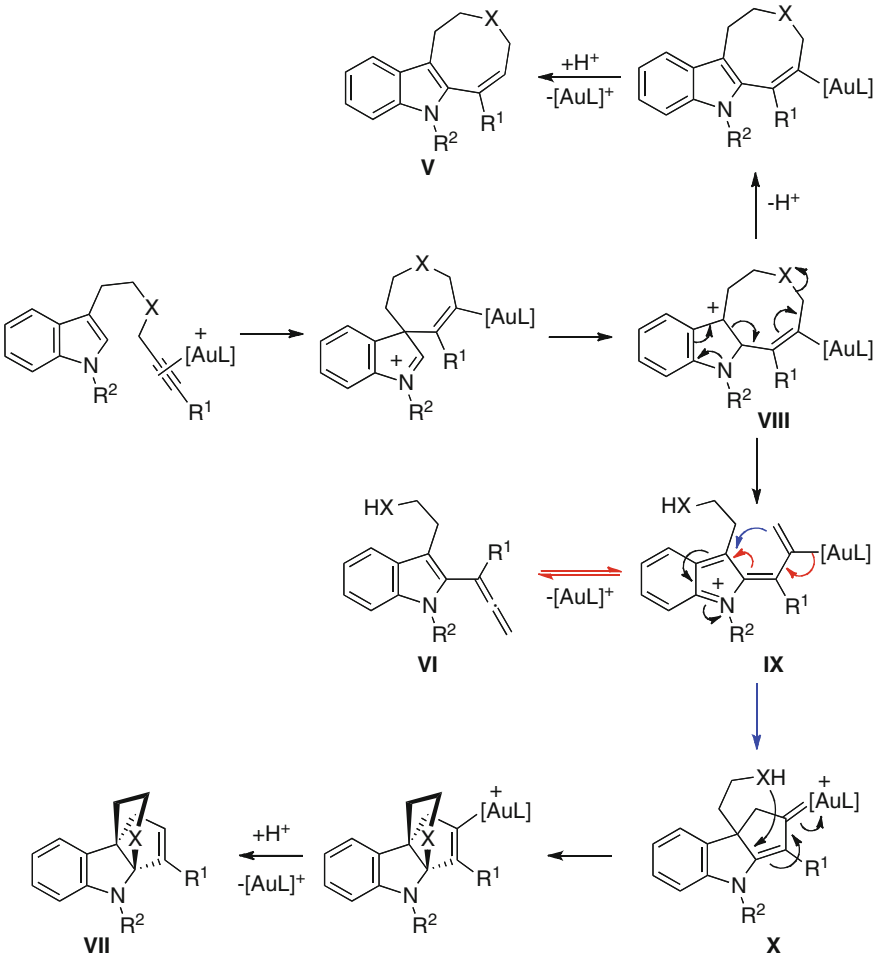
Scheme 1.8 Gold(I)-catalyzed synthesis of indenes from aryl propargyl acetates

The gold-catalyzed intramolecular reaction of indoles with alkynes is also a well-known reaction. Alkynyl indole of type **III** can lead to the formation of azepino[4,5-*b*]indole derivatives **IV**, via 7-*exo-dig* cyclization, or indoloazocine **V**, via 8-*endo-dig* cyclization (Scheme 1.9) [118, 133, 134].



Scheme 1.9 Intramolecular gold(I)-catalyzed reaction of indoles and alkynes

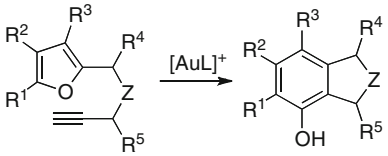
Cationic gold(I) complexes favor the formation of six- and seven-membered rings by 6-*endo-dig*, 6-*exo-dig*, and 7-*exo-dig* cyclization. However, indoloazocines **V** are selectively obtained with $AuCl_3$ via 8-*endo-dig* cyclization. Internal alkynes are also active in the intramolecular process leading to allenes **VI** and tetracyclic compounds **VII** (Scheme 1.10). In Scheme 1.10, the proposed mechanism for the formation of the different products is shown. Nucleophilic attack of the indole on the activated alkyne affords intermediate **VIII**, which arises from a 1,2-shift of the initially formed seven-membered ring iminium cation. Proton loss from **VIII** forms azocine **V**, while protonation of intermediate **VIII** leads to an open intermediate **IX**, which rearranges to the final allene **VI** or the tetracyclic compound **VII** via Michael-type addition of the XH group in intermediate **X**.



Scheme 1.10 Mechanism of the intramolecular reaction of indoles and alkynes

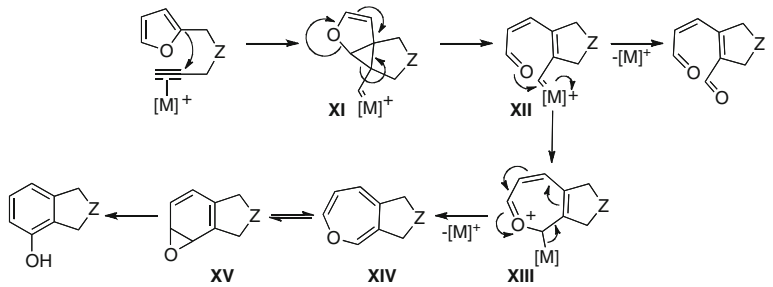
This methodology and its application on total synthesis will be discussed in more detail in Chap. 3.

Generally, the intramolecular reaction of furanes with alkynes forms phenols in good to excellent yields using catalytic gold(I) [135], $AuCl_3$ [62, 136–144], or heterogeneous gold [145] (Scheme 1.11).



Scheme 1.11 Synthesis of phenols via gold-catalyzed intramolecular reaction of furanes and alkynes

The mechanistic proposal depicted in Scheme 1.12 is based on experimental and theoretical studies using gold and platinum as catalysts [139, 145–147]. Nucleophilic attack of the furan to the activated alkyne gives cyclopropyl metal carbene **XI**. This intermediate rearranges to the conjugated metal carbene **XII**. In water, the carbene intermediate can evolve into the corresponding aldehyde, while in the absence of an external nucleophile, a [2+2] cycloaddition leads to **XIII**. Consequently, intermediate **XIII** undergoes metal elimination to form oxepine **XIV**, which is in equilibrium with the corresponding arene oxide **XV** [148].[10] Finally, intermediate **XV** aromatizes to provide the final phenol.



Scheme 1.12 Proposed mechanism for the formation of phenols

Another application of this methodology allows the synthesis of benzofurans [149], chromans [150], dihydrobenzofurans [150], dihydroindoles [150], tetrahydroquilones [150] or complex tetracyclic products [151] in a highly selective manner.

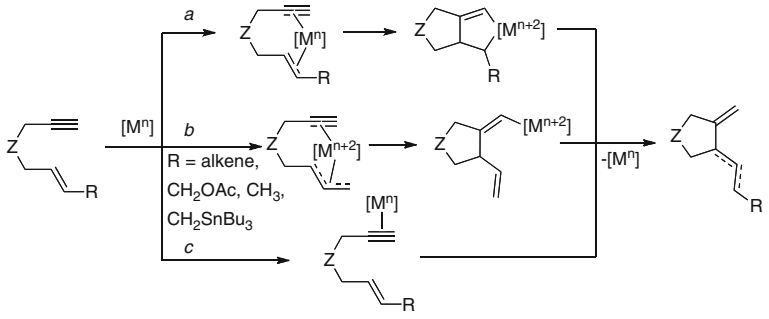
*1.4.3 Gold-Catalyzed Cyclization of 1,*n*-Enynes*

Metal-catalyzed cyclization of enynes has become an attractive and popular methodology for the straightforward synthesis of carbo- and heterocyclic

[10] The intermediate arene oxide XV was trapped by reaction with *N*-phenyltriazolinedione.

compounds. This versatile transformation can be promoted by a large array of transition metals.[11]

With regard to the mechanism, three pathways are possible depending on the type of coordination of the metal to the enyne (Scheme 1.13). In the first pathway, the simultaneous coordination of the metal to the alkyne and alkene leads to the formation of 1,3- and 1,4-dienes through metallacyclopentene intermediates (pathway a, Scheme 1.13). In this process, a two-electron oxidation of the metal takes place, which is favorable for palladium(0) and platinum(0), but highly unlikely for gold(I) under ordinary conditions. The second pathway is possible when the alkene motif bears a functional group that promotes the formation of a π-allylmetal intermediate (pathway b, Scheme 1.13). Finally, the third pathway is based on the selective activation of the alkyne moiety by the metal (pathway c, Scheme 1.13).



Scheme 1.13 Different pathways for the metal-catalyzed cycloisomerization of 1,*n*-enynes

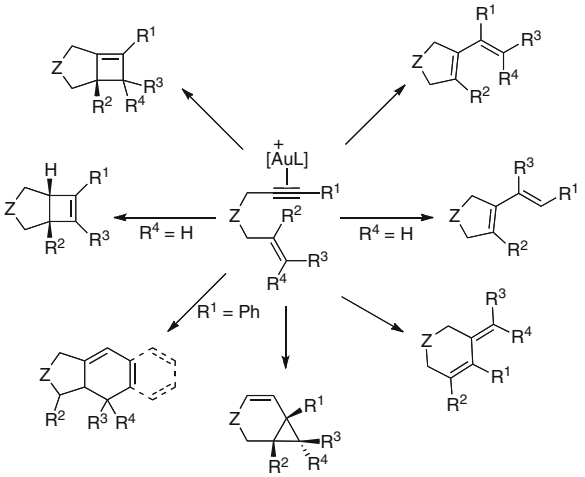
The cycloisomerization of 1,*n*-enynes promoted by gold complex catalysts, are known to go through only the third pathway. This high selectivity is due to two main reasons: (1) the fragment $[AuL]^+$ has only one vacant site, thus it can not coordinate simultaneously the alkyne and the alkene moieties, (2) oxidative addition processes are not facile for gold complexes [24, 157, 158]. In general, gold(I) complexes surpass the reactivity shown by platinum(II) and other electrophilic metals for the reaction of enynes.[12]

[11] General reviews for the behavior of 1,*n*-enynes in the presence of transition metals: [152–156].

[12] Selected reviews: [155, 159–164].

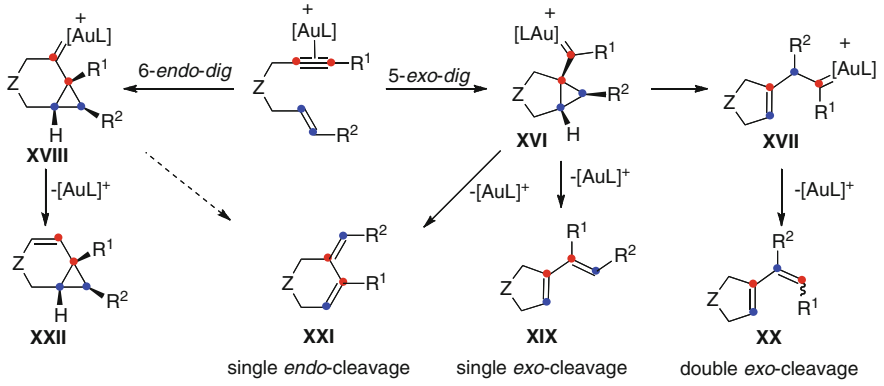
1.4.3.1 Gold-Catalyzed Cycloisomerization of 1,6-Enynes

The cycloisomerization of 1,6-enynes is one of the most widely studied and developed reaction within gold catalysis. In the absence of nucleophiles, a variety of products can be obtained (Scheme 1.14) [8, 159–164].



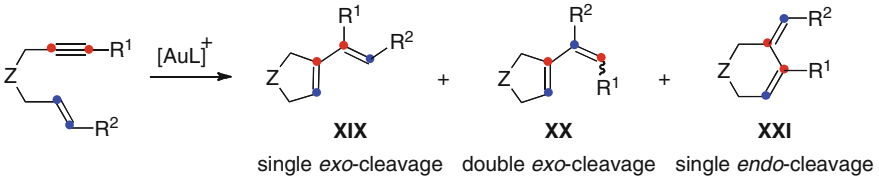
Scheme 1.14 Selected products in the gold-catalyzed cyclization of 1,6-enynes

The mechanism of this reaction starts with the activation of the alkyne moiety by the gold complex, followed by the *anti* attack of the alkene via 5-*exo-dig* or 6-*endo-dig* pathway (Scheme 1.15) [155]. In the absence of a nucleophile, cyclopropyl gold(I) carbene **XVI** evolves by skeletal rearrangement to afford diene **XIX** (single *exo*-cleavage) and/or **XX** (double *exo*-cleavage), where diene **XX** is formed through the rearranged gold carbene **XVII**. Furthermore, cyclopropyl gold carbene **XVI** can lead to diene **XXI** (single *endo*-cleavage) [165]. Bicyclic compound **XXII** is obtained by e*ndo*-cyclization via carbene **XVIII** [28, 163, 166, 167].



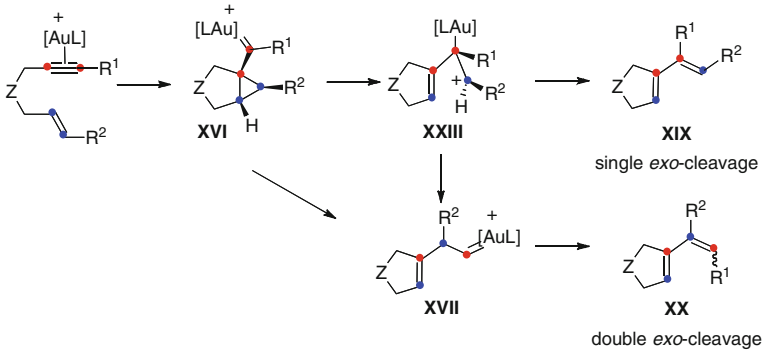
Scheme 1.15 Mechanism for the gold-catalyzed cyclization of 1,6-enynes

Dienes **XIX** and **XXI** are the products of single cleavage rearrangement characterized by the migration of the external alkene carbon to the terminus of the alkyne (Scheme 1.16). Dienes **XX** are the products of double rearrangement in which both the alkene and the alkyne are cleaved. The double *exo*-cleavage skeletal rearrangement often leads to dienes **XX** with predominant *Z* configuration [168].



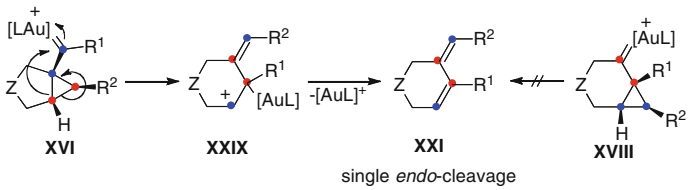
Scheme 1.16 Dienes of single and double cleavage rearrangement

The mechanism for the single cleavage skeletal rearrangement is consistent with the formation of a gold(I)-stabilized carbocation **XXIII**, by opening of the *anti*-cyclopropyl gold carbene **XVI**, followed by metal-elimination to give diene **XIX** (Scheme 1.17). The single *exo*-cleavage is similar to the metathesis of enynes [160, 169], although the mechanism is completely different. Nevertheless, the double cleavage rearrangement takes place through cyclopropyl gold carbene **XVII**, which can be formed by diotropic rearrangement from carbene **XVI** [170–172] or by carbocation 1,2-shift of the cyclic alkenyl group in **XXIII** [15]. Formation of the diene **XX**, form carbene **XVII**, involves loss of a α-proton, followed by protodemetallation.



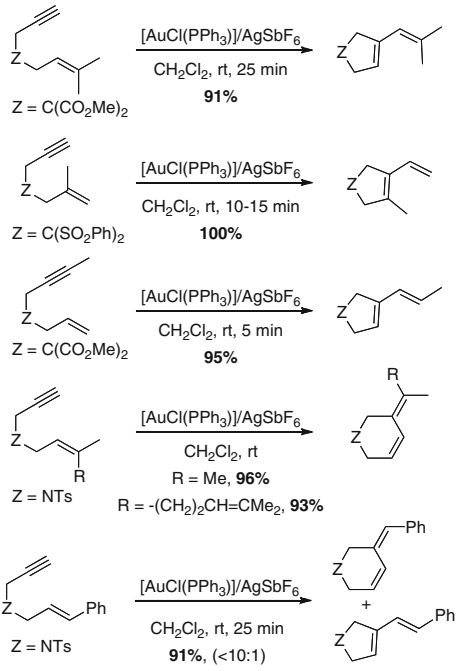
Scheme 1.17 Single- and double-cleavage exocyclic skeletal rearrangement

The formation of the six-membered ring **XXI** was initially proposed to take place through cyclopropyl gold carbene **XVIII** via 6-*endo-dig* cyclization (Scheme 1.18) [27]. However, DFT calculations support a mechanism in which cyclopropyl gold carbene **XVI** rearranges to cation **XXIX**, followed by protodemetallation [165].



Scheme 1.18 Endocyclic rearrangement of 1,6-enynes

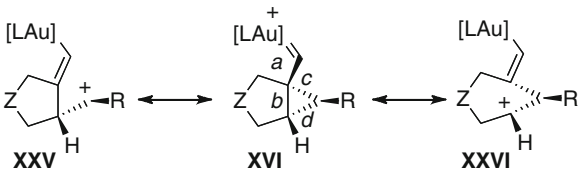
Selected examples of single *exo*-, double *exo*- and single *endo*-cleavage products are shown in Scheme 1.19 [15, 165].



Scheme 1.19 Selected examples of gold-catalyzed cycloisomerization of 1,6-enynes

Intermediates **XVI**, **XVII** and **XVIII** (Scheme 1.15) are usually drawn as cyclopropyl gold carbenes. However, these species are distorted structures that can also be represented as gold-stabilized homoallylic carbocations. DFT calculations of cyclopropyl gold carbenes **XVI** show that the cationic or carbenic character is depending on the substitution pattern of the enyne and the nature of the ligand (Table 1.1) [15, 18, 165, 173, 174]. Thus, when R=H or Me, the most relevant resonance form is **XXVI** where the longest bond is *b*. However, when R = *c*-C_3H_5, the most relevant resonance structure is **XXV**, due to the stabilization of the carbocation by the R group.

Table 1.1 Bond distances for cyclopropyl gold carbene **XVI** determined by DFT calculations

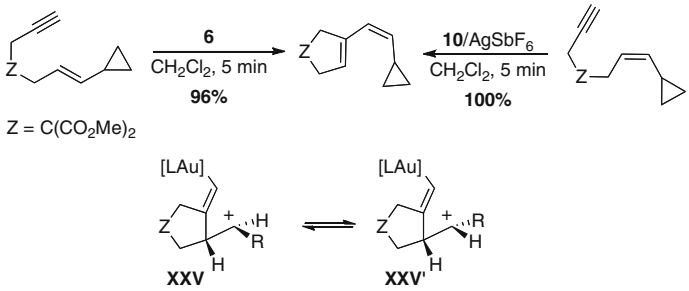


L = PPh_3

R	*a*	*b*	*c*
H	1.378	1.742	1.569
Me	1.372	1.720	1.622
c-C_3H_5	1.356	1.586	1.987

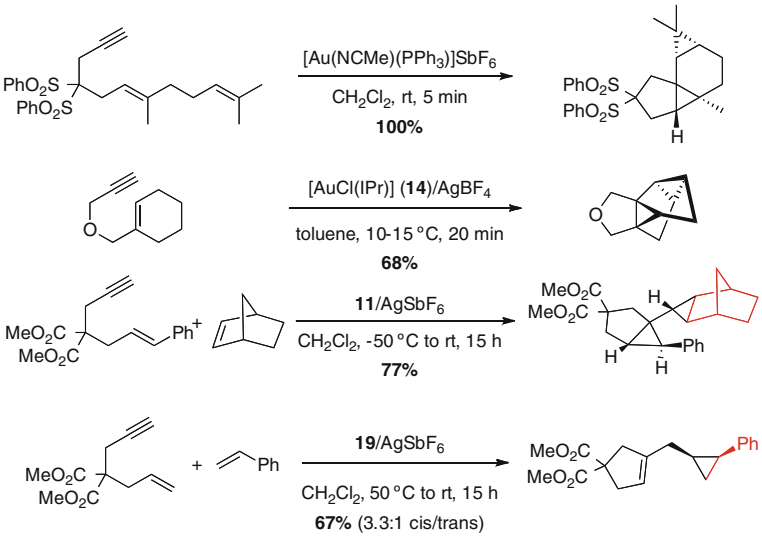
Bond distance in Å determined by DFT calculations at the B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au) level

Evidence for this dualism between gold(I) carbenes and homoallylic carbocations was found in the single-cleavage rearrangement of 1,6-enynes substituted at the alkene with an electron-donating group (Scheme 1.20) [174]. In this case, the reaction is non-stereospecific proceeding through an open carbocation of type **XXV** in which the rotational barrier for the *E*/*Z* interconversion is accessible at room temperature.



Scheme 1.20 Cis-selective single-cleavage rearrangement of (Z)- and (E)-1,6-enynes

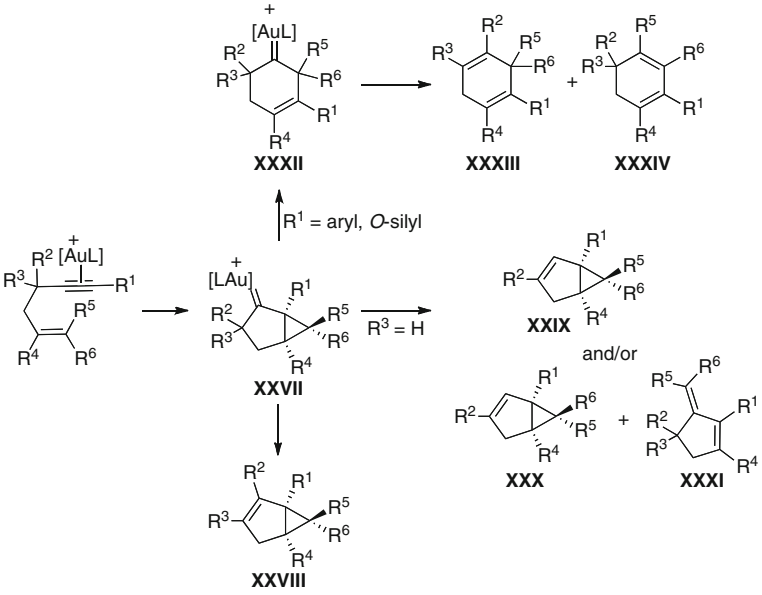
Although none of the key intermediates involved in the skeletal rearrangement have been spectroscopically characterized [175], the carbenic character of the carbene intermediates have been confirmed by trapping of the cyclopropyl gold carbenes **XVI** and **XVII** via intra-[27, 176, 177] and intermolecular [31, 178] cyclopropanation of alkenes (Scheme 1.21), as well as by formation of the corresponding aldehydes when the reaction is carried out in the presence of Ph_2SO [179]. Interestingly, a gold carbene has been generated in gas phase showing the reactivity expected for these species [180–183].



Scheme 1.21 Selected examples for the gold-catalyzed reaction of 1,6-enynes with olefins

1.4.3.2 Gold-Catalyzed Cyclization of 1,5-Enynes

Gold-catalyzed cyclization of 1,5-enynes allows the synthesis of a wide variety of synthetically useful products (Scheme 1.22) [24, 160]. The mechanism of 1,5-enynes resembles the one of 1,6-enynes, cyclizing through an endocyclic pathway.



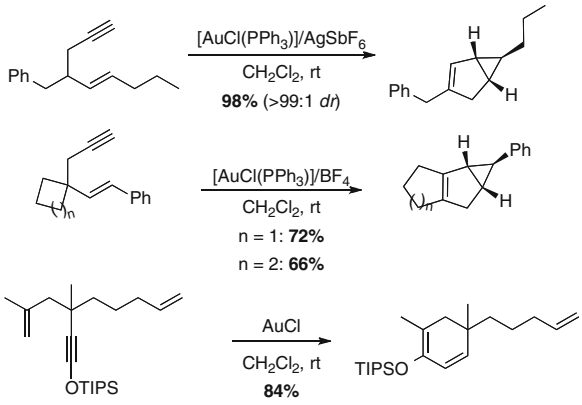
Scheme 1.22 General overview for the gold-catalyzed cyclization of 1,5-enynes

However, the *exo*-pathway is more favorable when terminal alkynes or iodoalkynes are used [184].

1,5-Enyne cycloisomerization gives bicyclo[3.1.0]hexanes **XXVIII**, **XXIX** and/or **XXX** in a stereoespecific transformation. The proposed mechanism starts by 5-*endo-dig* cyclization to give an internal cyclopropyl gold carbene **XXVII**, which undergoes hydride 1,2-shift to give **XXVIII** [33, 185–190]. On the other hand, cyclopropyl gold carbene **XXVII** can also suffer an alkyl 1,2-shift leading to the expected product **XXIX** along with stereoisomer **XXX** and the product of single cleavage rearrangement **XXXI** [187]. Stereoisomer **XXX** is expected to be produced from the *Z* isomer of the 1,5-enynes. Double cleavage products **XXXIII** and **XXXIV** are obtained from aryl- and silyloxy-1,5-enynes [191, 192]. The cycloisomerization occurs by reorganization of cyclopropyl gold carbene **XXVII** to form an internal gold carbene **XXXII**, which evolves by 1,2-migration of the substituents at the α-position.

As in the case of 1,5-enynes, the ligands on the gold catalysts influence the carbene or carbocation nature of the intermediates. Thus, gold complexes with electron-donating ligands, like NHCs, promote reactions that proceed via intermediates with carbene-like character, leading to products with a bicyclo[3.1.0]hexane skeleton **XXIX**. However, gold complexes with less donating ligands, like phosphite, favor the formation of 1,3-dienes of type **XXXI** via carbocationic intermediates [193].

Selected examples for the gold-catalyzed cyclization of 1,5-enynes are shown in Scheme 1.23 [185, 187].

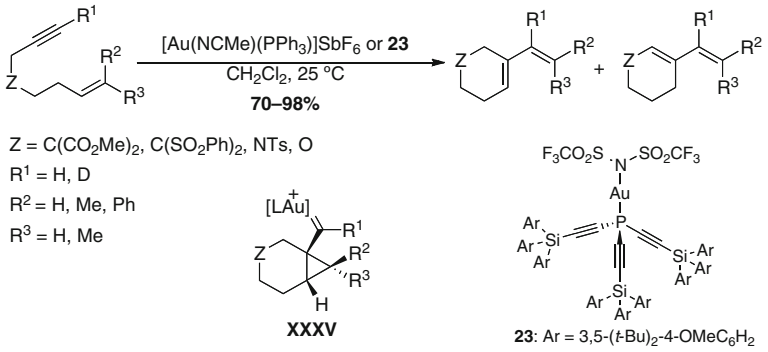


Scheme 1.23 Selected examples of gold-catalyzed cycloisomerization of 1,5-enynes

1.4.3.3 Gold-Catalyzed Cyclization of 1,*n*-Enynes (n > 6)

The skeletal rearrangement of 1,7-enynes is an extension of the cycloisomerization reaction of 1,6-enynes. 1,7-Enynes undergo single cleavage skeletal rearrangement

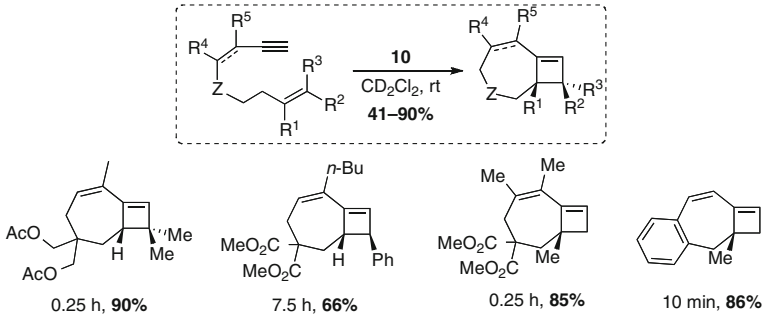
with different metals. In the case of gold, the reaction takes place at room temperature and with low catalyst loadings (Scheme 1.24) [96, 194]. Thus, 1,7-enynes react with $[Au(NCMe)(PPh_3)]SbF_6$ or **23** to give 1,3-dienes in good yield. The proposed mechanism is analogous to the one proposed for 1,6-enynes, which proceeds through cyclopropyl gold carbene **XXXV**. The product of the double cleavage rearrangement of 1,7-enynes has been reported using rhodium as a catalyst [195].



Scheme 1.24 Single cleavage rearrangement of 1,7-enynes

In the special case of 1,7- and 1,8-enynes seven-membered rings are obtained by a 7-*exo-dig* cyclization when the alkene moiety is a silylenolether [196].

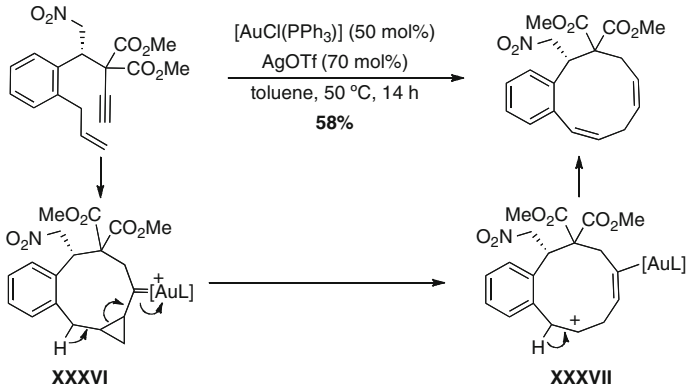
Gold(I)-catalyzed cyclization of 1,8-enynes gives cyclobutene compounds as the main product (Scheme 1.25) [145, 197]. These intermediates can also to give isomerization or fragmentation products after prolonged reaction times or in the presence of traces of acids. Furthermore, cyclobutene compounds can also be synthesized from certain 1,6- and 1,7-enynes [15]. The formation of cyclobutene compounds by gold-catalyzed cycloisomerization of 1,*n*-enynes will be discussed in Chap. 2.



Scheme 1.25 Formation of cyclobutene compounds by gold(I)-catalyzed cyclization of 1,8-enynes

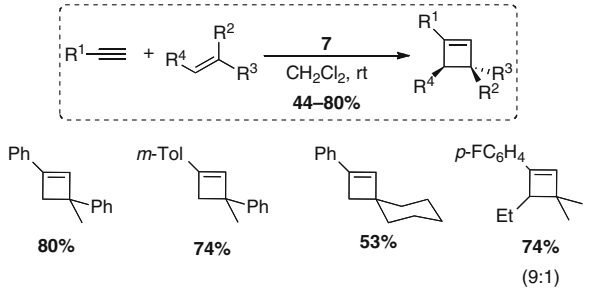
Alternatively, in the case of 1,7- and 1,8-enynes bearing a propargyl acetate group, cyclopropyl compounds are isolated in good yields [198, 199].

The largest 1,*n*-enyne that has been cyclized is a 1,9-enyne, which forms a 10-membered ring in the presence of a large amount of gold and silver complex (Scheme 1.26) [200]. The cycloisomerization presumably occurs via cyclopropyl gold carbene **XXXVI**, which can open to carbocation **XXXVII** or give directly the 10-membered ring.



Scheme 1.26 Gold(I)-catalyzed cyclization of 1,9-enyne

In addition, the gold-catalyzed intermolecular reaction of alkynes with alkenes leads to cyclobutene compounds (Scheme 1.27) [201]. This transformation shows that in the absence of constrains imposed by the tethers in the intramolecular processes, a [2+2] cycloaddition is the predominant mechanism.



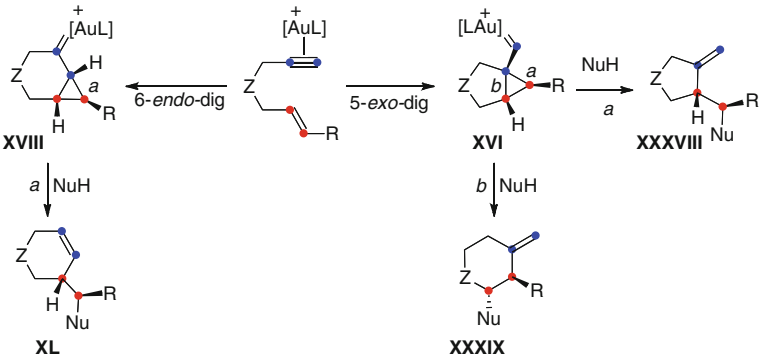
Scheme 1.27 Gold(I)-catalyzed intermolecular reaction of alkynes with alkenes

1.4.4 Gold-Catalyzed Nucleophilic Additions to 1,n-Enynes

One of the most emblematic reaction is the trapping of different intermediates of 1,*n*-enynes with different nucleophiles, which allows the formation of complicated structures from simple starting materials [202].

1.4.4.1 Hydroxy-, Alkoxy- and Aminocyclization of 1,*n*-Enynes

Water, alcohols, and amines have been studied as nucleophiles in the reaction of 1,6-enynes leading to alkoxy-, hydroxy- and aminocyclization products [202]. This process involves an opening of the cyclopropyl gold carbene intermediate **XVI** or **XVIII**, which results in a formal nucleophilic 1,4-addition (Scheme 1.28). Two different products can be synthesized by the 5-*exo-dig* cyclization pathway, **XXXVIII** and/or **XXXIX**. Methylenecyclopentene **XXXVIII** is obtained by cleavage of bond *a* in carbene **XVI**; however, cleavage of bond *b* leads to methylenecyclohexene **XXXIX**. Cyclohexene **XL** is also obtained from cyclopropyl gold carbene **XVIII** by the cleavage of bond *a*.



Scheme 1.28 General overview for the gold-catalyzed nucleophilic additions to 1,6-enynes

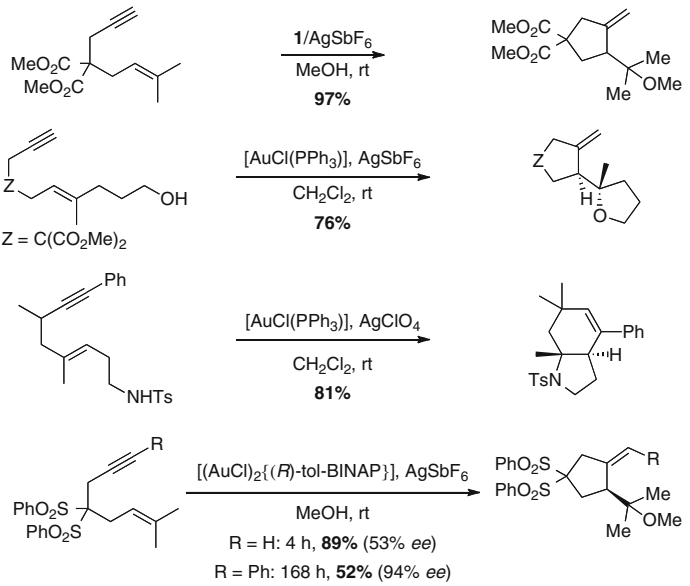
Water and alcohols can act as nucleophiles in the gold-catalyzed intra-[13] and intermolecular[14] reaction with 1,6-enynes. The asymmetric version of the reaction proceeds with good to excellent enantioselectivity using chiral gold complexes [208–210]. The hydroxy- and alkoxycyclization of 1,7-enynes takes place in a similar way [211]. Furthermore, this methodology has been extended to other

[13] For 1,6-enynes: For 1,5-enynes: [28, 50, 49–53, 203, 204].

[14] For 1,6-enyes: For 1,5-enynes: [28, 205–207].

nucleophiles, such as amines,[15] carbamates [50], carboxylic acids [213],[16] and phenols.[17]

Selected examples for the gold-catalyzed addition of nucleophiles to 1,5 and 1,6-enynes are shown in Scheme 1.29 [28, 209, 212].



Scheme 1.29 Selected examples for the hydroxy-, alkoxy- and aminocyclization of enynes

1.4.4.2 Addition of Carbon Nucleophiles to 1,*n*-Enynes

Electron-rich arenes [215–217], indoles [42], 1,3-dicarbonyl compounds [42] and allyl silanes [42] react intermolecularly with 1,5- and 1,6-enynes. However, in the case of cyclohexane-1,3-dione and 2-oxocyclohexanecarbaldehyde only the product of *O*-addition was observed. A strong effect of the ligand present in the gold complex was detected in the addition of indole and 1,3-dicarbonyl compounds (Table 1.2). In this reaction, the product of 1,2-addition is favored with more electron-donating ligands, such as NHC (Table 1.2, entries 5 and 6), as a result of the direct trapping of the gold(I) carbene by the nucleophile. Catalysts with more electrophilic ligands (such as phosphates) led to 1,4-addition products (Table 1.2, entries 2 and 3) [42, 51, 217]. In addition, asymmetric versions of the

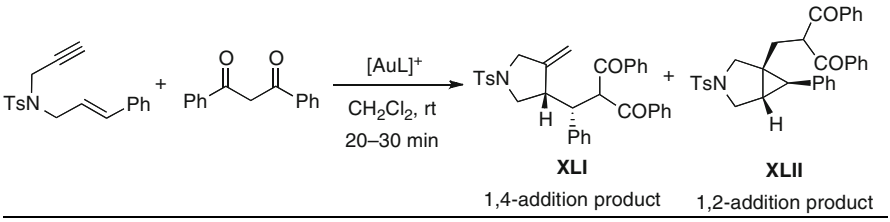
[15] For the intramolecular reaction of 1,5-enynes with amines: For the intramolecular reaction of 1,6-enynes with carbamates: [50, 212].

[16] For the intramolecular reaction of 1,6-enynes with carboxylic acids [28].

[17] For the intramolecular reaction of 1,5-enynes with phenols: [214].

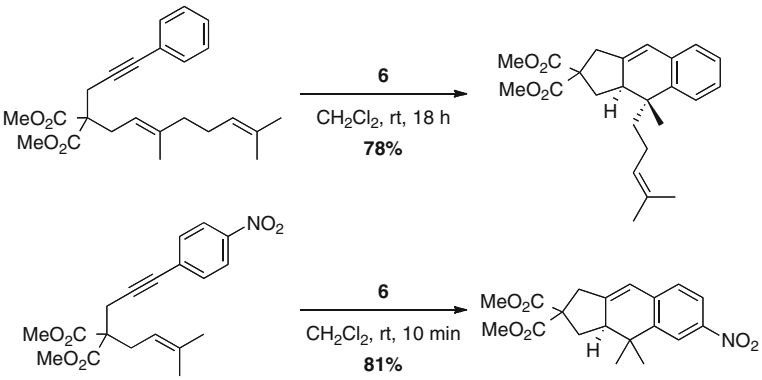
reaction with electron-rich arenes and 1,3-dicarbonyl compounds have been reported [213, 218].

Table 1.2 Ligand effect on the addition of 1,3-dicarbonyl compounds to 1,6-enynes



Entry	$[AuL]^+$	Yield (%) **XLI+XLII**	Ratio **XLI**:**XLII**
1	**6**	86	33:67
2	**19**, $AgSbF_6$	77	75:25
3	**20**	83	77:23
4	**11**, $AgSbF_6$	99	2:98
5	**15**	86	<1:99
6	**16**	87	<2:98

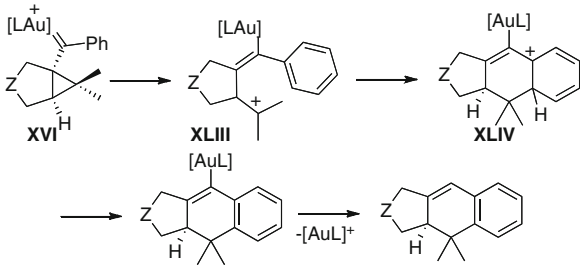
1,6-Enynes substituted at the alkyne position with an aryl group undergo a formal [2+2] cycloaddition yielding to tricyclic compounds (Scheme 1.30) [30, 219, 220]. Generally, the reaction is stereospecific and tolerates electron-donating and electron-withdrawing groups at several positions of the aryl moiety. However, olefins substituted with electron-releasing groups lead to a lack of stereospecicity in the reaction [174].



Scheme 1.30 Selected examples for [4+2]-cycloaddition of arylenynes

The reaction proceeds via the formation of cationic intermediate **XLIII** from *anti*-cyclopropyl gold carbene **XVI**. Intermediate **XLIII** is stabilized by a π-interaction with the aryl ring. A Friedel-Crafts-type reaction forms cationic

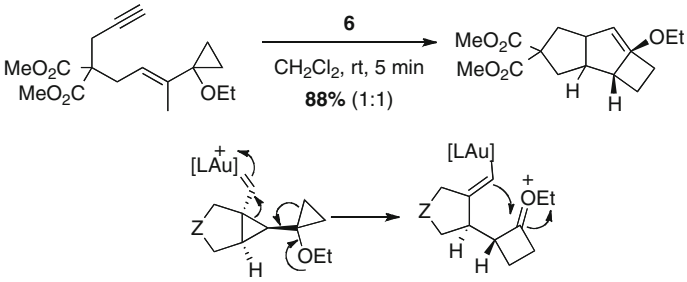
XLIV, which evolves by aromatization and protodemetallation to form the tricyclic compound (Scheme 1.31).



Scheme 1.31 Proposed mechanism for [4+2] cycloaddition of arylenynes

The *endo*-cyclization takes place as a minor pathway in certain cases, but is the favored one in platinum- and gold-catalyzed cycloaddition of related arylenynes with enesulfonamides or enamines [221–223]. Analogous tricylic products can be synthesized via gold-catalyzed [4+2] cycloaddition reaction of benzyl-substituted 1,5-enynes [193].

Hydrindanes can be synthesized from 1,8-dien-3-ynes by [4+2] cycloaddition [30, 219]. However, 1,3-dien-8-ynes undergo intramolecular Diels–Alder reactions to give formal [4+2] products or hexahydropentalene compounds [224, 225]. The reaction of cyclopropylenynes gives pentalenes via Prins cyclization (Scheme 1.32) [174]. Due to the lack of stereospecificity in the reaction, a non-concerted opening of the cyclopropyl gold carbene to an open carbocation is proposed.



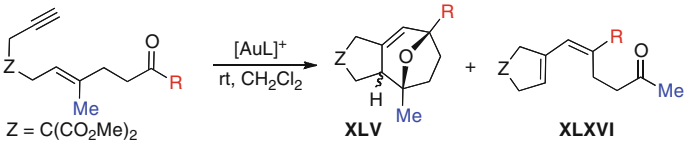
Scheme 1.32 Gold-catalyzed reaction of cyclopropylenynes

1.4.4.3 Other Nucleophilic Additions to 1,*n*-Enynes

Aldehydes and ketones can act as nucleophiles in gold-catalyzed reactions of 1,6-enynes. Only a brief view of this reactivity will be discussed in this introduction, since it will be presented in more detail in Chap. 1.

1,6-Enynes bearing a carbonyl group at the alkenyl side chain led to oxatricyclic compounds in the presence of AuCl as catalyst (Table 1.3) [226]. The reaction proceeds through a formal [2+2+2] cycloaddition, where two C–C and one C–O bonds are formed.

Table 1.3 Gold(I)-catalyzed cyclization of carbonyl 1,6-enynes

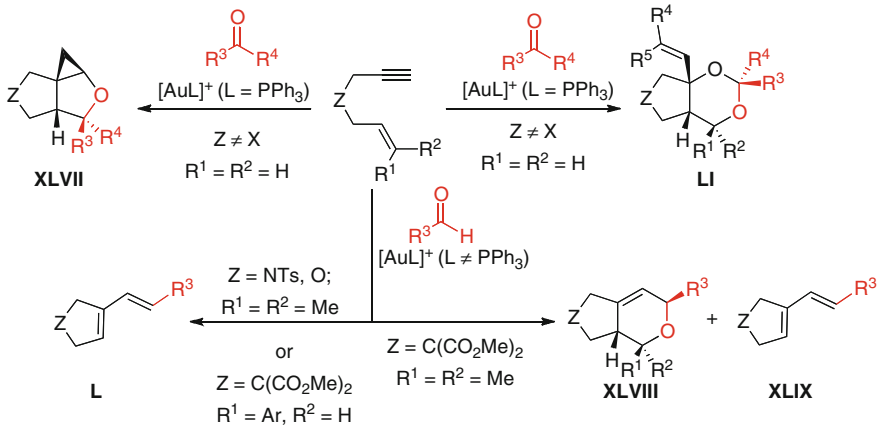


Z = C(CO2Me)2 **XLV** **XLXVI**

Entry	R	[AuL]+	Yield **XLV** (syn/anti)	Yield **XLVI** (%)
1	H	[AuCl(PPh3)]/AgSbF6	35 % (>50:1)	50
2	H	AuCl	58 % (>50:1)	18
3	Me	AuCl	79 % (>50:1)	10
4	*i*-Pr	AuCl	84 % (>50:1)	12

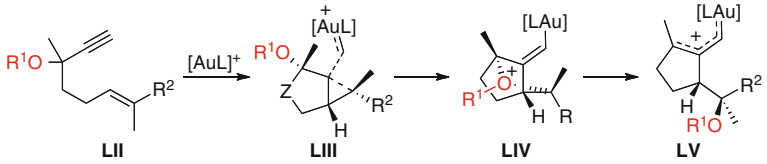
This valuable transformation has been successfully applied in the total synthesis of natural compounds like like (±)-pubinernoid B [227], (+)-orientalol F [227], and (−)-englerin A and B [228].

The gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes is also feasible. This methodology leads to a wide range of compounds (Scheme 1.33) [229–231]. Thus, tricyclic compounds **XLVII**, the products of formal [2+2+2] cycloaddition **XLVIII**, 1,3-dienes **XLIX** or 1,3-dioxolanes **L** can be selectively synthesized by changing the substitution pattern at the alkene moiety and using different gold(I) complexes. Moreover, the intermolecular addition of carbonyl compounds to 1,5-enynes has also been reported [230].



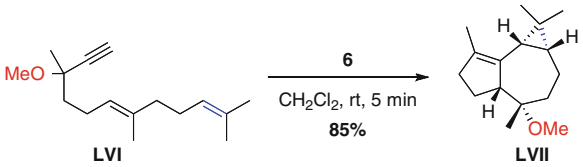
Scheme 1.33 General overview of the gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes

In this context it is worth mentioning a new type of gold-catalyzed cascade transformations. 1,6-Enynes substituted at the propargylic position with alcohols, ethers, or silyl ethers of type **LII** suffer a 1,5-migration of the OR group (Scheme 1.34) [231, 233]. The reaction proceeds through intermediate **LIII** and followed by the migration of the OR group to form **LV**, which then opens to give allylgold cation **LIV**.



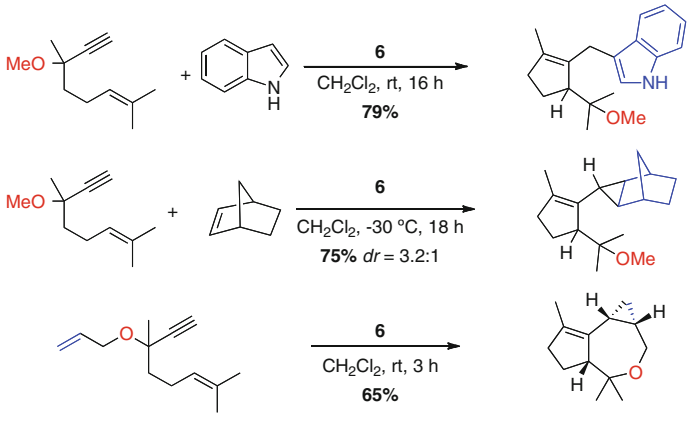
Scheme 1.34 Gold-catalyzed 1,5-migration of 1,6-enynes of type **LII**

This reaction leads to a range of different compounds depending on the nucleophile in the medium. For example, dienynes **LVI** gave tricyclic compounds **LVII** via intramolecular cyclopropanation of allylgold cation **LIV** in 85 % yield (Scheme 1.35) [232].Interestingly, this reaction leads to tricyclic compounds that are structurally related with globulol [234], epiglobulol [234] and halichonadin F [235].



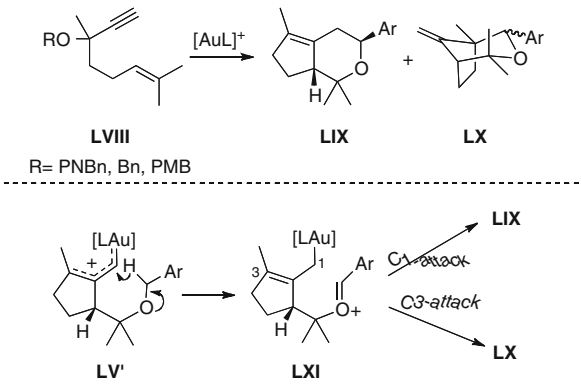
Scheme 1.35 Gold-catalyzed 1,5-migration of dienyne **LVI**

Intermediate **LIII** can also react with indoles, alkenes, or dienes to form products with a remarkable increase of molecular complexity (Scheme 1.36) [232, 233].



Scheme 1.36 Selected examples for the 1,5-migration of the enynes of type **LII**

On the other hand, 3-benzyloxy-1,6-enynes of type **LVIII** lead to **LIX** and **LX** via formal C–H insertion on intermediate **LV′** (Scheme 1.37). This reaction proceeds via proton abstraction from the CH_2Ar' group in **LV′** to form the η^1-allyl gold intermediate **LXI**, which reacts at C1 or C3 with the oxonium cation to give **LIX** or **LX**, respectively.

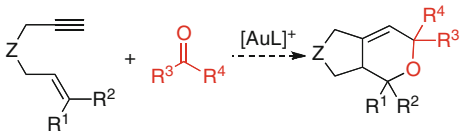


Scheme 1.37 1,5-Migration of 3-benzyloxy-1,6-enynes followed by formal C–H insertion

Another example of a cascade reaction is the cycloisomerization of 3-silyloxy1,5-enynes, which gives carbonyl compounds through a pinacol rearrangement [236–238].

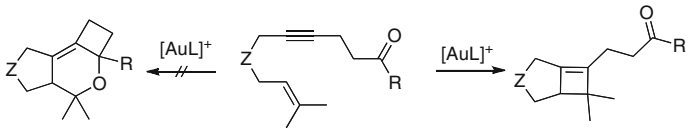
1.5 General Objectives

After many years in the shadow of palladium and rhodium, gold has become one of the most widely used late transition metals in homogeneous and heterogeneous catalysis [2–8]. Over the last few years, the Echavarren group reported new gold-based transformations mostly aimed at the activation of alkynes [3, 155]. Numerous methodologies have been developed that favor the attack of different nucleophiles, like olefins, indoles or aryls, to alkynes [3, 155]. For example, carbonyl compounds can act as nucleophiles in the intra-[226] and intermolecular [229–231] reaction of 1,6-enynes. Within this context, this PhD work focused on the intertwined reaction pathways at play in the gold(I)-catalyzed addition to 1,6-enynes. Our first objective was to study the intermolecular addition of carbonyl compounds to 1,6-enynes bearing a tri-substituted alkene moiety (Scheme 1.38).



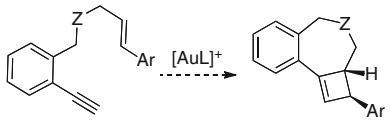
Scheme 1.38 Proposal for the study of the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes

Our second objective was to expand the methodology toward the intramolecular gold(I)-catalyzed cyclization of 1,6-enynes bearing a carbonyl group at the alkyne moiety (Scheme 1.39). Unexpectedly, this type of 1,6-enynes promoted the formation of cyclobutene compounds.



Scheme 1.39 Gold(I)-catalyzed cycloisomerization of 1,6-enynes bearing a carbonyl group at the alkyne side chain

Due to the high importance of the cyclobutene motif and the intrinsic difficulties of its synthesis, our third objective was to create new cyclobutene-containing compounds via gold(I)-catalyzed cyclization of 1,8-enynes (Scheme 1.40).



Scheme 1.40 Formation of cyclobutenes via gold(I)-catalyzed [2+2] cycloaddition

The last objective of this Doctoral Thesis was the application of the methodology developed in the group for the total synthesis of lundurines [133, 134]. Lundurines A–D are a new type of alkaloids characterized by a cyclopropylic fragment embedded within a hexacyclic ring system that includes a 1*H*–azocine[5,4–*b*]indole ring unit (Fig. 1.5). Importantly, lundurines B and D display significant cytoxicity in vitro toward B16 melanoma cells.

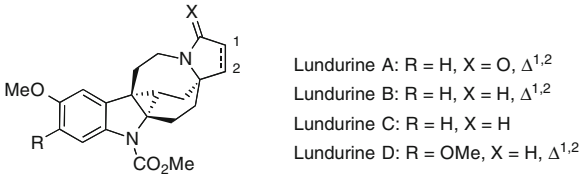
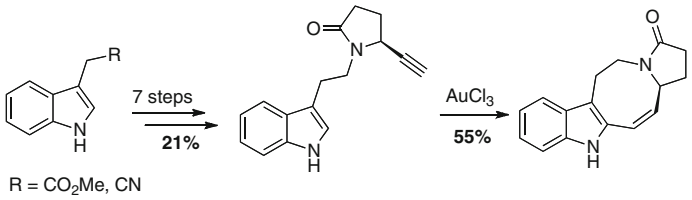


Fig. 1.5 Structures of lundurines A-D

The main tetracyclic core of these alkaloids has been synthesized via 8–*endo*–*dig* cyclization of alkynyl indole catalyzed by $AuCl_3$, which affords exclusively the desired azocine[5,4–*b*]indole derivative (Scheme 1.41) [239]. Thus, based on previously reported results, our objective was to develop an efficient approach toward the total synthesis of lundurines.



Scheme 1.41 Previous results for the synthesis of the tetracyclic core of lunduri

References

1. Lewis, G.N.: Valence and the Structure of Atoms and Molecules, p. 142 (1923)
2. Hashmi, A.: Gold Bulletin **36**, 3–9 (2003)
3. Jiménez-Núñez, E., Echavarren, A. M.,: Chem. Commun. 333–346 (2007)
4. Hashmi, A.S.K.: Chem. Rev. **107**, 3180–3211 (2007)
5. Fürstner, A., Davies, P.W.: Angew. Chem. Int. Ed. **46**, 3410–3449 (2007)
6. Li, Z., Brouwer, C., He, C.: Chem. Rev. **108**, 3239–3265 (2008)
7. Arcadi, A.: Chem. Rev. **108**, 3266–3325 (2008)
8. Fürstner, A.: Chem. Soc. Rev. **38**, 3208–3221 (2009)
9. Nechaev, M.S., Rayón, V.M., Frenking, G.J.: Phys. Chem. A **108**, 3134–3142 (2004)
10. Dewar, M.J.S.: Bull. Soc. Chim. Fr. **18**, C71–C79 (1951)
11. Chatt, J., Duncanson, L. A. J.: Chem. Soc. 2939–2947 (1953)
12. Nelson, J.H., Wheelock, K.S., Cusachs, L.C., Jonassen, H.B.J.: Am. Chem. Soc. **91**, 7005–7008 (1969)
13. Jolly, W.L.: Modern Inorganic Chemistry. New York: McGraw-Hill (1984). Additional references: Pearson, R.G.J.: Chem. Educ. **64**, 561–567 (1987)
14. Pearson, R.G.J.: Am. Chem. Soc. **85**, 3533–3539 (1963)
15. Nieto-Oberhuber, C., López, S., Muñoz, M.P., Cárdenas, D.J., Buñuel, E., Nevado, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **44**, 6146–6148 (2005)
16. Seidel, G., Mynott, R., Fürstner, A.: Angew. Chem. Int. Ed. **48**, 2510–2513 (2009)
17. Benitez, D., Shapiro, N.D., Tkatchouk, E., Wang, Y., Goddard, W.A., Toste, F.D.: Nat. Chem. **1**, 482–486 (2009)
18. Casanova, J., Kent, D.R., Goddard, W.A., Roberts, J.D.: Proc. Natl. Acad. Sci. U. S. A. **100**, 15–19 (2003)
19. Heinemann, C., Hertwig, R.H., Wesendrup, R., Knoch, W., Schwarz, H.J.: Am. Chem. Soc. **117**, 495–500 (1995)
20. Irikura, K.K., Goddard, W.A.J.: Am. Chem. Soc. **116**, 8733–8740 (1994)
21. Pyykkö, P.: Angew. Chem. Int. Ed. **41**, 3573–3578 (2002)
22. Schwarz, H.: Angew. Chem. Int. Ed. **42**, 4442–4454 (2003)
23. Pyykkö, P.: Angew. Chem. Int. Ed. **43**, 4412–4456 (2004)
24. Gorin, D.J., Toste, F.D.: Nature **446**, 395–403 (2007)
25. Teles, J.H., Brode, S., Chabanas, M.: Angew. Chem. Int. Ed. **37**, 1415–1418 (1998)

26. Mizushima, E., Sato, K., Hayashi, T., Tanaka, M.: Angew. Chem. Int. Ed. **41**, 4563–4565 (2002)
27. Nieto-Oberhuber, C., Muñoz, M.P., Buñuel, E., Nevado, C., Cárdenas, D.J., Echavarren, A.M.: Angew. Chem. Int. Ed. **43**, 2402–2406 (2004)
28. Nieto-Oberhuber, C., Muñoz, M.P., López, S., Jiménez-Núñez, E., Nevado, C., Herrero-Gómez, E., Raducan, M., Echavarren, A.M.: Chem. Eur. J. **12**, 1677–1693 (2006)
29. Ferrer, C., Raducan, M., Nevado, C., Claverie, C.K., Echavarren, A.M.: Tetrahedron **63**, 6306–6316 (2007)
30. Nieto-Oberhuber, C., López, S., Echavarren, A.M.: J. Am. Chem. Soc. **127**, 6178–6179 (2005)
31. López, S., Herrero-Gómez, E., Pérez-Galán, P., Nieto-Oberhuber, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **45**, 6029–6032 (2006)
32. Partyka, D.V., Robilotto, T.J., Zeller, M., Hunter, A.D., Gray, T.G.: Organometallics **27**, 28–32 (2007)
33. Mézailles, N., Ricard, L., Gagosz, F.: Org. Lett. **7**, 4133–4136 (2005)
34. Marion, N., Nolan, S.P.: Chem. Soc. Rev. **37**, 1776–1782 (2008)
35. Díez-González, S., Marion, N., Nolan, S.P.: Chem. Rev. **109**, 3612–3676 (2009)
36. Alcarazo, M., Stork, T., Anoop, A., Thiel, W., Fürstner, A.: Angew. Chem. Int. Ed. **49**, 2542–2546 (2010)
37. Nolan, S.P.: Acc. Chem. Res. **44**, 91–100 (2011)
38. Deetlefs, M., Raubenheimer, H.G., Esterhuysen, M.W.: Cat. Today **72**, 29–41 (2002)
39. Schneider, S.K., Herrmann, W.A., Herdtweck, E.Z.: Anorg. Allg. Chem. **629**, 2363–2370 (2003)
40. de Frémont, P., Scott, N.M., Stevens, E.D., Nolan, S.P.: Organometallics **24**, 2411–2418 (2005)
41. de Frémont, P., Singh, R., Stevens, E.D., Petersen, J.L., Nolan, S.P.: Organometallics **26**, 1376–1385 (2007)
42. Amijs, C.H.M., López-Carrillo, V., Raducan, M., Pérez-Galán, P., Ferrer, C., Echavarren, A.M.: J. Org. Chem. **73**, 7721–7730 (2008)
43. de Frémont, P., Stevens, E.D., Fructos, M.R., Díaz-Requejo, M.M., Pérez, P.J., Nolan, S.P: Chem. Commun. 2045–2047 (2006)
44. de Frémont, P., Marion, N., Nolan, S.P.: J. Organomet. Chem. **694**, 551–560 (2009)
45. Li, G., Zhang, L.: Angew. Chem. Int. Ed. **46**, 5156–5159 (2007)
46. Ricard, L., Gagosz, F.: Organometallics **26**, 4704–4707 (2007)
47. Gaillard, S., Slawin, A.M.Z., Nolan, S.P.: Chem. Commun. **46**, 2742–2744 (2010)
48. Gaillard, S., Bosson, J., Ramón, R.S., Nun, P., Slawin, A.M.Z., Nolan, S.P.: Chem. Eur. J. **16**, 13729–13740 (2010)
49. Bartolomé, C., Carrasco-Rando, M., Coco, S., Cordovilla, C., Martín-Alvarez, J.M., Espinet, P.: Inorg. Chem. **47**, 1616–1624 (2008)
50. Bartolomé, C., Ramiro, Z., Pérez-Galán, P., Bour, C., Raducan, M., Echavarren, A.M., Espinet, P.: Inorg. Chem. **47**, 11391–11397 (2008)
51. Bartolomé, C., Ramiro, Z., García-Cuadrado, D., Pérez-Galán, P., Raducan, M., Bour, C., Echavarren, A.M., Espinet, P.: Organometallics **29**, 951–956 (2010)
52. Bartolomé, C., García-Cuadrado, D., Ramiro, Z., Espinet, P.: Inorg. Chem. **49**, 9758–9764 (2010)
53. Hashmi, A.S.K., Hengst, T., Lothschütz, C., Rominger, F.: Adv. Synth. Catal. **352**, 1315–1337 (2010)
54. Shapiro, N.D., Toste, F.D.: Proc. Natl. Acad. Sci. U. S. A. **105**, 2779–2782 (2008)
55. Frey, G.D., Dewhurst, R.D., Kousar, S., Donnadieu, B., Bertrand, G.J.: Organomet. Chem. **693**, 1674–1682 (2008)
56. Zeng, X., Soleilhavoup, M., Bertrand, G.: Org. Lett. **11**, 3166–3169 (2009)
57. Zeng, X., Frey, G.D., Kousar, S., Bertrand, G.: Chem. Eur. J. **15**, 3056–3060 (2009)
58. Kilpin, K.J., Paul, U.S.D., Lee, A.-L., Crowley, J.D.: Chem. Commun. **47**, 328–330 (2011)

59. Teller, H., Flügge, S., Goddard, R., Fürstner, A.: Angew. Chem. Int. Ed. **49**, 1949–1953 (2010)
60. Fortman, G.C., Nolan, S.P.: Organometallics **29**, 4579–4583 (2010)
61. Annibale, G., Canovese, L., Cattalini, L., Marangoni, G., Michelon, G., Tobe, M.L.J.: Chem. Soc. Dalton Trans. 1641–1646 (1984)
62. Hashmi, A.S.K., Weyrauch, J.P., Rudolph, M., Kurpejović, E.: Angew. Chem. Int. Ed. **43**, 6545–6547 (2004)
63. García-Mota, M., Cabello, N., Maseras, F., Echavarren, A.M., Pérez-Ramírez, J., Lopez, N.: ChemPhysChem **9**, 1624–1629 (2008)
64. Müller, T.E., Grosche, M., Herdtweck, E., Pleier, A.-K., Walter, E., Yan, Y.-K.: Organometallics **19**, 170–183 (1999)
65. Mizushima, E., Hayashi, T., Tanaka, M.: Org. Lett. **5**, 3349–3352 (2003)
66. Istrate, F.M., Gagosz, F.: Org. Lett. **9**, 3181–3184 (2007)
67. Zhang, Y., Donahue, J.P., Li, C.-J.: Org. Lett. **9**, 627–630 (2007)
68. Kusama, H., Miyashita, Y., Takaya, J., Iwasawa, N.: Org. Lett. **8**, 289–292 (2005)
69. Kang, J.-E., Kim, H.-B., Lee, J.-W., Shin, S.: Org. Lett. **8**, 3537–3540 (2006)
70. Seregin, I.V., Schammel, A.W., Gevorgyan, V.: Org. Lett. **9**, 3433–3436 (2007)
71. Seregin, I.V., Gevorgyan, V.: J. Am. Chem. Soc. **128**, 12050–12051 (2006)
72. Gorin, D.J., Davis, N.R., Toste, F.D.: J. Am. Chem. Soc. **127**, 11260–11261 (2005)
73. Fukuda, Y., Utimoto, K.: J. Org. Chem. **56**, 3729–3731 (1991)
74. Antoniotti, S., Genin, E., Michelet, V., Genêt, J.-P.: J. Am. Chem. Soc. **127**, 9976–9977 (2005)
75. Liu, Y., Song, F., Song, Z., Liu, M., Yan, B.: Org. Lett. **7**, 5409–5412 (2005)
76. Belting, V., Krause, N.: Org. Lett. **8**, 4489–4492 (2006)
77. Barluenga, J., Diéguez, A., Fernández, A., Rodríguez, F., Fañanás, F.: J. Angew. Chem. Int. Ed. **45**, 2091–2093 (2006)
78. Engel, D.A., Dudley, G.B.: Org. Lett. **8**, 4027–4029 (2006)
79. Genin, E., Toullec, P.Y., Antoniotti, S., Brancour, C., Genêt, J.-P., Michelet, V.: J. Am. Chem. Soc. **128**, 3112–3113 (2006)
80. Buzas, A., Gagosz, F.: Org. Lett. **8**, 515–518 (2006)
81. Lim, C., Kang, J.-E., Lee, J.-E., Shin, S.: Org. Lett. **9**, 3539–3542 (2007)
82. Hashmi, A.S.K., Salathé, R., Frey, W.: Synlett **2007**, 1763–1766 (2007)
83. Jin, T., Yamamoto, Y.: Org. Lett. **9**, 5259–5262 (2007)
84. Hashmi, A.S.K., Weyrauch, J.P., Frey, W., Bats, J.W.: Org. Lett. **6**, 4391–4394 (2004)
85. Hashmi, A.S.K., Sinha, P.: Adv. Synth. Catal. **346**, 432–438 (2004)
86. Dai, L.-Z., Qi, M.-J., Shi, Y.-L., Liu, X.-G., Shi, M.: Org. Lett. **9**, 3191–3194 (2007)
87. Shu, X.-Z., Liu, X.-Y., Xiao, H.-Q., Ji, K.-G., Guo, L.-N., Qi, C.-Z., Liang, Y.-M.: Adv. Synth. Catal. **349**, 2493–2498 (2007)
88. Shapiro, N.D., Toste, F.D.: J. Am. Chem. Soc. **129**, 4160–4161 (2007)
89. Davies, P.W., Albrecht, S.J.C.: Angew. Chem. Int. Ed. **48**, 8372–8375 (2009)
90. Nakamura, I., Sato, T., Yamamoto, Y.: Angew. Chem. Int. Ed. **45**, 4473–4475 (2006)
91. Nakamura, I., Sato, T., Terada, M., Yamamoto, Y.: Org. Lett. **9**, 4081–4083 (2007)
92. Norman, R.O.C., Parr, W.J.E., Thomas, C.B.J.: Chem. Soc. Perkin. Trans. **1**, 1983–1987 (1976)
93. Akana, J.A., Bhattacharyya, K.X., Müller, P., Sadighi, J.P.: J. Am. Chem. Soc. **129**, 7736–7737 (2007)
94. Kennedy-Smith, J.J., Staben, S.T., Toste, F.D.: J. Am. Chem. Soc. **126**, 4526–4527 (2004)
95. Staben, S.T., Kennedy-Smith, J.J., Toste, F.D.: Angew. Chem. Int. Ed. **43**, 5350–5352 (2004)
96. Ochida, A., Ito, H., Sawamura, M.J.: Am. Chem. Soc. **128**, 16486–16487 (2006)
97. Staben, S.T., Kennedy-Smith, J.J., Huang, D., Corkey, B.K., LaLonde, R.L., Toste, F.D.: Angew. Chem. Int. Ed. **45**, 5991–5994 (2006)
98. Linghu, X., Kennedy-Smith, J.J., Toste, F.D.: Angew. Chem. Int. Ed. **46**, 7671–7673 (2007)
99. Minnihan, E.C., Colletti, S.L., Toste, F.D., Shen, H.C.J.: Org. Chem. **72**, 6287–6289 (2007)

100. Pan, J.-H., Yang, M., Gao, Q., Zhu, N.-Y., Yang, D.: Synthesis **2007**, 2539–2544 (2007)
101. Ito, H., Makida, Y., Ochida, A., Ohmiya, H., Sawamura, M.: Org. Lett. **10**, 5051–5054 (2008)
102. Binder, J.T., Crone, B., Haug, T.T., Menz, H., Kirsch, S.F.: Org. Lett. **10**, 1025–1028 (2008)
103. Barabé, F., Bétournay, G.V., Bellavance, G., Barriault, L.: Org. Lett. **11**, 4236–4238 (2009)
104. Davies, P.W., Detty-Mambo, C.: Org. Biomol. Chem. **8**, 2918–2922 (2010)
105. Nevado, C., Echavarren, A.M.: Synthesis 167–182 (2005)
106. Yamamoto, Y., Gridnev, I.D., Patil, N.T., Jin, T.: Chem. Commun. 5075–5087 (2009)
107. de Mendoza, P., Echavarren, A.M.: Pure Appl. Chem. **82**, 801–820 (2010)
108. Kharasch, M.S., Isbell, H.S.J.: Am. Chem. Soc. **53**, 3053–3059 (1931)
109. Porter, K.A., Schier, A., Schmidbaur, H.: Organometallics **22**, 4922–4927 (2003)
110. Fuchita, Y., Ieda, H., Yasutake, M.: J. Chem. Soc. Dalton Trans. 271–274 (2000)
111. Fuchita, Y., Utsunomiya, Y., Yasutake, M.: J. Chem. Soc. Dalton Trans. 2330–2334 (2001)
112. Li, Z., Capretto, D.A., Rahaman, R.O., He, C.: J. Am. Chem. Soc. **129**, 12058–12059 (2007)
113. Mo, F., Yan, J.M., Qiu, D., Li, F., Zhang, Y., Wang, J.: Angew. Chem. Int. Ed. **49**, 2028–2032 (2010)
114. Lu, P., Boorman, T.C., Slawin, A.M.Z., Larrosa, I.: J. Am. Chem. Soc. **132**, 5580–5581 (2010)
115. Boorman, T.C., Larrosa, I.: Chem. Soc. Rev. **40**, 1910–1925 (2011)
116. Reetz, M.T., Sommer, K.: Eur. J. Org. Chem. **2003**, 3485–3496 (2003)
117. Shi, Z., He, C.: J. Org. Chem. **69**, 3669–3671 (2004)
118. Ferrer, C., Amijs, C.H.M., Echavarren, A.M.: Chem. Eur. J. **13**, 1358–1373 (2007)
119. Li, Z., Shi, Z., He, C.: J. Organomet. Chem. **690**, 5049–5054 (2005)
120. Hashmi, A.S.K., Blanco, M.C.: Eur. J. Org. Chem. 4340–4342 (2006)
121. Hashmi, A.S.K., Blanco, M.C., Kurpejović, E., Frey, W., Bats, J.W.: Adv. Synth. Catal. **348**, 709–713 (2006)
122. Menon, R.S., Findlay, A.D., Bissember, A.C., Banwell, M.G.J.: Org. Chem. **74**, 8901–8903 (2009)
123. Jurberg, I.D., Gagosz, F.J.: Organomet. Chem. **696**, 37–41 (2011)
124. Mamane, V., Hannen, P., Fürstner, A.: Chem. Eur. J. **10**, 4556–4575 (2004)
125. Liu, X.-Y., Che, C.-M.: Angew. Chem. Int. Ed. **47**, 3805–3810 (2008)
126. Zhou, Y., Feng, E., Liu, G., Ye, D., Li, J., Jiang, H., Liu, H.: J. Org. Chem. **74**, 7344–7348 (2009)
127. Marion, N., Díez-González, S., de Frémont, P., Noble, A.R., Nolan, S.P.: Angew. Chem. Int. Ed. **45**, 3647–3650 (2006)
128. Nun, P., Gaillard, S., Poater, A., Cavallo, L., Nolan, S.P.: Org. Biomol. Chem. **9**, 101–104 (2011)
129. Marion, N., Carlqvist, P., Gealageas, R., de Frémont, P., Maseras, F., Nolan, S.P.: Chem. Eur. J. **13**, 6437–6451 (2007)
130. Peng, L., Zhang, X., Zhang, S., Wang, J.: J. Org. Chem. **72**, 1192–1197 (2007)
131. Dudnik, A.S., Schwier, T., Gevorgyan, V.: Org. Lett. **10**, 1465–1468 (2008)
132. Dudnik, A.S., Schwier, T., Gevorgyan, V.: Tetrahedron **65**, 1859–1870 (2009)
133. Ferrer, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **45**, 1105–1109 (2006)
134. Ferrer, C., Escribano-Cuesta, A., Echavarren, A.M.: Tetrahedron **65**, 9015–9020 (2009)
135. Hashmi, A.S.K., Haufe, P., Schmid, C., Rivas, N.A., Frey, W.: Chem. Eur. J. **12**, 5376–5382 (2006)
136. Hashmi, A.S.K., Frost, T.M., Bats, J.W.: J. Am. Chem. Soc. **122**, 11553–11554 (2000)
137. Hashmi, A.S.K., Frost, T.M., Bats, J.W.: Org. Lett. **3**, 3769–3771 (2001)
138. Shmi, A.S.K., Frost, T.M., Bats, J.W.: Cat. Today **72**, 19–27 (2002)
139. Hashmi, A.S.K., Weyrauch, J.P., Kurpejović, E., Frost, T.M., Miehlich, B., Frey, W., Bats, J.W.: Chem. Eur. J. **12**, 5806–5814 (2006)
140. Hashmi, A.S.K., Salathé, R., Frey, W.: Chem. Eur. J. **12**, 6991–6996 (2006)
141. Hashmi, A.S.K., Kurpejović, E., Frey, W., Bats, J.W.: Tetrahedron **63**, 5879–5885 (2007)
142. Hashmi, A., Ata, F., Kurpejovic, E., Huck, J., Rudolph, M.: Top. Catal. **44**, 245–251 (2007)

143. Hashmi, A.S.K., Schäfer, S., Bats, J.W., Frey, W., Rominger, F.: Eur. J. Org. Chem. **2008**, 4891–4899 (2008)
144. Hashmi, A.S.K., Ata, F., Haufe, P., Rominger, F.: Tetrahedron **65**, 1919–1927 (2009)
145. Carrettin, S., Blanco, M.C., Corma, A., Hashmi, A.S.K.: Adv. Synth. Catal. **348**, 1283–1288 (2006)
146. Hashmi, A.S.K., Rudolph, M., Siehl, H.-U., Tanaka, M., Bats, J.W., Frey, W.: Chem. Eur. J. **14**, 3703–3708 (2008)
147. Hashmi, A.S.K.; Weyrauch, J.P.; Rudolph, M.; Kurpejović, E. Angew. Chem. Int. Ed. **43**, 6545–6547 (2004)
148. Hashmi, A.S.K., Kurpejović, E., Wölfle, M., Frey, W., Bats, J.W.: Adv. Synth. Catal. **349**, 1743–1750 (2007)
149. Hashmi, A.S.K., Enns, E., Frost, T.M., Schäfer, S., Frey, W., Rominger, F: Synthesis 2707–2718 (2008)
150. Hashmi, A.S.K., Rudolph, M., Bats, J.W., Frey, W., Rominger, F., Oeser, T.: Chem. Eur. J. **14**, 6672–6678 (2008)
151. Hashmi, A.S.K., Rudolph, M., Huck, J., Frey, W., Bats, J.W., Hamzić, M.: Angew. Chem. Int. Ed. **48**, 5848–5852 (2009)
152. Aubert, C., Buisine, O., Malacria, M.: Chem. Rev. **102**, 813–834 (2002)
153. Lloyd-Jones, G.C.: Org. Biomol. Chem. **1**, 215–236 (2003)
154. Michelet, V., Toullec, P.Y., Genêt, J.-P.: Angew. Chem. Int. Ed. **47**, 4268–4315 (2008)
155. Jiménez-Núñez, E., Echavarren, A.M.: Chem. Rev. **108**, 3326–3350 (2008)
156. Echavarren, A., Jiménez-Núñez, E.: Top. Catal. **53**, 924–930 (2010)
157. Nakanishi, W., Yamanaka, M., Nakamura, E.: J. Am. Chem. Soc. **127**, 1446–1453 (2005)
158. Lauterbach, T., Livendahl, M., Rosellón, A., Espinet, P., Echavarren, A.M.: Org. Lett. **12**, 3006–3009 (2010)
159. Echavarren, A.M., Nevado, C.: Chem. Soc. Rev. **33**, 431–436 (2004)
160. Diver, S.T., Giessert, A.J.: Chem. Rev. **104**, 1317–1382 (2004)
161. Bruneau, C.: Angew. Chem. Int. Ed. **44**, 2328–2334 (2005)
162. Zhang, L., Sun, J., Kozmin, S.A.: Adv. Synth. Catal. **348**, 2271–2296 (2006)
163. Nieto-Oberhuber, C., López, S., Jiménez-Núñez, E., Echavarren, A.M.: Chem. Eur. J. **12**, 5916–5923 (2006)
164. Abu Sohel, S.M., Liu, R.-S.: Chem. Soc. Rev. **38**, 2269–2281 (2009)
165. Cabello, N., Jiménez-Núñez, E., Buñuel, E., Cárdenas, D.J., Echavarren, A.M.: Eur. J. Org. Chem. **2007**, 4217–4223 (2007)
166. Lee, S.I., Kim, S.M., Choi, M.R., Kim, S.Y., Chung, Y.K., Han, W.-S., Kang, S.O.: J. Org. Chem. **71**, 9366–9372 (2006)
167. Chao, C.-M., Beltrami, D., Toullec, P.Y., Michelet, V.: Chem. Commun. 6988–6990 (2009)
168. Ota, K., Chatani, N.: Chem. Commun. 2906–2907 (2008)
169. Mori, M.: Adv. Synth. Catal. **349**, 121–135 (2007)
170. Reetz, M.T.: Angew. Chem. Int. Ed. Engl. **11**, 129–130 (1972)
171. Reetz, M.T.: Angew. Chem. Int. Ed. Engl. **11**, 130–131 (1972)
172. Nouri, D.H., Tantillo, D.J.J.: Org. Chem. **71**, 3686–3695 (2006)
173. Pérez-Galán, P., Martin, N.J.A., Campaña, A.G., Cárdenas, D.J., Echavarren, A.M.: Chem. Asian J. **6**, 482–486 (2011)
174. Jiménez-Núñez, E., Claverie, C.K., Bour, C., Cárdenas, D.J., Echavarren, A.M.: Angew. Chem. Int. Ed. **47**, 7892–7895 (2008)
175. Hashmi, A.S.K.: Angew. Chem. Int. Ed. **49**, 5232–5241 (2010)
176. Nieto-Oberhuber, C., López, S., Muñoz, M.P., Jiménez-Núñez, E., Buñuel, E., Cárdenas, D.J., Echavarren, A.M.: Chem. Eur. J. **12**, 1694–1702 (2006)
177. Kim, S.M., Park, J.H., Choi, S.Y., Chung, Y.K.: Angew. Chem. Int. Ed. **46**, 6172–6175 (2007)
178. Pérez-Galán, P., Herrero-Gómez, E., Hog, D.T., Martin, N.J.A., Maseras, F., Echavarren, A.M.: Chem. Sci. **2**, 141–149 (2011)

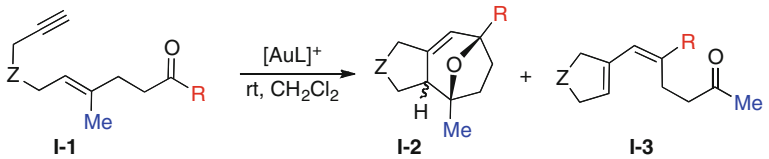
179. Witham, C.A., Mauleón, P., Shapiro, N.D., Sherry, B.D., Toste, F.D.: J. Am. Chem. Soc. **129**, 5838–5839 (2007)
180. Fedorov, A., Moret, M.-E., Chen, P.: J. Am. Chem. Soc. **130**, 8880–8881 (2008)
181. Fedorov, A., Chen, P.: Organometallics **28**, 1278–1281 (2009)
182. Batiste, L., Fedorov, A., Chen, P.: Chem. Commun. **46**, 3899–3901 (2010)
183. Fedorov, A., Chen, P.: Organometallics **29**, 2994–3000 (2010)
184. Shibata, T., Ueno, Y., Kanda, K.: Synlett 4411–4414 (2006)
185. Luzung, M.R., Markham, J.P., Toste, F.D.: J. Am. Chem. Soc. **126**, 10858–10859 (2004)
186. Mamane, V., Gress, T., Krause, H., Fürstner, A.: J. Am. Chem. Soc. **126**, 8654–8655 (2004)
187. Gagosz, F.: Org. Lett. **7**, 4129–4132 (2005)
188. Fürstner, A., Schlecker, A.: Chem. Eur. J. **14**, 9181–9191 (2008)
189. Horino, Y., Yamamoto, T., Ueda, K., Kuroda, S., Toste, F.D.: J. Am. Chem. Soc. **131**, 2809–2811 (2009)
190. Liu, Y., Zhang, D., Zhou, J., Liu, C.J.: Phys. Chem. A **114**, 6164–6170 (2010)
191. Zhang, L., Kozmin, S.A.: J. Am. Chem. Soc. **126**, 11806–11807 (2004)
192. Sun, J., Conley, M.P., Zhang, L., Kozmin, S.A.J.: Am. Chem. Soc. **128**, 9705–9710 (2006)
193. López-Carrillo, V., Huguet, N., Mosquera, Á., Echavarren, A.M.: Chem. Eur. J. **17**, 10972–10978 (2011)
194. Cabello, N., Rodríguez, C., Echavarren, A.M.: Synlett. 1753–1758 (2007)
195. Ota, K., Lee, S.I., Tang, J.-M., Takachi, M., Nakai, H., Morimoto, T., Sakurai, H., Kataoka, K., Chatani, N.: J. Am. Chem. Soc. **131**, 15203–15211 (2009)
196. Ito, H., Ohmiya, H., Sawamura, M.: Org. Lett. **12**, 4380–4383 (2010)
197. Odabachian, Y., Gagosz, F.: Adv. Synth. Catal. **351**, 379–386 (2009)
198. Moreau, X., Goddard, J.-P., Bernard, M., Lemière, G., López-Romero, J.M., Mainetti, E., Marion, N., Mouriès, V., Thorimbert, S., Fensterbank, L., Malacria, M.: Adv. Synth. Catal. **350**, 43–48 (2008)
199. Boyer, F.-D., Le Goff, X., Hanna, I.: J. Org. Chem. **73**, 5163–5166 (2008)
200. Comer, E., Rohan, E., Deng, L., Porco, J.A.: Org. Lett. **9**, 2123–2126 (2007)
201. López-Carrillo, V., Echavarren, A.M.: J. Am. Chem. Soc. **132**, 9292–9294 (2010)
202. Abu Sohel, S.M.; Liu, R.-S. Chem. Soc. Rev. **38**, 2269–2281 (2009)
203. Fürstner, A., Morency, L.: Angew. Chem. Int. Ed. **47**, 5030–5033 (2008)
204. Zhang, L., Kozmin, S.A.: J. Am. Chem. Soc. **127**, 6962–6963 (2005)
205. Lee, S.I., Kim, S.M., Choi, M.R., Kim, S.Y., Chung, Y.K., Han, W.-S., Kang, S.O.: J. Org. Chem. **71**, 9366–9372 (2006)
206. Chao, C.-M., Toullec, P.Y., Michelet, V.: Tetrahedron Lett. **50**, 3719–3722 (2009)
207. Buzas, A.K., Istrate, F.M., Gagosz, F.: Angew. Chem. Int. Ed. **46**, 1141–1144 (2007)
208. Muñoz, M.P., Adrio, J., Carretero, J.C., Echavarren, A.M.: Organometallics **24**, 1293–1300 (2005)
209. Widenhoefer, R.A.: Chem. Eur. J. **14**, 5382–5391 (2008)
210. Sengupta, S., Shi, X.: ChemCatChem. **2**, 609–619 (2010)
211. Cabello, N.; Rodríguez, C.; Echavarren, A.M. Synlett. 1753–1758 (2007)
212. Leseurre, L., Toullec, P.Y., Genêt, J.-P., Michelet, V.: Org. Lett. **9**, 4049–4052 (2007)
213. Sethofer, S.G., Mayer, T., Toste, F.D.: J. Am. Chem. Soc. **132**, 8276–8277 (2010)
214. Toullec, P.Y., Blarre, T., Michelet, V.R.: Org. Lett. **11**, 2888–2891 (2009)
215. Toullec, P.Y., Genin, E., Leseurre, L., Genêt, J.-P., Michelet, V.: Angew. Chem. Int. Ed. **45**, 7427–7430 (2006)
216. Leseurre, L., Chao, C.-M., Seki, T., Genin, E., Toullec, P.Y., Genêt, J.-P., Michelet, V.: Tetrahedron **65**, 1911–1918 (2009)
217. Seo, H., Roberts, B.P., Abboud, K.A., Merz, K.M., Hong, S.: Org. Lett. **12**, 4860–4863 (2010)
218. Chao, C.-M., Vitale, M.R., Toullec, P.Y., Genêt, J.-P., Michelet, V.: Chem. Eur. J. **15**, 1319–1323 (2009)

219. Nieto-Oberhuber, C., Pérez-Galán, P., Herrero-Gómez, E., Lauterbach, T., Rodríguez, C., López, S., Bour, C., Rosellón, A., Cárdenas, D.J., Echavarren, A.M.: J. Am. Chem. Soc. **130**, 269–279 (2007)
220. M.-C.P., Tsao, W.-C., Lee, B.-J., Lin, T.-L.: Organometallics **27**, 5326–5332 (2008)
221. Harrison, T.J., Patrick, B.O., Dake, G.R.: Org. Lett. **9**, 367–370 (2007)
222. Kozak, J.A., Dodd, J.M., Harrison, T.J., Jardine, K.J., Patrick, B.O., Dake, G.R.J.: Org. Chem. **74**, 6929–6935 (2009)
223. Kozak, J.A., Patrick, B.O., Dake, G.R.J.: Org. Chem. **75**, 8585–8590 (2010)
224. Fürstner, A., Stimson, C.C.: Angew. Chem. Int. Ed. **46**, 8845–8849 (2007)
225. Kusama, H., Karibe, Y., Onizawa, Y., Iwasawa, N.: Angew. Chem. Int. Ed. **49**, 4269–4272 (2010)
226. Jiménez-Núñez, E., Claverie, C.K., Nieto-Oberhuber, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **45**, 5452–5455 (2006)
227. Jiménez-Núñez, E., Molawi, K., Echavarren, A.M.: Chem. Commun. 7327–7329 (2009)
228. Molawi, K., Delpont, N., Echavarren, A.M.: Angew. Chem. Int. Ed. **49**, 3517–3519 (2010)
229. Schelwies, M., Dempwolff, A.L., Rominger, F., Helmchen, G.: Angew. Chem. Int. Ed. **46**, 5598–5601 (2007)
230. Escribano-Cuesta, A., López-Carrillo, V., Janssen, D., Echavarren, A.M.: Chem. Eur. J. **15**, 5646–5650 (2009)
231. Schelwies, M., Moser, R., Dempwolff, A.L., Rominger, F., Helmchen, G.: Chem. Eur. J. **15**, 10888–10900 (2009)
232. Jiménez-Núñez, E., Raducan, M., Lauterbach, T., Molawi, K., Solorio-Alvarado, C.R., Echavarren, A.M.: Angew. Chem. Int. Ed. **48**, 6152–6155 (2009)
233. Solorio-Alvarado, C.S., Echavarren, A.M.: J. Am. Chem. Soc. **132**, 11881–11883 (2010)
234. Caine, D.S., Gupton, J.T.: J. Org. Chem. **40**, 809–810 (1975)
235. Ishiyama, H., Kozawa, S., Aoyama, K., Mikami, Y., Fromont, J., Kobayashi, J.i: J. Nat. Prod. **71**, 1301–1303 (2008)
236. Kirsch, S.F., Binder, J.T., Crone, B., Duschek, A., Haug, T.T., Liébert, C., Menz, H.: Angew. Chem. Int. Ed. **46**, 2310–2313 (2007)
237. Baskar, B., Bae, H.J., An, S.E., Cheong, J.Y., Rhee, Y.H., Duschek, A., Kirsch, S.F.: Org. Lett. **10**, 2605–2607 (2008)
238. Menz, H., Binder, J.T., Crone, B., Duschek, A., Haug, T.T., Kirsch, S.F., Klahn, P., Liébert, C.: Tetrahedron **65**, 1880–1888 (2009)
239. Ferrer, C., Escribano-Cuesta, A., Echavarren, A.M.: Tetrahedron **65**, 9015–9020 (2009)

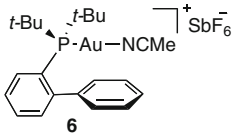
Chapter 2
Gold(I)-Catalyzed Reactions of 1, 6-Enynes with Aldehydes: Cycloaddition Versus Metathesis-Type Reactions

2.1 Introduction

The intra- and intermolecular nucleophilic trapping of gold intermediates starting from 1,n-enynes, allows the synthesis of very complicated structures in a highly efficient and selective manner (See general introduction) [Ref. 155 in Chap. 1]. In this context, 1,6-enynes with a carbonyl group at the alkenyl side chain such as **I-1** react in the presence of AuCl and other gold(I) catalysts to give oxatricyclic compounds **I-2** by a domino process in which two C–C bonds and one C–O bond are formed (Scheme 2.1) [Ref. 223 Chap. 1]. Fragmentation products **I-3** are also obtained as minor products.



Z	R	[AuL]$^+$	**I-2** (*syn*/*anti*)	**I-3**
$C(CO_2Me)_2$	Me	AuCl	79 (50:1)	10
$C(CO_2Me)_2$	*i*-Pr	**6**	44 (26.1)	39



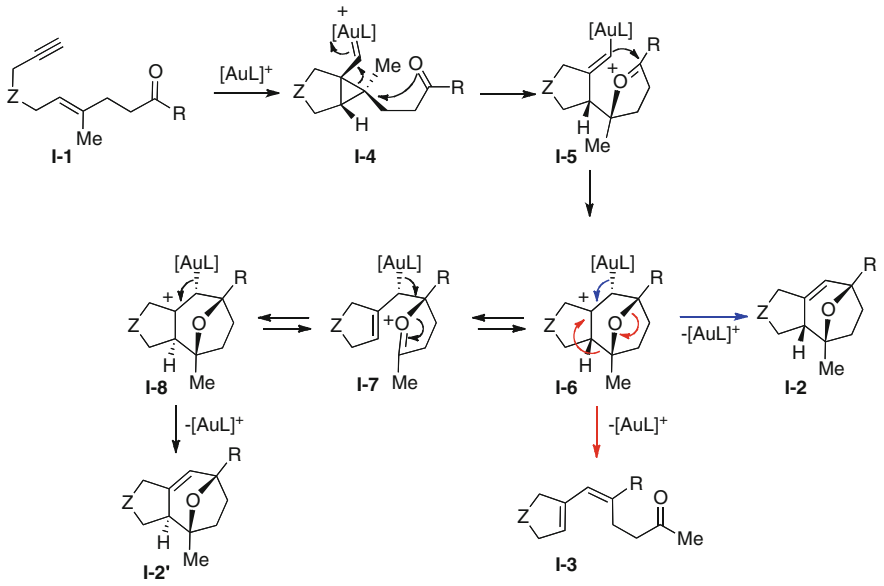
Scheme 2.1 Gold(I)-catalyzed cyclization of **I-1** enynes

This formal [2+2+2] alkyne/alkene/carbonyl cycloaddition proceeds through the opening of the cyclopropyl carbene intermediate **I-4** by the carbonyl group to form oxonium cation **I-5**, which undergoes nucleophilic attack by the vinylgold intermediates in a Prins-type cyclization to give tetrahydropyranyl cation **I-6**.

Part of these results have been published in: Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J.* **2009**, *15*, 5646–5650.

A. Escribano Cuesta, *New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids*, Springer Theses, DOI: 10.1007/978-3-319-00702-1_2,

Intermediate **I-6** can evolve by metal loss to give tricyclic compound **I-2,** or by fragmentation to form methyl ketone **I-3** (Scheme 2.2). The competitive 2-oxonia-Cope rearrangement of intermediate **I-6** via **I-7** forms **I-8**, which results in the minor epimer **I-2′** of the tricyclic compound. As other gold(I)-catalyzed reactions of enynes, this reaction is stereospecific [Refs. 4, 8, 154 in Chap. 1] [1].



Scheme 2.2 Proposed mechanism for the cyclization of **I-1** enynes

This is a powerful method to increase molecular complexity in one step, which has been applied as a key step in the total synthesis of natural products like (±)-pubinernoid B [Ref. 224 in Chap. 1], (+)-orientalol F [Ref. 224 in Chap. 1], and (−)-englerin A and B [Ref. 225 in Chap. 1] (Fig. 2.1).

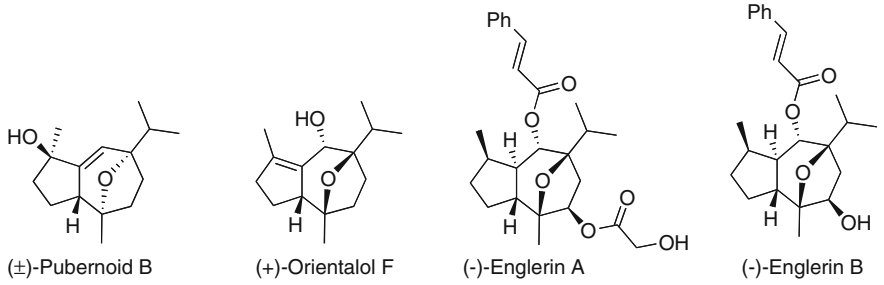
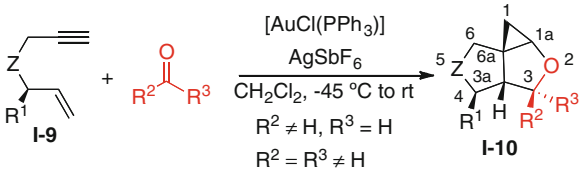


Fig. 2.1 Structures of (±)-pubernoid B, (+)-orientalol F, (−)-englerin A and (–)-englerin B

Intermolecular addition of aldehydes and ketones to 1,6-enynes is also feasible. 1,6-Enynes with a terminally monosubstituted alkene **I-9** react with carbonyl compounds to give tricyclic derivatives of type **I-10** with a highly diastereoselective control (Scheme 2.3) [Ref. 229 in Chap. 1]. The reaction proceeds with complete diastereoselectivity with respect to the stereogenic centers C1a, C3, C3a, and C6a.



Scheme 2.3 Gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes

The reaction proceeds with 1,6- and 1,7-enynes in the presence of aromatic and aliphatic aldehydes, but remarkably also with ketones. Selected examples using this methodology are shown in Fig. 2.2.

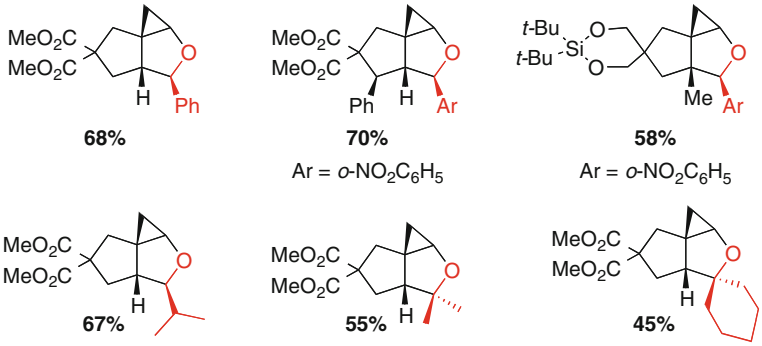
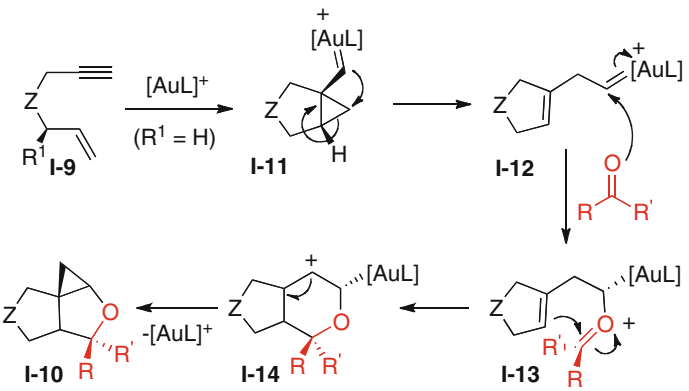


Fig. 2.2 Products of the intermolecular addition of different aldehydes and ketones to 1,6-enynes **I-9**

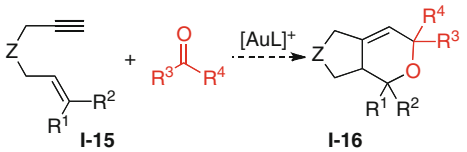
The gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enyne **I-9** presumably proceeds by trapping rearranged gold carbene intermediate **I-12** with the carbonyl compounds (Scheme 2.4). Thereby forming the oxonium cation **I-13**, which undergoes a Prins-type reaction to give **I-10**, probably via intermediate **I-14**.



Scheme 2.4 Proposed mechanism for the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes **I-9**

2.2 Objective

The precedent results shown in Scheme 2.3 suggested that aldehydes could react intermolecularly with 1,6-enynes possessing a terminal alkene moiety through cyclopropyl carbene **I-12** see (Scheme 2.4). Nevetheless, based on our observation of the intramolecular reaction of carbonyl compounds with 1,6-enynes **I-1** possesing a tri-substituted olefinic group (Scheme 2.1), we instead postulated that 1,6-enynes of type **I-15** give bicyclic compounds **I-16** in a formal [2+2+2] cycloaddition (Scheme 2.5).



Scheme 2.5 Proposal for the study of the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes **I-15**

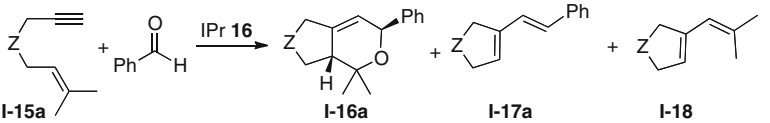
Therefore, the aim of the research was to study the intermolecular addition of carbonyl compounds to 1,6-enynes bearing a tri-substituted alkene (**I-15**) catalyzed by gold(I) complexes. This would provide a new methodology for the synthesis of bicyclic compounds of type **I-16**.

2.3 Results and Discussion

2.3.1 Optimization of the Reaction Conditions

To study the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes substituted at the alkene, like in **I-15**, we used enyne **I-15a** and benzaldehyde as our model (Table 2.1). Using the standard conditions for the intermolecular trapping of 1,6-enynes with nucleophiles, [Ref. 31 in Chap. 1] the formation of the expected [2+2+2] product **I-16a** and the skeletal rearrangement product **I-18** was observed. Surprisingly, an unpredicted metathesis-type product **I-17a** was also detected (Table 2.1, entry 1). Interestingly, we were able to decrease the yield of **I-18** by increasing the reaction time to 12 h at −40 °C (Table 2.1, entry 2). It should be noted that when this reaction was tested at room temperature, only the skeletal rearrangement product **I-18** was formed.

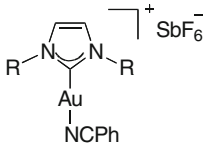
Table 2.1 Gold(I)-catalyzed intermolecular reaction of enyne **I-15a** and benzaldehyde



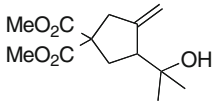
Z = $C(CO_2Me)_2$

Entry	Equiv aldehyde	Conditions	Conv. (%)	**I-16a**:**I-17a**:**I-18** ratio[a]
1	2	−40 °C (2 h) to rt (10 h)	100	28:18:55
2	5	−40 °C (12 h) to rt (10 h)	100	50:33:17[b]

Reaction conditions: Aldehyde (5 equiv) and IPr gold(I) **16** (5 mol %) in 0.1 M CH_2Cl_2 from −40 °C (12 h) to rt (10 h). [a] Ratios determined by ^{1}H-NMR; [b] Traces of hydroxycyclization **I-19** were observed

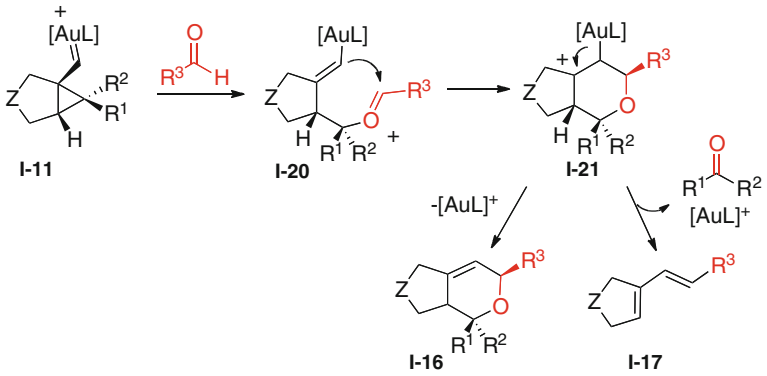


16: R = 2,6-*i*-$Pr_2C_6H_3$



I-19

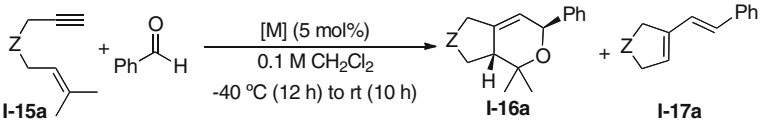
The mechanism for this reaction is analogous to its intramolecular version [Ref. 223 in Chap. 1], and starts with the formation of the cyclopropyl carbene **I-11** (Scheme 2.6). Direct attack of the aldehyde to the cyclopropyl gold(I) intermediate **I-11** leads to the oxonium cation **I-20**, which suffers Prins-type cyclization to give tetrahydropyranyl cation **I-21**. Intermediate **I-21** can undergo metalation to yield bicycle **I-16** or can evolve by a fragmentation reaction to form 1,3-diene **I-17**.



Scheme 2.6 Proposed mechanism for the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes substituted at the alkene **I-15**

In order to optimize the reaction conditions, a series of complexes were screened (Table 2.2). The best ratios were obtained with cationic gold(I) complexes (Table 2.2, entries 1–3). $[AuCl(PPh_3)]/AgSbF_6$ gave a nearly 1:1 mixture of dihydropyran **I-16a** and metathesis-type product **I-17a** (Table 2.2, entry 1). However, a similar ratios of **I-16a/I-17a =** 2.3:1 were observed with phosphine gold(I) **16** and phosphite gold(I) **20** (Table 2.2, entries 2–3). No difference between the results with the cationic phosphite gold(I) **20** and the in situ form

Table 2.2 Screening of catalysts for the gold(I)-catalyzed intermolecular reaction of enyne **I-15a** with benzaldehyde



Z = $C(CO_2Me)_2$

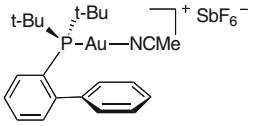
Entry	[M]	Conv. (%)	**I-16**:**I-17a**:**I-18** ratio[b]	Entry	[M]	Conv.(%)	**I-16**:**I-17a**:**I-18** ratio[a]
1	$[AuCl(PPh_3)]/AgSbF_6$	100	41:59:0	8	$PtCl_2$	0	–
2	**6**	100	37:63:0	9	$PtCl_4$	0	–
3	**19**/$AgSbF_6$ or **20**	100	33:67:0	10	**24**	100	13:8:63[b]
4	**14**	100	35:48:16	11	$PdCl_2$	0	–
5	**15**	100	38:27:35	12	$AgSbF_6$	0	–
6	**16**	100	50:33:17	13	$InCl_3$	7	0:71:29
7	AuCl	100	0:0:100	14	$GaCl_3$	5	0:95:5

Reaction conditions: Aldehyde (5 equiv) and [M] (5 mol %) in 0.1 M CH_2Cl_2 from −40 °C (12 h) to rt (10 h)

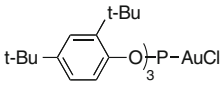
[a] Ratios determined by ^{1}H-NMR

[b] Traces of hydroxycyclization product **I-19** were observed

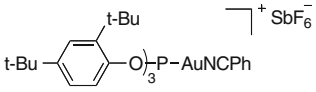
19/$AgSbF_6$ were found (Table 2.2, entry 3). In the examples with gold(I) carbene complexes **14**, **15**, and **16** quantitative conversion was observed but with low selectivity (Table 2.2, entries 4–6).



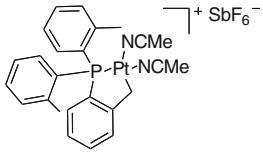
6



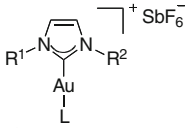
19



20



24

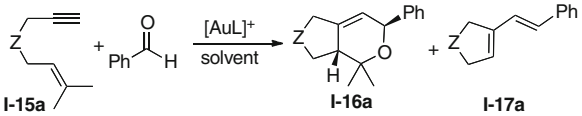


14: R^1 = Me, R^2 = Et, L = 2,4,6-$(MeO)_3C_6H_2CN$
15: $R^1 = R^2$ = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$
16: $R^1 = R^2$ = 2,6-i-$Pr_2C_6H_3$, L = PhCN

In the reaction catalyzed by AuCl and platinacycle **24** [Ref. 29 in Chap. 1] the rearranged product **I-18** was observed as the major product (Table 2.2, entries 7 and 10), whereas very low conversions ($\leq$7 %) were obtained when using $PtCl_2$, $PtCl_4$, $PdCl_2$, $AgSbF_6$, $InCl_3$, or $GaCl_3$ as catalysts (Table 2.2, entries 8, 9, 11–14).

The choice of solvent influenced both the activity and the selectivity of the catalytic system. Consequently, the reactions with the best cationic complexes phosphine gold(I) **6**, phosphite gold(I) **20**, and IPr gold(I) **16** were tested in different solvents (Table 2.3). In CH_2Cl_2, phosphine complex **6** gave a similar ratio to phosphite complex **20** (Table 2.3, entries 1 and 6), but in Et_2O the major product was the hydroxycyclization product **I-19**, due to traces of residual water (Table 2.3, entry 2). DMF completely inhibited the reaction of all the complexes (Table 2.3, entries 4, 9, and 13).

Table 2.3 Screening of solvents for the gold(I)-catalyzed intermolecular reaction of enyne **I-15a** with benzaldehyde



I-15a **I-16a** **I-17a**

Z = $C(CO_2Me)_2$

Entry	$[AuL]^+$	Solvent	Conv. (%)	**I-16**:**I-17a**:**I-18** ratio[a]
1	**6**	CH_2Cl_2	100	38:63:0
2		Et_2O	100	18:15:0[b,c]
3		DCE	50	23:32:45
4		DMF	0	–
5[d]		Dioxane	50	–
6	**20**	CH_2Cl_2	100	33:67:0
7		Et_2O	44	38:62:0
8		DCE	100	33:67:0
9		DMF	5	0:0:100[d]
10	**16**	CH_2Cl_2	100	38:27:35
11		Et_2O	58	72:29:0[b]
12		DCE	100	26:21:53
13		DMF	0	–

Reaction conditions: Aldehyde (5 equiv) and $[AuL]SbF_6$ (5 mol %) in 0.1 M solution from −40 °C (12 h) to rt (10 h)

[a] Ratios determined by ^{1}H-NMR

[b] Complex mixture

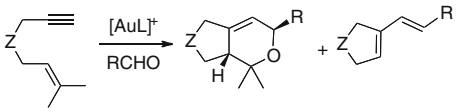
[c] 67 % of hydroxycyclization **I-19**. [d] rt (12 h) only hydroxycyclization product **I-19**

In CH_2Cl_2, Et_2O and DCE, the use of phosphite complex **20** gave the metathesis-type product **I-17a** as the major product (Table 2.3, entries 6–8), whereas low conversion of **I-15a** was observed in Et_2O (Table 2.3, entry 7).

2.3.2 Scope of the Reaction

Once we determined the best reaction conditions, the scope was explored. Products **I-16a-h** of [2+2+2] cycloaddition were isolated from enyne **I-15a** in 21–85 % yield, along with 1,3-dienes **I-17a-h** (Table 2.4). The reaction proceeded readily with electron-rich aldehydes. Conversely, in the reaction of **I-15a** with *o*-nitrobenzaldehyde, no adduct was formed (Table 2.4, entry 17), which is in contrast with the previously reported results for 1,6-enynes bearing a terminal alkene moiety **I-9** [Refs. 226, 228 in Chap. 1].

Table 2.4 Study of the gold(I)-catalyzed intermolecular reaction of enyne **I-15a** with different aldehydes



I-15a Z = $C(CO_2Me)_2$ **I-16** **I-17**

Entry	R	$[AuL]^+$	**I-16** yield (%)	**I-17** yield (%)
1	Ph	**6**	**I-16a** (35)[a]	**I-17a** (25)[b,c]
2		**16**	**I-16a** (21)[a]	**I-17a** (11)[b,c]
3		**20**	**I-16a** (29)[a]	**I-17a** (61)
4	4-MeC_6H_4	**16**	**I-16b** (41)	**I-17b** (21)[b,c]
5		**20**	**I-16b** (22)	**I-17b** (71)
6	2,4-$Me_2C_6H_3$	**16**	**I-16c** (77)	**I-17c** (19)
7		**20**	**I-16c** (41)	**I-17c** (59)[b]
8	2,4,6-$Me_3C_6H_2$	**16**	**I-16d** (85)	**I-17d** (39)
9		**20**	**I-16d** (53)	**I-17d** (9)
10	4-$MeOC_6H_4$	**6**	**I-16e** (25)	**I-17e** (27)
11		**16**	**I-16e** (58)	**I-17e** (12)
12		**20**	**I-16e** (30)	**I-17e** (23)
13	2,4-$(MeO)_2C_6H_3$	**16**	**I-16f** (63)	**I-17f** (29)
14		**20**	**I-16f** (50)	**I-17f** (34)[b]
15	2,4,6-$(MeO)_3C_6H_2$	**16**	**I-16g** (39)	**I-17g** (57)
16		**20**	**I-16g** (22)	**I-17g** (76)
17	4-$O_2NC_6H_4$	**20**	–	–
18	*c*-C_3H_5	**20**	**I-16h** (24)	**I-17h** (70)

Reaction conditions: Aldehyde (2 equiv) and $[AuL]SbF_6$ (2 mol %) in 0.1 M CH_2Cl_2 at −40 °C, 12 h

[a] 9:1–1:1 mixture of **I-16** and its $\Delta^{[4a,5]}$ isomer

[b] Yield determined by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as standard)

[c] Skeletal rearrangement product was also formed (10–50 % yield)

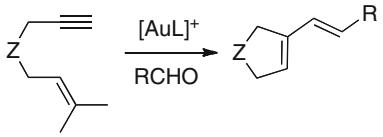
The metathesis-type products **I-17a-c** and **I-17g** were the major products observed with benzaldehyde, 4-methylbenzaldehyde, 2,4-dimethylbenzaldehyde, and 2,4,6-trimethoxy-benzaldehyde using phosphite complex **20** as catalyst (Table 2.4, entries 3, 5, 7, and 16). In contrast, with 2,4-dimethylbenzaldehyde, 2,4,6-trimethylbenzaldehyde, 4-methoxybenz-aldehyde, and 2,4-dimethoxybenz-aldehyde, the major products were the dihydropyran **I-16c-f** using IPr NHC complex **16** (Table 2.4, entries 6, 8, 11 and 13).

In general, we observed an increase in the yield of the dihydropyran products **I-16** using IPr gold(I) complex **16** (Table 2.4, entries 4, 6, 8, 13, 16 and 18). On the other hand, using phosphite complex **20**, the metathesis product **I-17** is favored (Table 2.4, entries 3, 5, 7 and 16).

On the other hand, complete selectivity toward 1,6-dienes **I-17** was obtained with 1,6-enynes **I-15b-c**, which only differ from **I-15a** in the heteroatom in the

enyne backbone (Table 2.5) [2]. Enynes **I-15b-c**, which in the absence of nucleophiles reacted by a 6-*endo-dig* pathway, reacted here by a 5-*exo-dig* process to give 1,3-dienes **I-17** [Refs. 28, 29, 154 in Chap. 1] [3], in moderate to good yields (Table 2.5, entries 1–7). It is worth mentioning than 1,6-enyne **I-15b** react with *p*-bromobenzaldehyde, which is the only example involving a deactivated aldehyde, in 67 % yield (Table 2.5, entry 4). Reactions were carried out routinely with two equivalents of aldehyde. Although acetone was released in the metathesis-like reactions of substrates **I-15a-c**, this ketone did not compete with the aldehydes. Consequently, this reaction can be applied to the ready synthesis of C1-substituted 1,3-dienes **I-17**, which would be otherwise difficult to prepare by other methods. For example, the reaction of 1,6-enynes **I-15b** with 1-pyrenecarboxaldehyde in the presence of phosphine gold(I) complex **6** (2 mol %) at −40 °C gave prenyl pyrenyl diene **I-17o** in 76 % yield (Table 2.5, entry 5).

Table 2.5 Study of the gold(I)-catalyzed intermolecular reaction of enyne **I-15b-c** with different aldehydes



I-15b Z = NTs **I-17**

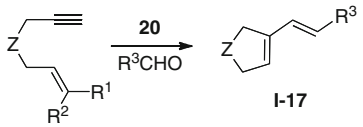
I-15c Z = O

Entry	**I-15**	$[AuL]^+$	R	**I-17** yield (%)
1	**b**	**20**	Ph	**I-17i** (65)
2		**20**	4-MeC_6H_4	**I-17j** (63)
3		**20**	2,4,6-$Me_3C_6H_2$	**I-17 k** (91)
4		**20**	4-BrC_6H_4	**I-17 l** (67)
5		**6**	1-pyrenyl	**I-17 m** (76)
6	**c**	**20**	4-MeC_6H_4	**I-17n** (34)
7			2,4,6-$Me_3C_6H_2$	**I-17o** (60)

Reaction conditions: Aldehyde (2 equiv) and $[AuL]SbF_6$ (2 mol %) in 0.1 M CH_2Cl_2 at −40 °C, 12 h

In addition, enynes **I-15d-f** with an aryl substituent at the alkene exclusively gave 1,3-dienes **I-17** by intermolecular metathesis with aldehydes in good yields (Table 2.6, entries 1–6) [Ref. 173 in Chap. 1]. Surprisingly, electron-rich aldehydes, such as 4-methoxybenzaldehyde or 3,4-dimethoxy-benzaldehyde, only led to decomposition or low yield using enynes with an aryl substituent at the alkene **I-15b-f** (Tables 2.5 and 2.6).

Table 2.6 Study of the gold(I)-catalyzed intermolecular reaction of enyne **I-15d-f** with different aldehydes



I-17

I-15d Z = $C(CO_2Me)_2$, R^1= Ph, R^2 = H

I-15e Z = $C(CO_2Me)_2$, R^1= 3,4-$(MeO)_2C_6H_3$, R^2 = H

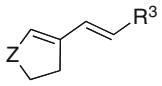
I-15f Z = $C(CO_2Me)_2$, R^1= 3,4,5-$(MeO)_3C_6H_2$, R^2 = H

Entry	**I-15**	R^3	**I-17** yield (%)
1	**d**	4-MeC_6H_4	**I-17b** (78)[a]
2		2,4-$Me_2C_6H_3$	**I-17c** (58)[b]
3		2,4,6-$Me_3C_6H_2$	**I-17d** (75)[b]
4	**e**	2,4,6-$Me_3C_6H_2$	**I-17d** (70)
5	**f**	4-MeC_6H_4	**I-17b** (41)
6		2,4,6-$Me_3C_6H_2$	**I-17d** (81)

Reaction conditions: Aldehyde (2 equiv) and **20** (2 mol %) in 0.1 M CH_2Cl_2 at −40 °C, 12 h

[a] 1:1 mixture of **I-17** and **1-22** isomer

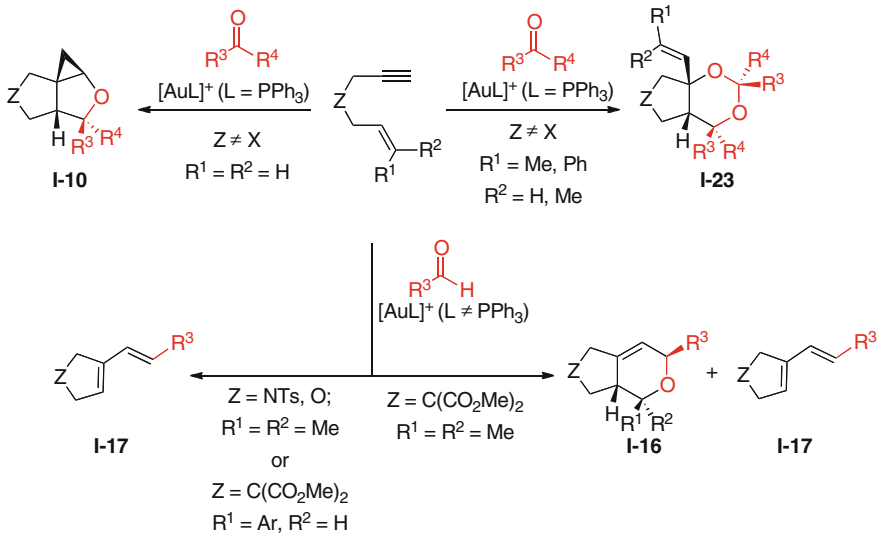
[b] 1:5 mixture of **I-17** and **1-22** isomer



I-22

2.4 Conclusions

In summary, a clearer picture of the intertwined reaction pathways at play in the intermolecular gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes has emerged from this study. Ultimately, this work complements the investigations leading to tricyclic compound **I-10** and 1,3-dioxolanes **I-23** reported by the Helmchen group (Scheme 2.7) [Ref. 226, 228 in Chap. 1].

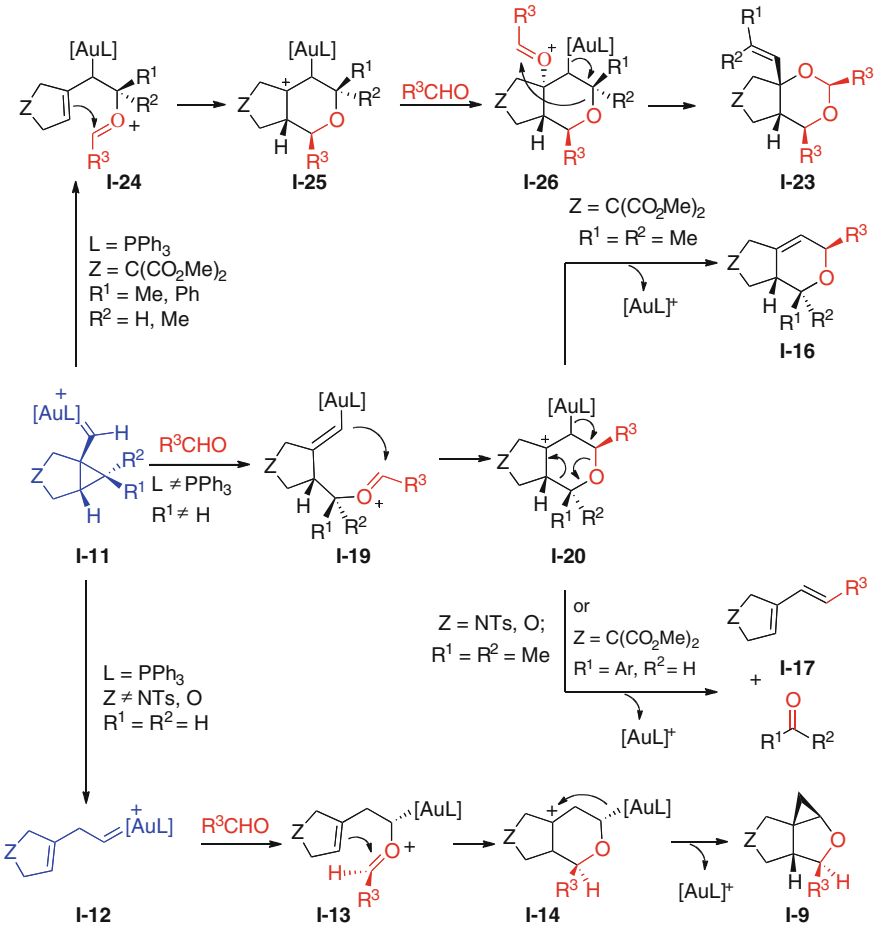


Scheme 2.7 General overview of the gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes

We conclude that changing the substitution pattern of the alkene, the heteroatom in the tether, or using different gold(I) complexes has a tremendous influence in the selective formation of tricyclic compound **I-10**, the product of formal [2+2+2] cycloaddition **I-16**, 1,3-dienes **I-17** or 1,3-dioxolanes **I-23** [Ref. 226 in Chap. 1].

Depending on the substitution pattern of different 1,6-enynes used and the ligand on the gold(I) complex, either gold carbene **I-11** or **I-12** could be trapped, thus giving different type of products (Scheme 2.8). In the case of 1,6-enynes substituted at the alkene, the formation of three different products is possible, the [2+2+2] cycloaddition product **I-16**, the 1,3-diene **I-17** and the 1,3-dioxolanes **I-23**.

Using 1,6-enynes **I-15** ($Z = C(CO_2Me)_2$, $R^1 \neq H$, $R^2 \neq H$), the formation of the expected [2+2+2] cycloaddition product **I-16** was observed in a mixture with 1,3-diene **I-17** from 1,6-dienes **I-15a** ($Z = C(CO_2Me)_2$, $R^1 = R^2 = Me$). However, 1,3-dienes **I-17** were synthesized selectively in moderate to high yields using 1,6-enynes with a heteroatom in the enyne backbone **I-17b-c** ($Z = NTs$, O, $R^1 = R^2 = Me$) or 1,6-enynes with an electron-donating aryl substituent at the alkene **I-15d-f** ($Z = C(CO_2Me)_2$, $R^1 = Ar$, $R^2 = H$). This reaction proceeds by a fragmentation of the tetrahydropyranyl cation **I-20** formed by an intramolecular Prins reaction.



Scheme 2.8 Mechanism hypothesis concerning the formation of the different products from 1,6-enynes and carbonyl compounds

On the other hand, in the case of enynes substituted at the alkene the double addition of aldehydes is also possible, although it is not a general process. Addition of the carbonyl compound to the gold cyclopropyl carbene **I-11** gives the oxonium cation **I-24**. Subsequent Prins-type addition leads to the gold stabilized carbocation **I-25**, which suffers nucleophilic attack by a second carbonyl compound. Then, the oxonium cation **I-26** rearranges to the final 1,3-dioxolane **I-23**.

To conclude, a wide array of products can be synthesized via intermolecular gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes by changing the substitution pattern of the alkene, the heteroatom in the tether, or using different gold(I) complexes. Within this work, we have shed some light into the necessary conditions to selectively synthesize these compounds.

2.5 Experimental Section

2.5.1 General Methods

All reactions were carried out under Ar in solvents dried using a Solvent Purification System (SPS). Extractive workup refers to portioning of the crude reaction between an organic solvent and water, phase separation, drying (Na_2SO_4 or $MgSO_4$), and evaporation under reduced pressure.

Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm). HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector.

NMR spectra were recorded at 23 °C on a Bruker Advance 400 Ultrashield apparatus.

Mass spectra were recorded on Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid. Melting points were determined using a Büchi melting point apparatus. Optical rotations were recorded on a P-1030 polarimeter from Jasco at the sodium D line.

2.5.2 Preparation of Substrates

The metal salts AuCl (Strem), $PdCl_2$ (Johson Matthey), $InCl_3$ (SDS), $GaCl_3$ (Aldrich), $PtCl_2$ (Johson Matthey), $AgSbF_6$ (Aldrich), complex [AuCl(PPh_3)] (Strem) and phosphine complex **6** (Aldrich) were used as received. Complex IME gold(I) **14** [Ref. 43 in Chap. 1], IMes gold(I) **15** [Ref. 43 in Chap. 1 IPr gold(I) **16** [Ref. 43 in Chap. 1], phosphite gold(I) **19** [Ref. 31 in Chap. 1] cationic phosphite gold(I) **20** [Ref. 42 in Chap. 1], platinacycle **24** [Ref. 29 in Chap. 1] were prepared according to the reported procedure.

The starting 1,6-enynes were synthesized following the literature procedures: **I-15a** [4], **I-15b** [5], **I-15c** [6], **I-15d** [7], **I-15e**, [Ref. 173 in Chap. 1] and **I-15d** [Ref. 173 in Chap. 1].

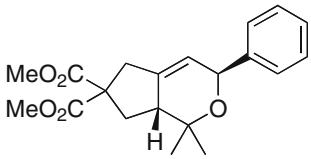
2.5.3 Cyclization Products

General procedure for the reaction of 1,6-enynes with aldehydes (Table 2.1). A solution of 1.6-enyne (80 mg) and the corresponding aldehyde (2 equiv) in CH_2Cl_2 (concentration. ca. 0.1 M) was cooled to −40 °C and the gold complex **6**, **16** or **20** (2 mol %) was added after 15 min. The solution was kept at −40 °C for 12 h.

A 0.1 M solution of Et_3N in hexane was added and the solution was filtered through Celite. After evaporation, the crude was chromatographed.

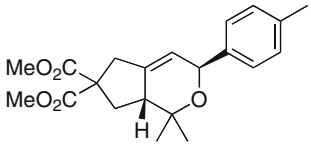
Characterization of the following compounds have been reported previously: **I-17a** [8], **I-17c** [Ref. 173 in Chap. 1], **I-17e**, [Ref. 28 in Chap. 1] **I-17f**, [Ref. 173 in Chap. 1]. **I-17g** [Ref. 173 in Chap. 1], and **I-17h** [Ref. 173 in Chap. 1].

Dimethyl 1,1-dimethyl-3-phenyl-3,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate (**I-16a**).



Compound **I-16a** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (82.0 mg, 0.34 mmol) and benzaldehyde (0.07 mL, 0.69 mmol) with catalyst **20**. The residue was purified by column chromatography (from 12:1 to 10:1 hexane/EtOAc) to give 34.1 mg of the compound **I-16a** (29 %, 1:0.16 mixture of estereoisomers) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.31 (m, 5H), 5.51 (quintuplet, $J = 2.1$ Hz, 1H), 5.01 (quintuplet, $J = 2.7$ Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.14 (br d, $J = 17.5$ Hz, 1H), 2.95 (dq, $J = 17.5$ Hz, $J = 2.1$ Hz, 1H), 2.70–263 (m, 1H), 2.54 (dd, $J = 12.8$ Hz, $J = 7.6$ Hz, 1H), 1.81 (t, $J = 12.4$ Hz, 1H), 1.34 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) Mixture of isomers δ 172.5 (C), 172.4 (C), 141.9 (C), 136.9 (C), 128.6 (2CH), 127.8 (CH), 127.4 (2CH), 120.4 (CH), 74.4 (C), 73.4 (CH), 58.1 (C), 53.1 (CH_3), 53.0 (CH_3), 47.5 (CH), 38.7 (CH_2), 36.3 (CH_2), 29.6 (CH_3), 19.0 (CH_3). HRMS-ESI *m/z* calcd for $C_{20}H_{24}O_5Na$ $[M+Na]^+$ 367.1521, found 367.1537. The structure was confirmed by HMBC, HSQC and COSY experiments and configuration assigned by NOESY.

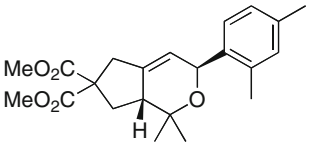
Dimethyl 1,1-dimethyl-3-*p*-tolyl-3,5,7,7a-tetrahydrocyclopenta [*c*] pyran-6,6(1*H*)-dicarboxylate (**I-16b**).



Compound **I-16b** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (91.2 mg, 0.38 mmol) and *p*-tolualdehyde (0.09 mL, 0.77 mmol) with catalyst **20**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 30.3 mg of the compound **I-16b** (22 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 5.50 (quintuplet, $J = 2.1$ Hz, 1H), 4.98 (quintuplet, $J = 2.9$ Hz 1H), 3.77(s, 3H), 3.74 (s, 3H), 3.13 (br d, $J = 17.2$ Hz, 1H), 2.95 (dq, $J = 17.4$, 2.1 Hz, 1H), 2.68-2.61 (m, 1H), 2.53 (dd,

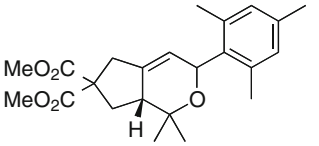
J = 12.4, 7.9 Hz, 1H), 2.32 (s, 3H), 1.80 (t, J = 12.4 Hz, 1H), 1.33 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, PENDANT) δ 172.5 (C), 172.4 (C), 138.9 (C), 137.5 (C), 136.8 (C), 129.3 (CH), 127.4 (2CH), 120.5 (CH), 74.4 (C), 73.2 (CH), 58.1 (C), 53.1 (CH_3), 53.0 (CH_3), 47.5 (CH), 38.7 (CH_2), 36.3 (CH_2), 29.6 (CH_3), 21.3 (CH_3), 19.0 (CH_3); HRMS-ESI *m/z* calcd for $C_{21}H_{26}O_5Na$ [M+Na]$^+$ 381.1678, found 381.1694. The structure was confirmed by HMBC, HSQC and COSY experiments and configuration assigned by NOESY.

Dimethyl 3-(2,4-dimethylphenyl)-1,1-dimethyl-3,5,7,7a-tetrahydro-cyclopenta[c]pyran-6,6(1*H*)-dicarboxylate (I-16c).



Compound **3ac** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (82.6 mg, 0.35 mmol) and 2,4-dimethylbenzaldehyde (0.10 mL, 0.69 mmol) with catalyst **16**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 99.8 mg of the compound **I-16c** (77 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.6 Hz, 1H), 6.98–6.95 (m, 2H), 5.51 (quintuplet, J = 1.9 Hz, 1H), 5.19 (quintuplet, J = 3.0 Hz, 1H), 3.77(s, 3H), 3.75 (s, 3H), 3.15 (br d, J = 17.3 Hz, 1H), 2.96 (br dd, J = 17.4, 2.0 Hz, 1H), 2.67–2.60 (m, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 1.82 (t, J = 12.3 Hz, 1H), 1.32 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.5 (C), 172.4 (C), 137.3 (C), 137.3 (C), 136.3 (C), 136.2 (C), 131.6 (CH), 128.0 (CH), 126.9 (CH), 119.4 (CH), 74.4 (C), 70.5 (CH), 58.1 (C), 53.1 (CH_3), 53.0 (CH_3), 47.4 (CH), 38.8 (CH_2), 36.2 (CH_2), 29.6 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 19.0 (CH_3). HRMS-ESI *m/z* calcd for $C_{22}H_{28}O_5Na$ [M+Na]$^+$ 395.1834, found 395.1848. The structure was confirmed by HMBC, HSQC and COSY experiments and configuration assigned by NOESY.

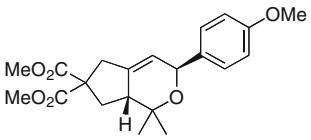
Dimethyl 3-mesityl-1,1-dimethyl-3,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate (I-16d).



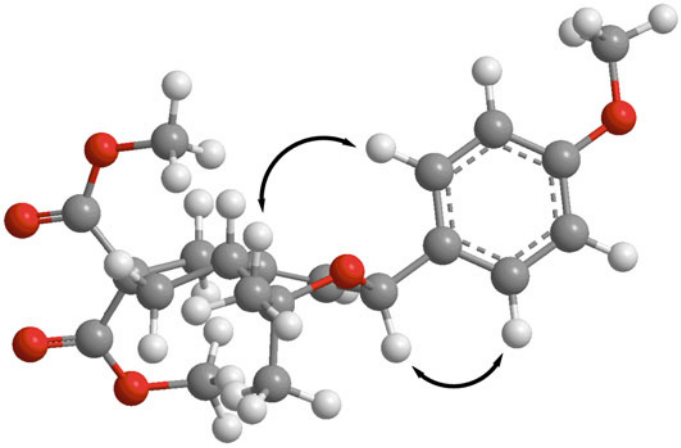
Compound **I-16d** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (84.6 mg, 0.36 mmol) and mesitaldehyde (0.11 mL, 0.71 mmol) with catalyst **16**. The residue was purified by column chromatography (15:1 hexane/EtOAc) to give 116.2 mg of the compound **I-16d** (85 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H), 5.47-5.44 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.13 (br d, J = 17.7 Hz, 1H),

2.93 (br d, $J = 13.3$ Hz, 1H), 2.66–2.61 (m, 1H), 2.53 (dd, $J = 12.5$, 7.9 Hz, 1H), 2.32 (s, 6H), 2.23 (s, 3H), 1.89 (t, $J = 12.2$ Hz, 1H), 1.32 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.5 (C), 172.4 (C), 137.1(C), 136.8 (C), 133.2 (C), 130.0 (CH), 118.7 (CH), 74.4 (C), 69.1 (CH), 58.1 (C), 53.1 (CH_3), 53.0 (CH_3), 46.9 (CH), 38.6 (CH_2), 36.2 (CH_2), 29.4 (CH_3), 20.9 (CH_3), 20.4 (CH_3), 19.3 (CH_3). HRMS-ESI *m/z* calcd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$ 409.1991, found 409.1987. The structure was confirmed by HMBC, HSQC and COSY experiments.

Dimethyl 3-(4-methoxyphenyl)-1,1-dimethyl-3,5,7,7a-tetrahydro-cyclopenta[*c*] pyran-6,6(1*H*)-dicarboxylate (**I-16e**).

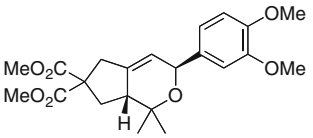


Compound **3ae** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (92.5 mg, 0.39 mmol) and *p*-methoxybenzaldehyde (0.10 mL, 0.78 mmol) with catalyst **16**. The residue was purified by column chromatography (7:1 hexane/EtOAc) to give 84.6 mg of the compound **I-16e** (58 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.48 (quintuplet, $J = 2.3$ Hz, 1H), 4.96 (quintuplet, $J = 2.7$ Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.14 (br d, $J = 17.4$ Hz, 1H), 2.95 (dq, $J = 17.4$, 2.0 Hz, 1H), 2.67–2.61 (m, 1H), 2.52 (dd, $J = 12.6$, 7.8 Hz, 1H), 1.80 (t, $J = 12.5$ Hz, 1H), 1.32 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, PENDANT) δ 172.5 (C), 172.4 (C), 159.4 (C), 136.9 (C), 134.0 (C), 128.8 (CH), 120.5 (CH), 114.0 (CH), 74.4 (C), 72.9 (CH), 58,1 (C), 55.5 (CH_3), 53.1 (CH_3), 53.0 (CH_3), 47.5 (CH), 38.7 (CH_2), 36.3 (CH_2), 29.6 (CH_3), 19.0 (CH_3). HRMS-ESI *m/z* calcd for $C_{21}H_{26}O_6Na$ $[M+Na]^+$ 397.1627, found 397.1631. The structure was confirmed by HMBC, HSQC and COSY experiments and configuration assigned by NOESY.



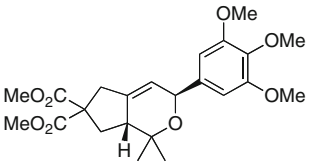
NOE effects shown in **I-16e** (conformation minimized by MM2).

Dimethyl 3-(3,4-dimethoxyphenyl)-1,1-dimethyl-3,5,7,7a-tetrahydro-cyclopenta[c-]pyran-6,6(1*H*)-dicarboxylate (I-16f).



Compound **I-16f** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (85.9 mg, 0.36 mmol) and 3,4-dimethoxybenzaldehyde (0.12 g, 0.72 mmol) with catalyst **16**. The residue was purified by column chromatography (from 5:1 to 3:1 hexane/EtOAc) to give 92.5 mg of the compound **I-16f** (63 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98–6.80 (m, 3H), 5.50 (br s, 1H), 4.95 (br s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.76 (d, $J = 0.9$ Hz, 3H), 3.74 (d, $J = 0.8$ Hz, 3H), 3.14 (d, $J = 17.5$ Hz, 1H), 2.96 (d, $J = 17.4$, 1H), 2.68–2.63 (m, 1H), 2.53 (dd, $J = 12.7$, 7.8 Hz, 1H), 1.80 (t, $J = 12.5$ Hz, 1H), 1.33 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.5 (C), 172.4 (C), 149.2 (C), 148.8 (C), 137.1 (C), 134.5 (C), 120.4 (CH), 119.9 (CH), 111.3 (CH), 110.8 (CH), 74.5 (C), 73.2 (CH), 58,1 (C), 56.1 (CH_3), 56.0 (CH_3), 53.1 (CH_3), 53.0 (CH_3), 47.5 (CH), 38.7 (CH_2), 36.2 (CH_2), 29.6 (CH_3), 19.0 (CH_3). HRMS-ESI *m/z* calcd for $C_{22}H_{28}O_7Na$ $[M + Na]^+$ 427.1733, found 427.1737. The structure was confirmed by HMBC, HSQC and COSY experiments and configuration assigned by NOESY.

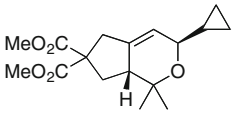
Dimethyl 1,1-dimethyl-3-(3,4,5-trimethoxyphenyl)-3,5,7,7a-tetrahydro-cyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate (**I-16g**).



Compound **I-16g** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (96.4 mg, 0.40 mmol) and 3,4,5-trimethoxybenzaldehyde (0.16 g, 0.81 mmol) with catalyst **20**. The residue was purified by column chromatography (from 4:1 to 3:1 hexane/EtOAc) to give 115.8 mg of the compound **I-16g** (76 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 2H), 5.51 (quintuplet, $J = 2.1$ Hz, 1H), 4.94 (quintuplet, $J = 3.0$ Hz, 1H), 3.86 (s, 6H), 3.80 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.15 (br d, $J = 17.2$ Hz, 1H), 2.97 (dq, $J = 17.4$, 1.9 Hz, 1H), 2.69–2.63 (m, 1H), 2.53 (dd, $J = 12.7$, 7.8 Hz, 1H), 1.80 (t, $J = 12.4$ Hz, 1H), 1.35 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.5 (C), 172.3 (C), 153.5 (2C), 137.4 (C), 137.4 (C), 120.1 (CH), 104.5 (CH), 74.6 (C), 73.5 (CH), 60.9 (CH_3), 58.0 (C),

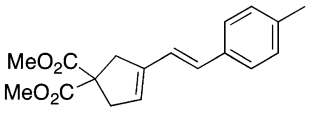
56.3 (CH_3), 53.1 (CH_3), 53.0 (CH_3), 47.4 (CH), 38.7 (CH_2), 36.2 (CH_2), 29.3 (CH_3), 19.0(CH_3). HRMS-ESI *m/z* calcd for $C_{23}H_{30}O_8Na$ $[M+Na]^+$ 457.1838, found 457.1843. The structure was confirmed by HMBC, HSQC and COSY experiments.

Dimethyl 3-cyclopropyl-1,1-dimethyl-3,5,7,7a-tetrahydrocyclopenta[*c*]pyran-6,6(1*H*)-dicarboxylate (**I-16h**).



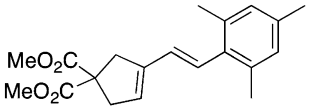
Compound **I-16h** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (90.0 mg, 0.38 mmol) and cyclopropranecarboxaldehyde (0.14 mL, 1.89 mmol) with catalyst **20**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 32.9 mg of the compound **I-16h** (24 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (quintuplet, $J = 2.1$ Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.22 (dd, $J = 5.8$, 3.0 Hz, 1H), 3.10 (dt, $J = 17.4$ Hz, 2.5 Hz, 1H), 2.89 (dq, $J = 17.3$, 2.0 Hz, 1H), 2.51-2.42 (m, 2H), 1.72 (t, $J = 11.2$ Hz, 1H), 1.28 (s, 3H), 0.96 (s, 3H), 0.89–0.81 (m, 1H), 0.59-0.52 (m, 1H), 0.49–0.42 (m, 1H), 0.37–0.31 (m, 1H), 0.22–0.16 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172. 5 (C), 172. 5 (C), 137.5 (C), 119.4 (CH), 75.2 (CH), 73.4 (C), 58.2 (C), 53.1 (CH_3), 53.0 (CH_3), 47.6 (CH), 38.6 (CH_2), 36.2 (CH_2), 29.6 (CH_3), 18.8 (CH_3), 15.7 (CH), 3.8 (CH_2), 1.2 (CH_2). HRMS-ESI *m/z* calcd for $C_{17}H_{24}O_5Na$ $[M+Na]^+$ 331.1521, found 331.1505. The structure was confirmed by HMBC, HSQC and COSY experiments.

(*E*)-Dimethyl 3-(4-methylstyryl)cyclopent-3-ene-1,1-dicarboxylate (**I-17b**).



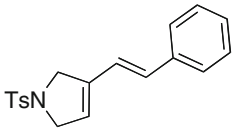
Compound **I-17b** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (91.2 mg, 0.38 mmol) and *p*-tolualdehyde (0.09 mL, 0.77 mmol) with catalyst **20**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 70.1 mg of the compound **I-17b** (71 %) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 7.9$ Hz, 2H), 6.85 (d, $J = 16.2$ Hz, 1H), 6.42 (d, $J = 16.2$ Hz, 1H), 5.67 (br s, 1H), 3.76 (s, 6H), 3.26 (br s, 2H), 3.16 (br s, 2H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.7 (C), 140.0 (C), 137.6 (C), 134.6 (C), 130.2 (CH), 129.5 (CH), 127.0 (CH), 126.5 (CH), 123.5 (CH), 59.0 (C), 53.0 ($2CH_3$), 41.2 (CH_2), 39.9 (CH_2), 21.9 (CH_3). HRMS-ESI *m/z* calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$ 323.1259, found 323.1265. The structure was confirmed by HMBC, HSQC and COSY experiments.

(*E*)-Dimethyl 3-(2,4,6-trimethylstyryl)cyclopent-3-ene-1,1-dicarboxylate (**I-17d**).



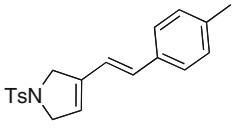
Compound **I-17d** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (84.6 mg, 0.36 mmol) and mesitaldehyde (0.11 mL, 0.71 mmol) with catalyst **16**. The residue was purified by column chromatography (15:1 hexane/EtOAc) to give 9.9 mg of the compound **I-17d** (9 %) as a colorless white solid: mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.44 (d, $J = 16.6$ Hz, 1H), 6.38 (d, $J = 16.6$ Hz, 1H), 5.59 (br s, 1H), 3.78 (s, 6H), 3.29 (d, $J = 1.5$ Hz, 2H), 3.16 (d, $J = 1.4$ Hz, 2H), 2.28 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.8 (C), 140.0 (C), 136.4 (C), 136.1 (2C), 133.8 (C), 129.5 (CH), 128.9 (CH), 128.3 (CH), 126.4 (CH), 58.9 (C), 53.1 (CH_3), 41.2 (CH_2), 39.8 (CH_2), 21.2 (CH_3), 21.1 (CH_3). HRMS-ESI m/z calcd for $C_{20}H_{24}O_4Na$ $[M+Na]^+$ 351.1572, found 351.1573. The structure was confirmed by HMBC, HSQC and COSY experiments.

(*E*)-3-Styryl-1-tosyl-2,5-dihydro-1*H*-pyrrole (**I-17i**).



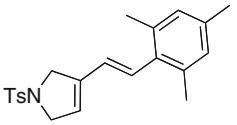
Compound **I-17i** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.4 mg, 0.30 mmol) and benzaldehyde (64.3 mg, 0.60 mmol) with catalyst **20**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 63.5 mg of compound **I-17i** (65 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.3$ Hz, 2H), 7.38–7.29 (m, 6H), 7.26–7.22 (m, 1H), 6.76 (d, $J = 16.4$ Hz, 1H), 6.32 (d, $J = 16.3$ Hz, 1H), 5.68 (t, $J = 1.8$ Hz, 1H), 4.34-4.32 (m, 2H), 4.23-4.21 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7 (C), 137.3 (C), 136.5 (C), 134.2 (C), 131.5 (CH), 130.0 (CH), 128.8 (2CH), 128.3 (CH), 127.6 (CH), 126.6 (CH), 123.5 (CH), 121.6 (CH), 55.3 (CH_2), 53.9 (CH_2), 21.6 (CH_3). HRMS-ESI *m/z* calcd for $C_{19}H_{19}NNaO_2S$ $[M+Na]^+$ 348.1040, found 348.1034.

(*E*)-3-(4-Methylstyryl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (**I-17j**).



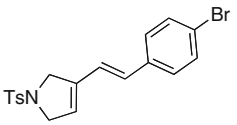
Compound **I-17j** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.4 mg, 0.30 mmol) and *p*-tolualdehyde (72.1 mg, 0.60 mmol) with catalyst **20**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 64.6 mg of the compound **I.17j** (63 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.71 (d, $J = 16.3$ Hz, 1H), 6.30 (d, $J = 16.2$ Hz, 1H), 5.65 (bt, $J = 1.9$ Hz, 1H), 4.34–4.31 (m, 2H), 4.23-4.20 (m, 2H), 2.41 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6 (C), 138.3 (C), 137.4 (C), 134.3 (C), 133.7 (C), 131.4 (CH), 129.9 (CH), 129.6 (CH), 127.6 (CH), 126.5 (CH), 122.9 (CH), 120.7 (CH), 55.3 (CH_2), 53.9 (CH_2), 21.6 (CH_3), 21.4 (CH_3). HRMS-ESI *m/z* calcd for $C_{20}H_{21}NNaO_2S$ $[M+Na]^+$ 362.1191, found 362.1179.

(*E*)-1-Tosyl-3-(2,4,6-trimethylstyryl)-2,5-dihydro-1*H*-pyrrole (**I-17k**).



Compound **I-17k** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.9 mg, 0.30 mmol) and mesitaldehyde (89.8 mg, 0.60 mmol) with catalyst **6**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 100.3 mg of compound **I-17k** (91 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 6.86 (s, 2H), 6.34 (d, $J = 16.5$ Hz, 1H), 6.26 (d, $J = 16.7$ Hz, 1H), 5.61 (bs, 1H), 4.37-4.35 (m, 2H), 4.23-4.20 (m, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6 (C), 137.5 (C), 136.9 (C), 136.0 (2C), 134.4 (C), 133.0 (C), 129.9 (CH), 129.8 (CH), 128.9 (CH), 127.6 (CH), 126.9 (CH), 122.7 (CH), 55.1 (CH_2), 53.7 (CH_2), 21.7 (CH_3), 21.1 ($3CH_3$). HRMS-ESI *m/z* calcd for $C_{22}H_{25}NNaO_2S$ $[M+Na]^+$ 390.1504, found 390.1521.

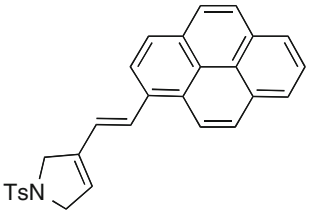
(*E*)-3-(4-Bromostyryl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (**I-17l**).



Compound **I-17l** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.6 mg, 0.30 mmol) and *p*-bromobenzaldehyde (111.1 mg, 0.60 mmol) with catalyst **6**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 81.2 mg of compound **I-17l** (67 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.3$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 6.74 (d, $J = 16.4$ Hz, 1H), 6.25 (d, $J = 16.4$ Hz, 1H), 5.71 (bt, $J = 2.0$ Hz, 1H), 4.32-4.30 (m, 2H), 4.23–4.20 (m, 2H), 2.42 (s, 3H). ^{13}C

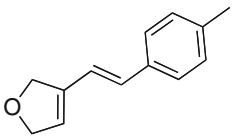
NMR (100 MHz, $CDCl_3$) δ 143.7 (C), 137.1 (C), 135.5 (C), 134.2 (C), 132.0 (CH), 130.2 (CH), 130.0 (CH), 128.0 (CH), 127.6 (CH), 124.3 (CH), 122.3 (CH), 122.1 (C), 55.3 (CH_2), 53.7 (CH_2), 21.6 (CH_3). HRMS-ESI *m/z* calcd for $C_{19}H_{18}BrNNaO_2S$ $[M+Na]^+$ 426.0139, found 426.0143.

(*E*)-3-(2-(pyren-1-yl)vinyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (**I-17m**).



Compound **I-17m** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.3 mg, 0.30 mmol) and 1-pyrenecarboxaldehyde (138.4 mg, 0.60 mmol) with catalyst **6**. The residue was purified by column chromatography (100 % CH_2Cl_2) to give 103.5 mg of compound **I-17o** (76 %) as a yellow solid: mp 213–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 9.3 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.9 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 15.8 Hz, 1H), 7.35 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 16.0 Hz, 1H), 5.77 (t, J = 1.8 Hz, 1H), 4.55-4.53 (m, 2H), 4.30-4.27 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7 (C), 137.8 (C), 134.3 (C), 131.6 (C), 131.3 (C), 131.0 (C), 130.7 (C), 130.0 (2CH), 128.5 (C), 128.2 (CH), 128.0 (CH), 127.7 (2CH), 127.6 (CH), 127.5 (CH), 126.2 (CH), 125.6 (CH), 125.4 (CH), 125.2 (CH), 125.1 (C), 125.0 (C), 124.4 (CH), 124.0 (CH), 123.4 (CH), 122.7 (CH), 55.4 (CH2), 54.0 (CH2), 21.7 (CH3). HRMS-ESI *m/z* calcd for $C_{29}H_{23}NNaO_2S$ $[M+Na]^+$ 472.1347, found 472.1346. UV–Vis (CH_2Cl_2) λ_{max} (ε_{max}) 388 nm (28830), 371 (31780), 289 (23470), 237 (34990). Fluorescence (395 nm excitation, c 0.05 M, CH_2Cl_2) 437 nm (2.88), 414 (4.12).

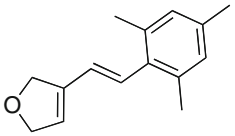
(*E*)-3-(4-Methylstyryl)-2,5-dihydrofuran (**I-17n**).



Compound **I-17n** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15c** (50.5 mg, 0.40 mmol) and *p*-tolualdehyde (96.3 mg, 0.80 mmol) with catalyst **6**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 13.5 mg of compound **I-17n** (34 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 16.4 Hz, 1H), 6.26 (d, J = 16.4 Hz, 1H), 5.90 (s, 1H), 4.86–4.84 (m, 2H), 4.76–4.74 (m, 2H), 2.34 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 138.4 (C), 137.9 (C), 134.2 (C), 130.9 (CH), 129.5 (CH), 126.4 (CH), 124.7 (CH), 120.2 (CH), 76.2 (CH_2), 74.4 (CH_2), 21.4 (CH_3). HRMS-APCI *m/z* calcd for C13H15O $[M+H]^+$ 187.1123, found 187.1124.

(*E*)-3-(2,4,6-Trimethylstyryl)-2,5-dihydrofuran (I-17o)



Compound **I-17o** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15c** (50.1 mg, 0.40 mmol) and mesitaldehyde (119.5 mg, 0.80 mmol) with catalyst **6**. The residue was purified by column chromatography (10:1 hexane/EtOAc) to give 51.8 mg of compound **I-17o** (59 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.50 (d, $J = 16.7$ Hz, 1H), 6.37 (d, $J = 16.6$ Hz, 1H), 5.92 (bt, $J = 1.8$ Hz, 1H), 4.99–4.96 (m, 2H), 4.85–4.83 (m, 2H), 2.35 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (C), 136.6 (C), 136.0 (C), 133.5 (C), 129.2 (CH), 128.9 (CH), 126.4 (CH), 124.4 (CH), 76.1 (CH_2), 74.4 (CH_2), 21.0 ($3CH_3$). HRMS-APCI *m/z* calcd for C15H19O $[M+H]^+$ 215.1436, found 215.1431.

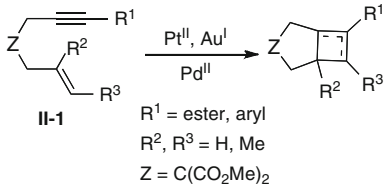
References

1. Gorin, D.J., Sherry, B.D., Toste, F.D.: Chem. Rev. **108**, 3351–3378 (2008)
2. Results carried out in collaboration with Dr. D. Janssen
3. Nevado, C., Cárdenas, D.J., Echavarren, A.M.: Chem. Eur. J. **9**, 2627–2635 (2003)
4. Trost, B.M., Braslau, R.: Tetrahedron Lett. **29**, 1231–1234 (1988)
5. Trost, B.M., Toste, F.D.: J. Am. Chem. Soc. **124**, 5025–5036 (2002)
6. Kataoka, T.; Yoshimatsu, M.; Noda, Y.; Sato, T.; Shimizu, H.; Hori, M.: *J. Chem. Soc., Perkin. Trans. 1* **1993**, 121–129
7. Chatani, N., Morimoto, T., Muto, T., Murai, S.: J. Am. Chem. Soc. **116**, 6049–6050 (1994)
8. Ma, S., Jiao, N., Zhao, S., Hou, H.: J. Org. Chem. **67**, 2837–2847 (2002)

Chapter 3
Formation of Cyclobutene Compounds via Gold(I)-Catalyzed Cycloisomerization of 1,n-Enynes

3.1 Introduction

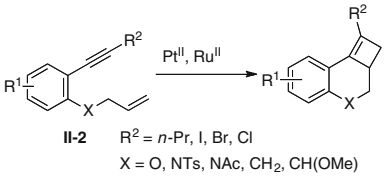
The importance of cyclobutene-containing compounds is notably due to their presence in a high number of naturally occurring and/or biologically active substances [1–3]. The cyclobutene unit is found as a basic structural motif in a wide range of molecules in bacteria, fungi, plants, and marine invertebrates. These compounds have shown many biological activities and may provide new ideas for the study of enzyme mechanisms, and/or organic synthesis. The preparation of cyclobutene-containing compounds has been a ubiquitous topic in organic synthesis since chemists realized the potential associated with the inherent ring strain. In the context of metal-catalyzed cycloisomerization of 1,n-enynes, several examples of cyclobutenes have been synthesized [Ref. 162 in Chap. 1] or postulated as intermediates [Ref. 162 in Chap. 1]. Despite the fact that the formation of cyclobutene compounds by [2+2] cycloaddition is less common than in cycloisomerization processes, it can be observed when a specific substitution pattern on the alkene and/or alkyne takes place and disfavors the skeletal rearrangement. It is not easy to formulate a general rule for the formation of cyclobutene compounds starting from 1,6- and 1,7-enynes. Certain 1,6-enynes possessing an acyclic alkene and an aryl- or esteralkyne moiety, as in **II-1**, can be transformed into the corresponding cyclobutenes in the presence of palladium(II) [4], platinum(II) [5], or gold(I) [Refs. 30, 162, Chap. 1] as catalysts (Scheme 3.1).



Scheme 3.1 Metal-catalyzed synthesis of cyclobutenes from 1,6-enynes **II-1**

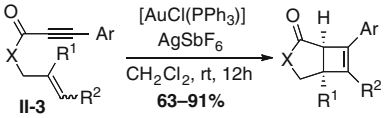
A. Escribano Cuesta, *New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids*, Springer Theses, DOI: 10.1007/978-3-319-00702-1_3,

In addition, 1,7-enynes possessing an acyclic alkene and a haloalkyne moiety **II-2** produce cyclobutene compounds via platinum(II)-[6] or ruthenium(II)-catalyzed [7] cycloisomerization (Scheme 3.2).



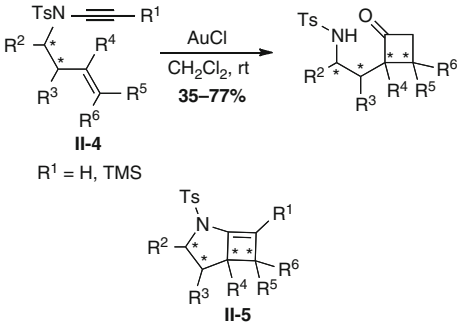
Scheme 3.2 Metal-catalyzed synthesis of cyclobutenes from 1,7-enynes **II-2**

In the case of amide- or ester-tethered 1,6-enynes **II-3**, bicyclo[3.2.0]hept-6-en-2-ones have been synthesized via gold(I)-catalyzed cycloisomerization in a general way (Scheme 3.3) [8].



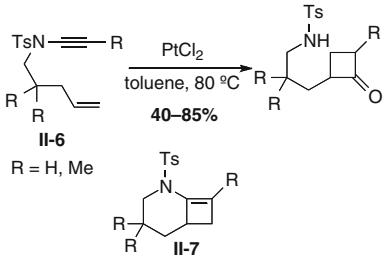
Scheme 3.3 Gold(I)-catalyzed cyclization of amide- or ester-tethered 1,6,enynes **I-3**

One of the principal problems in the synthesis of cyclobutene compounds is the isolation process, because of the general instability of the final products. As a result, cyclobutanones are isolated via gold(I)-catalyzed cyclization of 1,6-eneynamides **II-4** (Scheme 3.4) [9, 10]. The formation of cyclobutene intermediate **II-5** only takes place if the ynamides are terminal or substituted by a trimethysilyl group (R^1 = H, TMS). Skeletal rearrangement products were also obtained as minor products. Conversely, in the reaction of the same substrates catalyzed by $PtCl_2$, the 1,3-dienes were isolated as the major products in good yields [11, 12].



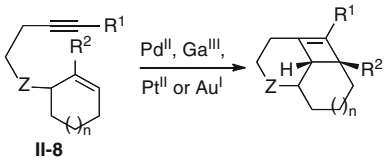
Scheme 3.4 Synthesis of cyclobutanones via gold(I)-catalyzed cycloisomerization of 1,6-eneynamides **II-4**

In addition, cyclobutanones are synthesized via platinum(II)-catalyzed cyclization of 1,7-ene-ynamides **II-6** (Scheme 3.5). The cyclobutanones are formed after hydrolysis of the corresponding bicycle[4.2.0] compounds **II-7.**



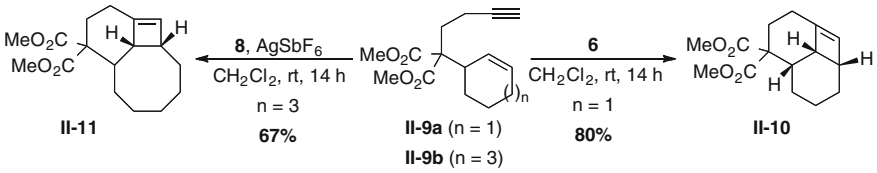
Scheme 3.5 Synthesis of cyclobutanones via platinum(II)-catalyzed cycloisomerization of 1,7-ene-ynamides **II-6**

In the particular case of 1,7-enynes bearing an endocyclic alkene moiety **II-8**, cyclobutenes are obtained in a general way using palladium(II) [13], gallium(III) [14], platinum(II) [15], or gold(I) [Ref. 15 in Chap. 1] as catalysts (Scheme 3.6). Other cyclobutene compounds have also been isolated from 1,6-enynes bearing an endocyclic alkene moiety via platinum(II)-[7] or gold(I)-catalyzed [Ref. 165 in Chap. 1] [2+2] cycloaddition.



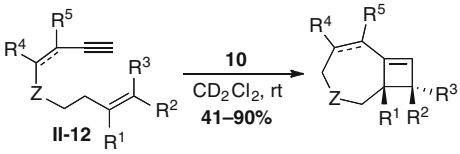
Scheme 3.6 Formation of cyclobutene compounds from 1,7-enynes **II-8**

By using cationic gold(I) complexes, bicyclo[4.2.0]oct-6-ene **II-10** or **II-11** are obtained starting from 1,7-enynes **II-9a** or **II-9b** (Scheme 3.7) [Ref. 15 in Chap. 1]. Ring opening to form 1,3-dienes does not occur even after heating at 120–150 °C.



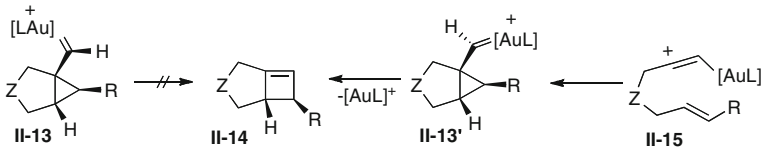
Scheme 3.7 Gold(I)-catalyzed cyclization of 1,7-enynes **II-9**

One of the most general methods for the isolation of stable cyclobutene compounds is to start from 1,8-enynes. In the case of gold(I)-catalyzed cyclization of 1,8-enynes **II-12,** cyclobutenes are isolated in a general way (Scheme 3.8) [Ref. 196 in Chap. 1]. The formation of 1,3-dienes was observed after prolonged reaction times and in the presence of trace acids.



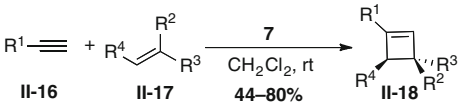
Scheme 3.8 Gold(I)-catalyzed cyclization of 1,8-enynes **II-12**

DFT calculations have been carried out to shed some light on the mechanism for cyclobutene formation. No direct pathway for the formation of cyclobutene **II-14** from *anti-exo*-cyclopropyl gold carbene **II-13** was found (Scheme 3.9). In contrast, *syn-exo*-cyclopropyl gold carbene **II-13′** forms cyclobutene **II-14** by a cyclopropane ring expansion. The formation of *syn-exo*-cyclopropyl gold carbene **II-13′** has been postulated to occur by a *syn*-type attack of the alkene to the alkyne gold moiety in **II-15**. However the *anti* attack is more favorable; the *syn* attack could compete if the substitution at the alkene and/or the alkyne does not favor the skeletal rearrangement [Ref. 15 in Chap. 1].



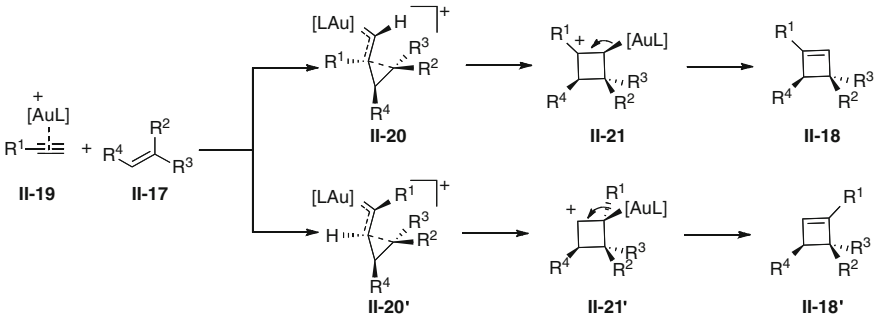
Scheme 3.9 Mechanism for gold(I)-catalyzed formation of cyclobutenes **II-14**

The intermolecular reaction of alkynes **II-16** with alkenes **II-17** catalyzed by gold(I) leads to cyclobutenes **II-18** with complete regio- and diastereoselectivity. Moderate to good yields are obtained when gold(I) complex **7** with a very bulky phosphine ligand is used (Scheme 3.10) [Ref. 192 in Chap. 1]. This transformation shows that [2+2] cycloaddition predominates in the reaction between alkynes and alkenes when the constraints imposed by the tethers are absent, like in the intermolecular process.



Scheme 3.10 Gold(I)-catalyzed intermolecular [2+2] cycloaddition of alkynes and alkenes

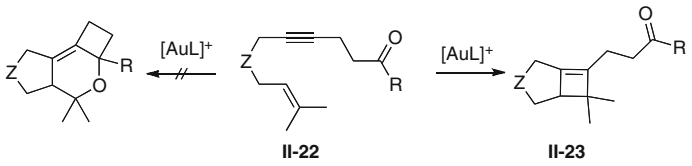
Based on the general reactivity of 1,n-enynes with gold(I), it is assumed that the reaction proceeds through similar cyclopropyl gold(I) carbenes **II-20/II-20′**. These intermediates are formed via the nucleophilic attack of alkenes **II-17** to cationic gold(I)-alkyne complexes **II-19**. Intermediates **II-20/II-20′** evolve toward cyclobutenes **II-18/II-18′** via carbocations **II-21/II-21′** (Scheme 3.11). The selective formation of regioisomers **II-18** is probably more favorable due to electronic and steric effects in intermediates **II-20** and **II-21**, which are analogous to the *exo*-type intermediates in the gold(I)-catalyzed cyclization of 1,n-enynes.



Scheme 3.11 Mechanism for the gold(I)-catalyzed intermolecular [2+2] cycloaddition of alkynes and alkenes

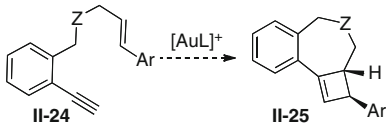
3.2 Objectives

Based on the results shown for the intermolecular gold(I)-catalyzed reaction of 1,6-enynes with carbonyl compounds (Chap. 1), our first objective was to study of the intramolecular gold(I)-catalyzed cyclization of 1,6-enynes bearing a carbonyl group at the alkyne moiety of type **II-22** (Scheme 3.12). Unexpectedly, the cyclization of these types of 1,6-enynes **II-22** led to the isolation of cyclobutenes **II-23**.



Scheme 3.12 Gold(I)-catalyzed cycloisomerization of 1,6-enynes **II-22**

Due to the high importance of the cyclobutene motif and the intrinsic difficulties of its synthesis [1–3], we decided to develop methodologies leading to cyclobutene-containing compounds via gold(I)-catalyzed cyclization of type **II-24** 1,8-enynes (Scheme 3.13).

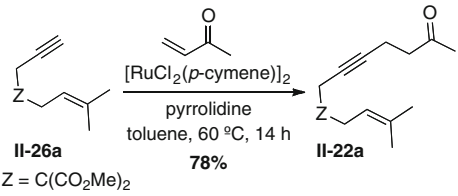


Scheme 3.13 Formation of cyclobutenes **II-25** via gold(I)-catalyzed [2+2] cycloaddition

3.3 Results and Discussion

3.3.1 Synthesis of Cyclobutene Compounds via Gold(I)-Catalyzed Intramolecular Addition of Carbonyl Compounds to 1,6-Enynes

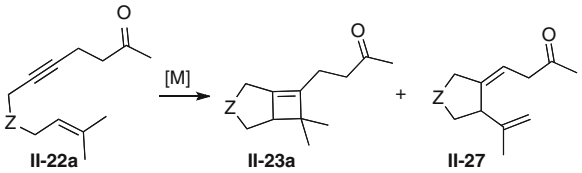
In order to study the intramolecular gold(I)-cyclization of 1,6-enynes bearing a carbonyl group at the alkyne moiety, enyne **II-22a** was synthesized via ruthenium(II)-catalyzed 1,4-addition of the terminal alkyne **II-26a** to methyl vinyl ketone with a 78 % yield (Scheme 3.14) [16].



Scheme 3.14 Synthesis of 1,6-enyne **II-22a**

We were pleased to observe the formation of cyclobutene **II-23a** with 38 % yield when 1,6-enyne **II-22a** was exposed to $[AuCl(PPh_3)]/AgSbF_6$ (Table 3.1, entry 1). In order to improve the yield, several complexes were tested. The desired cyclobutene compound **II-23a** was obtained with 58 % yield using phosphine gold(I) complex **6** (Table 3.1, entry 2). Unfortunately, the most active complex, phosphite gold(I) **20**, only resulted in decomposition of the starting material (Table 3.1, entry 3). At this point, we decided to test the mild activity of the NHC complexes. Thus, cyclobutene **II-23a** was formed in 80 % yield using IPr gold(I) **16** (Table 3.1, entry 4). Whereas low yield or no reaction was observed with IMes gold(I) **15**, IME gold(I) **14**, AuCl, $AuCl_3$, $AgSbF_6$, $PdCl_2$, $PtCl_2/P(o\text{-Tol})_3$, $GaCl_3$ and $InCl_3$ (Table 3.1, entries 5–13). A new product, 1,3-diene **II-27** of a single cleavaged rearrangement was isolated using platinacycle **24** [Ref. 29 in Chap. 1] in a 41 % yield (Table 3.1, entry 14).

Table 3.1 Screening of catalysts for the intramolecular gold(I)-catalyzed cycloisomerization of 1,6-enyne **II-22a**

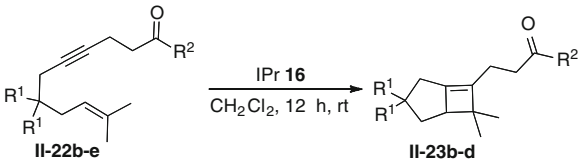


II-22a **II-23a** **II-27**

Z = $C(CO_2Me)_2$

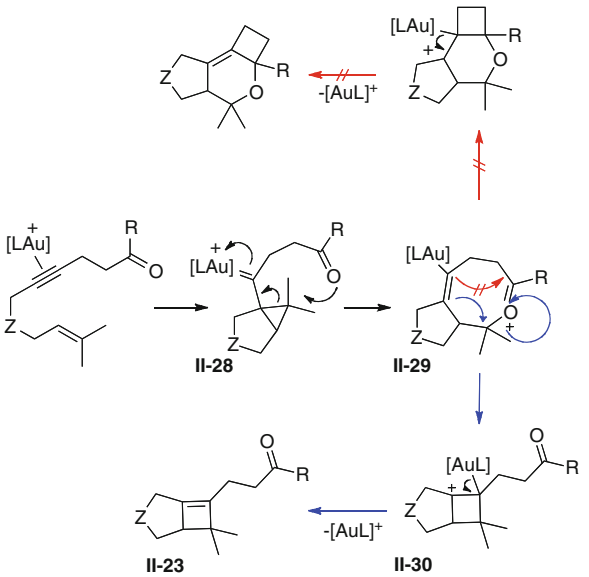
Entry	[M]	Time	Conv. (%)	Yield (%)[a]
1	$[AuCl(PPh_3)]/AgSbF_6$	2.5 h	100	**II-23a** (38)
2	**6**	3 h	100	**II-23a** (58)
3	**20**	2.5 h	100	–[b]
4	**16**	2 h	100	**II-23a** (80)
5	**15**	9 d	100	**II-23a** (30)
6	**14**	9 d	0	–
7	AuCl	9 d	0	–
8	$AuCl_3$	9 d	0	–
9	$AgSbF_6$	9 d	0	–
10	$PdCl_2$	9 d	0	–
11	$PtCl_2/P(o\text{-Tol})_3$	9 d	0	–
12	$GaCl_3$	9 d	0	–
13	$InCl_3$	9 d	0	–
14	**24**	8 d	100	**II-27** (41)[c]

Reaction conditions [M] (5 mol %) in 0.1 M CH_2Cl_2 at rt.
[a] Yield determined by ^{1}H-NMR crude analysis using 1,3,5-trimethoxybenzene as internal standard
[b] Complex mixture
[c] Isolated yield



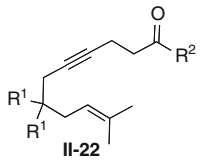
II-22b-e **II-23b-d**

Scheme 3.15 shows a possible mechanism for the formation of cyclobutene **II-23**. In analogy with the intramolecular cycloisomerization of 1,6-enynes bearing the carbonyl function at the alkene moiety **I-1** (Chap. 1, Scheme 1.1), this [2+2] cycloaddition proceeds via the opening of cyclopropyl gold carbene **II-28** thought the nucleophilic attack of the pendant carbonyl substituent to form oxonium cation **II-29**. However, in contrast with the previous methodology, the nucleophilic attack of the vinyl gold moiety in intermediate **II-29** does not take place via Prins-type cyclization (Scheme 3.15, red arrow), but at the quaternary *gem*-dimethyl carbon (Scheme 3.15, blue arrow), allowing the formation of cyclobutane intermediate **II-30**, which finally evolves via metal loss to give cyclobutene **II-23**.



Scheme 3.15 Proposed mechanism for the formation of cyclobutene **II-23**

Unfortunately, all attempts to purify cyclobutene **II-23a** (column chromatography with SiO_2, deactivated SiO_2, alumina and preparative TLC) were unsatisfactory due to the instability of the bicyclo[3.2.0]hept-5-ene moiety. Therefore, in order to form a more stable compound and confirm the cyclobutene structure, different modifications in the backbone of 1,6-enyne **II-22** were carried out (Fig. 3.1) [17].



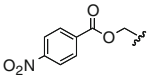
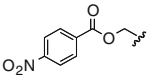
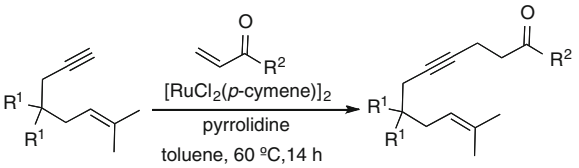
	R^1	R^2		R^1	R^2
II-22b		*p*-$NO_2C_6H_4$	**II-22d**	CO_2Me	*p*-$NO_2C_6H_4$
II-22c		CH_3	**II-22e**	SO_2Ph	*p*-$NO_2C_6H_4$

Fig. 3.1 Different modifications in the backbone of 1,6-enyne **II-22**

1,6-Enynes **II-22b-e** were synthesized via ruthenium(II)-catalyzed 1,4-addition of terminal alkyne to the corresponding conjugated enone in moderate yields (Scheme 3.16) [16].



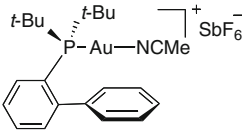
II-26a ($R^1 = CO_2Me$)
II-26b ($R^1 = CH_2OCO(p\text{-}NO_2C_6H_4)$)
II-26c ($R^1 = SO_2Ph$)

II-22b (30%)
II-22c (46%)
II-22d (45%)
II-22e (41%)

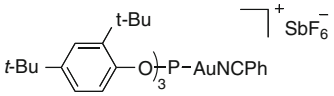
Scheme 3.16 Synthesis of 1,6-enynes **II-22** via 1,4-addition to conjugated enones

When the different 1,6-enynes **II-22b-e** were exposed to optimized conditions, the cyclobutenes **II-23b-d** were isolated in moderate to good yields (Table 3.2, entries 1–3). The only exception was the case of 1,6-enyne **II-22e**, where a complex mixture was detected (Table 3.2, entry 4).

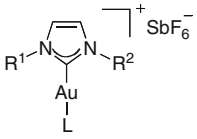
Table 3.2 Gold(I)-catalyzed cycloisomerization of 1,6-enynes **II-22b-d**

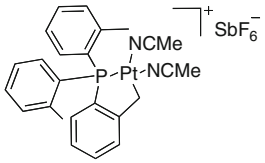


6



20





24

14: R^1 = Me, R^2 = Et, L = 2,4,6-$(MeO)_3C_6H_2CN$
15: $R^1 = R^2$ = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$
16: $R^1 = R^2$ = 2,6-*i*-$Pr_2C_6H_3$, L = PhCN

Entry		Conv. (%)	Yield (%)[a]
1	**II-22b**	100	**II-23b** (37)
2	**II-22c**	100	**II-23c** (64)
3	**II-22d**	100	**II-23d** (88)
4	**II-22e**	100	–[b]

Reaction conditions **16** (5 mol %) in 0.1 M CH_2Cl_2 at rt.
[a] Isolated yields of chromatographied products
[b] Complex mixture

In the case of compound **II-23d**, the proposed structure was confirmed by X-ray diffraction via formation of the 2,4-dinitrophenylhydrazone derivative **II-31** (Fig. 3.2). Therefore, the formation of a cyclobutene compound was unambiguously confirmed.

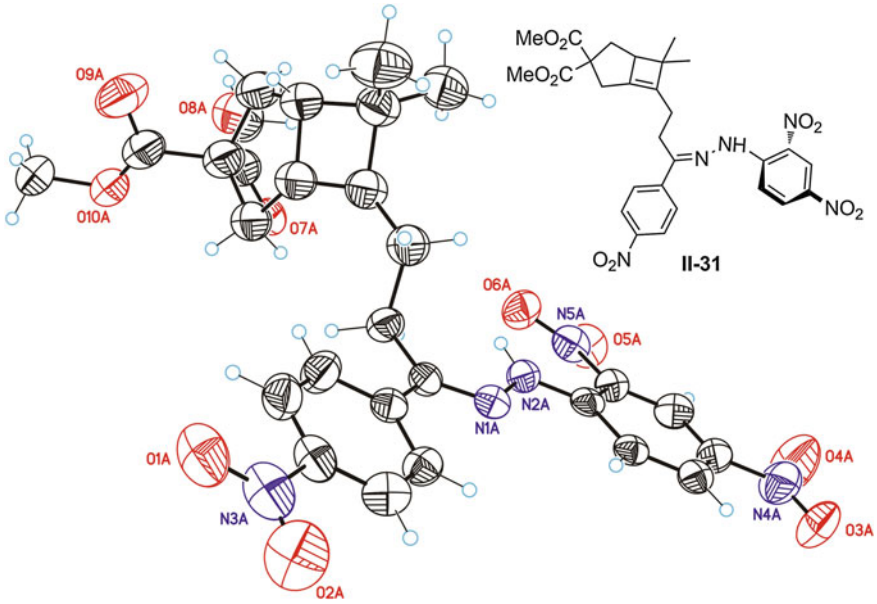
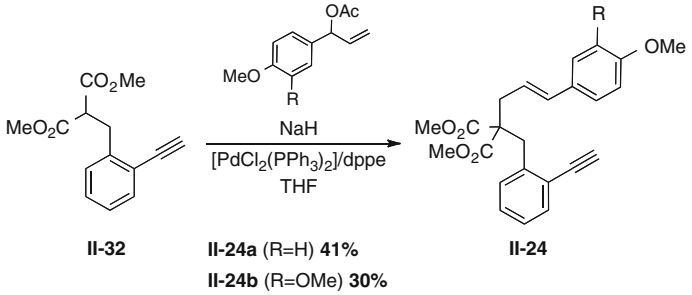


Fig. 3.2 X-ray structure of hydrazone **II-31**

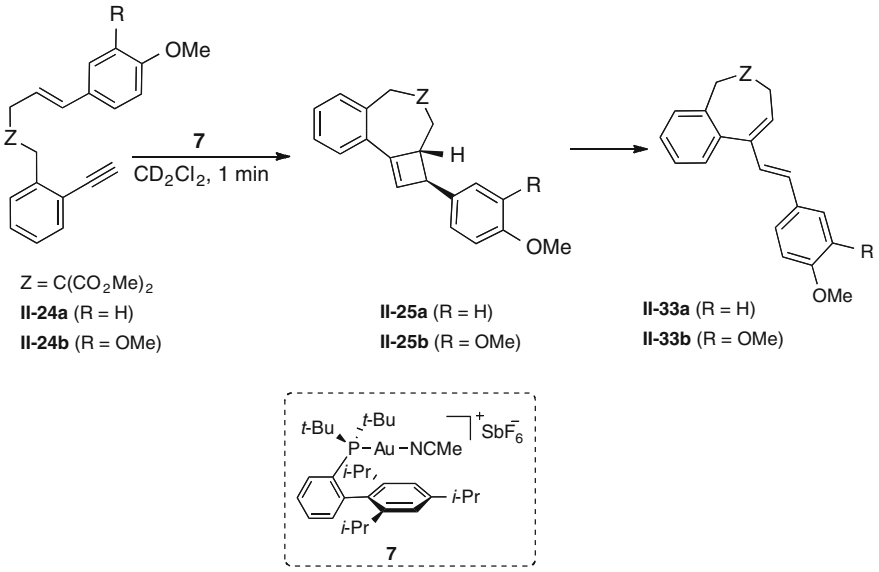
3.3.2 *Synthesis of Cyclobutene Compounds via Gold(I)-Catalyzed Cycloisomerization of 1,8-Enynes*

To obtain other compounds with the cyclobutene motive, we synthesized the 1,8-enynes **II-24a-b** in moderate yields via allylic Tsuji-Trost alkylation (Scheme 3.17) [Ref. 173 in Chap. 1].



Scheme 3.17 Synthesis of 1,8-enynes **II-24a-b**

Appling the Gagosz conditions for the cyclization of 1,8-enynes [Ref. 196 in Chap. 1], we observed the complete conversion toward cyclobutenes **II-25** after 1 min, which rearranged to 1,3-dienes **II-33** in 14 or 17 h (Scheme 3.18). Nevertheless, all attempts to purify and isolate cyclobutene compounds **II-25** were unsatisfactory (column chromatography or preparative TLC). Only 1,3-dienes **II-33** were isolated in high yields (**II-33a**, quant.; **II-33b**, 81 %). However, when the purification of cyclobutene **II-25a** was preformed over alumina [18], a mixture of **II-25a/II-33a** = 1.3:1.0 was isolated.



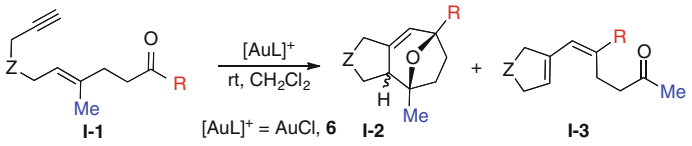
Scheme 3.18 Gold(I)-catalyzed cycloisomerization of 1,8-enynes **II-24**

It was observed that cyclobutenes **II-25** rearranged to 1,3-dienes **II-33** in 17 h, even in the absence of gold complex [19]. Furthermore, after only 14 h 1,3-diene **II-33a** was detected by ^{1}H-NMR in the presence of proton sponge or 2,6-di(*t*-butyl)pyridine, which indicates that the opening also takes place in the absence of acid. In conclusion, the gold(I)-catalyzed cycloisomerization of 1,8-enynes **II-24** allows the efficient synthesis of bicyclo[3.2.0]nonenes **II-25**, which are reactive intermediates toward the corresponding 1,3-dienes **II-33**. These results are in complete agreement with Gagosz's proposal. On the other hand, only the formation of *trans*-1,3-dienes **II-33** was observed, contrary to the results reported with 1,6-enynes substituted at the olefin with a electron-donating group (Scheme 3.19, Introduction) [Ref. 173 in Chap. 1].

3.4 Conclusions

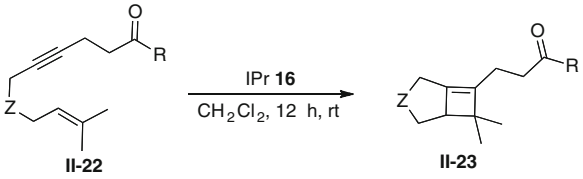
As an extension of the previous chapter, we decided to clarify the picture for the gold(I)-catalyzed intramolecular addition of carbonyl compounds to 1,6-enynes.

The formation of oxatricyclic compounds **I-2** and/or fragmentation products **I-3** was previously reported from 1,6-enynes with a carbonyl group at the alkenyl side chain such as **I-1** (Scheme 3.19) [Ref. 223 in Chap. 1].



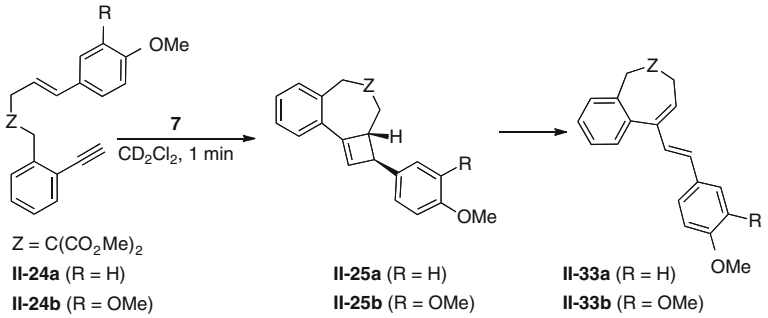
Scheme 3.19 Gold(I)-catalyzed cyclization of **I-1** enynes

With this precedent, our objective was to study the gold(I)-catalyzed cyclization of type **II-22** 1,6-enynes, which are characterized by a carbonyl unit at the alkynyl chain (Scheme 3.20). Selective formation of **II-23** was observed under mild conditions in lieu to the expected cyclization product. The bicyclo[3.2.0]hept-5-ene motif in **II-23** was confirmed by X-ray diffraction studies.



Scheme 3.20 Synthesis of cyclobutene compounds **II-23** via gold(I)-catalyzed [2+2] cycloaddition

Two more examples presenting the cyclobutene motif (**II-25**) were synthesized via gold(I)-catalyzed reaction of 1,8-enynes (Scheme 3.21). Although their isolations were unsuccessful, despite numerous attempts, it was possible to confirm that cyclobutenes **II-25** are intermediates in the formation of the corresponding 1,3-dienes **II-33**.



Scheme 3.21 Synthesis of intermediates **II-25** via gold(I)-catalyzed reaction of 1,8-enynes

3.5 Experimental Section

3.5.1 General Methods

All reactions were carried out under Ar in solvents dried using a Solvent Purification System (SPS). Extractive workup refers to portioning of the crude reaction between an organic solvent and water, phase separation, drying (Na_2SO_4 or $MgSO_4$), and evaporation under reduced pressure.

Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm). HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector.

NMR spectra were recorded at 23 °C on a Bruker Advance 400 Ultrashield apparatus.

Mass spectra were recorded on Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid. Melting points were determined using a Büchi melting point apparatus. Optical rotations were recorded on a P-1030 polarimeter from Jasco at the sodium D line.

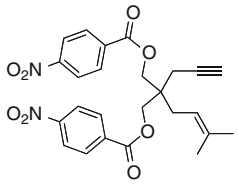
3.5.2 Preparation of Substrates

The metal salts AuCl (Strem), $AuCl_3$ (Sigma Aldrich), $PdCl_2$ (Johson Matthey), $InCl_3$ (SDS), $GaCl_3$ (Aldrich), $PtCl_2$ (Johson Matthey), $AgSbF_6$ (Aldrich), complex [AuCl(PPh_3)] (Strem) and phosphine gold(I) complex **6** (Aldrich) were used as received. Complex IME gold(I) **14** [Refs. 43, 44 in Chap. 1], IMes gold(I) **15** [Refs. 43, 44 in Chap. 1], IPr gold(I) **16** [Refs. 43, 44 in Chap. 1], cationic

phosphite gold(I) **20** [Ref. 42 in Chap. 1], and platinacycle **24** [Ref. 29 in Chap. 1], were prepared according to the reported procedure.

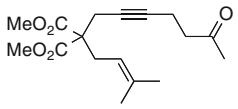
The starting 1,6-enynes were synthesized following the literature procedures: **I-26a** [20], and **II-26c** [20].

2-(3-Methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diyl bis(4-nitrobenzoate) (II-26b) [21]



4-Nitrobenzoyl chloride (4.99 g, 26.31 mmol, 2.4 equiv), *N,N*-dimethylpyridin-4-amine (0.27 g, 2.20 mmol, 0.2 equiv) and Et_3N (15.29 ml, 110 mmol, 10 equiv) were successively added to a slurry of 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diol (2.02 g, 10.97 mmol) in CH_2Cl_2 (21 mL) at 0 °C. The resulting mixture was then allowed to warm up to room temperature and stirred for 5 h. The reaction mixture was diluted by adding CH_2Cl_2, and precipitations generated during the reaction was removed by filtration. The reaction was quenched by adding 10 % HCl. The organic layer was washed by 0.5 M HCl and sat. $NaHCO_3$, then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to produce a crude mixture resembling a brown gummy solid. The purification was done by silica gel column chromatography (5:1, c-Hex/EtOAc) to give **II-26b** as a yellow–brown solid (2.42 g, 46 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (dt, $J = 8.8$, 2.0 Hz, 4H), 8.18 (dt, $J = 8.8$, 2.0 Hz, 4H), 5.20 (br t, $J = 7.8$ Hz, 1H), 4.33 (s, 4H), 3.48 (d, $J = 2.6$ Hz, 2H), 2.48 (d, $J = 2.6$ Hz, 2H), 2.39 (br d, $J = 7.8$ Hz, 2H), 2.08 (t, $J = 2.6$ Hz, 1H), 1.74 (s, 3H), 1.63 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 164.5 (2C), 151.0 (2C), 137.1 (2C), 135.0 (C), 130.9 (4CH), 123.9 (4CH), 117.1 (CH), 79.4 (C), 72.0 (CH), 67.2 ($2CH_2$), 41.6 (C), 30.8 (CH_2), 26.3 (CH_3), 23.0 (CH_2), 18.2 (CH_3). HRMS-ESI Caldc for $C25H24N_2O_8$ $[M+Na]^+$ 503.1430, found 503.1425.

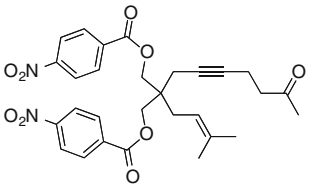
Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(6-oxohept-2-yn-1-yl)malonate (II-22a)



Pyrrolidine (0.07 mL, 0.84 mmol, 0.2 equiv) was added to a stirred solution of $[RuCl_2(p\text{-cymene})_2]$ (0.13 g, 0.21 mmol, 5 mol %) in toluene (8 mL). The mixture was stirred for 10 min at room temperature, which was followed by the

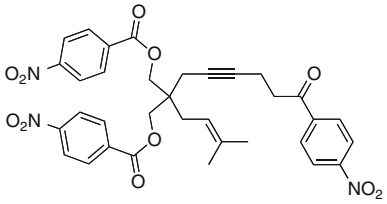
addition of a solution of 1,6-enyne **II-26a** (1.00 g, 4.21 mmol, 1 equiv) and methyl vinyl ketone (1.82 mL, 21.03 mmol, 5 equiv) in toluene (8 mL). The mixture was stirred for 13 h at 60 °C, and was then filtered over Celite and concentrated under low pressure. The purification was done via silica gel column chromatography (8:1, c-Hex/EtOAc) to give **II-22a** as a colorless oil (1.02 g, 78 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.87 (apparent t septuplet, $J = 7.8$ Hz, 1H), 3.70 (s, 6H), 2.71–2.68 [overlapping signals (2.71,d, $J = 7.8$ Hz, 2H), (2.69, t, $J = 2.5$ Hz, 2H), 4H], 2.59 (apparent t, $J = 7.0$ Hz, 2H), 2.39–2.34 (m, 2H), 2.15 (s, 3H), 1.68 (d, $J = 0.7$ Hz, 3H), 1.63 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 206.8 (C), 170.9 (2C), 136.8 (C), 117.4 (CH), 82.0 (C), 75.6 (C), 57.6 (C), 52.8 ($2CH_3$), 42.9 (CH_2), 20.9 (CH_2), 30.0 (CH_3), 26.2 (CH_3), 23.0 (CH_2), 18.1 (CH_3), 13.5 (CH_2). HRMS-ESI Caldc for $C_{17}H_{24}O_5$ $[M+Na]^+$ 331.1521, found 331.1528.

2-(3-Methylbut-2-en-1-yl)-2-(6-oxohept-2-yn-1-yl)propane-1,3-diyl bis(4-nitrobenzoate) (II-22b)



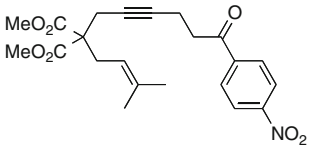
Pyrrolidine (0.03 mL, 0.38 mmol, 0.2 equiv) was added to a stirred solution of $[RuCl_2(p\text{-cymene})_2]$ (58.52 mg, 0.09 mmol, 5 mol %) in toluene (8 mL). The mixture was stirred at room temperature for 10 min, which was followed by the addition of 1,6-enyne **II-26b** (900 mg, 1.873 mmol, 1 equiv) and methyl vinyl ketone (0.780 mL, 9.37 mmol, 5 equiv). The mixture was stirred at 60 °C for 15 h. After it was cooled to room temperature, the resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain crude mixture as a black gummy solid. Purification was done via silica gel column chromatography (4:1, *c*-Hex/EtOAc) to give **II-22b** (930 mg, 90 %) as yellow gummy solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (dt, $J = 9.0$, 2.1 Hz, 4H), 8.18 (dt, $J = 9.0$, 2.1 Hz, 4H), 5.18 (apparent t septuplet, $J = 6.6$ Hz, 1H), 4.39 (d, $J = 1.9$ HZ, 4H), 2.61 (t, $J = 7.2$ Hz, 2H), 2.42-2.38 [overlapping signals (m, 2H), (2.41, br d, $J = 2.4$ Hz, 2H), 4H], 2.34 (br d, $J = 7.8$ Hz, 2H), 2.14 (s, 3H), 1.73 (d, $J = 0.4$ Hz, 3H), 1.62 (d, $J = 0.8$ Hz, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 205.5 (C), 164.5 (2C), 150.9 (2C), 136.7 (2C), 135.4 (C), 130.9 (4CH), 123.9 (4CH), 117.3 (CH), 82.5 (C), 75.4 (C), 67.3 ($2CH_2$), 42.8 (C), 41.8 (CH_2), 30.8 (CH_2), 30.0 (CH_3), 26.4 (CH_3), 23.1 (CH_2), 18.2 (CH_3), 13.5 (CH_2). HRMS-ESI Caldc for $C_{29}H_{30}N_2O_9$ $[M+Na]^+$ 570.1829, found 570.1849.

2-(3-Methylbut-2-en-1-yl)-2-(6-(4-nitrophenyl)-6-oxohex-2-yn-1-yl)propane-1,3-diyl bis(4-nitrobenzoate) (II-22c)



Pyrrolidine (0.03 mL, 0.38 mmol, 0.2 equiv) was added to a stirred solution of $[RuCl_2(p\text{-cymene})_2]$ (59.03 mg, 0.09 mmol,) in toluene (8 mL). The resulting mixture was stirred for 10 min at room temperature, which was followed by the addition of 1,6-enyne **II-26b** (908.09 mg, 1.89 mmol, 1 equiv) and 1-(4-nitrophenyl)prop-2-en-1-one (385.97 mg, 2.17 mmol, 1.1 equiv). The resulting mixture was stirred at 60 °C for 15 h. After it was cooled to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to obtain crude mixture as a black gummy solid. Purification was done via silica gel column chromatography (4:1, *c*-Hex/EtOAc) to give **II-22c** (570 mg, 46 %) as brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31–8.24 [overlapping signals (dt, 2H), (2.27, dt, $J = 9.1$, 1.9 Hz, 2H), 6H], 8.16 (dt, $J = 8.9$, 2.0 Hz, 4H), 8.09 (dt, $J = 8.9$, 2.1 Hz, 2H), 5.17 (br t, $J = 7.8$ HZ, 1H), 4.39 (d, $J = 4.0$ Hz, 4H), 3.21 (t, $J = 7.0$ Hz, 2H), 2.63–2.60 (m, 2H), 2.41 (t, $J = 2.1$ Hz, 2H), 2.33 (br d, $J = 7.8$ Hz, 2H), 1.72 (s, 3H), 1.60 (s, 3H). ^{13}C ($CDCl_3$, 400 MHz) δ 196.5 (C), 164.5 (2C), 150.9 (2C), 150.6 (C), 141.0 (C), 136.8 (2C), 135.3 (C), 130.8 (4CH), 129.2 (2CH), 124.1 (2CH), 123.8 (4CH), 117.3 (CH), 82.5 (C), 76.0 (C), 67.2 ($2CH_2$), 41.8 (C), 38.6 (CH_2), 30.9 (CH_2), 26.3 (CH_3), 23.2 (CH_2), 18.1 (CH_3), 13.7 (CH_2). HRMS-ESI Caldc for $C_{34}H_{31}N_3O_{11}$ $[M+Na]^+$ 680.1856, found 680.1857.

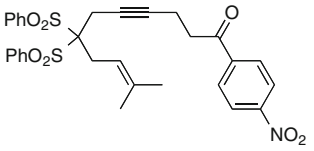
Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(6-(4-nitrophenyl)-6-oxohex-2-yn-1-yl)malonate (II-22d)



Pyrrolidine (0.08 mL, 0.94 mmol, 0.2 equiv) was added to a stirred solution of $[RuCl_2(p\text{-cymene})_2]$ (0.15 g, 0.24 mmol, 5 mol %) in toluene (20 mL). The reaction mixture was stirred for 10 min at room temperature, which was followed by the addition of 1,6-enyne **II-26a** (1.1 g, 4.7 mmol, 1 equiv) and 1-(4-nitrophenyl)prop-2-en-1-one (1.01 g, 5.63 mmol, 5 equiv). The mixture was stirred for

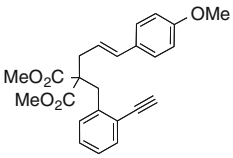
13 h at 60 °C. The resulting mixture was cooled to room temperature and quenched by sat. NH_4Cl solution. The organic layer was extracted by Et_2O, washed with water and brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification was done via silica column chromatography (6:1, *c*-Hex/EtOAc) to obtain **II-22d** as a yellow sticky liquid (880 mg, 45 %). After several weeks in the fridge, the product became crystalline yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$,) δ 8.33 (dm, $J = 8.8$ Hz, 2H), 8.11 (dm, $J = 8.8$ Hz, 1H), 4.88 (br t, $J = 7.8$ Hz, 1H), 3.69 (apparent t, $J = 1.1$ Hz, 6H), 3.20 (t, $J = 7.3$ Hz, 2H), 2.70–2.69 (m, 4H), 2.58 (apparent td, $J = 6.5$, 1.1 Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 196.6 (C), 170.8 (2C), 150.6 (C), 141.2 (C), 136.9 (C), 129.2 (2CH), 124.1 (2CH), 117.3 (CH), 81.6 (C), 76.2 (C), 57.6 (C), 52.8 ($2CH_3$), 38.8 (CH_2), 31.0 (CH_2), 29.2 (CH_3), 23.0 (CH_2), 18.1 (CH_3), 13.7 (CH_2).

10-Methyl-1-(4-nitrophenyl)-7,7-bis(phenylsulfonyl)undec-9-en-4-yn-1-one (II-22e)



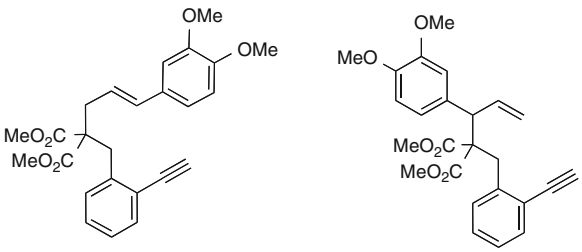
Pyrrolidine (0.07 ml, 0.85 mmol, 0.2 equiv) was added to a stirred solution of [$RuCl_2$(*p*-cymene)$_2$] (0.13 g, 0.21 mmol, 5 mol %) in toluene (20 mL). The mixture was stirred at room temperature for 10 min, then 1,6-enyne **II-26c** (1.75 g, 4.22 mmol, 1 equiv) and 1-(4-nitrophenyl)prop-2-en-1-one (1.13 g, 6.21 mmol, 1.1 equiv) were added stepwise. The mixture was stirred at 60 °C for 15 h. After it was cooled to room temperature, the resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to obtain a crude mixture as a black gummy solid. Purification was done via silica gel column chromatography (4:1, *c*-Hex/EtOAc) to give **II-22e** (1.07 g 41 %) as yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (dt, $J = 8.8$, 2.3 Hz, 2H), 8.11–8.07 [overlapping signals (d, 4H), (dt, 2H), 6H], 7.69 (br t, $J = 7.5$ Hz, 2H), 7.57 (br t, $J = 8.0$ Hz, 4H), 5.34 (apparent t septuplet, $J = 6.7$ Hz, 1H), 3.19 (t, $J = 7.0$ Hz, 2H), 3.10 (t, $J = 2.0$ Hz, 2H), 2.98 (br d, $J = 6.6$ Hz, 2H), 2.54 (tt, $J = 7.1$, 2.4 Hz, 2H), 1.74 (d, $J = 0.7$ Hz, 3H), 1.56 (s, 3H).

(*E*)-Dimethyl 2-(2-Ethynylbenzyl)-2-(3-(4-methoxyphenyl)allyl)malonate (II-24a)



A solution of 1-(4-methoxyphenyl)allyl acetate [Ref. 173 in Chap. 1] (189.03 mg, 0.92 mmol, 1.1 equiv) in dry THF (1.4 mL) was added to a suspension of $Pd(PPh_3)_2Cl_2$ (65.75 mg, 0.09 mmol, 11 mol %) and dppe (37.73 mg, 0.09 mmol, 11 mol %) in dry THF (1.4 mL). A solution of dimethyl 2-(2-ethynylbenzyl)malonate anion was prepared in a different flask by the addition of dimethyl 2-(2-ethynylbenzyl)malonate [22] (205.42 mg, 0.83 mmol, 1 equiv) to an NaH (36.78 mg, 0.92 mmol, 1.1 equiv) suspension in dry THF (2.8 mL) at 0 °C. The anion was added over the former acetate mixture via cannula and the mixture was stirred at room temperature for 3 h. Aqueous work-up with saturated NH_4Cl and Et_2O was performed and the organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude material was chromatographed (12:1, c-Hex/EtOAc) to yield **II-24a** as a colorless oil (132.63 mg, 41 %). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50 (dd, $J = 7.6$, 1.3 Hz, 1H), 7.30 (td, $J = 7.6$, 1.5 Hz, 1H), 7.26 (dt, $J = 8.8$, 2.0 Hz, 2H), 7.22 (td, $J = 7.6$, 1.4 Hz, 1H), 7.18 (dd, $J = 7.8$, 0.9 Hz, 1H), 6.83 (dt, $J = 8.8$, 2.9 Hz, 2H), 6.36 (d, $J = 5.6$ Hz, 1H), 6.11 (dt, 15.8, 7.4 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 6H), 3.56 (s, 2H), 3.33 (s, 1H), 2.70 (dd, $J = 7.4$, 1.3 Hz, 2H). ^{13}C (400 MHz, $CDCl_3$) δ 171.5 (2C), 159.2 (C), 139.0 (C), 133.5 (CH), 133.2 (CH), 130.4 (C), 130.0 (CH), 128.9 (CH), 127.5 (2CH), 127.0 (CH), 123.6 (C), 122.7 (CH), 114.1 (2CH), 82.8 (C), 81.5 (CH), 60.0 (C), 55.5 (CH_3), 56.2 ($2CH_3$), 37.0 (CH_2), 36.7 (CH_2).

(*E*)-Dimethyl 2-(3-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (II-24b) and dimethyl 2-(1-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (II-24b′)



A solution of 1-(3,4-dimethoxyphenyl)allyl acetate [Ref. 173 in Chap. 1] (234.04 mg, 0.99 mmol, 1.1 equiv) in dry THF (1.5 mL) was added to a suspension of $Pd(PPh_3)_2Cl_2$ (70.97 mg, 0.01 mmol, 11 mol %) and dppe (40.79 mg, 0.01 mmol, 11 mol %) in dry THF (1.5 mL). A solution of dimethyl

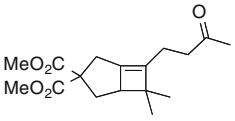
2-(2-ethynylbenzyl)malonate anion was prepared in a different flask by the addition of dimethyl 2-(2-ethynylbenzyl)malonate (221.75 mg, 0.90 mmol, 1 equiv) to an NaH (39.67 mg, 0.99 mmol, 1.1 equiv) suspension in dry THF (3 mL) at 0 °C. The anion was added over the former acetate mixture via cannula, and the mixture was stirred at room temperature for 3 h. Aqueous work-up with saturated NH_4Cl and Et_2O was performed, and the organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude material was chromatographed (6:1–5:1, c-Hex/EtOAc) to afford **II-24b** (112.5 mg, 30 %) and **II-24b′** (52.4 mg, 14 %).

(*E*)-Dimethyl 2-(3-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (**II-24b**): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.59 (dd, J = 7.4, 1.1 Hz, 1H), 7.37 (td, J = 7.5, 1.5 Hz, 1H), 7.22–7.16 (overlapping signals, 2H), 6.87–6.85 [overlapping signals (dd, 1H), (6.85, br s, 1H), 2H], 6.79 (br d, J = 8.2 Hz, 1H), 6.34 (br d, J = 15.7 Hz, 1H), 6.08 (dt, J = 15.7, 7.4 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.71 (s, 6H), 3.60 (s, 2H), 3.25 (s, 1H), 2.75 (dd, J = 7.4, 1.2 Hz, 2H). ^{13}C (500 MHz, $CDCl_3$) δ 171.5 (2C), 149.1 (C), 148.8 (C), 139.0 (C), 133.5 (2CH), 130.7 (C), 130.0 (CH), 129.0 (CH), 127.1 (CH), 123.5 (C), 122.9 (CH), 119.0 (2CH), 111.2 (CH), 109.1 (CH), 82.8 (C), 81.4 (CH), 59.9 (C), 56.1 (CH_3), 56.1 (CH_3), 52.6 ($2CH_3$), 37.1 (CH_2), 36.8 (CH_2). HRMS-ESI *m/z* calcd for $C_{25}H_{26}O_6$ $[M+Na]^+$ 445.1627, found 445.1625.

Dimethyl 2-(1-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (**II-24b′**): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.41 (dd, J = 7.6, 1.4 Hz, 1H), 7.31 (dd, J = 7.8, 0.8 Hz, 1H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.12 (td, J = 7.55, 1.4 Hz, 1H), 6.83 (br s, 1H), 6.80–6.79 (overlapping signals, 2H), 6.48 (ddd, J = 17.0, 10.2, 8.3 Hz, 1H), 5.16 (ddd, J = 10.2, 1.7, 0.9 Hz, 1H), 5.07 (ddd, J = 17.0, 1.6, 1.2 Hz, 1H), 4.11 (br d, J = 8.3 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H), 3.53–3.42 [overlapping signals, (3.50, s, 3H), (2H), 5H], 3.19 (s, 1H).^{13}C (400 MHz, $CDCl_3$) δ 170.8 (C), 170.6 (C), 148.7 (C), 148.3 (C), 140.4 (C), 137.8 (CH), 132.7 (CH), 131.7 (C), 129.8 (CH), 128.7 (CH), 126.5 (CH), 123.3 (C), 122.0 (CH), 117.6 (CH_2), 113.1 (CH), 111.0 (CH), 82.5 (C), 63.9 (C), 56.1 (CH_3), 56.0 (CH_3), 52.3 (CH_3), 52.2 (CH_3), 38.6 (CH_2).

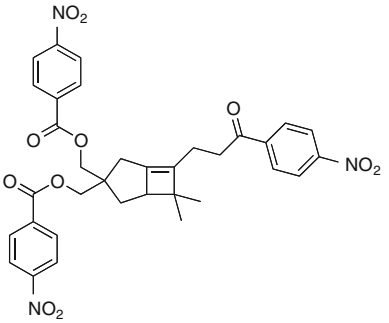
3.5.3 Cyclization Products

Dimethyl 7,7-Dimethyl-6-(3-oxobutyl)bicyclo[3.2.0]hept-5-ene-3,3-dicarboxylate (II-23a)



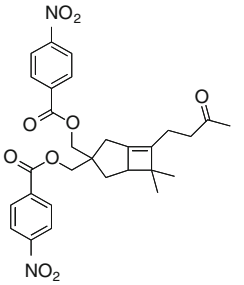
IPr gold(I) **16** (0.02 g, 0.03 mmol, 5 mol %) was added to a solution of **II-22a** (0.15 g, 0.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After 1.5 h, the reaction was quenched with Et_3N/*c*-Hex (0.1 M; 1 mL), and the resulting mixture was passed through a membrane filter. The solvent was removed under reduced pressure to obtain a crude mixture resembling a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.71 (s, 3H), 2.77 (br d, $J = 1.5$ Hz, 2H), 2.60 (dt, $J = 7.2$, 6.5 Hz, 2H), 2.39 (dt, $J = 12.9$, 7.2 Hz, 1H), 2.29 (br t, $J = 7.6$ Hz, 1H), 2.20–2.16 [overlapping signals (tm, $J = 7.0$ Hz, 2H), (2.16, s, 3H), 5H], 1.72 (dd, $J = 12.9$, 9.4 Hz, 3H), 1.14 (s, 3H), 0.95 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 208.2 (C), 172.9 (C), 172.5 (C), 141.1 (C), 140.1 (C), 65.3 (C), 53.0 (CH_3), 52.9 (CH_3), 51.6 (CH), 41.6 (C), 40.8 (CH_2), 35.1 (CH_2), 33.8 (CH_2), 30.0 (CH_3), 26.2 (CH_3), 20.8 (CH_2), 20.3 (CH_3). HRMS-ESI Caldc for $C_{17}H_{24}O_5$ [*M*+Na]$^+$ 331.1521, found 331.1537.

(7,7-Dimethyl-6-(3-(4-nitrophenyl)-3-oxopropyl)bicyclo[3.2.0]hept-5-ene-3,3-diyl)bis(methylene) bis(4-nitrobenzoate) (II-23b)



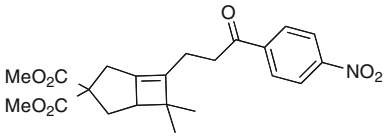
IPr gold (I) **16** (23.11 mg, 0.025 mmol, 5 mol %) was added to a solution of **II-22b** (329.87 mg, 0.50 mmol, 1 equiv) in CH_2Cl_2 (3 mL). After 12 h, the reaction was quenched by the addition of a Et_3N/*c*-Hex (0.1 M; 1 mL) solution. The resulting mixture was separated through membrane filter. The filtrate was concentrated under reduced pressure to obtain a crude mixture. **II-23b** was isolated via silica gel column chromatography (10:1 to 4:1, *c*-Hex/EtOAc) (120.69 mg, 37 %) as a pale yellow solid (trace amount of byproduct remained). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27–8.12 (m, 8H), 8.13 (dt, $J = 7.2$, 1.6 Hz, 2H), 8.08 (dt, $J = 7.1$, 1.7 Hz, 2H), 4.43 (d. $J = 1.9$ Hz, 2H), 4.36 (d, $J = 0.7$ Hz, 2H), 3.19 (t, $J = 5.6$ Hz, 2H), 2.43–2.39 (m, 1H), 2.24 (d, $J = 12.2$ Hz, 1H), 2.15 (d, $J = 12.2$ Hz, 1H), 1.89 (dd, $J = 10.8$, 6.3 Hz, 1H), 1.73–1.69 [overlapping signals (1.73, d, $J = 2.5$ Hz, 1H), (1.70, d, $J = 7.6$ Hz, 1H), 2H], 1.32 (dd, $J = 10.8$, 7.3 Hz, 1H), 1.21 (s, 3H), 1.03 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 197.7 (C), 146.7 (C), 146.6 (C), 150.8 (2C), 150.4 (C), 146.2 (C), 141.2 (C), 140.8 (C), 135.3 (C), 135.2 (C), 130.8 (2CH), 130.8 (2CH), 129.1 (2CH), 124.0 (2CH), 123.8 (2CH), 123.8 (2CH), 68.9 (CH_2), 68.3 (CH_2), 53.1 (C), 50.9 (CH), 42.3 (C), 36.5 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 26.5 (CH_3), 20.8 (CH_2), 20.7 (CH_3). HRMS-ESI Caldc for $C_{34}H_{31}N_3O_{11}$ [*M*+Na]$^+$ 680.1856, found 680.1887.

(7,7-Dimethyl-6-(3-oxobutyl)bicyclo[3.2.0]hept-5-ene-3,3-diyl)bis(methylene) bis(4-nitrobenzoate) (II-23c)



IPr gold(I) **16** (19.23 mg, 0.02 mmol, 5 mol %) was added to a solution of **II-22c** (225.45 mg, 0.41 mmol, 1 equiv) in CH_2Cl_2 (3 mL) at room temperature. The reaction was stirred overnight, then quenched by adding a solution of Et_3/*c*-Hex (0.1 M; 1 mL). The resulting mixture was filtered through membrane filter. The filtrate was concentrated under reduced pressure to obtain a crude mixture. The target product was isolated by silica gel column chromatography (10:1 to 5:1, *c*-Hex/EtOAc) to give **II-23c** (144.27 mg, 64 %) as a pale yellow solid (trace amount of byproduct remained). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (dt, $J = 7.1$, 1.5 Hz, 2H), 8.17 (dt, $J = 7.2$, 1.6 Hz, 2H), 4.42 (s. 2H), 4.37 (d, $J = 2.0$ Hz, 2H), 2.50–2.56 (m, 2H), 3.73 (s, 3H), 2.40 (t, $J = 7.3$ Hz, 1H), 2.27 (d, $J = 12.2$ Hz, 1H), 2.23–2.14 (m, 4H), 2.13 (s, 3H), 1.86 (dd, $J = 10.7$, 6.2 Hz, 1H), 1.17 (s, 3H), 0.98 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 207.9 (C), 164.6 (C), 164.6 (C), 150.8 (2C), 146.4 (C), 140.4 (C), 135.4 (C), 135.3 (C), 130.8 (4CH), 1238 (4CH), 69.0 (CH_2), 68.3 (CH_2), 53.1 (C), 50.8 (CH), 42.1 (C), 40.9 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 29.9 (CH_3), 26.4 (CH_3), 20.8 (CH_2), 20.6 (CH_3). HRMS-ESI Caldc for $C_{29}H_{30}N_2O_9$ $[M+Na]^+$ 573.1849, found 573.1855.

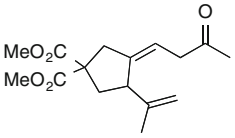
Dimethyl 7,7-dimethyl-6-(3-(4-nitrophenyl)-3-oxopropyl)bicyclo[3.2.0]hept-5-ene-3,3-dicarboxylate (II-23d)



IPr gold(I) **16** (23.11 mg, 0.03 mmol, 5 mol %) was added to a solution of **II-22d** (208.44 mg, 0.50 mmol, 1 equiv) in CH_2Cl_2. After stirring at room temperature for 12 h, the reaction was quenched by the addition of a Et_3N/*c*-Hex (0.1 M; 1 mL) solution and the resulting mixture was filtered through a membrane filter. The filtrate was concentrated under reduced pressure to obtain a crude mixture. The target product was isolated by silica gel column chromatography (10:1 to 4:1, *c*-Hex/EtOAc) to give **II-23d** (182.03 mg, 88 %) as a sticky yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (br d, $J = 7.0$ Hz, 2H), 8.14 (dt, $J = 7.1$, 1.7 Hz, 2H),

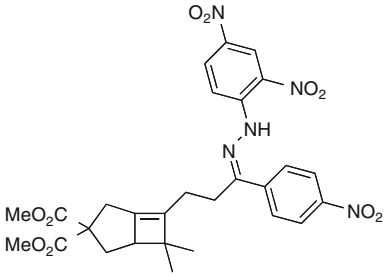
3.74 (s, 3H), 3.73 (s, 3H), 3.24–3.20 (m, 2H), 2.81 (br d, $J = 12.4$ Hz, 1H), 2.77 (br dd, $J = 12.4$, 1.4 Hz, 1H), 2.43 (dd, $J = 10.5$, 5.9 Hz, 1H), 2.40–2.32 (m, 3H), 1.76 (dd, $J = 10.5$, 6.1 Hz, 3H), 1.18 (s, 3H), 0.99 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 197.9 (C), 172.7 (C), 172.3 (C), 150.4 (C), 145.8 (C), 141.4 (C), 140.4 (C), 129.1 (2CH), 1240 (2CH), 65.2 (C), 52.9 (CH_3), 52.8 (CH_3), 51.5 (CH), 41.7 (C), 36.3 (CH_2), 34.9 (CH_2), 33.8 (CH_2), 26.1 (CH_3), 20.8 (CH_2), 20.3 (CH_3). HRMS-ESI Caldc for $C_{22}H_{25}NO_7$ $[M+Na]^+$ 438.1529, found 438.1518. HRMS-ESI Caldc for $C_{29}H_{30}N_2O_9$ $[M+Na]^+$ 573.1849, found 573.1855.

(*Z*)-Dimethyl 3-(3-Oxobutylidene)-4-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (II-27)



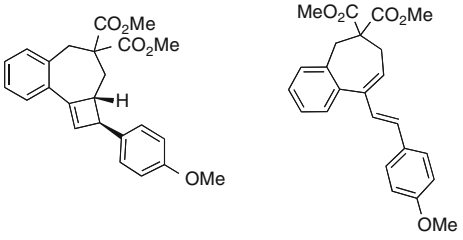
Platinacycle **24** (15.7 mg, 0.02 mmol, 5 mol %) was added to a solution of dimethyl **II-22a** (118.62 mg, 0.39 mmol, 1 equiv) in a vessel filled with argon. The reaction mixture was stirred at room temperature for 8 d, then quenched by the addition of a Et_3N/*c*-Hex solution (0.1 M; 1 mL). The resulting mixture was passed through a pad of Celite, and the solvent was removed under reduced pressure to obtain a crude mixture as a yellow oil. Purification was done via silica column chromatography (10:1, *c*-Hex/EtOAc) to obtain **II-27** as a colorless oil (49.25 mg, 41 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.06 (tquin, $J = 7.4$, 2.9 Hz, 1H), 4.82 (hex, $J = 1.3$ Hz, 1H), 4.79–4.78 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.22 (br t, $J = 1.5$ Hz, 1H), 3.08 (dhex, $J = 17.0$, 0.8 Hz, 1H), 2.78 (dhep, $J = 17.0$, 1.4 Hz, 1H), 2.49–2.42 (m, 3H), 2.26 (br q, $J = 7.2$ Hz, 2H), 2.12–2.09 [overlapping signals (2.12, s, 3H), (2.09, dd $J = 12.8$, 11.6 Hz, 1H), 3H], 1.59–1.58 (m, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 208.5 (C), 172.3 (2C), 145.0 (C), 140.8 (C), 121.8 (CH), 113.9 (CH), 58.9 (C), 53.0 (CH_3), 53.0 (CH_3), 51.3 (CH), 43.0 (CH_2), 38.5 (CH_2), 37.5 (CH_2), 30.9 (CH_3), 24.0 (CH_2), 18.0 (CH_3). HRMS-ESI Caldc for $C_{17}H_{24}O_5$ $[M+Na]^+$ 331.1521, found 331.1526.

(*Z*)-Dimethyl 6-(3-(2-(2,4-Dinitrophenyl)hydrazono)-3-(4-nitrophenyl)propyl)-7,7-dimethylbicyclo[3.2.0]hept-5-ene-3,3-dicarboxylate (II-31)



A solution of 2,4-2,dinitrophenylhydrazine (1.03 g, 3.38 mmol, 0.97 equiv) in sulfuric acid (3.31 ml, 60.9 mmol, 18 equiv) was added to a mixture of H_2O (5 mL) and EtOH (17 mL) and stirred for 10 min at room temperature. This reaction mixture was added to a solution of **II-23d** (147 mg, 0.35 mmol, 1 equiv) in a mixture of EtOH (1 mL) and CH_2Cl_2 (0.5 mL) and stirred for 15 min. Precipitation occurred. The mixture was diluted with CH_2Cl_2, then water was added. The organic layer was extracted by CH_2Cl_2, washed with sat $NaHCO_3$ and brine; dried over MgSO4, and finally filtrated and evaporated. The target product was isolated by silica gel column chromatography (10:1 to 6:1, c-Hex/EtOAc) to give **II-31** (100.43 mg, 48 %) as an orange solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.16 (d, $J = 2.5$ Hz, 1H), 8.41 (dd, $J = 9.5$, 2.6 Hz, 1H), 8.31 (dt, $J = 9.0$, 2.4 Hz, 2H), 8.12 (d, $J = 9.5$ Hz, 1H), 8.02 (dt, $J = 9.0$, 2.4 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.09 (td, $J = 15.4$, 6.5 Hz, 2H), 2.94 (d, $J = 15.5$ Hz, 1H), 2.80 (dd, $J = 15.6$, 1.6 Hz, 1H), 2.49 (dd, $J = 13.2$, 7.6 Hz, 1H), 2.40 (br t, $J = 9.0$ Hz, 1H), 2.28 (t, $J = 8.6$ Hz, 1H), 1.80 (dd, $J = 13.2$, 8.9 Hz, 1H), 1.62 (d, $J = 1.4$ Hz, 1H), 1.20 (s, 3H), 1.00 (s, 3H). ^{13}C (400 MHz, $CDCl_3$) δ 172.6 (C), 172.4 (C), 152.9 (C), 148.6 (C), 144.8 (C), 144.3 (C), 142.7 (C), 142.3 (C), 139.1 (C), 130.6 (C), 130.4 (C), 127.4 (2CH), 124.2 (2CH), 123.5 (CH), 116.9 (CH), 65.1 (CH_2), 53.1 (CH_3), 53.0 (CH_3), 51.7 (CH), 42.2 (C), 34.7 (CH_2), 34.0 (CH_2), 23.6 (CH_3), 25.3 (CH_2), 22.6 (CH_2), 20.4 (CH_3). HRMS-ESI Caldc for $C_{28}H_{29}N_5O_{10}$ $[M-H]^-$ 594.1836, found 594.1849.

(2*S*,2a*R*)-Dimethyl 2-(4-methoxyphenyl)-2a,3-dihydro-2*H*-benzo[*a*]cyclobuta[*c*] [7]annulene-4,4(5*H*)-dicarboxylate (II-25a) and (*E*)-dimethyl 9-(4-Methoxystyryl)-5*H*-benzo[7]annulene-6,6(7*H*)-dicarboxylate (II-33a)



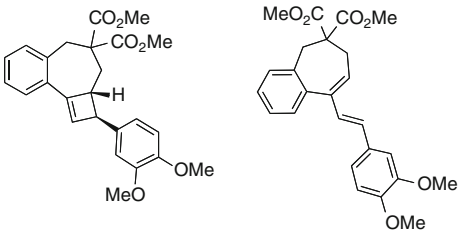
Complex **7** (3.32 mg, 3.41 μmol, 5 mol %) was added to a solution of 1,8-enyne **II-24a** (26.8 mg, 0.068 mmol, 1 equiv) in CD_2Cl_2 (1 mL). After 1 min, cyclobutene **II-24a** was observed and characterized by ^{1}H-NMR techniques. Moreover, after 17 h, 1,3-diene **II-33a** was detected and the reaction was stopped by the addition of a Et_3N/*c*Hex solution (0.1; 1 mL). After filtration through a pad of Celite and washing with CH_2Cl_2, the 1,3-diene **II-33a** was isolated. Purification via column chromatography (8:1 to 5:1, c-Hex/EtOAc) yielded **I-33** as a colorless oil (36.43 mg, quant.).

(2*S*,2a*R*)-dimethyl 2-(4-methoxyphenyl)-2a,3-dihydro-2*H*-benzo[*a*]cyclobuta[*c*] [7]annulene-4,4(5*H*)-dicarboxylate (**II-25a**): ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.48 (br d, $J = 7.3$ Hz, 1H), 7.24–721 [overlapping signals (7.22, d, $J = 8.6$ Hz,

2H), (m, 1H)], 7.18–716 (m, 2H), 6.85 (td, $J = 8.7$, 3.0 Hz, 2H), 6.42 (s, 1H), 3.78(s, 3H), 3.64 (s, 6H), 3.63 (s, 2H), 3.15 (d, $J = 14.8$ Hz, 1H), 3.09 (ddd, $J = 12.8$, 4.5, 1.4 Hz, 1H), 2.71 (dd, $J = 13.9$, 4.6 Hz, 1H), 2.39 (dd, $J = 13.9$. 12.9 Hz, 1H). ^{13}C (500 MHz, CD_2Cl_2) 172.3 (C), 172.0 (C), 158.8 (C), 151.0 (C), 136.0 (C), 134.9 (C), 134.2 (C), 132.3 (CH), 128.2 (CH), 128.2 (2CH), 127.7 (C), 127.7 (CH), 127.4 (CH), 125.9 (CH), 114.1 (2CH), 57.6 (C), 55.6 (CH3), 52.9 (CH_3), 52.8 (CH_3), 51.0 (CH), 50.8 (CH), 39.6 (CH_2), 37.0 (CH_2).

(*E*)-dimethyl 9-(4-methoxystyryl)-5*H*-benzo[7]annulene-6,6(7*H*)-dicarboxylat (**II-33a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, $J = 7.4$, 1.1 Hz, 1H), 7.39 (dd, $J = 7.6$, 1.3 Hz, 1H), 7.35–7.25 [overlapping signals (7.32, dd, $J = 8.6$, 1.6 Hz, 2H), (m, 2H)], 6.87–6.83 [overlapping signals (6.84, dd, $J = 8.8$, 1.9 Hz, 2H), (m, 1H)], 6.48 (d, $J = 16.2$ Hz, 1H), 6.26 (t, $J = 7.4$ Hz, 1H), 3.80 (s, 3H), 3.74 (s, 6H), 3.14 (s, 2H), 2.43 (d, $J = 7.3$ Hz, 2H). ^{13}C (400 MHz, $CDCl_3$) δ 171.7 (2C), 159.3 (C), 142.4 (C), 137.6 (C), 137.2 (C), 130.8 (CH), 130.3 (C), 130.0 (CH), 128.9 (CH), 128.0 (CH), 127.6 (2CH), 127.6 (CH), 127.0 (CH), 126.9 (CH), 114.2 (2CH), 67.2 (C), 55.5 (CH_3), 52.9 ($2CH_3$), 37.6 (CH_2), 31.5 (CH_2). HRMS-ESI Caldc for $C_{24}H_{24}O_5$ $[M+Na]^+$ 425.1521, found 415.1525.

(2*S*,2a*R*)-Dimethyl 2-(3,4-dimethoxyphenyl)-2a,3-dihydro-2*H*-benzo[*a*]cyclobuta[*c*][7]annulene-4,4(5*H*)-dicarboxylate (II-37b) and (*E*)-dimethyl 9-(3,4-dimethoxystyryl)-5*H*-benzo[7]annulene-6,6(7*H*)-dicarboxylate (II-33b)



Complex **7** (3.73 mg, 4.0 μmol, 5 mol %) was added to a solution of 1,8-enyne **II-24b** (38.24 mg, 0.08 mmol, 1 equiv) in CD_2Cl_2 (1.3 mL) After 1 min, cyclobutene **II-25b** was observed and characterized by NMR techniques. After 14 h, 1,3-diene **II-33b** was formed and the reaction was stopped by addition of a Et_3N/*c*-Hex solution (0.1 M; 1 mL). After filtration through a pad of Celite and washing with CH_2Cl_2. The 1,3-diene **II-33b** was isolated. Purification via column chromatography (6:1, c-Hex/EtOAc) yielded **II-33b** (26.95 mg, 82 %).

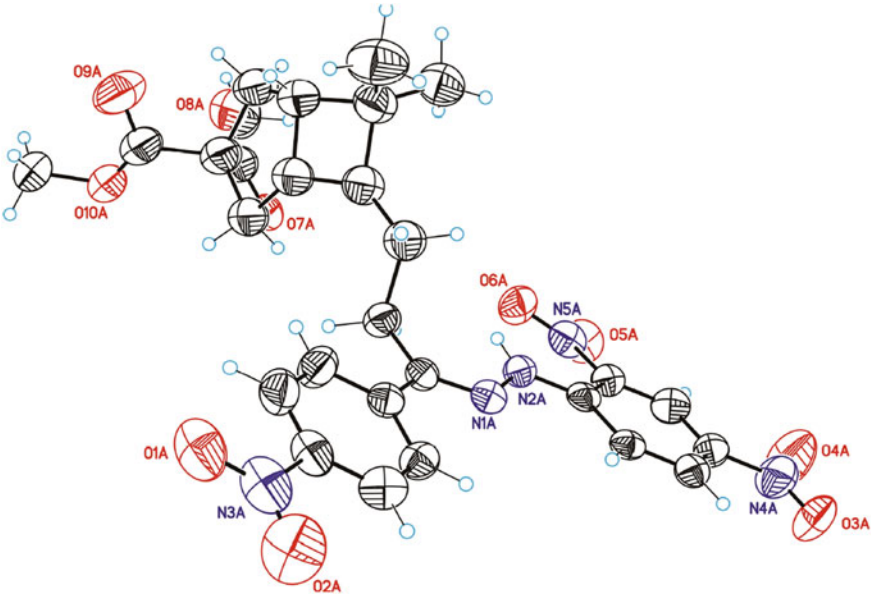
(2*S*,2a*R*)-Dimethyl 2-(3,4-dimethoxyphenyl)-2a,3-dihydro-2*H*-benzo[*a*]cyclobuta[*c*][7]-annulene-4,4(5*H*)-dicarboxylate (**II-25b**): ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.50 (dd, $J = 8.2$, 0.9 Hz, 1H), 7.24 (td, $J = 7.6$, 1.9 Hz, 1H), 7.19–7.14 (m, 2H), 6.84–6.82 (m, 3H), 6.42 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.60 (d, $J = 14.7$ Hz, 1H), 3.57 (br s, 1H), 3.15 (d, $J = 14.7$ Hz, 1H), 3.11 (dd, $J = 12.7$, 4.9, 1.2 Hz, 1H), 2.71 (dd, $J = 13.9$, 4.5 Hz, 1H), 2.40 (dd, $J = 13.6$, 12.9 Hz, 1H). ^{13}C (500 MHz, CD_2Cl_2) δ 172.3 (C), 172.0 (C), 151.0 (C), 149.6 (C), 148.8 (C), 136.0 (C), 135.5 (C), 134.1 (C), 132.2 (CH), 128.3 (CH),

127.5 (CH), 127.4 (CH), 125.9 (CH), 119.2 (CH), 111.8 (CH), 110.6 (CH), 57.6 (C), 56.1 (CH_3), 56.1 (CH_3), 52.9 (CH_3), 52.8 (CH_3), 51.5 (CH), 50.8 (CH), 39.0 (CH_2), 36.9 (CH_2).

(*E*)-Dimethyl 9-(3,4-dimethoxystyryl)-5*H*-benzo[7]annulene-6,6(7*H*)-dicarboxylate (**II-33b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 [overlapping signals (7.42 dd, $J = 7.4$, 1.0 Hz, 1H), (7.39, dd, $J = 7.8$, 1.5 Hz, 1H), 2H], 7.34 (td, $J = 7.4$, 1.4 Hz, 1H), 7.27 (td, $J = 7.4$, 1.6 Hz, 1H), 6.95–6.90 (overlapping signals, 2H), 6.85 (d, $J = 16.1$ Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 6.47 (d, $J = 16.2$ Hz, 1H),6.28 (t, $J = 7.4$ Hz, 1H), 3.90 (s, 3H), 388 (s, 3H), 3.74 (s, 6H), 3.14 (s, 2H), 2.44 (d, $J = 7.4$ Hz, 2H). ^{13}C (400 MHz, $CDCl_3$) δ 171.7 (2C), 149.2 (C), 148.9 (C), 142.2 (C), 137.6 (C), 137.2 (C), 130.8 (CH), 130.6 (C), 130.3 (CH), 128.9 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 126.9 (CH), 119.8 (CH), 111.3 (CH), 108.9 (CH), 67.2 (C), 56.5 (CH_3), 56.0 (CH_3), 52.9 ($2CH_3$), 37.6 (CH_2), 31.5 (CH_2). HRMS-ESI *m/z* calcd for $C_{25}H_{26}O_6$ $[M+Na]^+$ 445.1627, found 445.1627.

3.5.4 Crystallographic Data

Crystallographic data for compound II-31



Tables 3.3, 3.4 and 3.5.

Table 3.3 Crystal data and structure refinement for **II-31**

Empirical formula	$C_{28}H_{29}N_5O_{10}$	
Formula weight	595.56 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.1962(10) Å	$\alpha = 87.116(7)°$
	b = 13.6978(16) Å	$\beta = 76.553(7)°$
	c = 20.614(2) Å	$\gamma = 68.060(7)°$
Volume	2849.8(5) $Å^3$	
Z	4	
Density (calculated)	1.388 Mg/m^3	
Absorption coefficient	0.904 mm^{-1}	
F(000)	248	
Crystal size	0.20 × 0.20 × 0.04 mm^3	
Theta range for data collection	3.48–67	
Index ranges	−12 <=h <=13, −13 <=k <=13, 0 <=l <=23	
Reflections collected	7,193	
Independent reflections	7,193 [R(int) = 0.0556]	
Completeness to theta = 67.04°	0.693 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9647 and 0.8399	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	7193/462/1054	
Goodness-of-fit on F^2	0.999	
Final R indices [I > 2sigma(I)]	R1 = 0.1066, wR2 = 0.2549	
R indices (all data)	R1 = 0.1353, wR2 = 0.2805	
Largest diff. peak and hole	0.577 and −0.524 e.$Å^{-3}$	

Table 3.4 Bond lengths (Å) and angles (°) for II-34

Bond lengths	
C1A–N1A	1.292(6)
C1A–C2A	1.485(8)
C1A–C14A	1.501(6)
C2A–C7A	1.388(7)
C2A–C3A	1.394(7)
C3A–C4A	1.388(8)
C4A–C5A	1.377(8)
C5A–C6A	1.366(8)
C5A–N3A	1.484(8)
C6A–C7A	1.379(9)
C8A–N2A	1.350(6)
C8A–C9A	1.412(6)
C8A–C13A	1.421(7)
C9A–C10A	1.364(7)
C10A–C11A	1.400(8)
C11A–C12A	1.366(7)
C11A–N4A	1.456(7)
C12A–C13A	1.387(7)
C13A–N5A	1.454(6)
C14A–C15A	1.546(8)
C15A–C16A	1.427(7)
C16A–C17′	1.327(9)
C16A–C17A	1.366(8)
C16A–C22A	1.536(8)
C16A–C21′	2.040(5)
C17A–C21A	1.509(12)
C17A–C18A	1.534(5)
C18A–C19A	1.538(5)
C19A–C25A	1.537(4)
C19A–C20A	1.537(5)
C19A–C27A	1.539(3)
C20A–C21A	1.524(5)
C21A–C22A	1.549(7)
C22A–C23A	1.482(9)
C22A–C24A	1.520(9)
C22A–C21′	1.533(4)
C25A–O7A	1.182(6)
C25A–O8A	1.376(6)
C26A–O8A	1.452(5)
C27A–O9A	1.252(9)
C27A–O10A	1.287(10)
C28A–O10A	1.454(5)
C17′–C21′	1.505(11)
C17′–C18′	1.534(5)
C18′–C19′	1.527(11)

(continued)

Table 3.4 (continued)

Bond lengths	
C19′–C25′	1.534(5)
C19′–C27′	1.538(5)
C19′–C20′	1.540(5)
C20′–C21′	1.508(5)
C25′–O7A′	1.178(6)
C25′–O8A′	1.369(6)
C26′–O8A′	1.454(6)
C27′–O9A′	1.250(9)
C27′–O10′	1.288(9)
C28′–O10′	1.456(6)
C25″–O7A″	1.210(10)
C25″–O8A″	1.423(11)
C26″–O8A″	1.431(11)
C27″–O9A″	1.04(3)
C27″–O10″	1.45(3)
C28″–O10″	1.44(3)
N1A–N2A	1.377(6)
N3A–O1A	1.216(6)
N3A–O2A	1.218(7)
N4A–O3A	1.224(6)
N4A–O4A	1.238(7)
N5A–O5A	1.220(6)
N5A–O6A	1.244(5)
C1B–N1B	1.283(5)
C1B–C2B	1.490(6)
C1B–C14B	1.541(5)
C1B–C14″	1.545(5)
C2B–C3B	1.388(6)
C2B–C7B	1.412(7)
C3B–C4B	1.400(6)
C4B–C5B	1.376(7)
C5B–C6B	1.377(7)
C5B–N3B	1.477(5)
C6B–C7B	1.379(6)
C8B–N2B	1.362(6)
C8B–C9B	1.400(8)
C8B–C13B	1.407(6)
C9B–C10B	1.356(8)
C10B–C11B	1.375(8)
C11B–C12B	1.338(9)
C11B–N4B	1.476(8)
C12B–C13B	1.423(8)
C13B–N5B	1.461(8)
C14B–C15B	1.543(4)
C15B–C16B	1.542(5)

(continued)

Table 3.4 (continued)

Bond lengths	
C14″–C15″	1.539(5)
C15″–C16B	1.542(5)
C16B–C17″	1.294(13)
C16B–C17B	1.302(7)
C16B–C22B	1.522(6)
C16B–C22″	1.556(8)
C17B–C21B	1.494(8)
C17B–C18B	1.515(8)
C18B–C19B	1.547(4)
C17″–C21″	1.498(16)
C17″–C18″	1.516(16)
C18″–C19B	1.575(16)
C19B–C25B	1.527(4)
C19B–C27B	1.533(4)
C19B–C20″	1.540(3)
C19B–C20B	1.549(4)
C20B–C21B	1.541(4)
C21B–C22B	1.550(3)
C22B–C24B	1.529(6)
C22B–C23B	1.530(6)
C20″–C21″	1.542(5)
C21″–C22″	1.553(4)
C22″–C24″	1.529(6)
C22″–C23″	1.532(6)
C25B–O7B	1.215(8)
C25B–O7B″	1.228(8)
C25B–O8B	1.315(5)
C26B–O8B	1.436(6)
C27B–O9B″	1.207(8)
C27B–O9B	1.227(7)
C27B–O10B	1.354(5)
C28B–O10B	1.435(5)
N1B–N2B	1.363(5)
N3B–O2B	1.229(6)
N3B–O1B	1.230(5)
N4B–O4B	1.206(7)
N4B–O3B	1.232(9)
N5B–O5B	1.228(5)
N5B–O6B	1.232(6)
Angles	
N1A–C1A–C2A	115.8(4)
N1A–C1A–C14A	124.6(5)
C2A–C1A–C14A	119.2(4)
C7A–C2A–C3A	118.6(5)
C7A–C2A–C1A	120.8(4)

(continued)

Table 3.4 (continued)

Bond lengths	
C3A–C2A–C1A	120.6(4)
C4A–C3A–C2A	120.0(5)
C5A–C4A–C3A	119.4(5)
C6A–C5A–C4A	121.8(6)
C6A–C5A–N3A	118.0(5)
C4A–C5A–N3A	120.2(5)
C5A–C6A–C7A	118.6(6)
C6A–C7A–C2A	121.6(5)
N2A–C8A–C9A	121.2(5)
N2A–C8A–C13A	122.2(4)
C9A–C8A–C13A	116.6(4)
C10A–C9A–C8A	121.2(5)
C9A–C10A–C11A	120.0(4)
C12A–C11A–C10A	121.4(5)
C12A–C11A–N4A	119.3(5)
C10A–C11A–N4A	119.3(5)
C11A–C12A–C13A	118.5(5)
C12A–C13A–C8A	122.2(4)
C12A–C13A–N5A	116.0(5)
C8A–C13A–N5A	121.7(4)
C1A–C14A–C15A	108.7(4)
C16A–C15A–C14A	115.1(5)
C17′–C16A–C17A	35.9(7)
C17′–C16A–C15A	135.8(7)
C17A–C16A–C15A	136.3(6)
C17′–C16A–C22A	95.5(5)
C17A–C16A–C22A	90.1(5)
C15A–C16A–C22A	127.4(5)
C17′–C16A–C21′	47.5(4)
C17A–C16A–C21′	49.7(5)
C15A–C16A–C21′	173.9(5)
C22A–C16A–C21′	48.3(2)
C16A–C17A–C21A	96.9(6)
C16A–C17A–C18A	132.9(8)
C21A–C17A–C18A	119.2(5)
C17A–C18A–C19A	103.7(5)
C25A–C19A–C20A	118.5(6)
C25A–C19A–C18A	114.3(6)
C20A–C19A–C18A	101.8(5)
C25A–C19A–C27A	110.4(4)
C20A–C19A–C27A	98.7(5)
C18A–C19A–C27A	111.9(6)
C21A–C20A–C19A	120.2(6)
C17A–C21A–C20A	94.3(6)
C17A–C21A–C22A	84.5(5)

(continued)

Table 3.4 (continued)

Bond lengths	
C20A–C21A–C22A	139.4(8)
C23A–C22A–C24A	111.2(5)
C23A–C22A–C21′	124.4(6)
C24A–C22A–C21′	104.7(6)
C23A–C22A–C16A	118.1(5)
C24A–C22A–C16A	112.1(5)
C21′–C22A–C16A	83.3(4)
C23A–C22A–C21A	94.4(6)
C24A–C22A–C21A	131.3(6)
C21′–C22A–C21A	31.8(6)
C16A–C22A–C21A	88.5(5)
O7A–C25A–O8A	124.2(7)
O7A–C25A–C19A	125.3(7)
O8A–C25A–C19A	106.0(5)
O9A–C27A–O10A	126.2(7)
O9A–C27A–C19A	124.6(8)
O10A–C27A–C19A	108.5(6)
C25A–O8A–C26A	114.2(7)
C27A–O10A–C28A	117.0(8)
C16A–C17′–C21′	91.9(6)
C16A–C17′–C18′	150.8(10)
C21′–C17′–C18′	111.7(6)
C19′–C18′–C17′	95.9(6)
C18′–C19′–C25′	102.1(7)
C18′–C19′–C27′	117.9(7)
C25′–C19′–C27′	110.2(5)
C18′–C19′–C20′	116.2(5)
C25′–C19′–C20′	94.6(6)
C27′–C19′–C20′	112.4(6)
C21′–C20′–C19′	96.2(5)
C17′–C21′–C20′	105.3(7)
C17′–C21′–C22A	88.7(4)
C20′–C21′–C22A	154.6(7)
C17′–C21′–C16A	40.5(4)
C20′–C21′–C16A	143.5(7)
C22A–C21′–C16A	48.4(3)
O7A′–C25′–O8A′	124.7(7)
O7A′–C25′–C19′	126.7(7)
O8A′–C25′–C19′	107.1(5)
O9A′–C27′–O10′	126.3(6)
O9A′–C27′–C19′	121.3(8)
O10′–C27′–C19′	112.3(6)
C25′–O8A′–C26′	114.5(6)
C27′–O10′–C28′	116.7(7)
O7A″–C25″–O8A”	114(2)

(continued)

Table 3.4 (continued)

Bond lengths	
O9A″–C27″–O10″	128(3)
C25″–O8A″–C26″	99(2)
C28″–O10″–C27″	112(2)
C1A–N1A–N2A	116.3(4)
C8A–N2A–N1A	121.1(4)
O1A–N3A–O2A	124.9(6)
O1A–N3A–C5A	118.4(5)
O2A–N3A–C5A	116.6(5)
O3A–N4A–O4A	123.0(5)
O3A–N4A–C11A	118.5(5)
O4A–N4A–C11A	118.6(5)
O5A–N5A–O6A	122.5(4)
O5A–N5A–C13A	118.4(4)
O6A–N5A–C13A	119.1(5)
N1B–C1B–C2B	115.5(4)
N1B–C1B–C14B	123.0(4)
C2B–C1B–C14B	120.1(4)
N1B–C1B–C14″	118.2(4)
C2B–C1B–C14″	119.0(4)
C14B–C1B–C14″	37.7(4)
C3B–C2B–C7B	119.2(4)
C3B–C2B–C1B	122.4(4)
C7B–C2B–C1B	118.5(4)
C2B–C3B–C4B	120.6(5)
C5B–C4B–C3B	118.2(4)
C4B–C5B–C6B	122.8(4)
C4B–C5B–N3B	118.3(4)
C6B–C5B–N3B	118.9(4)
C5B–C6B–C7B	118.9(5)
C6B–C7B–C2B	120.3(4)
N2B–C8B–C9B	120.5(4)
N2B–C8B–C13B	122.2(5)
C9B–C8B–C13B	117.2(5)
C10B–C9B–C8B	121.8(5)
C9B–C10B–C11B	119.7(6)
C12B–C11B–C10B	122.2(6)
C12B–C11B–N4B	119.4(6)
C10B–C11B–N4B	118.4(6)
C11B–C12B–C13B	118.9(5)
C8B–C13B–C12B	120.1(5)
C8B–C13B–N5B	121.4(5)
C12B–C13B–N5B	118.5(5)
C1B–C14B–C15B	108.3(4)
C16B–C15B–C14B	107.3(4)
C15″–C14″–C1B	113.7(6)

(continued)

Table 3.4 (continued)

Bond lengths	
C14″–C15″–C16B	103.1(5)
C17″–C16B–C17B	20.3(11)
C17″–C16B–C22B	96.5(7)
C17B–C16B–C22B	95.1(4)
C17″–C16B–C15″	131.4(9)
C17B–C16B–C15″	120.4(6)
C22B–C16B–C15″	125.1(6)
C17″–C16B–C15B	123.1(10)
C17B–C16B–C15B	133.7(5)
C22B–C16B–C15B	128.3(4)
C15″–C16B–C15B	50.5(4)
C17″–C16B–C22″	93.3(8)
C17B–C16B–C22″	88.7(4)
C22B–C16B–C22″	10.5(3)
C15″–C16B–C22″	122.8(6)
C15B–C16B–C22″	136.6(4)
C16B–C17B–C21B	93.8(4)
C16B–C17B–C18B	145.5(7)
C21B–C17B–C18B	115.3(5)
C17B–C18B–C19B	100.5(4)
C16B–C17″–C21″	94.6(9)
C16B–C17″–C18″	150.1(15)
C21″–C17″–C18″	111.4(11)
C17″–C18″–C19B	97.1(11)
C25B–C19B–C27B	109.6(4)
C25B–C19B–C20″	88.0(4)
C27B–C19B–C20″	130.2(6)
C25B–C19B–C18B	108.8(5)
C27B–C19B–C18B	110.1(4)
C20″–C19B–C18B	107.1(5)
C25B–C19B–C20B	111.7(4)
C27B–C19B–C20B	108.7(3)
C20″–C19B–C20B	26.3(5)
C18B–C19B–C20B	108.0(4)
C25B–C19B–C18″	106.5(11)
C27B–C19B–C18″	111.1(11)
C20″–C19B–C18″	107.3(9)
C18B–C19B–C18″	2.3(12)
C20B–C19B–C18″	109.3(7)
C21B–C20B–C19B	105.1(3)
C17B–C21B–C20B	100.0(4)
C17B–C21B–C22B	86.7(4)
C20B–C21B–C22B	126.7(3)
C16B–C22B–C24B	115.1(5)
C16B–C22B–C23B	114.7(4)

(continued)

Table 3.4 (continued)

Bond lengths	
C24B–C22B–C23B	109.2(4)
C16B–C22B–C21B	83.5(3)
C24B–C22B–C21B	117.4(3)
C23B–C22B–C21B	115.1(4)
C19B–C20″–C21″	94.8(4)
C17″–C21″–C20″	104.3(9)
C17″–C21″–C22″	86.0(7)
C20″–C21″–C22″	126.0(5)
C24″–C22″–C23″	109.0(5)
C24″–C22″–C21″	117.2(5)
C23″–C22″–C21″	114.3(5)
C24″–C22″–C16B	106.6(8)
C23″–C22″–C16B	125.3(7)
C21″–C22″–C16B	82.9(4)
O7B–C25B–O7B”	48.5(7)
O7B–C25B–O8B	115.9(6)
O7B”–C25B–O8B	115.8(7)
O7B–C25B–C19B	125.0(6)
O7B”–C25B–C19B	119.5(7)
O8B–C25B–C19B	115.3(4)
O9B”–C27B–O9B	39.9(5)
O9B”–C27B–O10B	118.4(6)
O9B–C27B–O10B	120.1(5)
O9B”–C27B–C19B	124.8(6)
O9B–C27B–C19B	127.2(5)
O10B–C27B–C19B	109.7(4)
C1B–N1B–N2B	118.6(4)
C8B–N2B–N1B	118.0(4)
O2B–N3B–O1B	124.4(4)
O2B–N3B–C5B	117.4(4)
O1B–N3B–C5B	118.2(4)
O4B–N4B–O3B	124.6(6)
O4B–N4B–C11B	117.3(7)
O3B–N4B–C11B	118.0(6)
O5B–N5B–O6B	123.0(5)
O5B–N5B–C13B	116.9(5)
O6B–N5B–C13B	120.1(4)
C25B–O8B–C26B	118.4(5)
C27B–O10B–C28B	115.9(4)

Table 3.5 Torsion angles (°) for **II-34**

N1A–C1A–C2A–C7A	167.1(5)
C14A–C1A–C2A–C7A	−6.7(7)
N1A–C1A–C2A–C3A	−13.3(7)
C14A–C1A–C2A–C3A	172.9(5)
C7A–C2A–C3A–C4A	−0.2(8)
C1A–C2A–C3A–C4A	−179.8(5)
C2A–C3A–C4A–C5A	0.5(8)
C3A–C4A–C5A–C6A	−0.6(9)
C3A–C4A–C5A–N3A	177.4(5)
C4A–C5A–C6A–C7A	0.3(10)
N3A–C5A–C6A–C7A	−177.7(5)
C5A–C6A–C7A–C2A	0.0(10)
C3A–C2A–C7A–C6A	0.0(9)
C1A–C2A–C7A–C6A	179.5(5)
N2A–C8A–C9A–C10A	179.1(4)
C13A–C8A–C9A–C10A	1.9(7)
C8A–C9A–C10A–C11A	−1.0(7)
C9A–C10A–C11A–C12A	−0.1(8)
C9A–C10A–C11A–N4A	179.8(5)
C10A–C11A–C12A–C13A	0.1(8)
N4A–C11A–C12A–C13A	−179.9(5)
C11A–C12A–C13A–C8A	1.0(8)
C11A–C12A–C13A–N5A	−176.6(5)
N2A–C8A–C13A–C12A	−179.1(5)
C9A–C8A–C13A–C12A	−2.0(7)
N2A–C8A–C13A–N5A	−1.6(7)
C9A–C8A–C13A–N5A	175.5(4)
N1A–C1A–C14A–C15A	−82.6(7)
C2A–C1A–C14A–C15A	90.7(6)
C1A–C14A–C15A–C16A	−170.3(6)
C14A–C15A–C16A–C17′	−10.4(14)
C14A–C15A–C16A–C17A	42.3(13)
C14A–C15A–C16A–C22A	−174.2(6)
C14A–C15A–C16A–C21′	−131(6)
C17′–C16A–C17A–C21A	−100.9(11)
C15A–C16A–C17A–C21A	150.2(9)
C22A–C16A–C17A–C21A	−1.6(7)
C21′–C16A–C17A–C21A	−30.8(6)
C17′–C16A–C17A–C18A	40.6(11)
C15A–C16A–C17A–C18A	−68.3(17)
C22A–C16A–C17A–C18A	139.9(11)
C21′–C16A–C17A–C18A	110.7(14)
C16A–C17A–C18A–C19A	−125.1(11)
C21A–C17A–C18A–C19A	9.8(13)
C17A–C18A–C19A–C25A	122.6(8)
C17A–C18A–C19A–C20A	−6.4(9)

(continued)

Table 3.5 (continued)

C17A–C18A–C19A–C27A	−110.9(8)
C25A–C19A–C20A–C21A	−123.8(8)
C18A–C19A–C20A–C21A	2.5(10)
C27A–C19A–C20A–C21A	117.2(8)
C16A–C17A–C21A–C20A	140.8(8)
C18A–C17A–C21A–C20A	−7.6(12)
C16A–C17A–C21A–C22A	1.5(7)
C18A–C17A–C21A–C22A	−146.9(10)
C19A–C20A–C21A–C17A	2.7(10)
C19A–C20A–C21A–C22A	89.3(14)
C17′–C16A–C22A–C23A	131.3(8)
C17A–C16A–C22A–C23A	95.7(7)
C15A–C16A–C22A–C23A	−60.0(9)
C21′–C16A–C22A–C23A	125.6(7)
C17′–C16A–C22A–C24A	−97.5(8)
C17A–C16A–C22A–C24A	−133.1(7)
C15A–C16A–C22A–C24A	71.2(9)
C21′–C16A–C22A–C24A	−103.1(7)
C17′–C16A–C22A–C21′	5.6(9)
C17A–C16A–C22A–C21′	−29.9(7)
C15A–C16A–C22A–C21′	174.4(8)
C17′–C16A–C22A–C21A	37.1(8)
C17A–C16A–C22A–C21A	1.5(7)
C15A–C16A–C22A–C21A	−154.2(8)
C21′–C16A–C22A–C21A	31.4(6)
C17A–C21A–C22A–C23A	−119.4(7)
C20A–C21A–C22A–C23A	150.4(12)
C17A–C21A–C22A–C24A	117.3(9)
C20A–C21A–C22A–C24A	27.1(17)
C17A–C21A–C22A–C21′	78.3(9)
C20A–C21A–C22A–C21′	−11.9(8)
C17A–C21A–C22A–C16A	−1.4(7)
C20A–C21A–C22A–C16A	−91.5(12)
C20A–C19A–C25A–O7A	112.6(10)
C18A–C19A–C25A–O7A	−7.5(12)
C27A–C19A–C25A–O7A	−134.7(10)
C20A–C19A–C25A–O8A	−44.2(7)
C18A–C19A–C25A–O8A	−164.3(7)
C27A–C19A–C25A–O8A	68.5(8)
C25A–C19A–C27A–O9A	−125.5(11)
C20A–C19A–C27A–O9A	−0.5(12)
C18A–C19A–C27A–O9A	106.0(12)
C25A–C19A–C27A–O10A	44.8(10)
C20A–C19A–C27A–O10A	169.8(8)
C18A–C19A–C27A–O10A	−83.7(9)
O7A–C25A–O8A–C26A	23.1(15)

(continued)

Table 3.5 (continued)

C19A–C25A–O8A–C26A	−179.8(7)
O9A–C27A–O10A–C28A	−1.5(19)
C19A–C27A–O10A–C28A	−171.6(10)
C17A–C16A–C17′–C21′	76.7(10)
C15A–C16A–C17′–C21′	−172.9(9)
C22A–C16A–C17′–C21′	−5.7(9)
C17A–C16A–C17′–C18′	−68(3)
C15A–C16A–C17′–C18′	42(3)
C22A–C16A–C17′–C18′	−150(2)
C21′–C16A–C17′–C18′	−145(3)
C16A–C17′–C18′–C19′	153(2)
C21′–C17′–C18′–C19′	11.8(14)
C17′–C18′–C19′–C25′	115.3(9)
C17′–C18′–C19′–C27′	−123.9(9)
C17′–C18′–C19′–C20′	13.9(12)
C18′–C19′–C20′–C21′	−32.7(10)
C25′–C19′–C20′–C21′	−138.7(6)
C27′–C19′–C20′–C21′	107.3(7)
C16A–C17′–C21′–C20′	164.2(8)
C18′–C17′–C21′–C20′	−33.5(14)
C16A–C17′–C21′–C22A	5.7(9)
C18′–C17′–C21′–C22A	168.0(11)
C18′–C17′–C21′–C16A	162.3(17)
C19′–C20′–C21′–C17′	36.5(9)
C19′–C20′–C21′–C22A	157.8(16)
C19′–C20′–C21′–C16A	53.8(12)
C23A–C22A–C21′–C17′	−124.5(9)
C24A–C22A–C21′–C17′	106.3(8)
C16A–C22A–C21′–C17′	−4.9(8)
C21A–C22A–C21′–C17′	−103.0(12)
C23A–C22A–C21′–C20′	111.0(18)
C24A–C22A–C21′–C20′	−18.2(19)
C16A–C22A–C21′–C20′	−129.4(18)
C21A–C22A–C21′–C20′	133(2)
C23A–C22A–C21′–C16A	−119.6(8)
C24A–C22A–C21′–C16A	111.2(6)
C21A–C22A–C21′–C16A	−98.1(9)
C17A–C16A–C21′–C17′	−48.4(10)
C15A–C16A–C21′–C17′	125(6)
C22A–C16A–C21′–C17′	172.4(11)
C17′–C16A–C21′–C20′	−26.2(13)
C17A–C16A–C21′–C20′	−74.7(12)
C15A–C16A–C21′–C20′	99(6)
C22A–C16A–C21′–C20′	146.2(13)
C17′–C16A–C21′–C22A	−172.4(11)
C17A–C16A–C21′–C22A	139.2(9)

(continued)

Table 3.5 (continued)

C15A–C16A–C21′–C22A	−47(6)
C18′–C19′–C25′–O7A′	−3.6(11)
C27′–C19′–C25′–O7A′	−129.6(10)
C20′–C19′–C25′–O7A′	114.5(10)
C18′–C19′–C25′–O8A′	162.9(7)
C27′–C19′–C25′–O8A′	36.8(9)
C20′–C19′–C25′–O8A′	−79.1(7)
C18′–C19′–C27′–O9A′	123.4(10)
C25′–C19′–C27′–O9A′	−120.1(9)
C20′–C19′–C27′–O9A′	−15.9(11)
C18′–C19′–C27′–O10′	−60.6(10)
C25′–C19′–C27′–O10′	56.0(10)
C20′–C19′–C27′–O10′	160.1(8)
O7A′–C25′–O8A′–C26′	−12.1(14)
C19′–C25′–O8A′–C26′	−178.8(7)
O9A′–C27′–O10′–C28′	−2.8(16)
C19′–C27′–O10′–C28′	−178.6(8)
O7A″–C25″–O8A″–C26″	4(3)
O9A″–C27″–O10″–C28″	−8(5)
C2A–C1A–N1A–N2A	−177.6(4)
C14A–C1A–N1A–N2A	−4.1(7)
C9A–C8A–N2A–N1A	−6.9(7)
C13A–C8A–N2A–N1A	170.1(4)
C1A–N1A–N2A–C8A	−173.0(4)
C6A–C5A–N3A–O1A	−4.0(9)
C4A–C5A–N3A–O1A	177.9(6)
C6A–C5A–N3A–O2A	174.1(6)
C4A–C5A–N3A–O2A	−4.0(9)
C12A–C11A–N4A–O3A	−179.3(6)
C10A–C11A–N4A–O3A	0.8(8)
C12A–C11A–N4A–O4A	−0.2(9)
C10A–C11A–N4A–O4A	179.9(6)
C12A–C13A–N5A–O5A	13.8(7)
C8A–C13A–N5A–O5A	−163.9(5)
C12A–C13A–N5A–O6A	−167.9(5)
C8A–C13A–N5A–O6A	14.5(7)
N1B–C1B–C2B–C3B	−173.9(4)
C14B–C1B–C2B–C3B	−7.0(6)
C14″–C1B–C2B–C3B	36.6(7)
N1B–C1B–C2B–C7B	5.0(6)
C14B–C1B–C2B–C7B	171.8(4)
C14″–C1B–C2B–C7B	−144.5(6)
C7B–C2B–C3B–C4B	−1.6(7)
C1B–C2B–C3B–C4B	177.2(4)
C2B–C3B–C4B–C5B	1.3(7)
C3B–C4B–C5B–C6B	−1.0(7)

(continued)

Table 3.5 (continued)

C3B–C4B–C5B–N3B	179.7(4)
C4B–C5B–C6B–C7B	1.1(7)
N3B–C5B–C6B–C7B	−179.6(4)
C5B–C6B–C7B–C2B	−1.4(7)
C3B–C2B–C7B–C6B	1.7(7)
C1B–C2B–C7B–C6B	−177.2(4)
N2B–C8B–C9B–C10B	−179.7(5)
C13B–C8B–C9B–C10B	−2.1(8)
C8B–C9B–C10B–C11B	2.3(10)
C9B–C10B–C11B–C12B	−0.5(10)
C9B–C10B–C11B–N4B	−179.4(6)
C10B–C11B–C12B–C13B	−1.6(9)
N4B–C11B–C12B–C13B	177.3(5)
N2B–C8B–C13B–C12B	177.6(5)
C9B–C8B–C13B–C12B	0.0(7)
N2B–C8B–C13B–N5B	−2.6(7)
C9B–C8B–C13B–N5B	179.7(5)
C11B–C12B–C13B–C8B	1.8(8)
C11B–C12B–C13B–N5B	−178.0(5)
N1B–C1B–C14B–C15B	−84.6(6)
C2B–C1B–C14B–C15B	109.6(5)
C14″–C1B–C14B–C15B	10.1(5)
C1B–C14B–C15B–C16B	175.9(4)
N1B–C1B–C14″–C15″	95.9(8)
C2B–C1B–C14″–C15″	−115.4(7)
C14B–C1B–C14″–C15″	−12.6(6)
C1B–C14″–C15″–C16B	−175.7(6)
C14″–C15″–C16B–C17″	110.6(15)
C14″–C15″–C16B–C17B	131.8(7)
C14″–C15″–C16B–C22B	−105.6(7)
C14″–C15″–C16B–C15B	8.1(4)
C14″–C15″–C16B–C22″	−117.9(7)
C14B–C15B–C16B–C17″	−128.7(11)
C14B–C15B–C16B–C17B	−106.5(7)
C14B–C15B–C16B–C22B	97.9(6)
C14B–C15B–C16B–C15″	−9.6(6)
C14B–C15B–C16B–C22″	89.1(7)
C17″–C16B–C17B–C21B	−103(2)
C22B–C16B–C17B–C21B	−7.8(4)
C15″–C16B–C17B–C21B	128.4(6)
C15B–C16B–C17B–C21B	−168.9(5)
C22″–C16B–C17B–C21B	0.4(5)
C17″–C16B–C17B–C18B	46(2)
C22B–C16B–C17B–C18B	140.7(10)
C15″–C16B–C17B–C18B	−83.0(12)
C15B–C16B–C17B–C18B	−20.3(14)

(continued)

Table 3.5 (continued)

C22″–C16B–C17B–C18B	149.0(10)
C16B–C17B–C18B–C19B	−135.7(9)
C21B–C17B–C18B–C19B	9.1(8)
C17B–C16B–C17″–C21″	91(2)
C22B–C16B–C17″–C21″	4.1(12)
C15″–C16B–C17″–C21″	155.0(8)
C15B–C16B–C17″–C21″	−140.9(7)
C22″–C16B–C17″–C21″	14.1(11)
C17B–C16B–C17″–C18″	−60(4)
C22B–C16B–C17″–C18″	−147(4)
C15″–C16B–C17″–C18″	4(5)
C15B–C16B–C17″–C18″	68(4)
C22″–C16B–C17″–C18″	−137(4)
C16B–C17″–C18″–C19B	155(3)
C21″–C17″–C18″–C19B	6(2)
C17B–C18B–C19B–C25B	−108.7(5)
C17B–C18B–C19B–C27B	131.3(5)
C17B–C18B–C19B–C20″	−14.9(8)
C17B–C18B–C19B–C20B	12.7(7)
C17B–C18B–C19B–C18″	−112(24)
C17″–C18″–C19B–C25B	−128.6(14)
C17″–C18″–C19B–C27B	112.2(15)
C17″–C18″–C19B–C20″	−35.5(19)
C17″–C18″–C19B–C18B	48(23)
C17″–C18″–C19B–C20B	−7.8(19)
C25B–C19B–C20B–C21B	90.2(5)
C27B–C19B–C20B–C21B	−148.8(4)
C20″–C19B–C20B–C21B	62.8(9)
C18B–C19B–C20B–C21B	−29.4(6)
C18″–C19B–C20B–C21B	−27.4(13)
C16B–C17B–C21B–C20B	134.4(4)
C18B–C17B–C21B–C20B	−26.5(7)
C16B–C17B–C21B–C22B	7.7(4)
C18B–C17B–C21B–C22B	−153.3(6)
C19B–C20B–C21B–C17B	32.2(5)
C19B–C20B–C21B–C22B	125.6(5)
C17″–C16B–C22B–C24B	−89.4(11)
C17B–C16B–C22B–C24B	−109.7(5)
C15″–C16B–C22B–C24B	117.1(6)
C15B–C16B–C22B–C24B	52.9(6)
C22″–C16B–C22B–C24B	−162.0(13)
C17″–C16B–C22B–C23B	142.6(11)
C17B–C16B–C22B–C23B	122.3(5)
C15″–C16B–C22B–C23B	−10.9(8)
C15B–C16B–C22B–C23B	−75.1(6)
C22″–C16B–C22B–C23B	69.9(14)

(continued)

Table 3.5 (continued)

C17″–C16B–C22B–C21B	28.0(11)
C17B–C16B–C22B–C21B	7.6(4)
C15″–C16B–C22B–C21B	−125.5(6)
C15B–C16B–C22B–C21B	170.2(5)
C22″–C16B–C22B–C21B	−44.7(12)
C17B–C21B–C22B–C16B	−6.6(4)
C20B–C21B–C22B–C16B	−106.6(6)
C17B–C21B–C22B–C24B	108.4(5)
C20B–C21B–C22B–C24B	8.4(8)
C17B–C21B–C22B–C23B	−120.9(4)
C20B–C21B–C22B–C23B	139.0(5)
C25B–C19B–C20″–C21″	156.2(7)
C27B–C19B–C20″–C21″	−89.6(7)
C18B–C19B–C20″–C21″	47.2(8)
C20B–C19B–C20″–C21″	−49.1(6)
C18″–C19B–C20″–C21″	49.5(13)
C16B–C17″–C21″–C20″	−140.4(11)
C18″–C17″–C21″–C20″	25(2)
C16B–C17″–C21″–C22″	−14.2(11)
C18″–C17″–C21″–C22″	150.8(18)
C19B–C20″–C21″–C17″	−43.1(11)
C19B–C20″–C21″–C22″	−138.6(7)
C17″–C21″–C22″–C24″	116.8(12)
C20″–C21″–C22″–C24″	−138.4(11)
C17″–C21″–C22″–C23″	−113.8(11)
C20″–C21″–C22″–C23″	−9.1(11)
C17″–C21″–C22″–C16B	11.8(9)
C20″–C21″–C22″–C16B	116.5(9)
C17″–C16B–C22″–C24″	−130.0(11)
C17B–C16B–C22″–C24″	−149.8(6)
C22B–C16B–C22″–C24″	−21.8(13)
C15″–C16B–C22″–C24″	84.3(8)
C15B–C16B–C22″–C24″	19.0(9)
C17″–C16B–C22″–C23″	101.1(12)
C17B–C16B–C22″–C23″	81.4(7)
C22B–C16B–C22″–C23″	−150.7(16)
C15″–C16B–C22″–C23″	−44.6(9)
C15B–C16B–C22″–C23″	−109.9(8)
C17″–C16B–C22″–C21″	−13.7(11)
C17B–C16B–C22″–C21″	−33.4(5)
C22B–C16B–C22″–C21″	94.5(13)
C15″–C16B–C22″–C21″	−159.4(6)
C15B–C16B–C22″–C21″	135.4(6)
C27B–C19B–C25B–O7B	172.4(8)
C20″–C19B–C25B–O7B	−55.4(10)
C18B–C19B–C25B–O7B	52.0(9)

(continued)

Table 3.5 (continued)

C20B–C19B–C25B–O7B	−67.1(9)
C18″–C19B–C25B–O7B	52.1(12)
C27B–C19B–C25B–O7B″	−129.8(9)
C20″–C19B–C25B–O7B″	2.5(10)
C18B–C19B–C25B–O7B″	109.8(9)
C20B–C19B–C25B–O7B″	−9.3(10)
C18″–C19B–C25B–O7B″	110.0(12)
C27B–C19B–C25B–O8B	15.3(6)
C20″–C19B–C25B–O8B	147.6(7)
C18B–C19B–C25B–O8B	−105.0(6)
C20B–C19B–C25B–O8B	135.8(5)
C18″–C19B–C25B–O8B	−104.9(10)
C25B–C19B–C27B–O9B″	−139.3(8)
C20″–C19B–C27B–O9B″	116.2(8)
C18B–C19B–C27B–O9B″	−19.7(9)
C20B–C19B–C27B–O9B″	98.5(8)
C18″–C19B–C27B–O9B″	−21.9(12)
C25B–C19B–C27B–O9B	−89.5(8)
C20″–C19B–C27B–O9B	166.0(7)
C18B–C19B–C27B–O9B	30.1(9)
C20B–C19B–C27B–O9B	148.3(7)
C18″–C19B–C27B–O9B	27.9(12)
C25B–C19B–C27B–O10B	70.9(5)
C20″–C19B–C27B–O10B	−33.6(7)
C18B–C19B–C27B–O10B	−169.5(5)
C20B–C19B–C27B–O10B	−51.3(5)
C18″–C19B–C27B–O10B	−171.7(9)
C2B–C1B–N1B–N2B	178.4(4)
C14B–C1B–N1B–N2B	12.0(6)
C14″–C1B–N1B–N2B	−31.8(7)
C9B–C8B–N2B–N1B	2.0(7)
C13B–C8B–N2B–N1B	−175.5(4)
C1B–N1B–N2B–C8B	−178.8(4)
C4B–C5B–N3B–O2B	179.1(4)
C6B–C5B–N3B–O2B	−0.3(6)
C4B–C5B–N3B–O1B	−2.9(6)
C6B–C5B–N3B–O1B	177.8(4)
C12B–C11B–N4B–O4B	8.5(10)
C10B–C11B–N4B–O4B	−172.6(6)
C12B–C11B–N4B–O3B	−167.0(7)
C10B–C11B–N4B–O3B	12.0(10)
C8B–C13B–N5B–O5B	168.3(5)
C12B–C13B–N5B–O5B	−12.0(7)
C8B–C13B–N5B–O6B	−11.5(7)
C12B–C13B–N5B–O6B	168.2(5)
O7B–C25B–O8B–C26B	18.4(10)

(continued)

Table 3.5 (continued)

O7B″–C25B–O8B–C26B	−36.0(11)
C19B–C25B–O8B–C26B	177.6(5)
O9B″–C27B–O10B–C28B	27.1(9)
O9B–C27B–O10B–C28B	−18.9(9)
C19B–C27B–O10B–C28B	179.1(4)

References

1. Dembitsky, V.M.: J. Nat. Med. **62**, 1–33 (2008)
2. Sergeiko, A., Poroikov, V.V., Hanu, L.O., Dembitsky, V.M.: Open Med. Chem. J. 26–37 (2008)
3. Hansen, T.V., Stenstrøm, Y.: Organic Synthesis: Theory and Applications, vol. 5, pp. 1–38. Elsevier, Amsterdam (1996)
4. Trost, B.M., Tanoury, G.J.: J. Am. Chem. Soc. **110**, 1636–1638 (1988)
5. Fürstner, A., Davies, P.W., Gress, T.: J. Am. Chem. Soc. **127**, 8244–8245 (2005)
6. Bajracharya, G.B., Nakamura, I., Yamamoto, Y.: J. Org. Chem. **70**, 892–897 (2005)
7. Fürstner, A., Schlecker, A., Lehmann, C.W.: Chem. Commun. 4277–4279 (2007)
8. Lee, Y.T., Kang, Y.K., Chung, Y.K.: J. Org. Chem. **74**, 7922–7934 (2009)
9. Couty, S., Meyer, C., Cossy, J.: Angew. Chem. Int. Ed. **45**, 6726–6730 (2006)
10. Couty, S., Meyer, C., Cossy, J.: Tetrahedron **65**, 1809–1832 (2009)
11. Marion, F., Coulomb, J., Courillon, C., Fensterbank, L., Malacria, M.: Org. Lett. **6**, 1509–1511 (2004)
12. Marion, F., Coulomb, J., Servais, A., Courillon, C., Fensterbank, L., Malacria, M.: Tetrahedron **62**, 3856–3871 (2006)
13. Trost, B.M., Yanai, M., Hoogsteen, K.: J. Am. Chem. Soc. **115**, 5294–5295 (1993)
14. Chatani, N., Inoue, H., Kotsuma, T., Murai, S.: J. Am. Chem. Soc. **124**, 10294–10295 (2002)
15. Fürstner, A., Stelzer, F., Szillat, H.: J. Am. Chem. Soc. **123**, 11863–11869 (2001)
16. Chang, S., Na, Y., Choi, E., Kim, S.: Org. Lett. **3**, 2089–2091 (2001)
17. Results obtained in collaboration with Masaki Sekine (visiting PhD student from the group of Prof. Eiichi Nakamura, Tokyo University, Japan)
18. PPh_3-bound polymer was added before purification to completely remove the gold(I) complex
19. A 1 M solution of Et_3N in cyclohexane was added, followed by filtration through a plug of Celite to quench the gold(I) complex
20. Muñoz, M. P., Méndez, M., Nevado, C., Cárdenas, D.J., Echavarren, A.M.: Synthesis 2898–2902 (2003)
21. Blaszykowski, C., Harrak, Y., Brancour, C., Nakama, K., Dhimane, A.-L., Fensterbank, L., Malacria, M.: Synthesis 2037–2049 (2007)
22. Ramachary, D.B., Mondal, R., Venkaiah, C.: Org. Biomol. Chem. **8**, 321–325 (2010)

Chapter 4
Approach Toward the Total Synthesis of Lundurines

4.1 Introduction

4.1.1 The Importance of the Indole Nucleus: An Overview

Heterocyclic compounds are cyclic derivatives that have a least one non-carbon atom in the ring system. Specifically, indole is an important heterocyclic system characterized by a benzene ring fused to a pyrrole. Indole is obtained from coal tar or certain plants and produced by bacterial degradation of tryptophan in the intestine. Nonetheless, it has a flowery smell at very low concentrations, and is used in perfumery. In 1866, Adolf von Baeyer achieved the first isolation of indole, during the decomposition of indigo dye [1]. Since then, the indole scaffold is probably one of the most commonly occurring structural subunits among natural products and pharmaceutically important compounds, and is crucial for the discovery of new drugs [2–7].

The importance of the indole ring lies in its presence in many alkaloids. Indole alkaloids are presenced in more than 4,100 different known compounds (Fig. 4.1). Many of them possess significant biological activity (e.g. antifungal, insecticidal) and some of them are used in medicine (e.g. antitumor, opioid antagonist, anticancer, antiHIV) [8]. The action of some indole alkaloids has been known for ages. Aztecs and Mazatecs referred to psilocybin mushrooms, which contain alkaloids psilocybin and psilocin, as genius, divinatory, and wondrous mushrooms. In fact, they have psychedelic and hallucinogenic properties. Around 1000 BC, the flowering plant *Rauwolfia serpentina* was used in Indian medicine due to the antipsychotic and antihypertensive properties of reserpine. In Nigeria, people accused of a crime were forced to drink an infusion of Calabar bean seed, which contains physostigmine. Rejection by the stomach was regarded as a sign of innocence. Otherwise, the person was killed by heart and lung paralysis.

Part of these results have been published in: Ferrer, C., Escribano-Cuesta, A., Echavarren, A. M.: *Tetrahedron*, **65**, 9015–9020 (2009).

A. Escribano Cuesta, *New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids*, Springer Theses, DOI: 10.1007/978-3-319-00702-1_4,

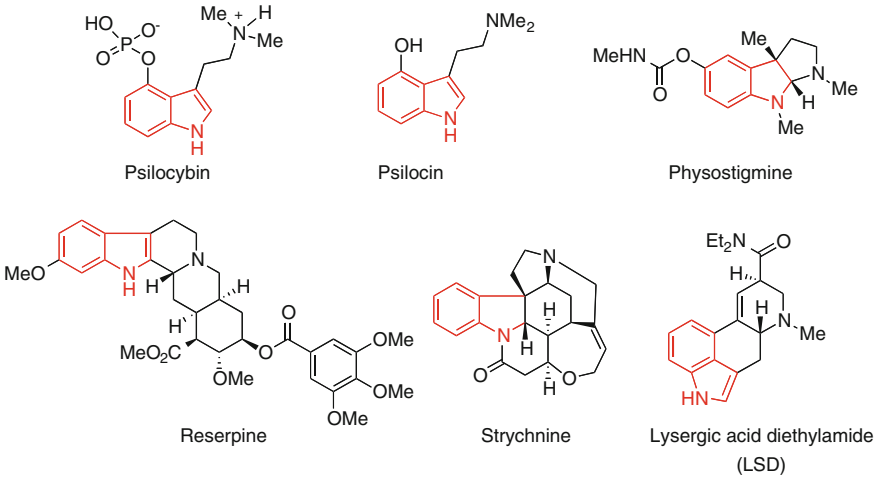


Fig. 4.1 Several examples of indole and indoline alkaloids

Strychinine was the first alkaloid isolated by Pierre Joseph Pelletier and Joseph Bienaimé Caventou in 1818, from the plants of the *Strychnos genus*. The structure was first determined in 1946 by Sir Robert Robinson, and in 1954 it was synthesized by Robert B. Woodward [9]. This is one of the most famous synthesis in the history of organic chemistry. Strychnine is a very well known compound, due to its powerful poisonous activity. Moreover, one of the most famous non-natural indole alkaloid derivatives is lysergic acid diethylamide (LSD), which was synthesized in 1938 by Albert Hofmann. LSD was a popular psychedelic drug in the 1960s and 1970s.

4.1.2 Indoloazocine Framework: Important Indole Alkaloids

Indoloazocine core is formed by the fusion of an eight-membered *N*-containing azocine ring with the indole nucleus (Fig. 4.2).

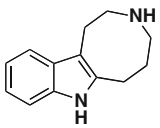


Fig. 4.2 Indoloazocine skeleton

This ring system is present in some indole alkaloids such as deoxyisoaustamide [10–12], okarimine N [13, 14], balasubramide [15, 16], lundurines [17, 18], appericine [19], and ervaticine (or conolidine) (Fig. 4.3) [20, 21].

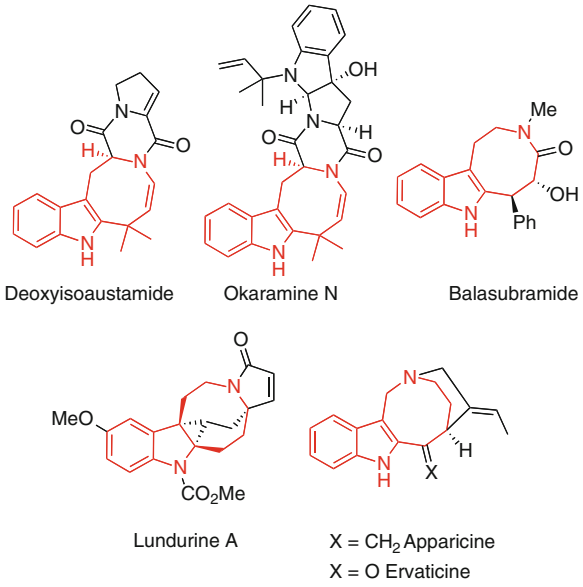


Fig. 4.3 Indole alkaloids containing the indoloazocine core

Traditionally, synthetic approaches toward this framework were characterized by a lack of generality, involving poorly available starting material that require multistep synthetic transformations [22–25]. More recent approaches include tandem cleavage of hydrogenated β-and α-carbolines [26], ring closing metathesis [27], and metal-catalyzed Friedel–Crafts-type reactions of indole derivatives with several electrophiles (such as alkynes, alkenes or epoxides) (see Refs. [118] and [133] in Chap. 1; [28–32]).

4.1.3 Lundurines A–D

Lundurines A–D [17, 18] are a new type of indole alkaloids characterized by the presence of a cyclopropyl moiety embedded within a hexacyclic ring system that includes a 1*H*-azocine[5,4-*b*]indole ring unit (Fig. 4.4).

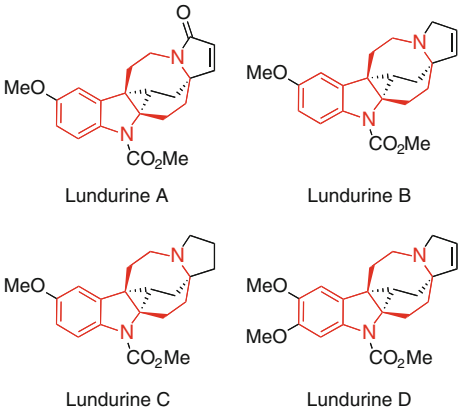


Fig. 4.4 Structures of lundurines

These novel dihydroindole derivatives have been isolated from plants of the genus *Kopsia*, and have proven to be rich sources of novel alkaloids with intriguing carbon skeletons that display a wide variety of interesting activities.[1]

In particular, lundurines B and D have shown significant in vitro cytotoxicity toward B16 melanoma cells, being lundurine B the one displaying the highest potency (IC_{50} 2.8 μl/mL). Moreover, lundurine B is also effective in circumventing multidrug resistance in vincristine-resistant KB cells. To date only three approaches toward the total synthesis of lundurines A–D have been reported (see Ref. [133] in Chap. 1 [37, 38]). Furthermore, various approaches toward related indoloazocine compounds have been published (in the next section, these syntheses will be briefly reviewed).

In Fig. 4.5, other examples of indole alkaloids isolated from the genus *Kopsia* are depicted [36, 39–41]. In particular, the indoloazocine derivative lapideilectine B has been synthetized by Pearson and coworkers in 23 linear steps [42, 43].

[1] Lead references on indole alkaloids form genus *Kopsia*: Subramaniam et al. [33, 34], Kam et al. [35], Awang et al. [36].

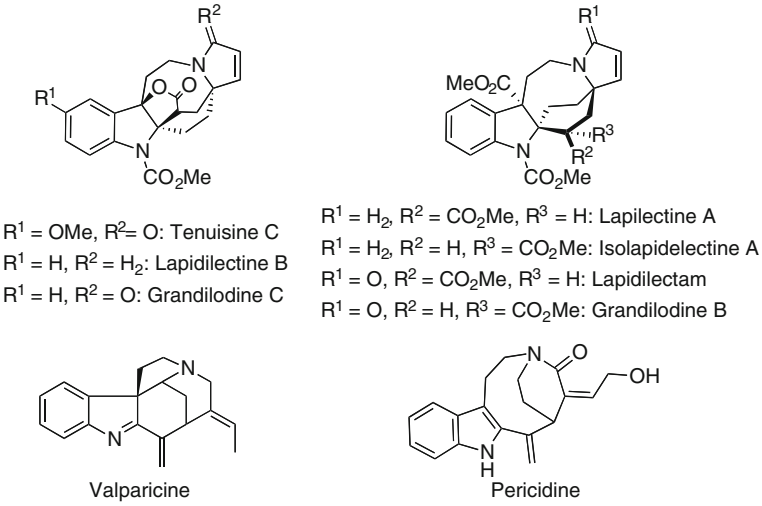
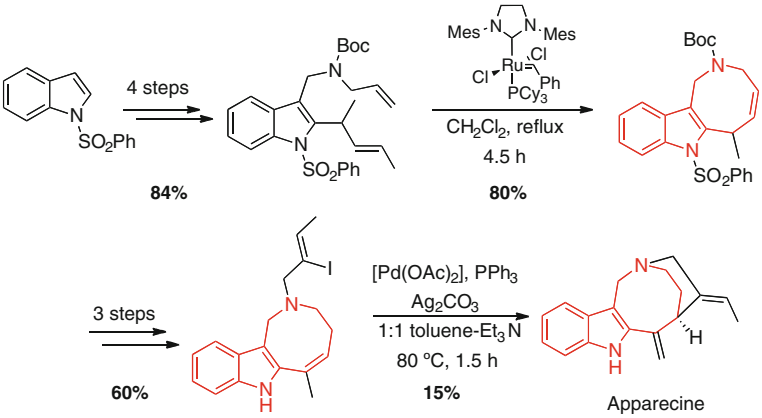


Fig. 4.5 Structures of indole alkaloids present in plants of genus Kopsia

4.1.4 Synthesis of Other Indoloazocine Derivatives

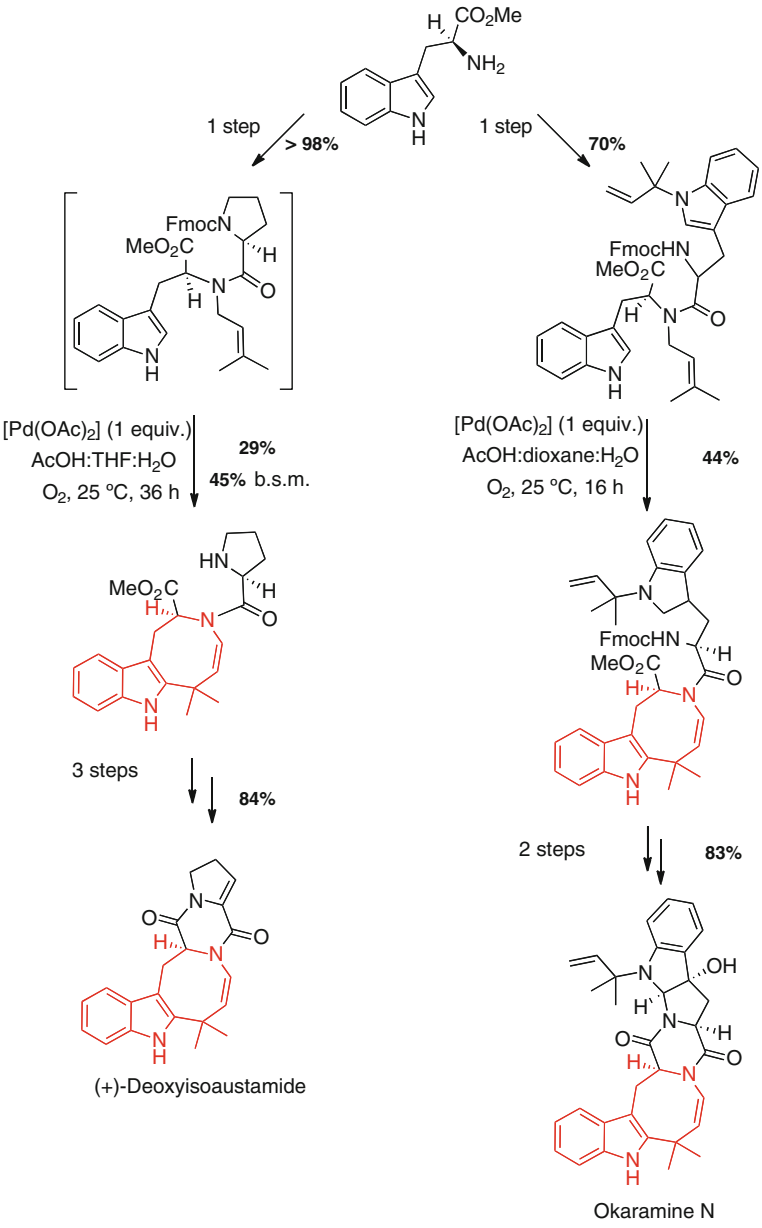
The importance of indoloazocine scaffold in indole alkaloids has been supported by several methodologies and total syntheses published through the years. One example is the total synthesis of (±)-apparicine by the Bennesar group (Scheme 4.1). Indeed, the indoloazocine scaffold was synthesized via an indole-template ring-closing metathesis reaction. Another key step was the Heck cyclization to finally assemble the bridged skeleton [27].

A major contribution toward the synthesis of indoloazocine skeletons is based on metal-mediated Friedel–Crafts-type reaction of indole derivates with several



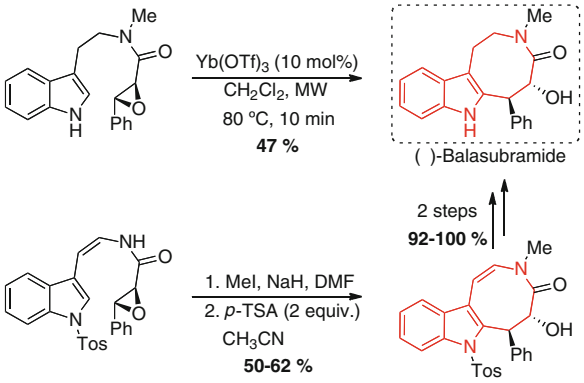
Scheme 4.1 Total synthesis of (±)-apparicine

electrophiles. In this context, Baran and Corey developed an impressive palladium-mediated transformation of *N*-prenylated tryptophan derivatives allowing the synthesis of the dihydroindoloazocine tricycle in one step. This straightforward methodology was applied to the total synthesis of (+)-deoxyisoaustamide [28] and okaramine N [40] in a remarkably short synthetic route (Scheme 4.2).



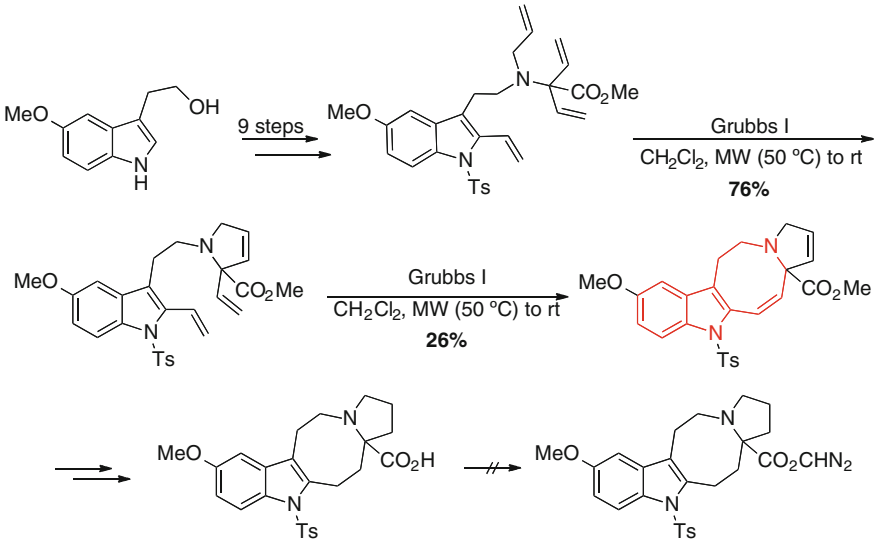
Scheme 4.2 Total synthesis of (+)-dexoxyisoaustamide and okaramine N

Another possibility is based on a biomimetic approach, a stereoselective 8-*endo*-epoxide-indole cyclization. Using this methodology, the Kerr group has reported the synthesis of (−) or (+)-balasubramide using ytterbium triflate as the catalyst [15], while the Zhang group used *p*-toluenesulfonic acid (*p*-TSA) [16] (Scheme 4.3).



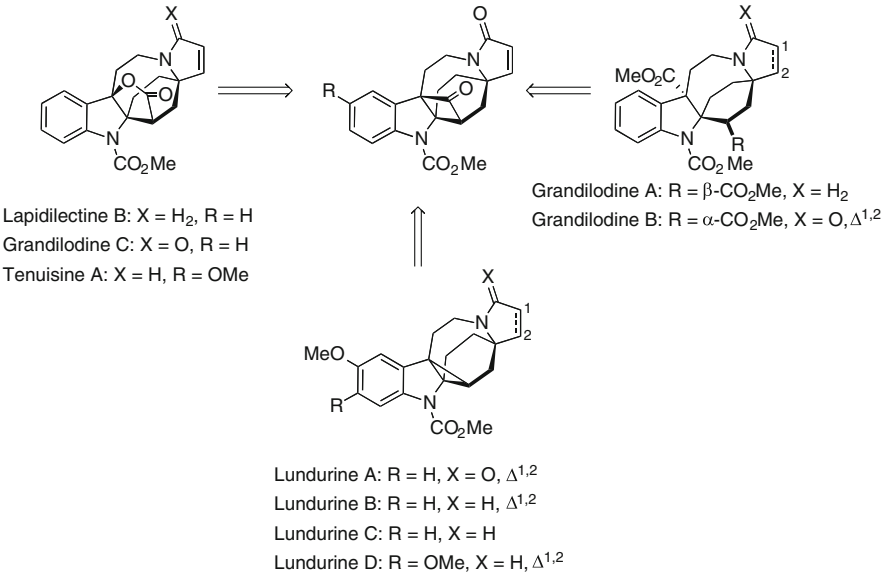
Scheme 4.3 Synthesis of balasubramide

In addition, the Martin group has reported the synthesis of the tetracyclic core of the lundurine by a double ring-closing olefin metathesis to form the five- and eight-membered ring (Scheme 4.4) [37]. This group also reported the synthesis of the tetracyclic framework of lundurine B in a racemic manner, even though all attempts to synthesize diazoketone, which allows the formation of the cyclopropyl moiety, were unsucessfull.



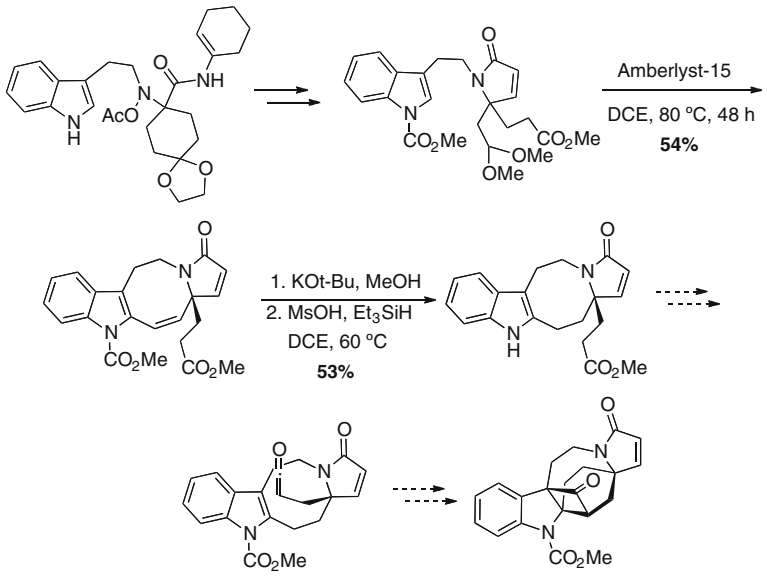
Scheme 4.4 Synthesis of the tetracyclic framework of lundurine B

Very recently, synthetic studies toward lapidilectine-type *Kopsia* alkaloids have been developed by Sarpong and co-workers [38]. They proposed a unified strategy for the synthesis of *Kopsia* alkaloids from a common cyclobutanone intermediate. This intermediate could be transformed in lapidilectine B, grandilodine C and tenuisine C by Baeyer–Villiger oxidation or in lundurines A–D using a C–C bond activation/decarboxylation sequence. Furthermore, a selective carbanion formation, which would open the γ-lactone moiety in lapilectine B and grandilodine C, could lead to grandilodine A and B. A carboxylation of lundurines instead could give rise to related tenuisine alkaloids (Scheme 4.5).



Scheme 4.5 Common intermediate for the synthesis of Kopsia alkaloids

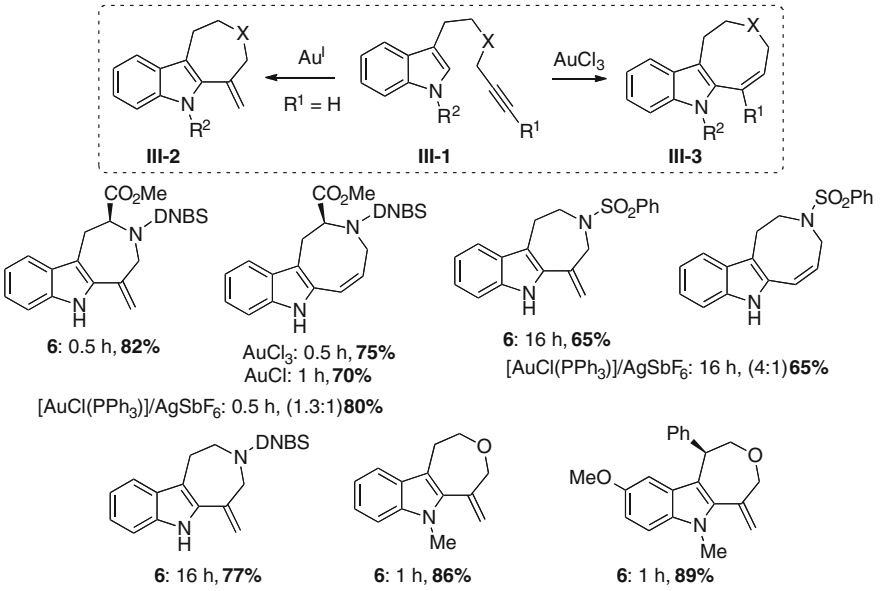
In Scheme 4.6 is shown the syntesis of the tetracyclic core of *Kopsia* alkaloids, which are related to lapidilectine. An Ugi four-component coupling allowed the synthesis of the β-aminoamide adduct from simple starting material. After several steps, a Fridel-Crafts-type transformation of dimethyl acetal using Amberlyst-15 led to the tetracyclic main core in a 54 % yield. Then, cleavage of the carbamate and selective removal of the alkene group gave indoloazocine compound. As an endgame scenario, they proposed that the methyl ester would be activated to form a ketene genaration/cycloaddition, which would provide the cyclobutanone intermediate.



Scheme 4.6 Key step of the synthetic studies toward lapidilectine-type alkaloids

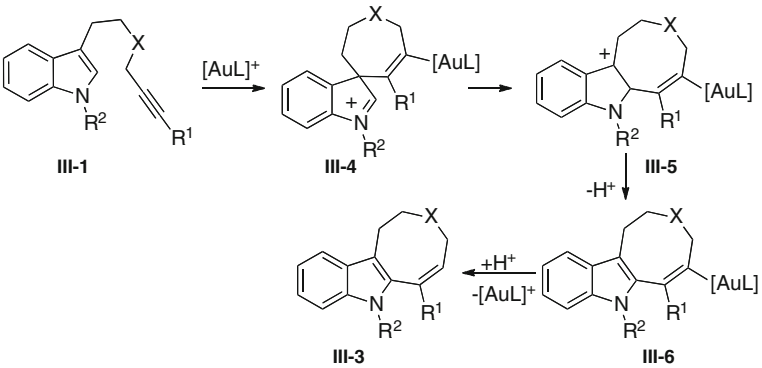
4.1.5 Gold-Catalyzed Reaction of Indoles with Alkynes

As part of our investigation of the hydroarylation of alkynes (or alkenylation of arenes) catalyzed by electrophilic transition metal complexes, our group reported the intra- and intermolecular reaction of indoles with alkynes catalyzed by gold (see Ref. [118, 133] in Chap. 1). Thus, alkynylindole **III-1** cyclizes readily in the presence of a cationic gold(I) complex to give azepino[4,5-*b*]indole derivative **III-2**, whereas the use of $AuCl_3$ leads to indoloazocine **III-3** by a 8-*endo-dig* process, this cyclization mode has not been observed in other hydroarylation of alkynes (Scheme 4.7). Under certain forcing conditions, allenes and tetracyclic compounds were also obtained (see Refs. [118, 133] in Chap. 1).



Scheme 4.7 7-*exo-dig* versus 8-*endo-dig* cyclization of alkenylindoles **III-1**

The proposed mechanism for the formation of the eight-membered ring compound starts with an initial activation of the triple bond, followed by a gold-catalyzed cyclization at the C3 position of the substituted alkynylindole **III-1** to form the seven-membered ring iminium cation **III-4** (Scheme 4.8). 1,2-Migration and proton loss then lead to **III-6**, from which the eight-membered ring compound **III-3** is formed by protodemetalation.



Scheme 4.8 Mechanism for the 8-*endo-dig* cyclization of alkenylindoles **III-1**

The formation of the spiro intermediate **III-4** is suggested by the isolation of spiro compounds during the study of the reaction. Similar intermediates are probably involved in the 7-*exo-dig* cyclization. In this case, intermediates of type **III-7** could be formed directly by a Friedel–Crafts-type reaction, or indirectly, by opening of cyclopropyl carbenes **III-8** at C–C bond *a* (Fig. 4.6).

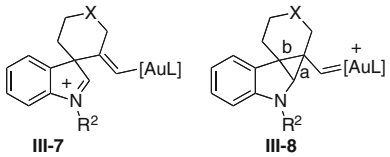
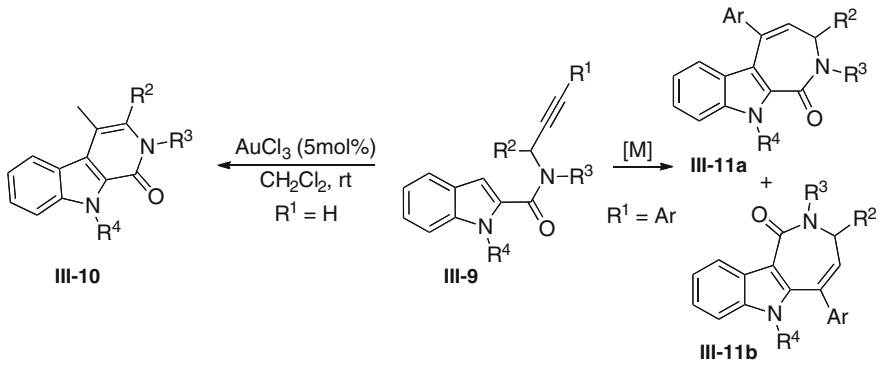


Fig. 4.6 Proposed intermediates in the 7-*exo-dig* cyclization of alkynylindole **III-1**

The Padwa group has reported the synthesis of substituted *β*-carbolines **III-10** via gold(III)-catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides **III-9** (R^1 = H) (Scheme 4.9) [44, 45]. Alkyne-substituted *N*-propargylindole-2-carboxamides **III-9** (R^1 = Ar) also cyclized to form azepino[3,4-*b*]insol-1-ones **III-11** using AuCl, $AuCl_3$, and $PtCl_2$ [46].



Scheme 4.9 6-*exo-dig* versus 7-*endo-dig* cyclization of alkenyl indoles **III-9**

The intermolecular reaction of indoles with alkynes and alkynyl alcohols takes place with gold(I), see Ref. [118] in Chap. 1, [47], gallium(III) [48], or platinum(II)[49] as catalysts. A remarkable transformation involving the indole nucleus was found by Zhang, who reported the formation of tetracyclic 2,3-indoline-fused cyclobutanes from propargylic 3-indoleacetates via sequential 3,3-rearrangement and [2+2] cycloaddition [50, 51]. Gold-catalyzed cascade and tandem cyclization of indole derivatives with alkynes have been applied to the formation of dihydrocyclohepta[*b*]indole [52], teracyclic indolines [53], 3-allenylindole derivatives [54], and indene-containing indole scaffolds through a new 1,2-indole migration [55]. A direct method has been developed by the Fujii group, which allows the

formation of aryl-annulated[*a*]carbazoles and azepinoindole derivatives from anilindiyne derivatives, through a gold-catalyzed cascade reaction [56]. Recently, the synthesis of functionalized carbazoles was achieved through gold-catalyzed deacylative cycloisomerization of 3-indolynes [57].

4.2 Objective

Lundurines are a new type of indole alkaloids, which are characterized by an unusual carbon skeleton (Fig. 4.7) [17, 18]. In addition, lundurines B and D have displayed in vitro cytotoxicity towards B16 melanoma cells (lundurine B: IC_{50} 2.8 μl/mL), and lundurine B is also proved effective in circumventing multidrug resistance in vincristine-resistant KB cells.

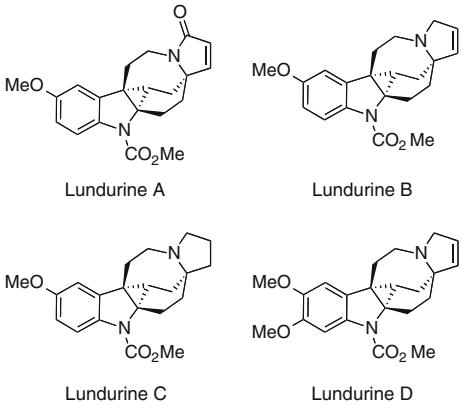
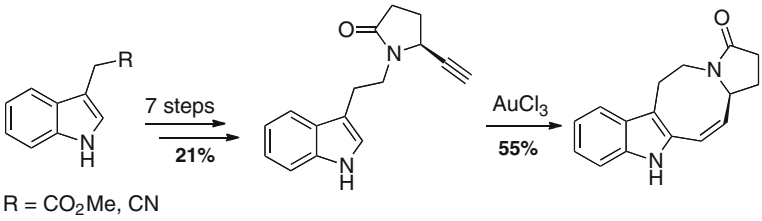


Fig. 4.7 Structures of lundurines A-D

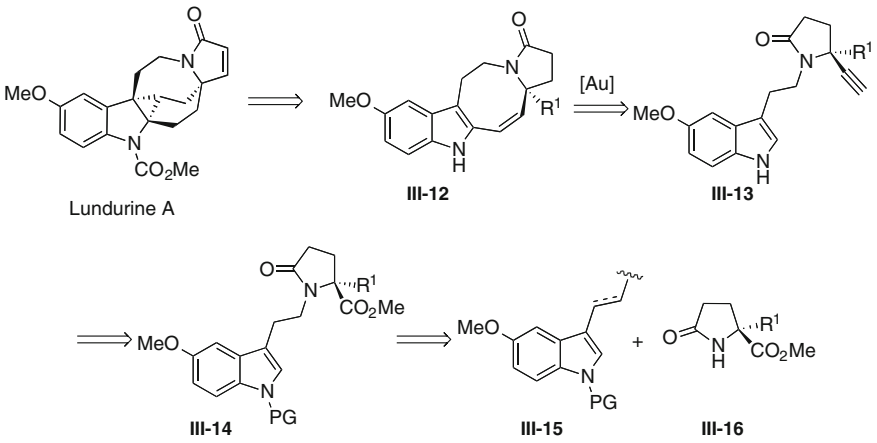
The main tetracyclic core of these alkaloid compounds has been synthesized by applying the methodology developed in the group for the intramolecular reaction of indoles with alkynes catalyzed by gold complexes (Scheme 4.10) (See Ref. [118] and [133] in Chap. 1), Thus, based on previously reported results, our objective was to develop an efficient approach toward the total synthesis of lundurines.



Scheme 4.10 Previous results for the synthesis of the tetracyclic core of lundurines

4.3 Results and Discussion

We decided to center our work on the synthesis of lundurine A. The retrosynthetic analysis that we envisioned for this compound is depicted in Scheme 4.11.



Scheme 4.11 Retrosynthetic analysis of the synthesis of lundurine A

Lundurine A could be synthesized from indoloazocine **III-12** after cyclopropanation of the indole ring.[2,3] The intermediate **III-12** would be formed by gold(III)-catalyzed cyclization of the alkynylindole **III-13**, (See Ref. [118] and [133] in Chap. 1) which arises from **III-14** upon conversion of the ester group into a homologated alkyne.[4] Compound **III-14** would be assembled from an enantiomerically pure pyroglutamic ester derivative **III-16** and an indole derivative **III-15**.[5]

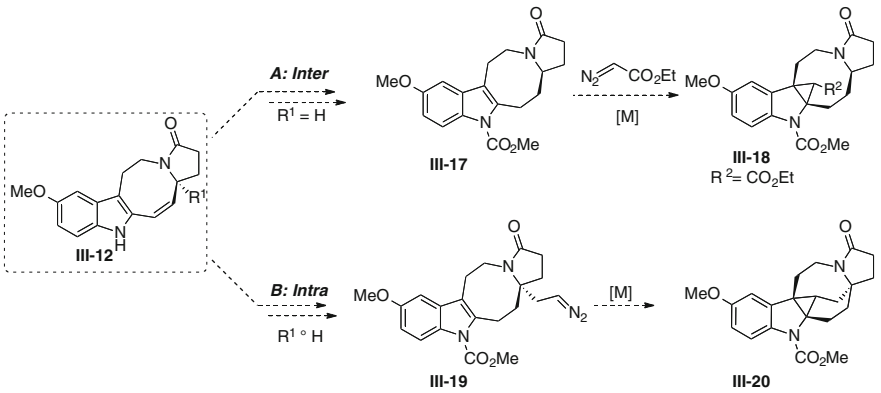
Two approaches were considered for the cyclopropanation reaction from **III-12** derivatives (Scheme 4.12): the intermolecular (A) and intramolecular (B).

[2] General review about cyclopropanation: Lebel et al. [58].

[3] General review about indole cyclopropanation: Zhang et al. [59].

[4] General review about conversion of carbonyl compounds to alkynes: Habrant et al. [60].

[5] General reviews about metal-catalyzed approaches to amide bond formation: Joullié and Lassen [61], Allen and Williams [62].



Scheme 4.12 Inter- and intramolecular strategies

In the intermolecular approach, the cyclopropylindole **III-18** would be formed after metal-catalyzed cyclopropanation of **III-17** with ethyl diazoacetate (EDA) [63–69]. In the intramolecular approach, cyclopropylindole **III-20** would be obtained from the diazoindole **III-19** [70–80].

4.3.1 Intermolecular Approach

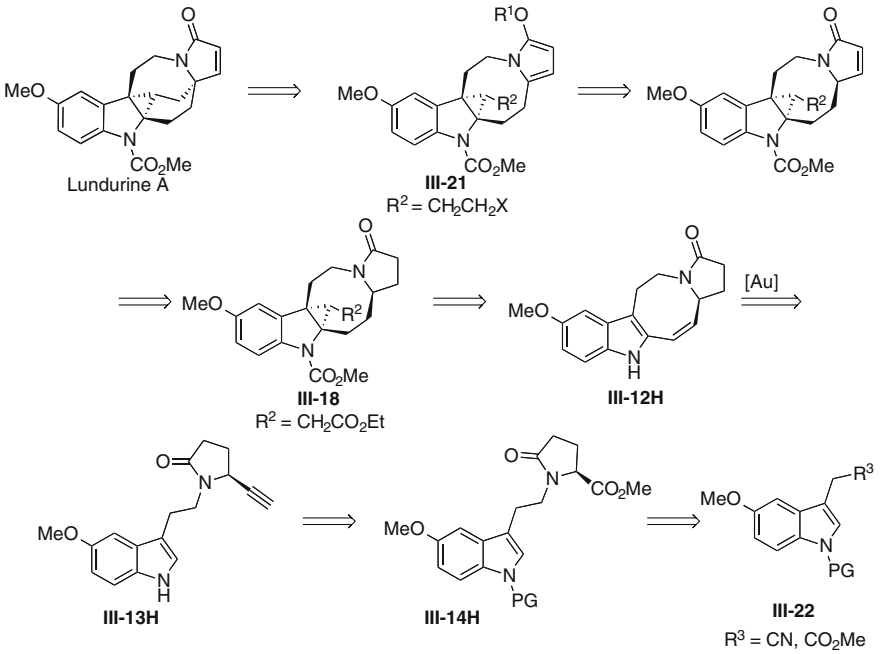
In this strategy toward the total synthesis of lundurine A (Scheme 4.13), the key steps involved are:

1. The condensation of **III-22** with dimethyl (*L*)-glutamate by reductive amination, followed by in situ lactamization to give **III-14H.**
2. Transformation of the remaining methyl ester group into the alkyne **III-13H** via the corresponding aldehyde [60].
3. Gold-catalyzed 8-*endo-dig*-cyclization to give **III-12H** (see [118, 151–155] in Chap. 1).
4. Catalytic hydrogenation of the alkene and formation of the carbamate, followed by metal-catalyzed cyclopropanation of the indole with EDA to stereoselectively form **III-18** [63–69].
5. Reduction of the ester to the alcohol (R^2), installation of the double bond in the lactam ring [81–84], and formation of the pyrrole-based silyl dienol ether **III-21**.[6,7,8] The final C–C bond in the lundurine A could be formed by intramolecular regioselective γ-alkylation of the pyrrole **III-21**in the presence of a Lewis acid [88].

[6] First example of synthesis and reactivity of pyrrole-based silyl dienol ether: Fiorenza et al. [85].

[7] Selected reviews: Rassu et al. [86, 87].

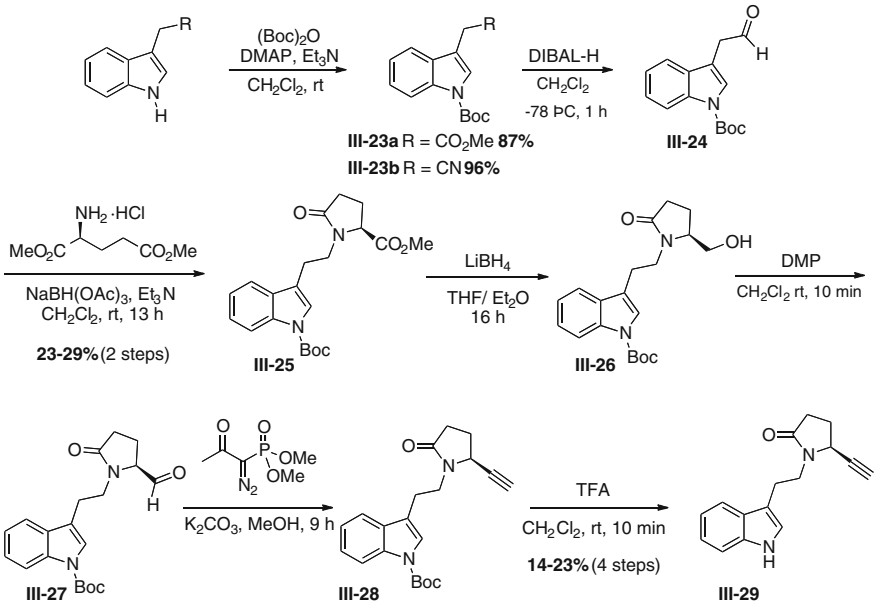
[8] Synthesis and γ-alkylation of pyrrole-based silyl dienol ether: Zanardi et al. [88].



Scheme 4.13 Retrosynthetic analysis of the intermolecular strategy

4.3.1.1 Synthesis of Alkynylindole

In order to obtain a suitable enantiomerically pure precursor for the synthesis of lundurine A, we started with the preparation of alkynylindole **III-29** following synthetic sequence shown in Scheme 4.14 [257]. Methyl 2-(1*H*-indol-3-yl)acetate was protected as a Boc-carbamate [89], which was reduced with DIBAL-H at low temperature to give aldehyde **III-24**. When we carried out the reductive amination of this aldehyde with dimethyl (*S*)-glutamate and triacetoxyborohydride, we observed the formation of lactam **III-25** in low yield, by in situ lactamization. Alternatively, aldehyde **III-24** could also be prepared from 2-(1*H*-indol-3-yl) acetonitrile [90, 91].



Scheme 4.14 Synthesis of alkynylindole **III-29**

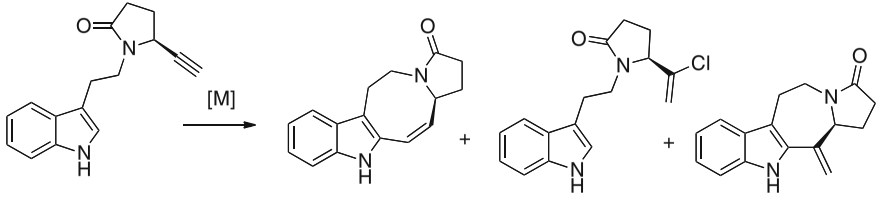
Ester **III-25** was reduced to alcohol **III-26** using lithium borohydride [92]. Alternatively, alcohol **III-26** could also be prepared using sodium borohydride and calcium chloride, but a with longer reaction time (1–2 days) [93–95]. When lithium aluminium hydride was used, competitive reduction of the lactam was also observed, even at low temperatures.

Dess–Martin oxidation of alcohol **III-26** gave aldehyde **III-27**, which was used in the next step without further purification. Aldehyde **III-27** reacted with the Bestmann–Ohira reagent [96–101] to give alkyne **III-28**, from which alkynylindole **III-29** was obtained by Boc cleavage after a brief exposure to trifluoroacetic acid. This four step procedure can be routinely carried out without purification of any intermediate in 14–23 % overall yield. Alternatively, alkyne **III-29** could be prepared from aldehyde **III-27** by the Corey-Fuchs procedure, although the overall yield was lower using this procedure [102].

4.3.1.2 Gold-Catalyzed Cyclization of Alkynylindole

Alkynylindole **III-29** cyclized in the presence of $AuCl_3$ at room temperature to give indoloazocine **III-30** as the major product in a 55 % isolated yield (Table 4.1, entry 1). Indoloazocine **III-30** contains the tetracyclic core present in lundurine A. Traces of vinyl chloride **III-31**, which is the product of Markonikov gold-catalyzed hydrochlorination in this reaction [103–105], were also observed using $AuCl_3$.

Table 4.1 Gold-catalyzed cyclization of alkynylindole **III-29**



III-29 **III-30** **III-31** **III-32**

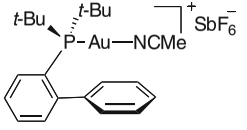
Entry	*[M]*	*Conv. (%)*	*Products (ratio)*	*Yield (%)*
1	$AuCl_3$	100	**III-30** : **III-31** (ca. 95:5)	55
2	**22**	66	**III-30**	34[a]
3	$HAuCl_4$	100	**III-30**	30[a]
4	$NaAuCl_4$	100	-[b]	–
5	**21**	82	**III-30** + **III-32** (61:39)	–
6	**25**	82	**III-30** + **III-32** (78:22)	–
7	**6**	80	**III-30** + **III-32** (27:73)	–
8	**15**	54	**III-30** + **III-32** (27:73)	-
9	**20**	100	**III-30** + **III-32** (13:87)	-
10	AuCl	82	**III-30**	42[a]
11	**24**	13	**III-30**	−17
12	$AgSbF_6$	100	**III-30**	
13	AgOTf	29	**III-30**	–
14	$GaCl_3$	–[c]	**–**	

(continued)

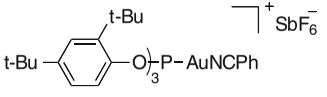
Table 4.1 (continued)

Entry	*[M]*	*Conv. (%)*	*Products (ratio)*	*Yield (%)*
15	$InCl_3$	–[c]	–[d]	–
16	TfOH	–[c]	–	–

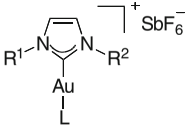
Reaction carried out with 5 mol % [M] in CH_2Cl_2 at room temperature for 24 h. [a] Determined by NMR using 1,3,5-trimethoxybenzene as standard
[b] Complex mixture
[c] Conversion < 5 %
[d] Traces of **III-30** were observed



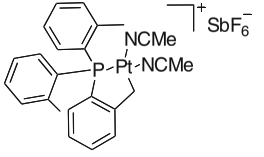
6



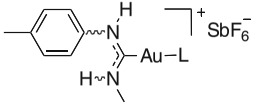
20



14: R^1 = Me, R^2 = Et, L = 2,4,6-$(MeO)_3C_6H_2CN$
15: $R^1 = R^2$ = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$
16: $R^1 = R^2$ = 2,6-i-$Pr_2C_6H_3$, L = PhCN



24



21: L = 2,4,6-$(MeO)_3C_6H_2CN$

The cyclization was less efficient using gold(III) complex **22** or $HAuCl_4$ as catalyst (Table 4.1, entries 2 and 3). In the case of $NaAuCl_4$, formation of a complex mixture was observed (Table 4.1, entry 4). Surprisingly, complex **21** and $[Au(NCMe)(PPh_3)]SbF_6$ (**25**) also favored the 8-*exo-dig* cyclization leading to indoloazocine **III-30** as the major product (Table 4.1, entry 5 and 6).

Alternatively, the 7-*endo-dig* cyclization, which afforded the azepinoindole **III-32** as the major product, was favored with related gold(I) complex **6**, bearing a bulkier phosphine, or IMes gold(I) complex (**15**) (Table 4.1, entries 7 and 8). Similar selectivity was observed using phosphite gold(I) **20** (Table 4.1, entry 9). As expected, higher conversions were observed with the gold(III) complexes and phosphite gold(I) complex **20**, both more electrophilic (Table 4.1, entries 1, 3, 4 and 9) and, in consequence, more reactive. On the other hand, lower conversions were achieved with the more electron-rich complexes, bearing electron-donating ligands like IMes gold(I) (**15**), which are less reactive.

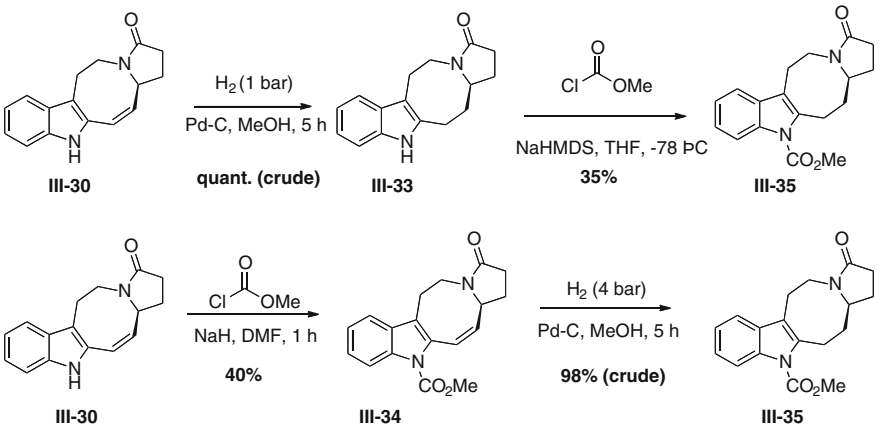
As was also observed that AuCl favored the formation of indoloazocine **III-30** (Table 4.1, entry 10) (see Ref. [118] in Chap. 1). On the other hand, only low conversion was achieved with cationic platinacycle **24** (see Ref. [29] in Chap. 1, Table 4.1, entry 11). Low yields of indoloazocine **III-30** were obtained using silver(I) salts such as $AgSbF_6$ and AgOTf [106] whereas, $GaCl_3$, $InCl_3$, and Brønsted acid (TfOH) were not effective (Table 4.1, entries 12–16).

The fact that very similar results were obtained using $AuCl_3$ and AuCl (Table 4.1, entries 1 and 10) suggests that gold(III) might be reduced to gold(I) under the reaction conditions [107]. Moreover, these results suggest that steric factors control the *exo* versus *endo* selectivity in this cyclization. Gold complexes bearing bulky ligands such as phosphine gold(I) **6**, IMes gold(I) **15** and phosphite gold(I) complex **20** (Table 1, entries 7–9) favor the 7-*exo-dig* pathway, whereas less bulky ligands favor the 8-*endo-dig* pathway (Table 4.1, entries 1–5 and 10–13).

4.3.1.3 Synthesis of Precursors for the Intermolecular Cyclopropanation

For the study of the cyclopropanation reaction, the precursor **III-35** was synthesized following two different pathways (Scheme 4.15):

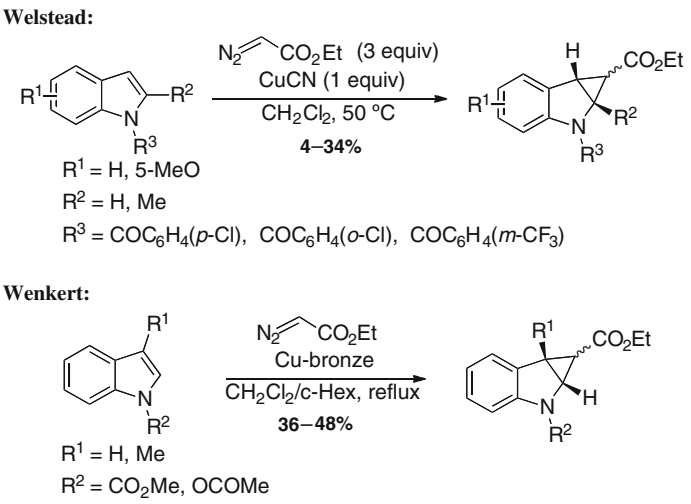
1. First, hydrogenolysis of indoloazocine **III-30**, followed by protection as methyl carbamate **III-35** using methyl cloroformate and NaHMDS, as base, in THF [108].
2. Protection as methyl carbamate **III-34** using methyl chloroformate and sodium hydride [109], and subsequent hydrogenolysis. In this case, a higher hydrogen pressure (4 bar) was needed to afford complete conversion.



Scheme 4.15 Synthesis of precursor **III-35**

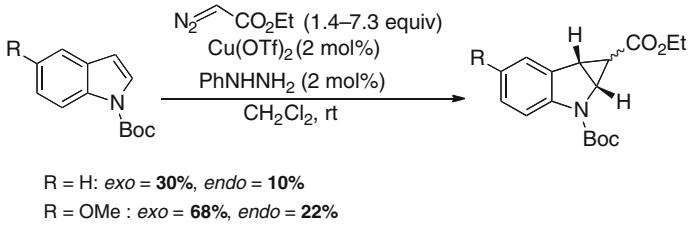
4.3.1.4 Study of Cyclopropanation Reaction

For the study of the cyclopropanation reaction of indoles with diethyl diazoacetate (EDA), we were inspired by the pioneering work of Welstead [63] and Wenkert [64]. They found that the deactivation of the indole nucleus, through electron-withdrawing substituents at N1, allows the addition of carbene moiety into the 2,3-double bond without the competitive rearrangement that leads to the C–H insertion product (Scheme 4.16).



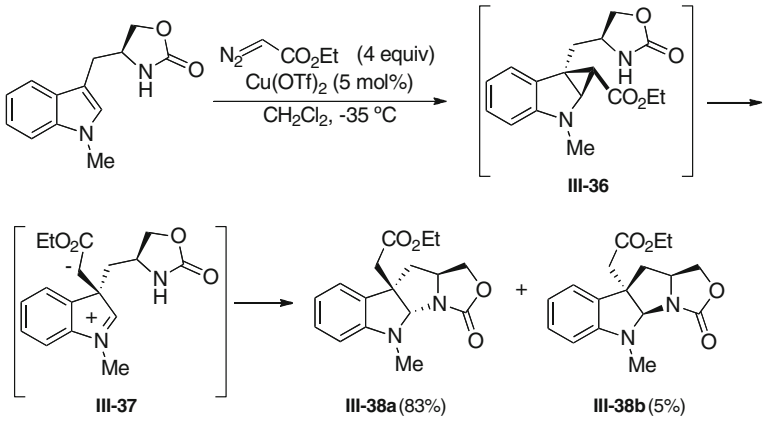
Scheme 4.16 Welstead and Wenkert results

In 1993, Reiser improved the yield toward the cyclopropanated adducts using copper(I) complex and Boc-protected indoles (Scheme 4.17) [65].



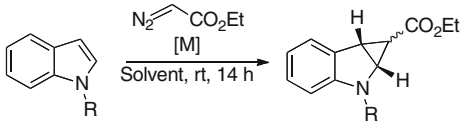
Scheme 4.17 Reiser results

More recently, Qin has developed a new cascade reaction to afford 3-substituted hexahydropyrroloindole **III-38** [67]. The key steps are the formation of a cyclopropane intermediate **III-36** and the consecutive nucleophilic attack of a pendant amine on the C=N bond of the resulting indolenium **III-37** (Scheme 4.18). This methodology has been applied for the total synthesis of (-)-ardeemin. [69]



Scheme 4.18 Qin results

We first decided to optimize the reaction conditions using simple indoles as a models (Scheme 4.19).

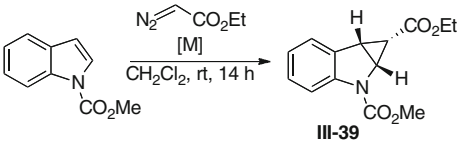


Scheme 4.19 Screening of conditions for the cyclopropanation reaction

To determine the best conditions several variables were tested, such as solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, $CHCl_3$, and $MeNO_2$), number of equivalents of EDA (1.1, 4.0 and 7.0 equiv), R of the indole (CO_2Me, Boc and H), and the order of addition of the reagents. Among the conditions screened, the best results were obtained using CH_2Cl_2 with 7.0 equiv of EDA and methyl carbamate (CO_2Me) as protecting group. In agreement with the published results, we also observed the importance of the protecting group at the indole moiety, where electron-donating groups favor the formation of *β*-alkylation products, while the electron-withdrawing groups favor the formation of the cyclopropane products [68, 110]

The use of metal complexes in cyclopropanation reactions allows the formation of metal carbenes or carbenoids, which are endowed with increasing stability, in comparison to free carbene. Although most of these metal carbenes and carbenoids are highly electrophilic, their reactivity profile is dependent on the metal [68]. Thus, for the cyclopropanation of methyl 1*H*-indole-1-carboxylate with EDA (Table 4.2), the best yield was observed using 5 mol % of $[Cu(hacac)_2]$ (hfacac = hexafluoroacetylacetonato) [110] as catalyst in CH_2Cl_2 at room temperature, affording the desired cyclopropanated product **III-39** in 72 % yield (Table 4.2, entry 1). The reaction was less efficient with $[Rh_2(OAc)_4]$, $Cu(OTf)_2$ and CuOTf (Table 4.2, entries 2–4).

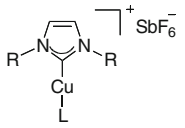
Table 4.2 Cyclopropanation of indole **III-39** with diethyl diazoacetate



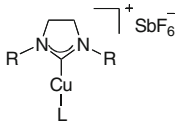
III-39

Entry	*[M]*	*Conv. (%)*	*Yield[a] (%)*
1	$[Cu(hfacac)_2]$	87	72
2	$[Rh_2(OAc)_4]$	100	56
3	$Cu(OTf)_2$	50	33
4	$(CuOTf)_2{\cdot}C_6H_6$	51	23
5	**26**	45	23
6	**27**	49	27
7	**29**	53	22
8	**28**	47	16
9	**30**	0	0

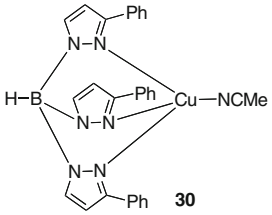
Reaction carried out with 7 equiv of EDA, 5 mol % [M] in CH_2Cl_2 at room temperature for 14 h.
[a] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard



26: R = 2,6-*i*-$Pr_2C_6H_3$, L = MeCN
27: R = 2,4,6-$Me_3C_6H_2$, L = MeCN



28: R = 2,6-*i*-$Pr_2C_6H_3$, L = MeCN
29: R = 2,4,6-$Me_3C_6H_2$, L = MeCN

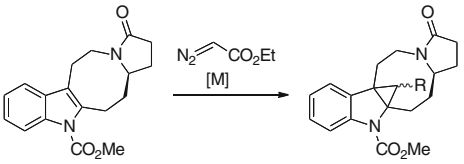


30

As expected, low yields were obtained with cationic NHC copper(I) complexes[111] (Table 2, entries 5–8), which are less reactive but more stable [112]. Furthermore, no conversion was observed using hydrotrispyrazolylborate (Tp^{Ph}) complex **30** [113], although $Tp^{x}Cu(I)$ complexes have efficiently catalyzed the cyclopropanation of styrene with EDA in high to very high yields both under homogeneous and heterogeneous conditions [114]. Gold(I) complexes such as phosphine gold(I) **6**, IPr gold(I) **16** and phosphite gold(I) **20** were not effective in this cyclopropanation. Although copper(II) salts are often used as catalyst precursor in the cyclopropanation of alkenes, it has been demonstrated that copper(I) salts are the catalytically active species in these reactions [115]. Nonetheless, better yields were obtained with copper(II) compared to copper(I) complexes (Table 4.2, compare entries 1, 3–8).

Unfortunately, the cyclopropanation reaction of indoloazocine **III-35** with EDA catalyzed by several metal complexes failed in all cases (Table 4.3). [Cu(hfacac)$_2$], which gave the best yield with methyl 1*H*-indole-1-carboxylate, was ineffective with indole **III-35** (Table 4.3, entry 1). Also, [$Rh_2(OAc)_4$] was unproductive in this transformation (Table 4.3, entry 2).

Table 4.3 Cyclopropanation of indole **III-35** with diethyl diazoacetate



III-35 R = CO_2Et

Entry	*[M]*	*Conditions*	*Conv. (%)*
1	[Cu(hfacac)$_2$]	rt, 21 h	0
2	[$Rh_2(OAc)_4$]	rt, 21 h	0
3	$Cu(OTf)_2$	−35 °C, 14 h	0
4	$Cu(OTf)_2$	rt, 23 h	0
5	$(CuOTf)_2{\cdot}C_6H_6$	rt, 16 h	0
6	**27**	40 °C, 14 h	0
7	**15**	rt, 23 h	0

Reaction carried out with 7 equiv, of EDA, 5 mol % [M]

The conditions reported by the Qin group for the intermolecular cyclopropanation of 3-substituted hexahydropyrroloindole provided unsuccessful results (Table 4.3, entry 3) [65, 69]. Furthermore, no conversion was observed using $Cu(OTf)_2$, CuOTf, IME copper(I) **27** or IMes gold(I) **15** complexes as catalysts (Table 4.3, entries 3–7) [116, 117]. Only starting material was recovered under the optimized conditions. This is probably due to the higher steric hindrance of the indole **III-35**, in comparison with methyl 1*H*-indole-1-carboxylate, preventing the nucleophilic attack of the enamine moiety.

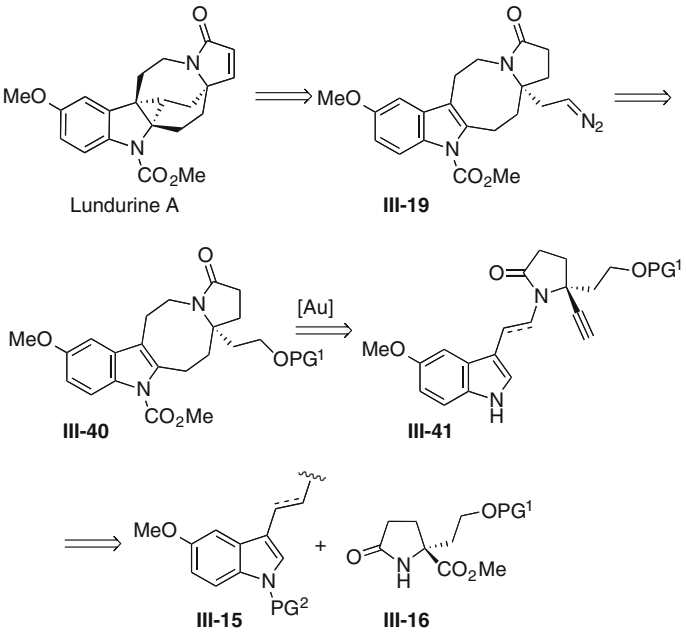
At this point, we decided to abandon the intermolecular approach, and focused our efforts on the intramolecular approach.

4.3.2 Intramolecular Approach

For this strategy, the key steps are described in Scheme 4.20:

1. The assembly of indole derivative **III-15** with an enantiomerically pure pyroglutamic ester derivative **III-16** [61, 62], followed by transformation of the ester moiety into an alkyne to afford alkynylindole **III-41** [60].

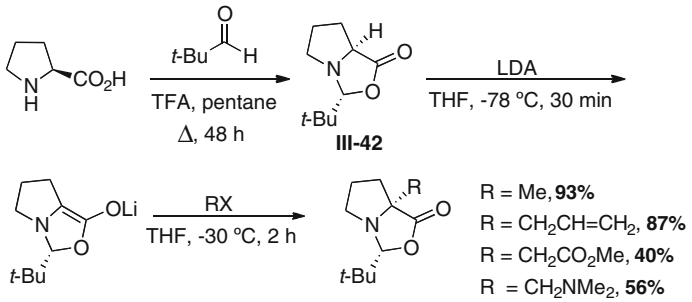
2. Gold-catalyzed 8-*endo-dig* cyclization, (see Refs. [118, 133] in Chap. 1) hydrogenation of the alkene and formation of the methyl carbamate to give indoloazocine **III-40**.
3. Finally, intramolecular cyclopropanation of diazo compound **III-19** [70–79] and formation of the α,β-unsaturated lactam to form lundurine A [80–83].



Scheme 4.20 Retrosynthetic analysis of the intramolecular strategy

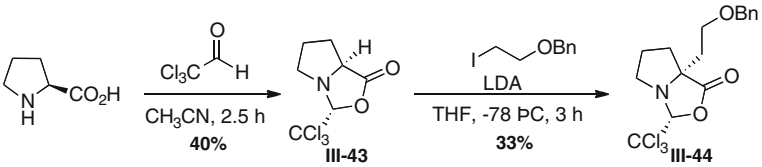
4.3.2.1 Synthesis of Substituted 2-Pyrrolidone

For the synthesis of 2-pyrrolidone **III-16**, we followed the procedure described by Germanas and coworkers for the enantioselective alkylation of proline [118]. This procedure was based on a method reported by Seebach [119], in which proline is condensed with pivaldehyde to give a single stereoisomer of 2-*t*-butyl-1-aza-3-oxabicylo[3.3.0]octan-4-one **III-42** [120], which is deprotonated with LDA to give a chiral enolate that can be alkylated with an electrophile (Scheme 4.21).



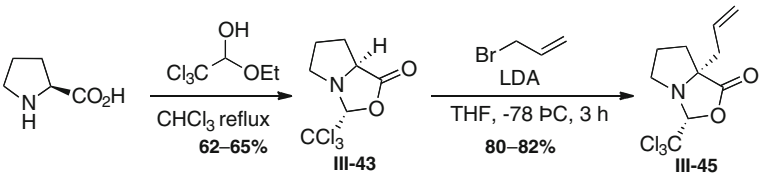
Scheme 4.21 Synthesis of α-substituted proline derivatives [119]

Germanas described the condensation of proline with chloral instead of pivaldehyde to give a more stable oxazolidinone **III-43** (Scheme 4.20). Thus, they reported the alkylation of **III-43** using LDA and ((2-iodoethoxy)methyl)benzene in 33 % yield [257] (Scheme 4.22).



Scheme 4.22 Alkylation of 2-trichloromethyloxazolidin-5-ones [257]

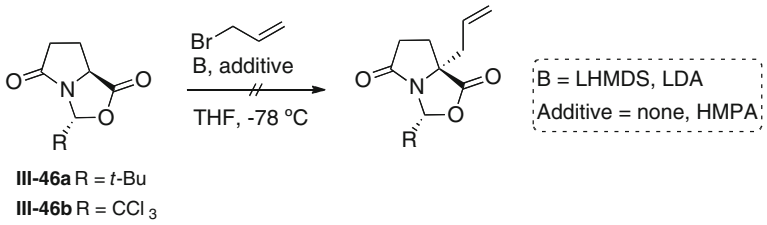
We decided to introduce the protected-alcohol after proper modification on an allyl moiety. 2-Trichloromethyloxazolidin-5-one **III-43** was alkylated using LDA and allyl bromide in 80–82 % yield (Scheme 4.23). Proline/chloral **III-43** was synthesized using 2,2,2-trichloro-1-ethoxyethanol [121]. The use of chloral was avoided, since it is a regulated substance, which greatly limits its commercial availability even in small quantities.



Scheme 4.23 Allylation of 2-trichloromethyloxazolidin-5-ones [121]

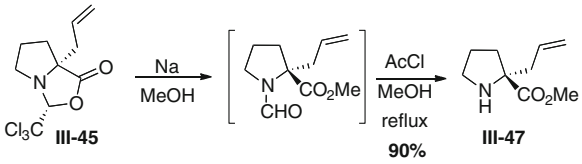
In addition, the analogous 2-*t*-butyloxazolidin-4-one **III-46a** [122, 123] and 2-trichloromethyloxazolidin-4-one **III-46b** [124, 125] precursor, derived from *S*-pyroglutamic acid, were also synthesized (Scheme 4.24). Unfortunately, the

alkylation of these oxazolidin-4-ones with LDA or LHMDS and allyl bromide afforded only complex mixtures. This was due to the lower nucleophilicity of oxazolindin-4-ones **III-46a** and **III-46b** in comparison with the oxazolidin-5-one **III-42** and **III-43**.



Scheme 4.24 Alkylation of oxazolidin-4-one precursors

Optically active α-branched proline derivative **III-47** was obtained by a one-pot procedure (Scheme 4.25) [121]. Proline/chloral precursor **III-45** was exposed to sodium methoxide, resulting in rapid conversion to the *N*-formyl ester at room temperature. Cleavage of the *N*-formyl group was efficient performed by heating with hydrochloric acid Thus, the desired *R*-allyl prolinate hydrochloride salt **III-47** was obtained reproducibility in a multigram scale.[9,10]

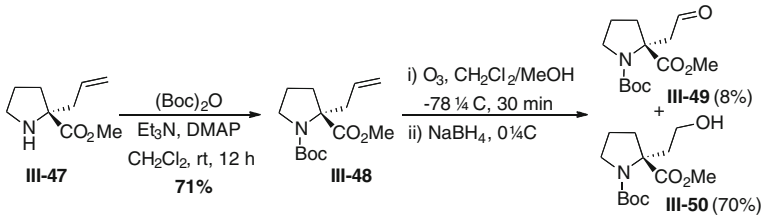


Scheme 4.25 Cleavage of the trichloro auxiliary [121]

Pyrrolidine **III-47** was protected as a Boc carbamate (Scheme 4.26). Subsequent ozonolysis of **III-48** and addition of sodium borohydride afforded a mixture of the alcohol **III-49** (70 %) and aldehyde **III-50** (8 %), [128] which were separated by column chromatography.

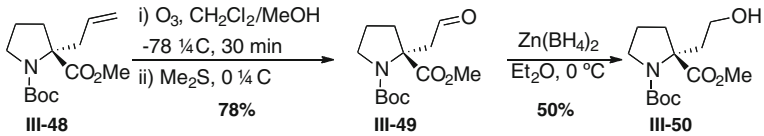
[9] **III-47** can be synthesized by Ireland-Claisen ester rearrangement but only on small scale: Kazmaier et al. [126], Chandan and Moloney [127].

[10] The reported *ee* of **III-47** was determined via conversion of the final product to the Mosher amide under Schotten-Bauman conditions [121]. The desired product was observed as a single peak, >99 % diasteromerically pure.



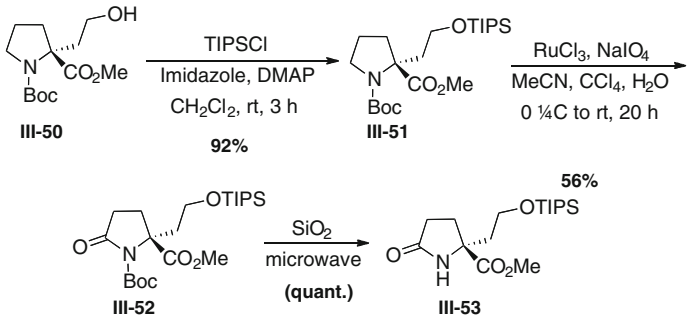
Scheme 4.26 Synthesis of alcohol **III-50**

In order to optimize the synthesis of alcohol **III-50**, the corresponding aldehyde **III-49** was isolated by treatment of alkene **III-48** with ozone followed by addition of dimethyl sulfide (Scheme 4.27) [129]. After an extensive screening of reducing agents ($NaBH_4$, DIBALH, H_2/PtO_2) [130, 131], solvents, and conditions, we obtained alcohol **III-50** using zinc borohydride in ether[132, 133] with 84 % yield without purification and 50 % after column chromatography.



Scheme 4.27 Optimized conditions for the synthesis alcohol **III-50**

Finally, the desired lactam **III-53** was synthesized following the sequence shown in Scheme 4.28. Thus, triisopropylsilyl ether-protection (TIPS) of alcohol **III-50** [134], oxidative of pyrrolidine **III-51**, using the Sharpless and Katsuki conditions [135], afforded 2-pyrrolidone **III-52** [140],[11] which was subsequently deprotected to give the lactam **III-53** [141].



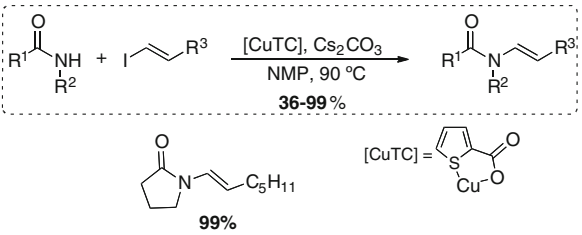
Scheme 4.28 Synthesis toward lactam **III-53**

[11] First example for the oxidation of cyclic amines with ruthenium tetraoxide: Sheehan and Tulis [136], Yoshifuji et al. [137, 138], Tanaka et al. 139].

4.3.2.2 Connection of 2-Pyrrolidine III-53 and the Indole Part[12]

Formation of C–N bond has raised of interest in the scientific community in the last 10 years. In this context, the formation of enamides is a valuable protocol. In addition to conventional approaches that include condensation of amides and aldehydes, addition of amides to alkynes, acylation of imines, Curtius rearrangement of α,β-unsaturated acyl azides, amide Peterson olefination, and Wittig and Horner-Wadsworth-Emmons reactions, several transition metal-catalyzed methods have been developed that allow the synthesis of enamides.[13] Inspired by the analogous arylation of amines catalyzed by palladium or copper complexes (Buchwald-Hartwig reaction), a new approach for the synthesis of enamides has been published recently, which allows to prepare enamides from readily available starting materials (amides and vinyl halides) proceeding under very mild conditions. Thus, we decided to test the Porco-Buchwald amidation of vinyl halides in our synthesis [144–146].

Although palladium[14] and copper-catalyzed cross-coupling of amides and vinyl halides are possible, copper catalysis appears to be the most spread. On the basis of the precedents reported by Ogawa [150], Porco developed an efficient approach for the assembly of enamides using Liebeskind catalyst, copper(I) thiophene carboxylate ([CuTC]), Cs_2CO_3 and disubtituted (*E*)-vinyl iodides in NMP or DMSO. Using this protocol, a series of (*E*)-enamides could be prepared in moderate yields under mild conditions (Scheme 4.29) [144, 145][15]. Under these conditions, the coupling of 2-pyrrolidine and (*E*)-1-iodohept-1-ene takes place in 99 % yield.



Scheme 4.29 CuTC-catalyzed coupling of vinyl iodides and amides

Later, Buchwald reported a general procedure for the synthesis of enamides under mild conditions that allows the use of substituted vinyl iodides and bromides using CuI and DMEDA (Scheme 4.30) [146]. The coupling required Cs_2CO_3 in

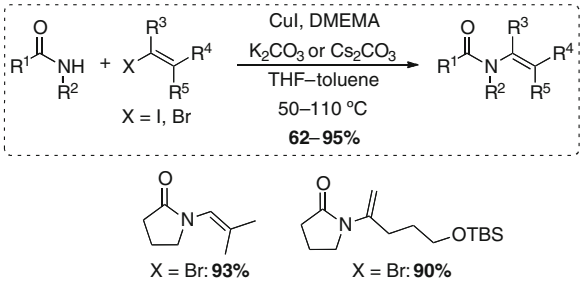
[12] In this part of the chapter, only the methodology that allowed the connection of both fragments is discussed. All of the previous attempts are discussed in the 3.3.4 Annex.

[13] Reviews about metal-catalyzed coupling reaction: Dehli et al. [142], Evano et al. [143].

[14] Synthesis of enamides starting from 2-pyrrolidine and vinyl triflates: Wallace et al. [147], Klapars et al. [148]. From vinyl chlorides: Hesse and Kirsch [149].

[15] For the synthesis of *N*-acyl vinylogous carbamic acids and ureas see: Han et al. [151].

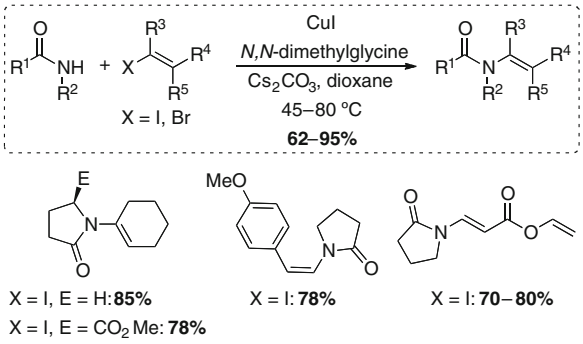
THF at temperatures ranging from 50 to 70 °C using vinyl iodides, whereas vinyl bromides required the use of K_2CO_3 in toluene at 110 °C.



Scheme 4.30 CuI/diamine-catalyzed synthesis of enamides

An interesting feature is that di- or trisubstituted vinyl bromides as well as (*Z*)-vinyl iodides perform well under the reaction conditions. Lactams and oxazolidinones were shown to be equally efficient reaction partners.

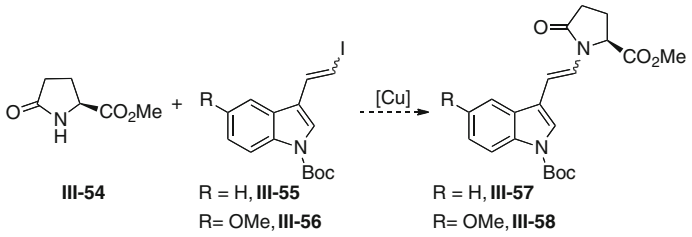
A year later than Buchwald, Ma reported the coupling of vinyl iodides and bromides with amides or oxazolidines using CuI in combination with *N*,*N*-dimethylglycine and Cs_2CO_3 in dioxane at temperatures ranging from 45 to 80 °C (Scheme 4.31) [152].



Scheme 4.31 CuI/N,N-dimethylglycine-catalyzed synthesis of enamides

Lam reported an alternative to vinylhalides using (*E*)-hexenylboronic acids as a room temperature vinylating agent [153]. However, this method lacks generality, and only three examples of amide-like substrates were reported. One of the potential problems with this route, compared to similar reactions of arylboronic acids, is the lower stability of alkenylboronic acids, particularly under oxidative conditions. An interesting alternative was found using of potassium alkenyltrifluoroborates, which allows the copper-catalyzed cross-coupling of amides and oxazolidines under base free conditions at 40 °C [154].

Encouraged by the previously reported results for the copper-catalyzed coupling of amides and heteroaryl vinyl halides,[16] we decided to study of the reaction with the model lactam **III-54** [159] and indolylvinyl iodide **III-55** (R=H) and **III-56** (R=OMe) (Scheme 4.32).



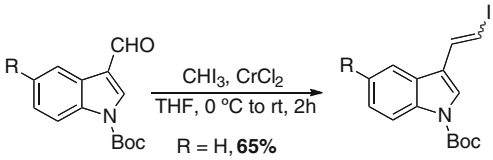
III-54

R = H, **III-55**
R= OMe, **III-56**

R = H, **III-57**
R= OMe, **III-58**

Scheme 4.32 Synthetic model for the study of the copper-catalyzed cross-coupling reaction

Indolylvinyl iodides **III-55** and **III-56** were synthesized using the Takai-Utimoto olefination [160], starting from the corresponding aldehydes, in moderate to high yields (Scheme 4.33). Unfortunately, when we tried this reaction catalytic, only traces of the iodides were detected [161].



R = H, **65%**
R = OMe, **71%**

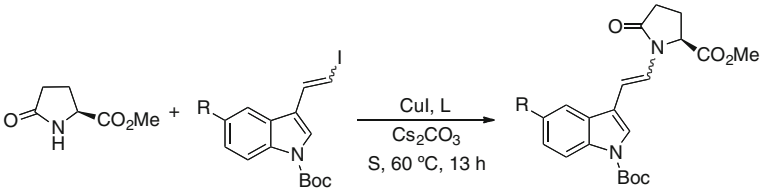
R = H, *Z*/*E* = 2.3:1.0 **III-55**
R= OMe, *Z*/*E* = 4.3:1.0 **III-56**

Scheme 4.33 Synthesis of indolylvinyl iodides

With the indolyl vinyl iodides in hand, the next step was to study the copper-catalyzed cross-coupling. When we exposed lactam **III-54** and indolyl vinyl iodide **III-55** to the Ma conditions [152], no reaction was observed (Table 4.4, entry 1). Nevertheless, enamides **III-57** and **III-58** were obtained in high yields using the Buchwald conditions [146] (Table 4.4, entries 2 and 3). It is worth mentioning that the *E*/*Z* ratio of the starting indolyl vinyl iodide is increased in the final enamides, since the (*Z*)-vinyl iodide is less reactive.

[16] Selected examples for the copper-catalyzed cross-coupling of lactam and heteroaryl vinyl halides: Sun et al. [155], Meketa and Weinreb [156, 157], Yang et al. [158].

Table 4.4 Study of the copper-catalyzed cross-coupling of lactam **III-54** and indolylvinyl iodides

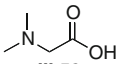


III-54 R = H, **III-55** (E/Z = 2.3:1.0) R= OMe, **III-56** (E/Z = 4.3:1.0)

R = H, **III-57** (E/Z = 5.6:1.0) R= OMe, **III-58** (E/Z = 5.2:1.0)

Entry	R	L	S	Conv (%)	Yield (%)
1	H	**III-59**	DMSO	0	–
2	H	DMEDA	THF	75	73
3	OMe	DMEDA	THF	100	82

Reactions carried out with 1 equiv of the iodide **III-55** or **III-56**, 1.2 equiv of amide **III-54**, 10 mol % of CuI, 20 mol % of additive and 2 equiv of Cs_2CO_3

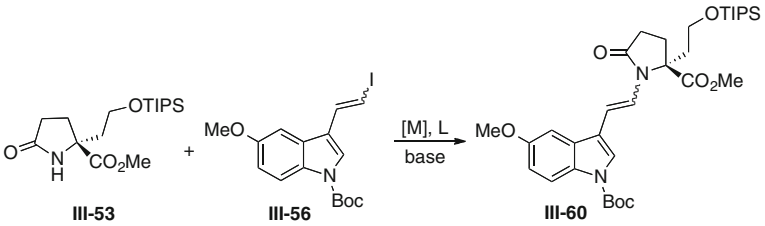


III-59

Although a systematic screening of the metal, ligand, base and the solvent was done, only selected conditions are shown in Table 4.5 using amide **III-53**. Unfortunately, only traces of the desired enamide **III-60** were detected when we applied the Buchwald conditions [146] for the copper-catalyzed cross-coupling of more complex lactam **III-53** and indolyl vinyl iodide **III-56** (Table 4.5, entry 1). Under more forcing conditions, only decomposition of the iodide was observed (Table 4.5, entry 2). The same result was achieved using the Porco conditions (Table 4.5, entry 3) [144, 145], the modified version using diamine **III-61** (Table 4.5, entry 4),[17] and palladium as catalyst (Table 4.5, entry 5).

[17] Optimizated conditions for the copper-catalyzed cross-coupling of protected maleimide hemianals: Coleman and Liu [162].

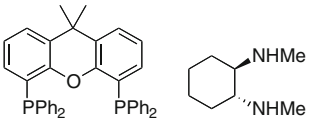
Table 4.5 Study of the metal-catalyzed cross-coupling of lactam **III-53** and indolylvinyl iodide **III-56**



III-53 III-56 III-60

Entry	[M]	L	Base	S	Cond.	Yield (%)
1	CuI	DMEDA	Cs_2CO_3	THF	60 °C, 13 h	27[a]
2	CuI	DMEDA	Cs_2CO_3	THF	MW, 110 °C, 12 h	–
3	[CuTC]	–	Cs_2CO_3	NMP	90 °C, 1 d	–
4	[CuTC]	**III-61**	K_3PO_4	Dioxane	90 °C, 1 d	–
5	$[Pd_2(dba)_3]$	Xantphos	Cs_2CO_3	Dioxane	110 °C, 1d	–

a Inseparable mixture, **I-53/I-60** = 2:1



xantphos III-61

Presumably, the higher steric hindrance of lactam **III-53** is responsible for the sluggishness of this reaction. Although not fully explored to date, our main hypothesis is that the side chain with TIPS appears to be blocking the attack toward one face of the ester (Fig. 4.8).

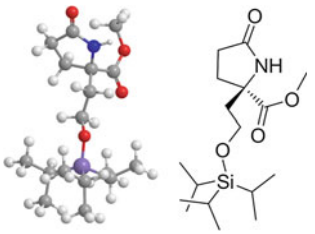
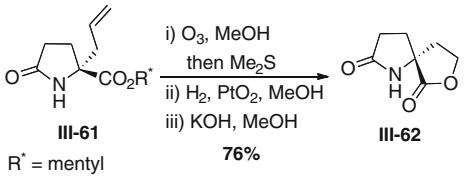


Fig. 4.8 Optimized structure of lactam **III-53** using MM2

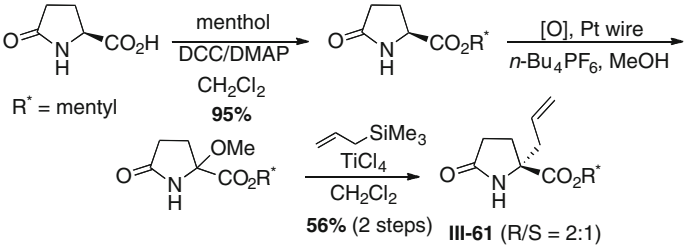
4.3.2.3 Outlook

To succeed in the total synthesis of lundurines, the next step will be the formation of a less sterically hindered lactam. The Moeller group has reported the synthesis of spiro lactam **III-62**, which was synthesized starting from lactam **III-61** by ozonolysis, reduction of the aldehyde, and finally lactonization (Scheme 4.34) [163].



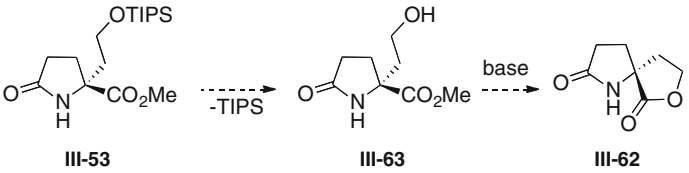
Scheme 4.34 Reported synthesis of spiro lactama **III-62**

The principal drawback of this approach is the generation of a 2:1 mixture of diastereoisomeric lactams **III-61**, which were separated by MPLC. Lactams **III-61** were isolated after the reaction of pyroglutamic acid with (+)-menthol, anodic oxidation, and treatment of the correspondening methoxylethers amide with allyltrimethylsilane and titanium tetrachloride (Scheme 4.35) [164, 165].



Scheme 4.35 Synthesis of lactam **III-61** [164, 165]

Based on this strategy, Scheme 4.36 shows the proposed approach for the synthesis of the spiro lactama **III-62**, which will be synthesized by removal the TIPS protecting-group and lactonization of alcohol **III-63**.



Scheme 4.36 Synthetic approach toward lactona-lactma **III-61**

This spiro lactam **III-62** is characterized by less hindrance around the quaternary carbon (Fig. 4.9), which should allow the C–N coupling reaction to go to completion.

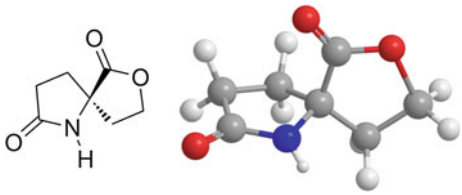


Fig. 4.9 Optimized structure of lactam **III-62** using MM2

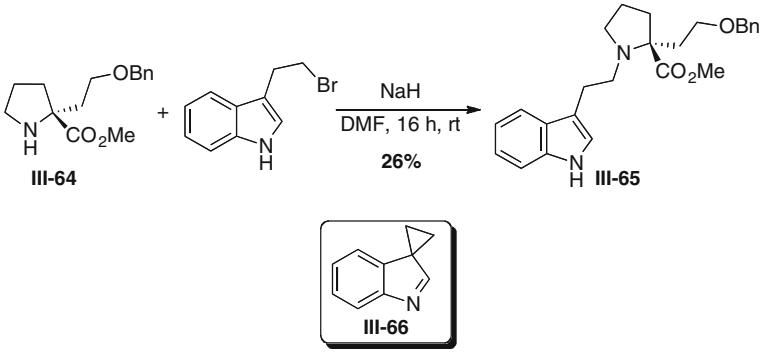
4.3.2.4 Annex: Other Methodologies Tested for the Connection of 2-pyrrolidine III-53 and the Indole Part

In order to find the suitable methodology that allowed the connection of the lactam and the indole moiety, several strategies were tested. In this annex, some of the main methodologies are discussed and the more significant results highlighted.

Nucleophilic Substitution (S_N2)

Following the precedents reported for the alkylation of proline and pyroglutamic derivatives [166], the nucleophilic substitution of 3-(2-bromoethyl)-1*H*-indole derivatives with lactam **III-53** was tried.

The alkylation of proline derivative **III-64** with 3-(2-bromoethyl)-1*H*-indole in 23 % yield had been carried before (Scheme 4.37) [166], during which the formation of spiro[cyclopropane-1,3′-indole] (**III-66**) was also observed. This compound was previously obtained by Rapoport in the alkylation of 2,3-piperidiendicarboxylate with 3-(2-bromoethyl)-1*H*-indole [167].

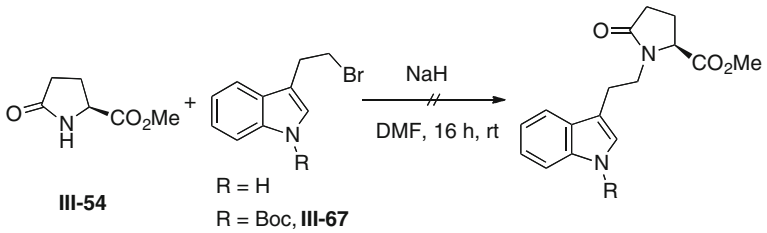


Scheme 4.37 Alkylation of proline derivative **III-64** with 3-(2-bromoethyl)-1*H*-indole [166]

In the work of Rapoport [168], the use of $NaHCO_3$ led to a more efficient alkylation. In this case, however, it only gave unchanged starting material.

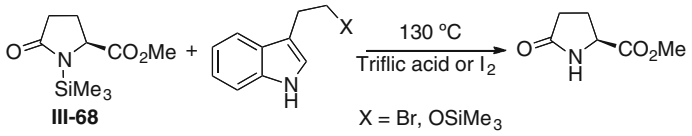
Moreover, the use of a *N*-Boc protected indole for the alkylation was also ineffective.

When the same conditions were tested with (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) and 3-(2-bromoethyl)-1*H*-indole or *tert*-butyl 3-(2-bromoethyl)-1*H*-indole-1-carboxylate (**III-67**) [168] (Scheme 4.38), the desired alkylated product was not detected.



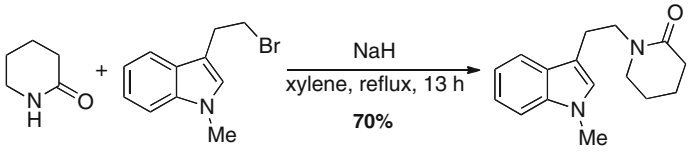
Scheme 4.38 Alkylation of lactam **III-54** with different *N*-protected bromoindoles

The Rigo methodology [169] was also found to be unsuccessful for the alkylation of (*S*)-methyl 5-oxo-1-(trimethylsilyl)pyrrolidine-2-carboxylate (**III-68**) with 3-(2-bromoethyl)-1*H*-indole or 3-(2-((trimethylsilyl)oxy)ethyl)-1*H*-indole (Scheme 4.39) [166]. Under these conditions, only (*L*)-methyl pyroglutamate was formed.



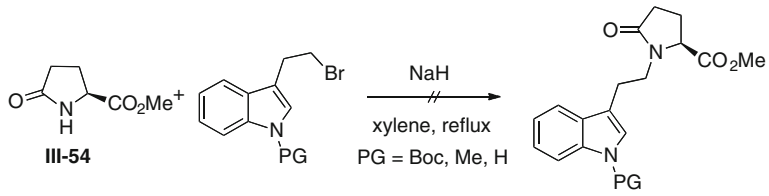
Scheme 4.39 Alkylation of pyroglutamate derivative **III-68** with several electrophiles [166]

Given these unsuccessful alkylation attempts, we decided to examine the methodology developed by Hwang and coworkers [170] in which 2-piperidone is alkylated with 1-methyltryptophylbromide using sodium hydride under reflux conditions (Scheme 4.40).



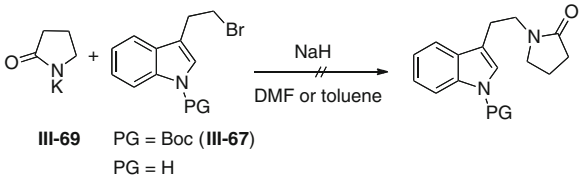
Scheme 4.40 Alkylation of 2-piperidone [170]

The reaction of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) with different 3-(2-bromoethyl)indole derivatives (PG=H, Boc, Me [171]) only provided a complex mixture of products (Scheme 4.41).



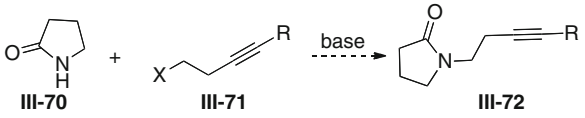
Scheme 4.41 Alkylation of pyroglutamate **III-54**

In order to improve the nucleophilicity of the lactam, we decided to pre-form the potassium salt of pyrrolidin-2-one **III-69** [172]. Unfortunately, no alkylated product was detected in the reaction of **III-69** with *N*-Boc indole **III-67** in DMF (Scheme 4.42) [173]. When the reaction was carried of using toluene as the solvent, only spiro[cyclopropane-1,3′-indole] (**III-66**) was detected. Futhermore, spiro[cyclopropane-1,3′-indole] (**III-66**) was the only product observed in the reaction of the potassium salt **III-69** with 3-(2-bromoethyl)-1*H*-indole in toluene.



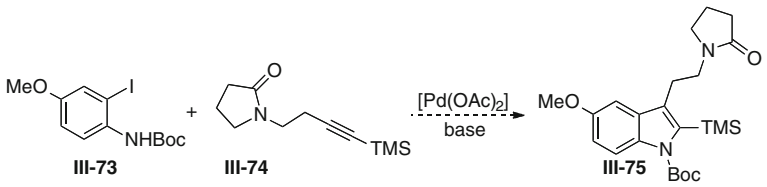
Scheme 4.42 S_N2 of the potassium salt **III-69** with indolylbromides

Since the alkylated product was not detected in any of the examples, we decided to change the halide agent. Therefore, we envisaged that lactam **III-72** could be synthesized by alkylation of pyrrolidin-2-one (**III-70**) with halide **III-71** (Scheme 4.43).



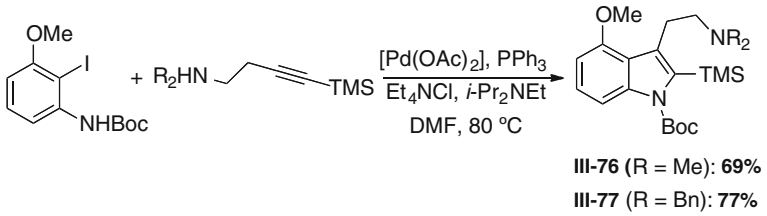
Scheme 4.43 Strategy for the synthesis of lactam **III-72**

Finally, lactam **III-74** could react with *o*-iodoaniline **III-73** [174], leading to indole **III-75** by the Larock indole synthesis (Scheme 4.44). [175, 176]



Scheme 4.44 Larock approach for the synthesis of indole derivative **III-75**

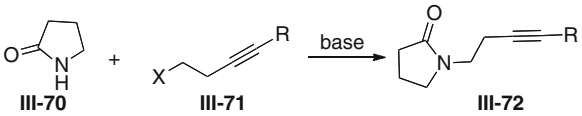
One of the precedents of this strategy was reported by Gaterhood and Scammells, who published the synthesis of *N*,*N*′-disubstituted tryptamines **III-76** and **III-77** with 69 and 77 % yield (Scheme 4.45) [177].



Scheme 4.45 Synthesis of *N*, *N*′-disubstituted tryptamine derivatives

During the study of the nucleophilic substitution, when pyrrolidin-2-one (**III-70**) was exposed to 4-(trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate or (4-iodobut-1-yn-1-yl)trimethylsilane and KH in THF [178, 179], no reaction was observed (Table 4.6, entries 1 and 2). The same result was also obtained using (4-iodobut-1-yn-1-yl)trimethylsilane and NaH in THF (Table 4.6, entry 3) [180]. Unfortunately, no nucleophilic subsitution was detected with 4-(iodobut-1-yn-1-yl)trimethylsilane or 4-iodobut-1-yne and NaHMDS in DMF (Table 4.6, entries 4 and 5) [181]. In the case of 4-iodobut-1-yne[182] and KOH in THF [178–180, 183], or NaOH in biphasic conditions [184], only starting material was detected (Table 4.6, entries 6 and 7).

Table 4.6 Study of the alkylation reaction of pyrrolidin-2-one (**III-70**)

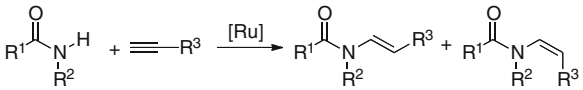


III-70 **III-71** **III-72**

Entry	X	R	Base	S	Cond.	Conv. (%)
1	TsO	TMS	KH	THF	rt, 13 h	0
2	I	TMS	KH	THF	rt, 13 h	0
3	I	TMS	NaH	THF	rt, 13 h	0
4	I	TMS	NaHMDS	DMF	Bu_4NI, 5 h	0
5	I	H	NaHMDS	DMF	Bu_4NI, 5 h	0
6	I	H	KOH	THF	Bu_4NBr, reflux, 13 h	0
7	I	H	NaOH	CH_2Cl_2/H_2O	Bu_4NHSO_4, 1d	0

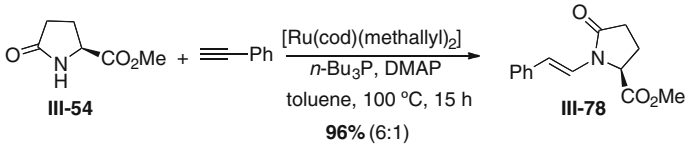
Synthesis of Enamides by Hydroamidation

The transition metal catalyzed addition of amides to alkynes provides a useful approach to the preparation of enamides.[18] In this context, Goo*β*en and coworkers have developed efficient ruthenium catalysts, which allow the anti-Markovnikov addition of amide to terminal alkynes (Scheme 4.46) [187].



Scheme 4.46 Ruthenium-catalyzed anti-Markovnikov addition of amides to alkynes[187]

The Goo*β*en group has identified bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II) [Ru(methallyl)$_2$(cod)] with *n*-Bu_3P and DMAP as an efficient catalyst for the selective formation of (*E*)-enamides [188]. For example, (*E*)-enamide **III-78** is obtained by the coupling of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) and phenylacetylene in 96 % yield (Scheme 4.47).



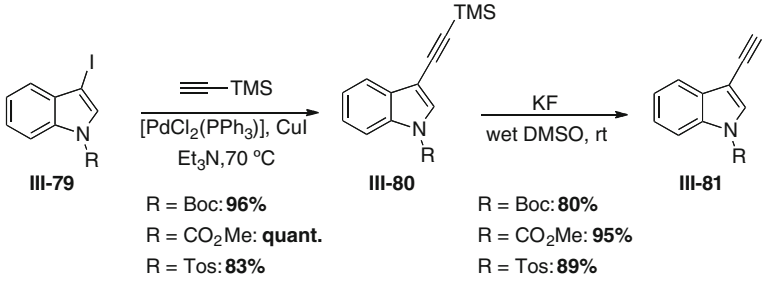
III-54 **III-78**

Scheme 4.47 Anti-Markovnikov addition of lactam **III-54** to phenylacetylene [188]

[18] Pioneer examples of ruthenium complexes, which mediate the addion of certain amides to terminal alkynes: Heider et al. [185], Kondo et al. [186].

Recently, Goo*β*en has reported a new protocol that draws on easily available ruthenium chloride trihydrate ($RuCl_3 \cdot 3H_2O$) as a catalyst precursor instead of the expensive [Ru(cod)(methallyl)$_2$] [189]. In this new protocol, the catalyst is generated in situ, affording comparable yields. Furthermore, in 2007 Kuninobu and Takai reported the synthesis of (*E*)-enamide by rhenium-catalyzed hydroamination of unactivated terminal alkynes [190]. However, this method proceeds with less efficiency and lower reaction scope with respect to the ruthenium one.

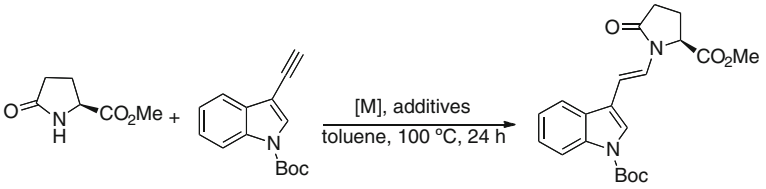
For the preparation of alkynylindole derivatives **III-81**, we followed the synthetic sequence shown in Scheme 4.48. Trimethylsilyl derivatives **III-80** [191–193] were obtained by Sonogashira cross-coupling of *N*-protected iodoindoles **III-79** [194], and ethynyltrimethylsilane with high yield in all the cases. Then, TMS-removal afforded the desired *N*–protected alkynylindole derivatives **III-81**.



Scheme 4.48 Synthesis of alkynylindoles derivatives

Unfortunately, when lactam **III-54** was allowed to react with *N*-Boc alkynylindole **III-81** using the Goo*β*en conditions with [Ru(cod)(methallyl)$_2$] (Table 4.7, entry 1) or $RuCl_3$ (Table 4.7, entry 2), no enamide **III-82Boc** was detected. Additionally, no formation of the desired product was observed when using [$Re_2(CO)_{10}$] as a catalyst (Table 4.7, entry 3).

Table 4.7 Study of the addition of lactam **III-54** to alkyne **III-81Boc**



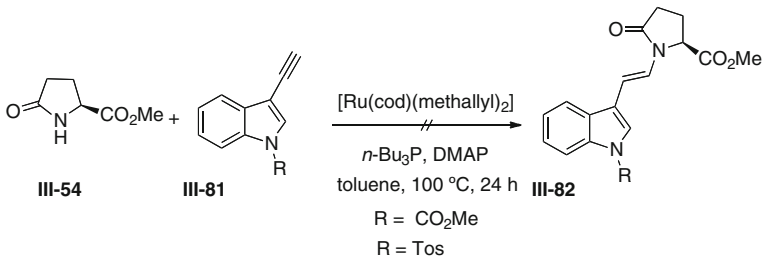
III-54 **III-81Boc** **III-82Boc**

Entry	[M]	Additive	Conv.
1	[Ru(cod)(methallyl)$_2$]	*n*-Bu_3P, DMAP	–[a]
2	$RuCl_3$	*n*-Bu_3P, DMAP, K_2CO_3	–[a]
3	[$Re_2(CO)_{10}$]	–	–[a]

[a] <0 % conversion

Furthermore, we decided to try an uncatalyzed method, where lactam **III-54** reacts with alkynylindole **III-81Boc** using NaH in DMF [195]. As before, no alkylated product was detected.

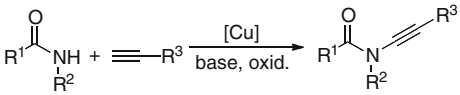
Finally, we tested the Goo*β*en conditions with the other *N*-protected alkynylindole derivatives **III-81** (R=CO_2Me or Tos) (Scheme 4.49). Again, no traces of the desired enamide product **III-82** were detected, neither with *N*-CO_2Me nor with *N*-Tos alkynylindole **III-81**.



Scheme 4.49 Study of the addition of lactam **III-54** to alkynes **III-81**

Synthesis of Ynamides: Amidative Cross-Coupling of Terminal Alkynes

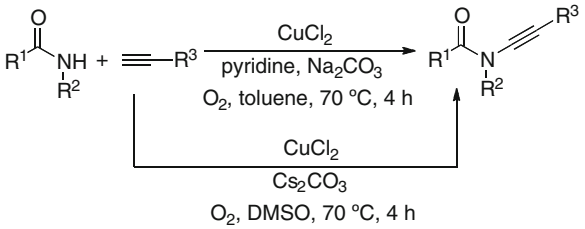
Ynamides can be easily synthesized by metal-catalyzed amidative cross-coupling of alkynes (Scheme 4.50).[19] Other alternatives employ lithiated amides with alkynyliodonium salts [196], or metal-catalyzed coupling of amides with alkynyl bromides [196], potassium alkynyltrifluoroborates [197], 1,1-dihalo-1-alkenes [198], or propylic acids [199].



Scheme 4.50 Copper-catalyzed amidative cross-coupling of alkynes

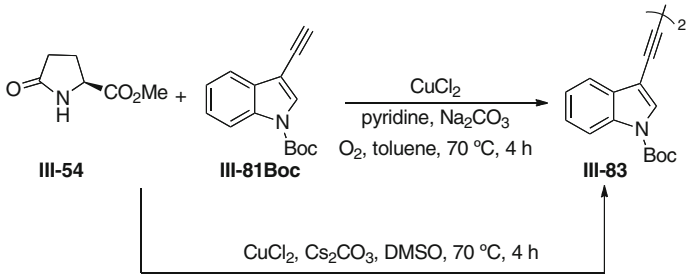
In 2008, the Stahl group published the first copper-catalyzed aerobic oxidative amidation of terminal alkynes [200]. An extensive screening of various copper sources, Brønsted bases, and solvents led to the optimal conditions shown in Scheme 4.51.

[19] See general review: DeKorver et al. [196].



Scheme 4.51 General conditions for the Stahl methodology

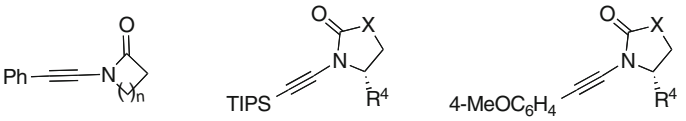
It was reported that a wide range of nitrogen nucleophiles (cyclic: 2-oxazalidinone, carbamate, amide, urea, and indole; acyclic: *N*,*O*-dimethylcarbamate, acetamide, and *N*,*N*′-dimethylurea) and alkynes (R^3 = TIPS, *n*-Bu, $(CH_2)_3OTBS$, CH_2OTBS, and *p*-$MeOC_6H_4$) could be used, and in most cases the desired ynamides were isolated in good to excellent yields. Figure 4.10 highlights the most relevant examples for the copper-catalyzed aerobic oxidative amidation of terminal alkynes using 2-pyrrolidone derivatives.



Scheme 4.52 Copper-catalyzed coupling of lactam **III-54** and alkynylindole **III-81Boc**

Ynamide preparation via oxidative coupling of amides and alkynes represents an efficient alternative to known multi-step methods, such as alkyne halogenation or the synthesis of alkynyliodonium salts followed by C–N formation. The only shortcoming of this system is that 5 equiv of the amide are necessary to achieve satisfactory yields.

When we applied the Stahl conditions to the copper-catalyzed coupling of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) and *N*-Boc ethynylindole derivate **III-81Boc**, only the Glaser-Hay product **III-83** was isolated together with starting material (Scheme 4.52). This result did not surprise us, since Stahl had reported the same problem during the coupling of 2-pyrrolidone and phenylacetylene (Fig. 4.10).



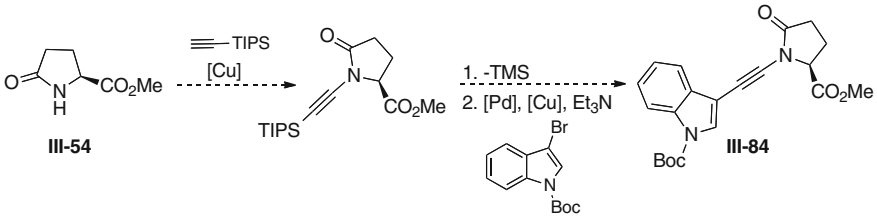
n = 2: **traces**
n = 1: **89%**

X = O, R^4 = H: **83%**
X = O, R^4 = Bn: **78%**
X = CH_2, R^4 = H: **95%**
X = NMe, R^4 = H: **70%**

X = O, R^4 = H: **81%**
X = O, R^4 = Bn: **81%**
X = NMe, R^4 = H: **80%**

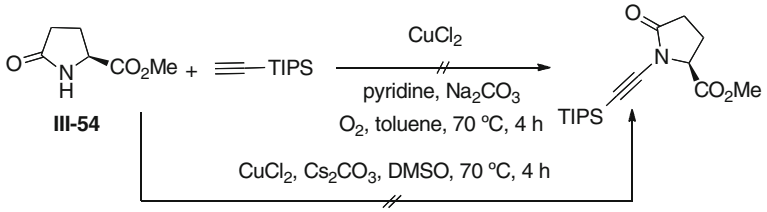
Fig. 4.10 Selected examples

Since Stahl has reported a good yield (95 %) for the coupling of 2-pyrrolidine and ethynyltriisopropylsilane (Fig. 4.10), we anticipated that the copper-catalyzed coupling of lactam **III-54** and ethynyltriisopropylsilane, followed by removing of the TIPS, and Sonogashira cross-coupling with *N*-Boc 3-bromo indole would allow the formation of the desired indolynamide **III-84** (Scheme 4.53).



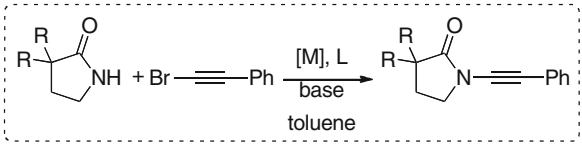
Scheme 4.53 Synthetic pathway to indolynamide **III-84**

Unfortunately, the copper-catalyzed coupling of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) and ethynyltriisopropylsilane was ineffective (Scheme 4.54).

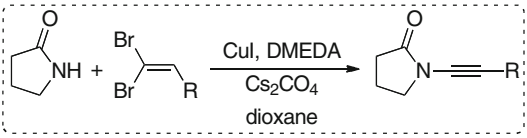


Scheme 4.54 Copper-catalyzed coupling of lactam **III-54** and ethynyltriisopropylsilane

Another plausible alternative is the metal-catalyzed coupling of amides with alkynyl bromides or 1,1-dibromo-1-alkene [196]. Scheme 4.55 shows the more significant reported results with 2-pyrrolidine derivatives.[20,21]



R	*[M]*	*L*	base	Yield (%)
Me	$CuSO_4{\cdot}5H_2O$	1,10-phen	Cs_2CO_3	58
H	$CuSO_4{\cdot}5H_2O$	1,10-phen	K_3PO_4	38
H	$FeCl_3{\cdot}6H_2O$	DMEDA	K_2CO_3	57



R	*Yield (%)*
Ph	80
p-$MeOC_6H_4$	66
t-Bu	34
Cy	43

Scheme 4.55 Selected results for the coupling of 2-pyrrolidine derivatives

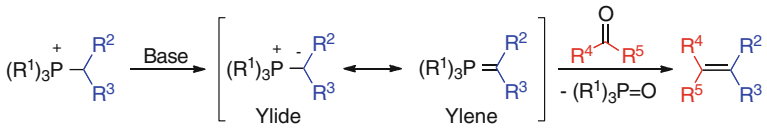
Since the yields are between low and moderate with (bromoethynyl)benzene and, in the case of 1,1-dibromo-1-alkene, a decreased in the yield is observed with electron-donating groups on the phenyl ring, we anticipated a low conversion when R = indole. Therefore, we decided to dismiss this approach at this point.

Synthesis of Enamides by Wittig Reaction

The Wittig reaction is a chemical reaction that allows the synthesis of an alkene by the reaction of an aldehyde or a ketone with an ylide generated from a phosphosnium salt (Scheme 4.56). The geometry of the resulting alkene depends on the reactivity of the ylide.

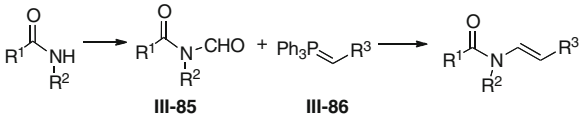
[20] For alkynyl bromides: Zhang et al. [201], Yao et al. [202].

[21] For 1,1-dibromo-1-alkene: Coste et al. 203].



Scheme 4.56 Wittig reaction

The Wittig reaction can be modified to allow the synthesis of enamides. In Scheme 4.57, the Wittig olefination of *N*-formyl imide precursor **III-85** [204] (pseudo-aldehyde) with a phosphonium ylide **III-86** is shown. The *N*-formyl imide **III-85** can be synthesized from the parent lactam unit.



Scheme 4.57 Imide olefination

In 2007, the group of Marquez reported the first synthesis of enamides through the use of *N*-formyl imides. [204] These *N*-formyl imides behave as carbonyls due to the presence of a second carbonyl unit, which effectively ties up the nitrogen lone pair (Fig. 4.11).

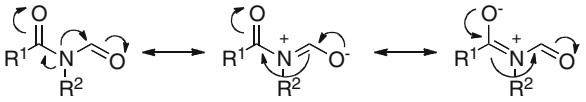
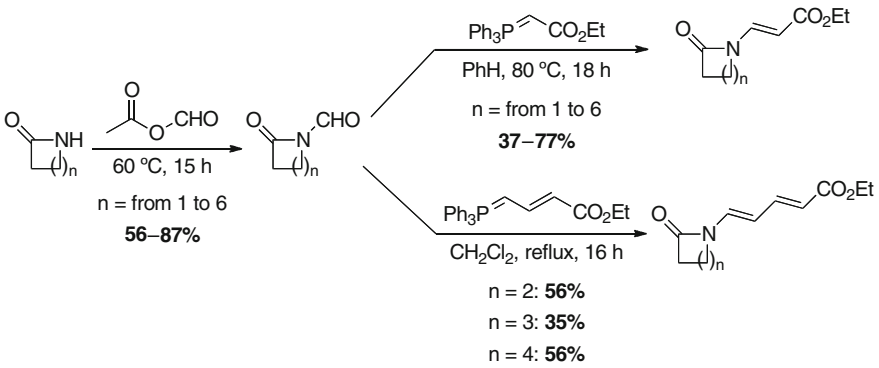


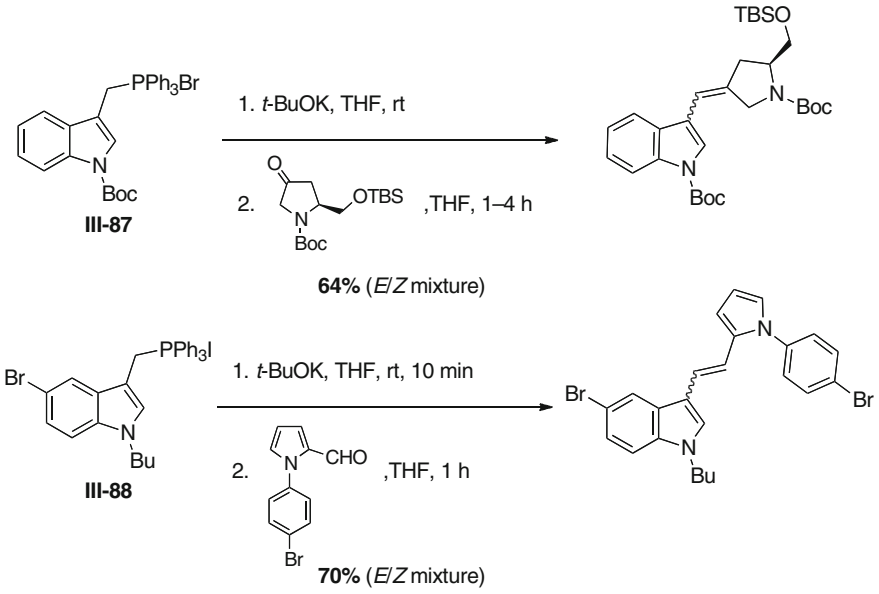
Fig. 4.11 Delocalization of the *N*-lone pair of the imide

In Scheme 4.56, the most relevant results with cyclic *N*-formyl imides are shown [204, 205]. Unfortunately, the scope of the phosphonium ylide is not very broad, since good yields are only reported when $R^3 = -CO_2R'$ or $-CH{=}CHCO_2Me$ (Scheme 4.58).



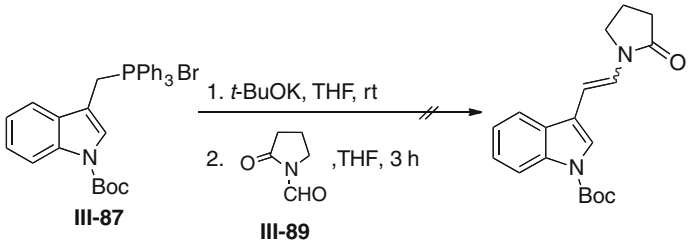
Scheme 4.58 Most relevant results for the cyclic *N*-formyl imide olefination

Regarding the phosphonium ylide derivative **III-86**, there are three publications of the Wittig olefination of carbonyl compounds with indolylmethyl phosphonium ylide derivatives [206–208]. In Scheme 4.59, two examples are highlighted: the reaction of *tert*-butyl 3-((bromotriphenylphosphoranyl)methyl)-1*H*-indole-1-carboxylate (**III-87**) with a ketone [206], and the reaction of 5-bromo-1-butyl-3-((iodotriphenylphosphoranyl)methyl)-1*H*-indole (**III-88**) with an aldehyde [207].



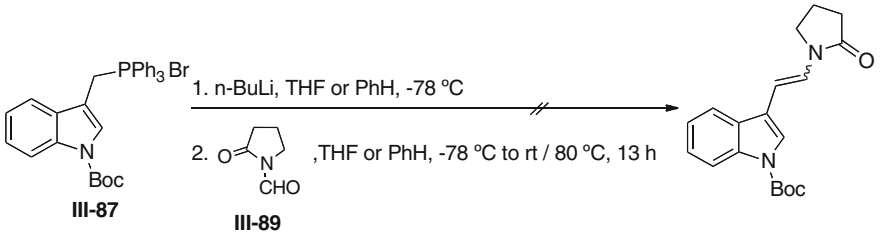
Scheme 4.59 Most relevant results of Wittig reaction using indolylmethyl phosphonium ylide derivatives [205]

The Wittig olefination of cyclic *N*-formyl imides and simple phosphonium ylide derivatives is possible (Scheme 4.56). Furthermore, the reaction of carbonyl compounds with indolylmethyl phosphonium ylide derivatives is also feasible (Scheme 4.59). Therefore, we decided to test the Wittig olefination of *N*-formyl imide **III-89** with indolylmethylphosphonium bromide derivative **III-87**. At room temperatute, using potassium *t*-butoxide to form the ylide in situ, no reaction was detected (Scheme 4.60). The reaction was repeated under reflux, but the formation of the olefin was not observed.



Scheme 4.60 Study of the Wittig reaction with N-formyl imide **III-89** and ylide **III-87**

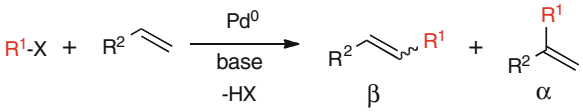
No improvement of the Wittig olefination was observed in changing the base to *n*-BuLi, whether in THF or in benzene, at room temperature or at 80 °C (Scheme 4.61).



Scheme 4.61 Witting reaction of *N*-formyl imide **III-89** and phosphinium bromide **III-87**

Synthesis of Enamides by Heck Reaction

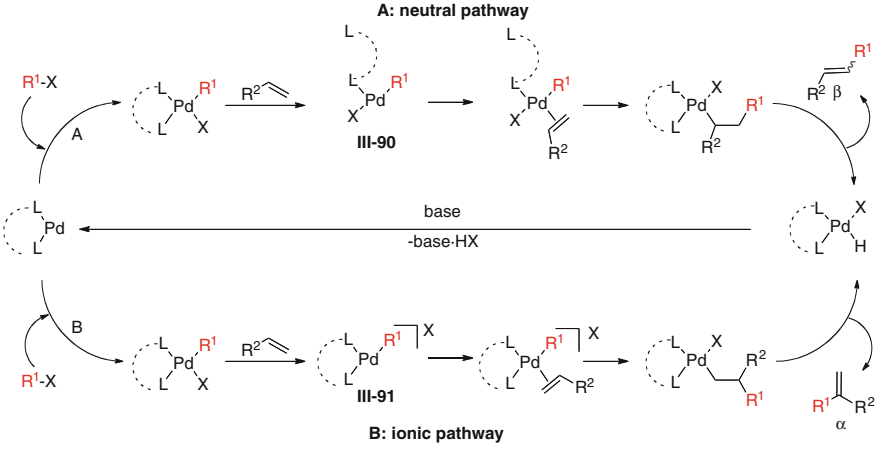
The Mizoroki–Heck reaction is one of the most versatile methods for generating new C–C bonds. Using palladium-based complexes, the reaction couples an unsaturated center, often a vinyl or aryl group, to one end of an alkene C=C bond (Scheme 4.62) [209]. Both inter- and intramolecular examples are known. This methodology is more often called the Heck reaction, and has recently been recognized with the 2010 Nobel Prize in chemistry.



Scheme 4.62 Mizoroki-Heck reaction

In general, the R^1 group can be aryl, vinyl, or any alkyl group without β-hydrogens on a sp^3 carbon atom. The group X can be halide or *pseudo*-halide (triflate, tosylate and mesilate). The alkene can be mono- or disubstituted and can be electron-rich, -poor, or –neutral.

The mechanism for the Heck reaction is shown in Scheme 4.63. The first step involves the oxidative addition of an aryl or vinyl halide, R^1–X, to a palladium(0) species. This species normally contains an auxiliary donor, L, where L is often a phosphine. This may be preceded by a reduction of the metal if a palladium(II) salt is employed initially. Thereafter, two different pathways are possible depending on which group dissociates to provide a vacant coordination site for the incoming alkene. If a neutral ligand (such as a phosphine) detaches and the halide is retained, the active species immediately prior to the C–C coupling step is the neutral complex **III-90**. Conversely, if the anionic ligand (such as a halide) dissociates, the active species is the cationic complex **III-91**.

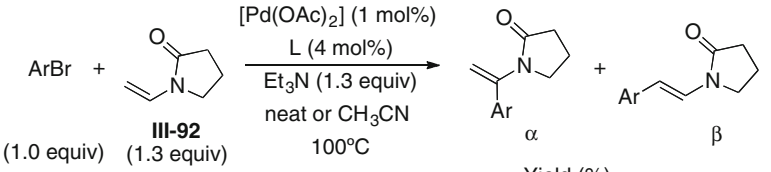


Scheme 4.63 Two competing pathways in the Heck reaction

The Heck reaction can give rise to two regioisomeric products. It is now generally accepted that the regioselectivity issue exists due to the two competing reaction pathways. The neutral pathway (Scheme 4.63, pathway A) yields the β-alkene, whereas the ionic pathway (Scheme 4.63, pathway B) produces the α-alkene [210]. In fact, a bidentate ligand would make the neutral pathway more likely, whereas a monodentate ligand would encourage the ionic pathway.

In general, when the Heck reaction proceeds with electron-deficient alkenes such as acrylonitriles and acrylates, the linear *β*-functionalized alkenes are formed. In this case, the regioselectivity is controlled by electronic factors favoring the neutral pathway. However, it has been reported very recently that it is possible to break the regioselectivity for the acrylate insertion by destabilizing the transition state of 2,1-insertion via steric interactions [211]. The regioselectivity of methyl acrylate insertion into Pd-methyl and -phenyl bonds is inverted to yield the opposite "regioirregular" olefin in stochiometric reactions.

The regioselectivity of the Heck reaction was considered less satisfactory with electron-rich olefins, such as acyclic enol ethers and enamides, which usually afforded a mixture of α- and *β*-functionalized alkenes. In 1978, Heck studied the arylation of *N*-vinylpyrrolidine **III-92**, observing regioselectivity changes depending on the substituent at the aryl bromide (Scheme 4.64) [212]. Thus, the α-alkene was the only product isolated using electron-donating groups such as dimethylamine.



Ar	*L*	*Time*	Yield (%) *α*	*β*
Ph	$P(o\text{-}Tol)_3$	8 h	40	60
Ph	$P(2,5\text{-}i\text{-}Pr_2C_6H_3)_3$	9.5 h	44	55
p-$Me_2NC_6H_4$	$P(o\text{-}Tol)_3$	2 d	57[a]	0

[a] Isolated as *p*-(dimethylamino)acetophenone (hydrolized product)

Scheme 4.64 Vinylic substitution of *N*-vinylpyrrolidone **III-92**

At present, due to extensive research by the groups of Cabri, Hallberg, and Larhed,[22] the α-regioselectivity of the Heck reaction with electron-rich olefins can be controlled. Therefore, the α-arylated alkene is favored by the correct choice of the ligand and the leaving group of aryl substrate. For example, using:

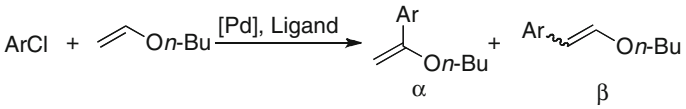
1. Aryl or vinyl halides with stoichiometric amounts of silver and thallium salts.
2. Bidentate ligand with aryl pseudo-halides.

The use of silver and thallium salts, as halide scavengers, promotes the ionic pathway (Scheme 4.61, pathway B). Similarly, the lability of the Pd–OTf bond facilitates the formation of the cationic $[Pd(alkene)]^{+2}$ species **III-91**. More recently, the Xiao group has reported the α-arylation of electron-rich alkenes with

[22] General review about α-arylation of electron-rich olefins: Ruan and Xiao [213].

aryl halides using alcohols (such as ethylene glycol) as solvents. This methodology avoids the use of silver or thallium additives, or aryl pseudo-halides.

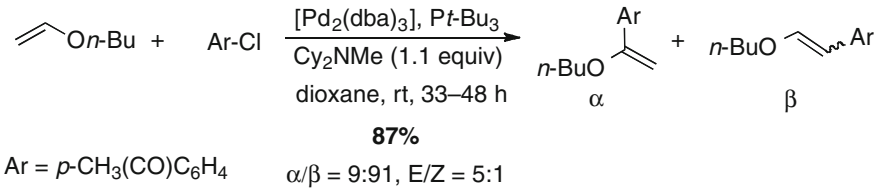
Favoring the β-regioselectivity of the Heck reaction with electron-rich alkenes is not so simple. In 1988, Andersson and Hallberg observed that the type of halide coordinating to the metal center had a profound influence on the regioselectivity, chloride favoring the formation of the β-alkene when using vinyl ethers [214, 215]. Scheme 4.65 shows the most relevant results in the literature toward the β-regioselective arylation of vinyl ethers.



	[Pd]	*Ligand*	*Ratio α/β*
Fu:	$[Pd_2(dba)_3]$	$P(t\text{-}Bu)_3$	9:91
Studer:	$[Pd(OAc)_2]$	$HPAd_2$	26:74
Larhded:	Herrmann's pallacycle	$[t\text{-}Bu_3PH]BF_4$	2:98–35:65
Nacci:	Pd nanoparticles	-	20:80

Scheme 4.65 Examples of Heck arylation of enol ethers with aryl chlorides

In 2001, Fu reported the first arylation of *n*-butyl vinyl ether with *p*-chloroacetophenone using $[Pd_2(dba)_3]$ and $P(t\text{-}Bu)_3$ (Scheme 4.66). The reaction proceeded at room temperature, furnishing a high α/β selectivity of 9:91 [216].



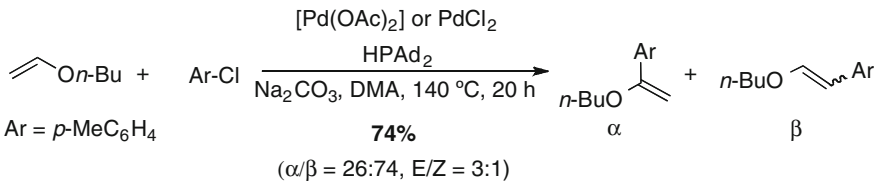
Scheme 4.66 Heck coupling of aryl halides at room temperature

The key to their success was the application of a electron-rich and bulky $P(t\text{-}Bu)_3$ ligand, which promotes smooth oxidative addition of aryl chlorides.[23,24] These conditions are also very efficient when using aryl bromides.

Studer reported the arylation of *n*-butyl vinyl ether with 4-chlorotoluene using palladium diacetate or palladium dichloride with $HPAd_2$ (Ad = adamantyl) as a ligand (Scheme 4.67) [219]. The reaction afforded α/β selectivity of 26:74.

[23] General review about palladium-catalyzed coupling reactions of aryl chlorides: Littke and Fu [217].

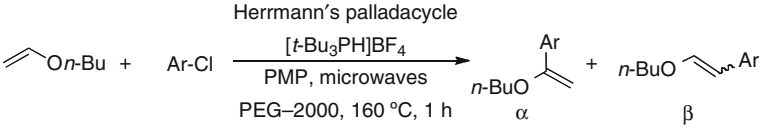
[24] First example of the Heck reaction using aryl chlorides and $P(t\text{-}Bu)_3$ as ligand: Littke and Fu [218].



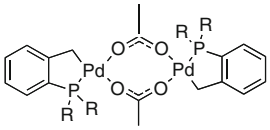
Scheme 4.67 Heck reaction of 4-chlorotoluene with $HPAd_2$ as a ligand

Later, the Chandrasekhar group reported high terminal regioselectivities with *n*-butyl vinyl ether and aryl bromides carrying electron-withdrawing or -donating groups using simple palladium diacetate without any ligand [220]. The key was the use of poly(ethylene glycol) polymer PEG-2000, as solvent.

In 2006, Larhed applied microvawe heating to the arylation of vinyl ether with various aryl chlorides using Herrmann's palladacycle[25] and $[t\text{-}Bu_3PH]BF_4$,[26] favoring the formation of the *β*-arylated alkenes in moderate yields [222]. A regioselective tendency is observed in the selected results shown in Scheme 4.68, where aryl chlorides with electron-withdrawing groups promote higher *β*-regioselectivity, and the *α*/*β* ratio increases with electron-donating groups on the aryl moiety. Similar results (*α*/*β* regioselectivities and yields) are obtained when the solvent is changed to aqueous DMF.



Ar	*Yield (%)*	*ratio α/β*
p-$NO_2C_6H_4$	60	2:98
p-$CF_3C_6H_4$	65	2:98
p-$CHOC_6H_4$	62	2:98
p-AcC_6H_4	70	2:98
o-Naphtyl	60	8:92
Ph	59	7:93
p-$CF_3C_6H_4$	52	17:83
o-$CF_3C_6H_4$	54	18:82
p-$MeOC_6H_4$	46	22:78



R = *o*-Tol

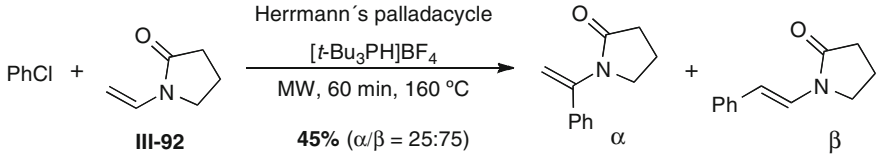
Herrmann's palladacycle

Scheme 4.68 Heck coupling of n-butyl vinyl ether with aryl chlorides

[25] Hermann's palladacycle is characterized by a high termal stability, prermitting it to be used with low cost, but poorly reactive, aryl chloride substrates. General review about application of palladacyles in Heck type reactions: Herrmann et al. [221].

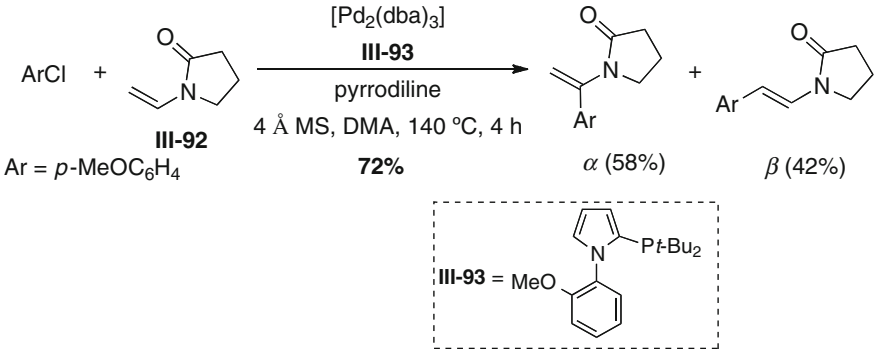
[26] $[(t\text{-}Bu_3)PH]BF_4$ is used as an air-stable preligand of $P(t\text{-}Bu)_3$.

In Scheme 4.69, the Heck arylation of vinyl pyrrolidine **III-92** with phenyl chloride is highlighted. Using the Lahred conditions, a mixture of α- and β-arylated alkenes are formed with moderate yield (45 %) and regioselectivity.



Scheme 4.69 Heck coupling of phenyl chloride and *N*-vinylpyrrolidone **III-92**

Recently, the Xiao group has reported the Heck arylation of vinyl pyrrolidine **III-92** with 1-chloro-4-methoxybenzene (Scheme 4.70) [223]. Despite the use of a bulky electron-rich monophosphine **III-93**, the α-arylated alkene is the major product. Alternatevely, when a bidentate ligand is used under ionizing conditions, the α-product can be exclusively obtained from **III-92** [224–228].



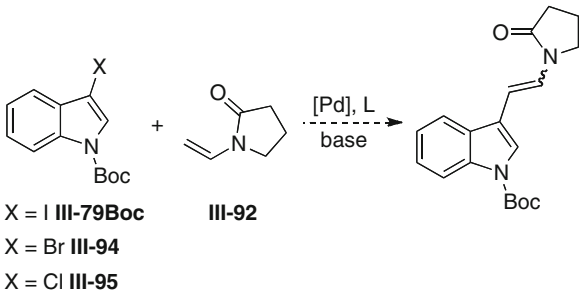
Scheme 4.70 Heck coupling of 1-chloro-4-methoxybenzene and *N*-vinylpyrrolidone **III-92**

Later, Calò and Nacci used Pd nanoparticles to catalyze the arylation with 4-chloroacetophone and chlorobenzene in ionic liquid [229]. An *α/β* selectivity of 20:80 was detected in both cases. Unfortunately a low yield (25 %) was obtained with the unactivated chlorobenzene.

With all of these precedents, it was clear that controlling the *β*-regioselectivity heteroarylation of *N*-vinyl pyrrolidine (**III-92**)[27] would not be easy. Despite these previous results, we decided to test the Heck reaction with different *N*-Boc

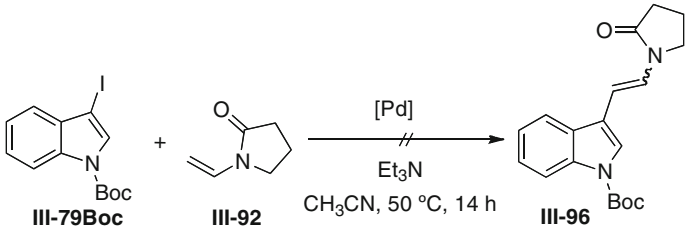
[27] The analogous *N*-vinyl pyrrolidine of lactam **III-53** could be synthesized by palladium(II)-catalyzed vinyl tranfer from vinyl ethers: Brice et al. [230].

3-haloindoles. We started the study with *N*-Boc 3-iodo indole **III-79Boc**[28] and *N*-Boc 3-bromo indole **III-94** [239] (Scheme 4.71).[29]



Scheme 4.71 General overview of the indol-functionalization of *N*-vinyl pyrrolidone

Starting with *N*-Boc iodo indole **III-79Boc**, only decomposition was observed using $[Pd(OAc)_2]$, $[Pd_2(dba)_3]$ or $[Pd(PPh_3)_4]$ as catalysts, without the addition of any ligand (Scheme 4.72). It should be noted that it has been reported that the presence of a ligand is not necessary when using aryl iodides [240].



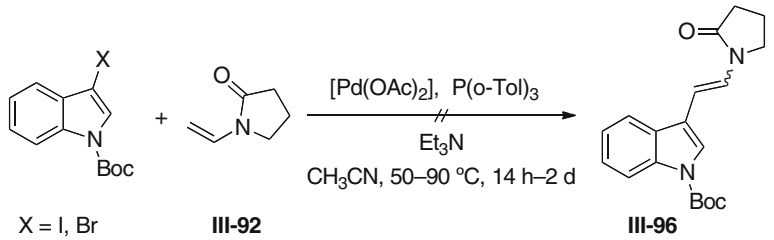
Scheme 4.72 Heck reaction of vinyl pyrrolidone **III-92** and iodo indole **III-79Boc**

When we tested the Heck conditions [212] with iodo indole **III-79Boc**, only complex mixture of product was observed and no traces of the desired enamide **III-96** were present (Scheme 4.73). On the other hand, in the case of bromo indole

[28] Complete *β*-regioselective Heck reaction has been reported using *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate (**III-62Boc**) with electron-poor alkenes: Yue and Larock [231], Yue et al. [232], Putey et al. [233], Mitsudo et al. [234], Della Sala et al. [235].

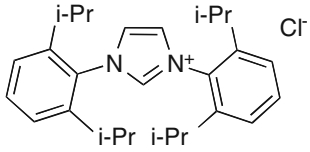
[29] Complete *β*-regioselective Heck reaction has been reported using *tert*-butyl 3-bromo-1*H*-indole-1-carboxylate (**III-73**) with electron-poor and -neutral alkenes: Busacca and Dong [236], Omura et al. [237], Hussain et al. 238].

III-93, almost no reaction was observed. Furthermore, under the same conditions, no improvement was achieved by changing the solvent to DMF.



Scheme 4.73 Heck conditions for the indol-functionalization of vinyl pyrrolidone **III-92**

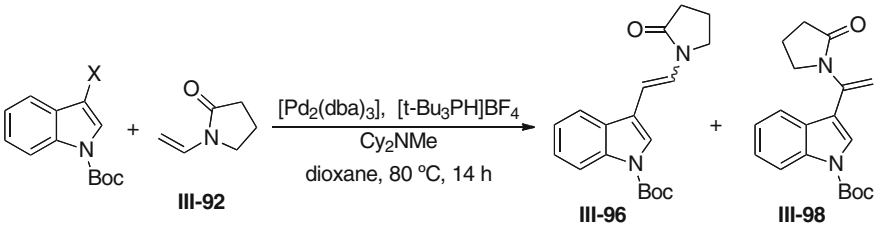
In the case of iodo indole **III-79Boc**, other ligands were tested such as [*t*-$Bu_3PH]BF_4$, PCy_3, or NHC **III-97** (Fig. 4.12), no reaction was detected in all the examples. However, in the case of Dipp NHC **III-97** in combination with Cs_2CO_3, a complex mixture of products was observed in a low conversion.



III-97

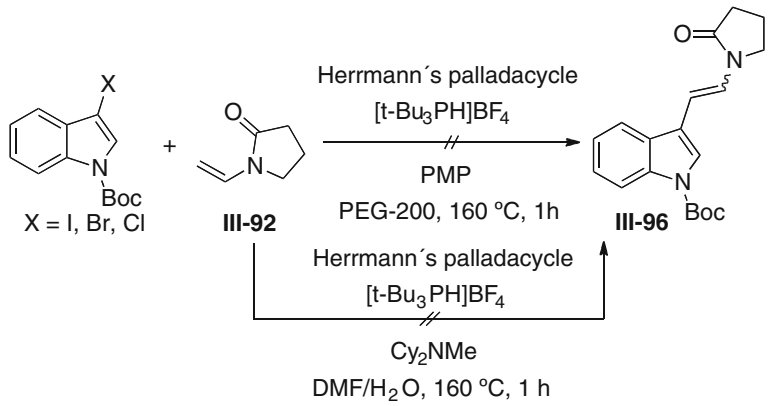
Fig. 4.12 *N*-heterocyclic carbene IPr

Using the Fu conditions, no reaction was observed at room temperature, neither with bromo indole **III-94** nor chloro indole **III-95** [216].However, in the case of bromo indole **III-94**, the reaction was done at 80 °C and the α-enamide **III-98** was formed in a 10 % yield. Alternatively, with *N*-Boc chloro indole **III-95**, a mixture of α-enamide **III-98** and *β*-enamide **III-96** was detected in a 7 and 16 % yield (Scheme 4.74).



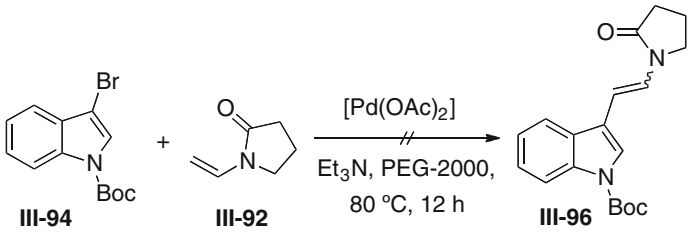
Scheme 4.74 Fu conditions for the indol-functionalization of vinyl pyrrolidine **III-92**

No traces of the β-functionalized alkene **III-96** were found when employing the Lahred conditions with *N*-Boc iodo indole **III-79Boc**, bromo indole **III-94** or chloro indole **III-95** (Scheme 4.75) [222]. Only complex mixtures were observed with iodo indole **III-79Boc** and bromo indole **III-94**. In the case of chloro indole **III-95**, only starting material was recovered.



Scheme 4.75 Larhed conditions for the indol-functionalization of enamide **III-92**

Finally, using the Chandrasekhar conditions [220] for the Heck reaction of *N*-vinyl pyrrolidone **III-92** and bromo indole **III-94** (Scheme 76), only a complex mixture was isolated.



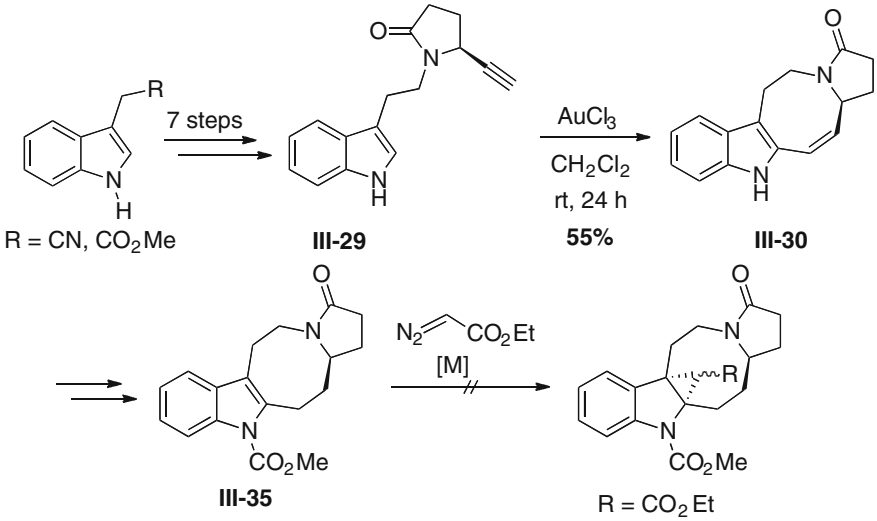
Scheme 4.76 Chandrasekhar conditions for the indol-functionalization of enamide **III-92**

In light of the fact that all the attempts to favor the formation of desired β-enamide **III-96** were unsatisfactory, we can conclude that,

- The oxidative addition with this type of *N*-Boc halide indole is very difficult, since in most cases only starting material was detected.
- To favor the formation of the desired β-enamide **III-96** working with electron-rich olefins and electron-rich halide is not a trivial issue, which would need more optimization to be undertaken.

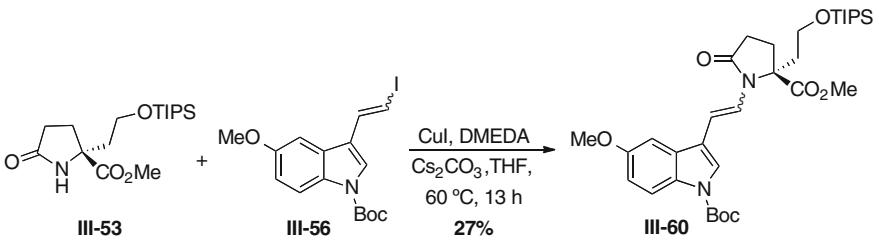
4.4 Conclusions

In the first part of this chapter, we have optimized the synthetic sequence to obtain alkynylindole **III-29** from 2-(1*H*-indol-3-yl)acetonitrile or methyl 2-(1*H*-indol-3-yl)acetate in 7 steps (Scheme 4.77). Furthermore, the azocino indole skeleton of lundurine A **III-30** has been readily synthesized using $AuCl_3$ or other gold complexes as catalysts via 8-*endo-dig* cyclization of alkynylindole substrate **III-29** (see Ref. [134] in Chap. 1). However, the intermolecular cyclopropanation of indoloazocine **III-35** was unsuccessful under all the tested conditions. Thus, we have demonstrated that the intermolacular approach is viable for the total synthesis of lundurines.



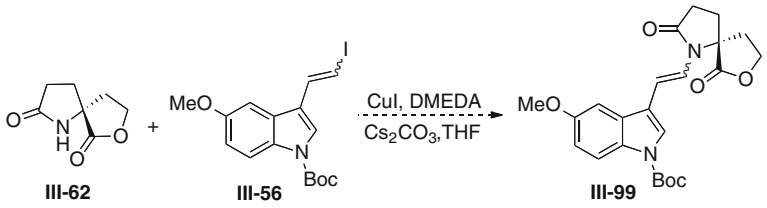
Scheme 4.77 Intermolecular approach toward the total synthesis of lundurines

In the second part of the chapter, the intramolecular approach has been reviewed. After several trials, we have found the adequate methodology to join the lactam and the indole part, which will allow the synthesis of an advance intermediate [146]. However, using enantiomerically pure lactam **III-53** and the indolylvinyl iodide **III-56**, the desired alkenylindole **III-60** was only obtained in a very low yield (Scheme 4.78). We believe that this is mainly due to the high steric hindrance around the quaternary center of the lactam **III-53**.



Scheme 4.78 Copper-catalyzed coupling of lactam **III-53** and alkenylindole **III-60**

Thus, the next step will involve the formation of a less bulky lactone-lactam **III-62** in order to decrease steric hindrance and allow the formation of the new alkenylindole **III-99** (Scheme 4.79). If this is accomplished, further functionalization will enable the intramolecular cyclopropanation to produce lundurine A. If the intramolecular cyclopropanation occurs at the undesired side of the indole, the required enantiomer of lundurine A will be obtained from the opposite enantiomer of proline. Reduction of the amide group in this molecule would lead to the formation of the other members of this family of natural products.



Scheme 4.79 Copper-catalyzed coupling of lactam **III-62** and alkenylindole **III-60**

In a similar way, the preparation of pericidine (**III-100**), pericine (**III-101**) and subincanadine D (**III-102**) (Fig. 4.13) will be also accessible using the gold(I)-catalyzed intramolecular reaction of indoles with alkynes.

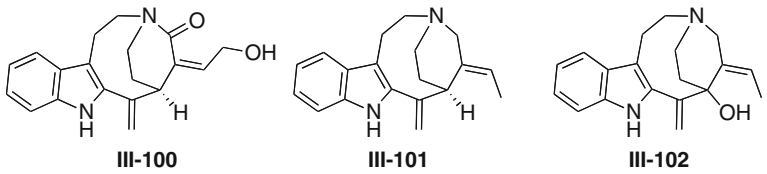


Fig. 4.13 Structure of pericidine, pericine and subincanidine D

4.5 Experimental Section

4.5.1 General Methods

All reactions were carried out under Ar in solvents dried using a Solvent Purification System (SPS). Extractive workup refers to portioning of the crude reaction between an organic solvent and water, phase separation, drying (Na_2SO_4 or $MgSO_4$), and evaporation under reduced pressure.

Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm). HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector.

NMR spectra were recorded at 23 °C on a Bruker Avance 400 Ultrashield apparatus.

Mass spectra were recorded on Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid. Melting points were determined using a Büchi melting point apparatus. Optical rotations were recorded on a P-1030 polarimeter from Jasco at the sodium D line.

4.5.2 Preparation of Substrates

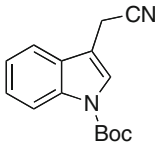
Catalyst phosphine gold(I) **6**, IMes gold(I) **15** (see Refs. [43, 44] in Chap. 1), phosphite gold(I) **20** (see Ref. [42] in Chap. 1), open carbene gold(I) **21** (see Ref. [49–53] in Chap. 1), gold(III) **22** (see Ref. [61, 62] in Chap. 1), platinacycle **24** (see Ref. [29] in Chap. 1), NHC copper(I) **25–29** [112], and copper(I) **30** [113] were synthesized according to reported procedure

Compound *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (**III-23a**) [89], *tert*-butyl 3-formyl-5-methoxy-1*H*-indole-1-carboxylate [241], (3*R*,7a*S*)-3-(trichloromethyl)-tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**III-43**) [118], (3*R*,7a*R*)-7a-allyl-3-(trichloromethyl)-tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**III-45**) [121], (3*R*,7a*S*)-3-(*tert*-butyl)dihydro-pyrrolo[1,2-*c*]oxazole-1,5(3*H*,6*H*)-dione (**III-46a**) [125], (3*R*,7a*S*)-3-(trichloromethyl)-dihydropyrrolo[1,2-*c*]oxazole-1,5(3*H*,6*H*)-dione (**III-46b**) [122], (*R*)-methyl 2-allylpyrrolidine-2-carboxylate (**III-47**) [121], (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) [159], 3-(2-bromoethyl)-1-methyl-1*H*-indole [171], potassium salt of the pyrrolidin-2-one **III-69** [172], (4-iodobut-1-yn-1-yl)trimethylsilane [242], 4-iodobut-1-yne [182], tert-butyl 3-iodo-1H-indole-1-carboxylate **III-79Boc** [194],1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole (**III-80Tos**) [193], *tert*-butyl 3-((bromotriphenylphosphoranyl)methyl)-1*H*-indole-1-carboxylate (**III-87**) [206], N-formyl imide **III-89** [204],

tert-butyl 3-bromo-1*H*-indole-1-carboxylate (**III-94**) [239], were synthesized according to reported procedures.

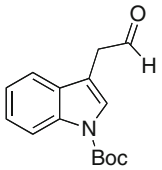
The 5 M $Zn(BH_4)_2$ solution in Et_2O[132, 133] was synthesized according to reported procedure.

***tert*-Butyl 3-(cyanomethyl)-1*H*-indole-1-carboxylate (III-23b)**



Et_3N (20.85 mL, 3.74 mmol, 2 equiv) was added to a mixture of 3-indoleacetonitrile (11.68 g, 74.80 mmol, 1 equiv), Boc_2O (17.14 g, 79.00 mmol, 1.05 equiv) and DMAP (457 mg, 3.74 mmol, 5 mol %) in CH_2Cl_2 (250 mL). The reaction was stirred at room temperature for 2 h, and then it was diluted with CH_2Cl_2. The organic phase was washed with 10 % HCl solution, brine and dried over Na_2SO_4. After removing of the solvent, the residue was purified by column chromatography (10:1 hexane/EtOAc) to give 18.39 g of **III-23b** as a white solid (96 %). mp = 90.4–92.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br d, J = 8,1 Hz, 1H), 7.64 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 3.77 (d, J = 1.6 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 149.3 (C), 135.58 (C), 128.5 (C), 125.2 (CH), 124.3 (CH), 123.0 (CH), 118.2 (CH), 117.1 (C), 115.6 (CH), 109.5 (C), 84.3 (C), 28.2 (CH_3, 3C), 14.3 (CH_2). HRMS-ESI *m/z* calcd for $C_{15}H_{16}N_2O_2Na$ $[M + Na]^+$ 279.1109, found 279.111

***tert*-Butyl 3-(2-oxoethyl)-1*H*-indole-1-carboxylate (III-24)**

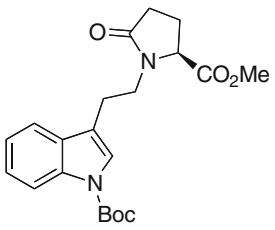


Procedure A:[243] DIBAL-H (1 M solution in CH_2Cl_2, 49.1 mL, 49.10 mmol, 2 equiv) was added to a solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (**III-23a**) (7.10 g, 24.54 mmol, 1 equiv) in CH_2Cl_2 (300 mL) at −78 °C. The solution was stirred for 1.5 h at this temperature and was then quenched with MeOH at −78 °C. Next, the solution was allowed to warm to room temperature for 2 h. The mixture was then diluted with EtOAc and washed with a Na/K tartrate saturated solution, the organic layer was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was purified by chromatography (10:1, hexane–EtOAc) to give 2.20 g of **III-24** as a yellow oil (37 %).

Procedure B: DIBAL-H (1 M solution in toluene 11.46 mL, 11.46 mmol, 1.5 equiv) was added to a solution of *tert*-butyl 3-(cyanomethyl)-1*H*-indole-1-carboxylate (**III-23b**) (1.96 g, 7.64 mmol, 1 equiv) in CH_2Cl_2 (76 mL) at −78 °C over 30 min. The solution was stirred for 30 min at this temperature and, then quenched with EtOH (1.5 ml) at −78 °C, and allowed to warm up to room temperature. The reaction was treated with sat. NH_4Cl solution (30 ml) and 3 M H_2SO_4 solution (100 ml). The aqueous phase was washed with CH_2Cl_2, the organic layer dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to produce aldehyde **III-24** as a yellow oil, which was used immediately without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, J = 2.3 Hz, 1H), 8.16 (br d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.35 (td, J = 7.2, 1.2 Hz, 1H), 7.26 (td, J = 7.6, 1.0 Hz, 1H), 3.76 (dd, J = 2.1, 1.0 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 198.5 (CH), 149.5 (C), 135.5 (C), 130.1 (C), 124.8 (CH), 124.8 (CH), 122.8 (CH), 118.7 (CH), 115.4 (CH), 110.9 (C), 83.9 (C), 40.0 (CH_2), 28.2 (CH_3, 3C). HRMS-ESI *m/z* calcd for $C_{16}H_{21}NO_4Na$ $[M + MeOH + Na]^+$ 314.1368, found, 314.1369.

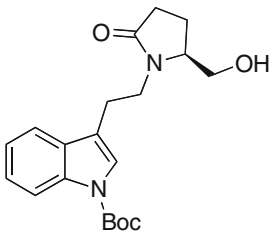
(S)-*tert*-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-25)



Et_3N (0.798 mL, 5.73 mmol, 1.5 equiv) was added to a solution of crude aldehyde **III-24** (3.82 mmol, 1 equiv) and (*L*)-glutamic acid methyl ester hydrochloride (889 mg, 4.20 mmol, 1.02 equiv) in CH_2Cl_2 (39 mL). After 15 min triacetoxyborohydride (1.21 g, 5.73 mmol, 1.5 equiv) was added. The mixture was stirred at room temperature for 12 h. Ther reaction mixture was diluted with EtOAc, washed 3 times with sat. $NaHCO_3$, and brine. After the evaporation of the solvent, it was purified by chromatography (1:1 to 1:2, hexane/EtOAc) to give 1.14 g of ester **III-25** as a yellow oil (39 % over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.41 (s, 1H), 7.31 (td, J = 7.4, 1.2 Hz, 1H), 7.24 (td, J = 7.3, 1.0 Hz, 1H), 4.08 (dd, J = 9.0, 3.1 Hz, 1H), 4.00 (ddd, J = 13.9, 9.0, 5.6 Hz, 1H), 3.73 (s, 3H), 3.24 (ddd, J = 13.9, 8.6, 6.7 Hz, 1H), 3.00 (dddd, J = 14.5, 9.0, 6.6, 0.8 Hz, 1H), 2.87 (dddd, J = 14.5, 8.7, 5.8, 0.9 Hz, 1H), 2.51 (ddd, J = 16.8, 9.3, 9.2 Hz, 1H), 2.36 (ddd, J = 16.7, 9.6, 3.8 Hz, 1H), 2.26–2.16 (m, 1H), 2.08–2.01 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 175.3 (C), 172.5 (C), 149.7 (C), 135.5 (C), 130.3 (C), 124.5 (CH), 123.0 (CH), 122.5 (CH), 118.8 (CH), 117.5 (C), 115.3

(CH), 83.6 (C), 60.2 (CH), 52.5 (CH_3), 42.1 (CH_2), 29.5 (CH_2), 28.2 (CH_3, 3C), 23.1 (CH_2, 2C). HRMS-ESI *m/z* calcd for $C_{21}H_{26}N_2O_5Na$ $[M + Na]^+$ 409.1739, found 409.1741. $[\alpha]_D$ = -6.61 (c = 1.16, $CHCl_3$).

(S)-*tert*-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-26)

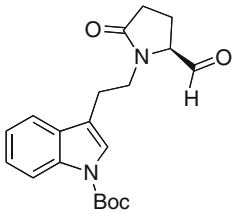


Procedure A: Lithium borohydride (198 mg, 8.19 mmol, 4 equiv) was added to a solution of ester **III-25** (1710 mg, 2.05 mmol, 1 equiv) in a mixture of THF (27 mL) and Et_2O (21 mL) at 0 °C. The reaction was allowed to warm up to room temperature and was left to stir for 16 h. Then, an appropriate amount of water necessary to react with $LiBH_4$ were added, as was $MgSO_4 \cdot 7H_2O$. The mixture was stirred until the evolution of gas ceased, was then filtered through a path of Celite. After the evaporation of the solvent, alcohol **III-26** was obtained as a colourless oil.

Procedure B:[243] Sodium borohydride (447 mg, 11.34 mmol, 4 equiv) was added to a solution of ester **III-25** (1.10 g, 2.83 mmol, 1 equiv) and calcium chloride (649 mg, 5.67 mmol, 2 equiv) in a mixture of THF (38 mL) and Et_2O (28 mL) at 0 °C. The reaction was allowed to warm up to room temperature and was left to stir for 1 day. Then, an appropriate amount of water necessary to react with the $NaBH_4$ were added and as was $MgSO_4 \cdot 7H_2O$. The mixture was stirred until the evolution of gas ceased, and was then filtered through a path of Celite. After the evaporation of the solvent, **III-26** was obtained as a colourless oil.

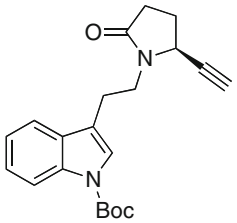
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.42 (s, 1H), 7.31 (td, J = 7.8, 1.1 Hz, 1H), 7.23 (td, J = 7.2, 0.9 Hz, 1H), 3.91 (ddd, J = 13.8, 9.2, 5.8 Hz, 1H), 3.77–3.73 (m, 1H), 3.62–3.55 (m, 2H), 3.36 (ddd, J = 13.8, 9.0, 6.2 Hz, 1H), 3.03 (ddd, J = 14.3, 9.1, 6.1 Hz, 1H), 2.90 (ddd, J = 14.3, 8.9, 5.9 Hz, 1H), 2.45 (ddd, J = 17.0, 9.9, 7.3 Hz, 1H), 2.33 (ddd, J = 17.0, 10.1, 5.3 Hz, 1H), 2.08–1.98 (m, 1H), 1.91–1.83 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 176.0 (C), 149.7 (C), 135.5 (C), 130.4 (C), 124.5 (CH), 123.1 (CH), 122.5 (CH), 118.9 (CH), 117.7 (C), 115.3 (CH), 83.6 (C), 63.5 (CH_2), 59.6 (CH), 41.3 (CH_2), 30.4 (CH_2), 28.2 (CH_3, 3C), 23.3 (CH_2), 21.3 (CH_2). HRMS-ESI *m/z* calcd for $C_{20}H_{26}N_2O_4Na$ $[M + Na]^+$ 381.1790, found 381.1773. $[\alpha]_D$ = 13.40 (c = 1.03, $CHCl_3$).

(*S*)-*tert*-Butyl 3-(2-(2-Formyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-27)



Dess-Martin periodinane (1.00 g, 2.35 mmol, 1.1 equiv) was added to a solution of alcohol **III-26** (0.77 g, 2.14 mmol, 1 equiv) in CH_2Cl_2 (24 mL). The reaction mixture was stirred at room temperature for 20 min, and then saturated aqueous $Na_2S_2O_3$ was added slowly. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to produce aldehyde **III-27** as a yellow oil, which was used immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, $J = 2.3$ Hz, 1H), 8.12 (br d, $J = 7.8$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.41 (s, 1H), 7.31 (td, $J = 7.8$, 1.1 Hz, 1H), 7.24 (td, $J = 7.6$, 1.0 Hz, 1H), 4.01–3.94 (m, 2H), 3.34 (ddd, $J = 13.9$, 8.5, 7.0 Hz, 1H), 3.01 (ddd, $J = 14.4$, 8.9, 6.8 Hz, 1H), 2.88 (dddd, $J = 14.5$, 8.5, 5.8, 0.8 Hz, 1H), 2.44–2.40 (m, 2H), 2.22–2.11 (m, 1H), 2.05–1.97 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 198.6 (CH), 175.3 (C), 149.6 (C), 136.1 (C), 135.5 (C), 124.6 (CH), 123.2 (CH), 122.6 (CH), 118.8 (CH), 117.2 (C), 115.3 (CH), 83.7 (C), 66.1 (CH), 42.6 (CH_2), 29.3 (CH_2), 28.2 (CH_3, 3C), 23.3 (CH_2), 19.4 (CH_2).

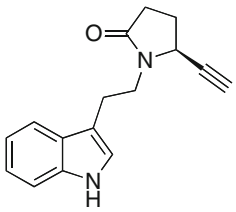
(*S*)-*tert*-Butyl 3-(2-(2-Ethynyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-28)



Potassium carbonate (614 mg, 4.44 mmol, 2.1 equiv) was added to a stirring solution of aldehyde **III-27** (765 mg, 2.15 mmol, 1 equiv) and dimethyldiazo-2-oxopropylphosphonate (495 mg, 2.58 mmol, 1.2 equiv) in MeOH (12 mL). The resulting solution was stirred for 12 h and was then quenched with water (0.34 ml) and extracted with CH_2Cl_2. The combined organic phases were washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to produce 25 mg of the alkyne **III-28** as a brown oil, which was used without further purification (36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.44 (s, 1H), 7.31 (td, $J = 7.6$, 1.3 Hz,

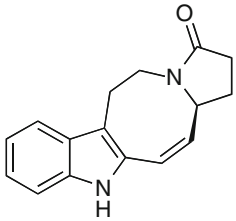
1H), 7.24 (td, $J = 7.2$, 1.0 Hz, 1H), 4.25 (ddd, $J = 7.4$, 5.1, 2.2 Hz, 1H), 3.93 (ddd, $J = 13.8$, 9.3, 5.9 Hz, 1H), 3.46 (ddd, $J = 13.6$, 9.1, 6.2 Hz, 1H), 3.06–2.90 (m, 2H), 2.56–2.48 (m, 1H), 2.41 (d, $J = 2.2$ Hz, 1H), 2.40–2.24 (m, 2H), 2.12–2.04 (m, 1H), 1.66 (s, 9H);.^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.2 (C), 149.7 (C), 135.5 (C), 130.4 (C), 124.5 (CH), 123.1 (CH), 122.5 (CH), 118.9 (CH), 117.5 (C), 115.3 (CH), 83.5 (C), 81.6 (CH), 73.5 (C), 49.5 (CH), 41.1 (CH_2), 29.9 (CH_2), 28.2 (CH_3, 3C), 26.3 (CH_2), 23.1 (CH_2). HRMS-ESI *m/z* calcd for $C_{21}H_{24}N_2O_3Na$ $[M + Na]^+$ 375.1685, found 375.1686.

(*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-5-ethynylpyrrolidin-2-one (III-29)



A solution of **III-28** (626 mg, 1.78 mmol, 1 equiv) in TFA/CH_2Cl_2 (18/5 mL) was stirred at room temperature for 10 min. Then, the solvent was evaporated and the residue was diluted in EtOAc and washed with $NaHCO_3$. The aqueous phase was extracted with EtOAc several times, and then the solvent was evaporated. After, purification by column chromotography (from 2:1 to 1:1 *c*-hexane/EtOAc), 243 mg of compound **III-29** was obtained as a colourless oil (23 % over 4 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.08 (s, 1H), 4.19 (ddd, $J = 7.6$, 5.1, 2.1 Hz, 1H), 4.05–3.98 (m, 1H), 3.48–3.41 (m, 1H), 3.12–2.99 (m, 2H), 2.51 (ddd, $J = 16.6$, 9.6, 6.6 Hz, 1H), 2.40 (d, $J = 2.2$ Hz, 1H), 2.33 (ddd, $J = 16.4$, 9.2, 6.3 Hz, 1H), 2.27–2.17 (m, 1H), 2.09–2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.3 (C), 136.2 (C), 127.5 (C), 122.1 (CH), 121.8 (CH), 119.4 (CH), 118.7 (CH), 112.9 (C), 111.2 (CH), 81.6 (C), 73.4 (CH), 49.3 (CH), 41.4 (CH_2), 30.0 (CH_2), 26.2 (CH_2), 23.1 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$ $[M + Na]^+$ 275.1160, found: 275.1168. $[\alpha]_D = -20.22$ (c = 0.93, $CHCl_3$).

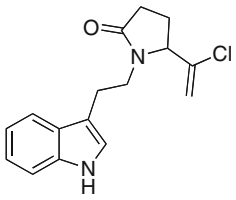
Tetracyclic Compound III-30



$AuCl_3$ (3 mg, 0.008 mmol, 5 mol %) was added to a solution of **III-29** (45 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 16 h. The residue was purified by chromatography (1:2 hexane–

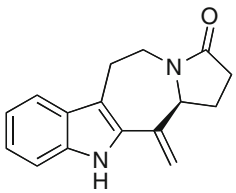
EtOAc) to give 25 mg of tetracyclic compound **III-30** (55 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 1H), 7.20 (t, $J = 8.1$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 6.68 (d, $J = 10.9$ Hz, 1H), 5.65 (dd, $J = 10.7$, 7.1 Hz, 1H), 4.52–4.47 (m, 1H), 3.90 (dt, $J = 14.0$, 4.6 Hz, 1H), 3.83–3.76 (m, 1H), 3.09 (dd, $J = 5.9$, 4.8 Hz, 2H), 2.50 (ddd, $J = 16.3$, 9.2, 6.6 Hz, 1H), 2.42–2.24 (m, 2H), 1.90–1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.1 (C), 136.1 (C), 131.1 (CH), 129.7 (C), 128.6 (C), 124.6 (CH), 123.1 (CH), 119.8 (CH), 118.6 (CH), 113.6 (C), 110.6 (CH), 56.7 (CH), 37.8 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 26.3 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$ $[M + Na]^+$ 275.1160, found 275.1164. $[\alpha]_D = 478.5$ ($c = 0.46$, $CHCl_3$).

(*S*)-1-(2-(1*H*-indol-3-yl)ethyl)-5-(1-chlorovinyl)pyrrolidin-2-one (III-31)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 1H), 7.22 (td, $J = 7.9$, 0.8 Hz, 1H), 7.14 (td, $J = 7.7$, 0.7 Hz, 1H), 7.07 (d, $J = 2.0$ Hz, 1H), 5.33 (d, $J = 1.5$ Hz, 1H), 5.18 (d, $J = 1.5$ Hz, 1H), 4.07–3.96 (m, 2H), 3.18–2.95 (m, 3H), 2.55 (ddd, $J = 17.3$, 10.1, 7.6 Hz, 1H), 2.35 (ddd, $J = 17.0$, 10.1, 5.2 Hz, 1H), 2.12–1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.4 (C), 142.0 (C), 136.4 (C), 127.7 (C), 122.3 (CH), 122.0 (CH), 119.6 (CH), 118.9 (CH), 115.5 (CH_2), 113.3 (C), 111.3 (CH), 64.2 (CH), 53.6 (CH), 41.6 (CH_2), 30.2 (CH_2), 26.4 (CH_2), 23.3 (CH_2). LRMS *m/z* $[M]^+$ 287. HRMS-ESI *m/z* calcd for $C_{16}H_{17}N_2O_{35}ClNa$ $[M + Na]^+$ 311.0927, found 311.0919.

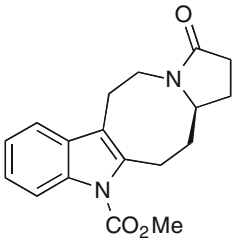
Tetracyclic Compound III-32[166]



A mixture of **III-30** and **III-32** was separated by HPLC chromatography using a NH_2 column (95:5 hexane/ethanol), flow = 1.5 mL/min, $\lambda = 254$ nm. Retention times: 14.24 min, compound **III-30**; 16.35 min, compound **III-32**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.2$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 5.38 (s, 1H), 5.32 (s, 1H), 4.68 (d, $J = 7.7$ Hz, 1H), 4.20–4.15 (m, 1H), 3.43–3.30 (m, 2H),

2.94–2.89 (m, 1H), 2.47–2.24 (m, 3H), 1.92–1.81 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$; DEPT) δ 174.3 (C), 160.9 (C), 142.2 (C), 135.8 (C), 128.8 (C), 123.3 (CH), 119.9 (CH), 119.1 (CH_2), 113.2 (C), 112.8 (CH), 110.5 (CH), 65.1 (CH), 39.8 (CH_2), 30.9 (CH_2), 27.9 (CH_2), 25.1 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$ $[M + Na]^+$ 275.1160, found 275.1156

Tetracylic Compound III-35



Procedure A: Compound **III-30** (36 mg, 0.14 mmol, 1 equiv) and Pd/C (10 wt. % palladium on activated carbon, 7.4 mg, 0.007 mmol, 5 mol %) were dissolved in dry MeOH (1.5 mL). The mixture was put under hydrogen atmosphere and stirred at room temperature for 2.5 h. Then, it was filtered through Celite washing with CH_2Cl_2 and concentrated under reduced pressure. 35 mg of compound **III-33** was used at the next step without further purification (100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.48 (br d, J = 7.6 Hz, 1H), 7.27 (br s, 1H), 7.16–7.07 (overlapping signals (7.14, dt, J = 7.1, 1.3 Hz, 1H), 7.09, dt, J = 7.1, 1.1 Hz, 1H), 2H), 4.16 (ddd, J = 15.0, 9.0, 3.0 Hz, 1H), 3.72 (apparent hept., J = 3.4 Hz, 1H), 3.47 (ddd, J = 14.0, 8.0, 3.4 Hz, 1H), 3.21 301 (m, 3H), 2.86 (dt, J = 15.6, 4.7 Hz, 1H), 3.51 (dt, J = 16.7,9.2 Hz, 1H), 2.30 (ddd, J = 16.7, 9.8, 4.0 Hz, 1H), 2.21–2.14 (m, 1H), 2.12–2.06 (m, 2H), 1.91 (apparent oct., J = 4.6 Hz, 1H), 1.68 (ddt, J = 12.4, 6.9, 3.4 Hz, 1H).

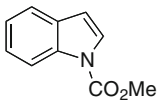
NaHMDS (1 M solution in THF, 170 μL, 0.17 mmol, 1.2 equiv) was added to a solution of compound **III-33** (35 mg, 0.14 mmol, 1 equiv) in dry THF (2 mL) at − 78 °C. After 30 min, methyl chloroformate (14 μL, 0.18 mmol, 1.3 equiv) was added dropwise. The reaction was quenched by addition of MeOH (0.3 mL) after 3.5 h, and was warmed to room temperature. The residue was purified by chromatography (1:5 hexane/EtOAc) to afford 15 mg of compound **III-35** (35 %).

Procedure B: Methyl chloroformate (10 μL, 0.12 mmol, 1.6 equiv) was added to a solution of compound **III-30** (17 mg, 0.07 mmol, 1 equiv) in DMF (0.14 mL) at 0 °C. After 15 min, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. Combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Silica gel chromatography (5.1 hexane: EtOAc) yielded 40 mg of **III-34** as a colourless oil (40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 6.6 Hz, 1H), 7.52 (br d, J = 6.3 Hz, 1H), 7.34 (td, J = 5.9, 1.0 Hz, 1H), 7.28 (td, J = 6.2, 0.9 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 5.77 (dd, J = 8.9, 5.5 Hz, 1H), 4.26 (ddd, J = 9.4, 7.4, 2.0 Hz, 1H), 4.04 (s, 3H), 4.00–3.97 (m, 1H), 3.11 (ddd, J = 12.1,7.4, 2.0 Hz, 1H), 2.95 (ddd, J = 10.6, 6.4,

1.7 Hz, 1H), 2.59–2.52 (m, 2H), 2.33–2.19 (m, 2H), 1.96 (ddt, $J = 9.6$, 6.7, 1.6 Hz, 1H). Compound **III-34** (5.8 mg, 0.02 mmol, 1 equiv) and Pd/C (10 wt. % on activated carbon, 1 mg, 0.001 mmol, 5 mol %) were dissolved in dry MeOH (0.2 mL). The mixture was put under hydrogen atmosphere (4 bar) and stirred at room temperature for 5 h. The reaction mixture was filtered through a pad of Celite washing with CH_2Cl_2 and concentrated under reduced pressure. 6.6 mg of compound **III-35** was obtained (quant.).

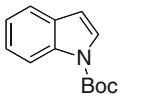
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br dd, $J = 7.2$, 2.2 Hz, 1H), 7.45 (br dd, $J = 6.8$, 1.8 Hz, 1H), 7.31–7.23 (overlapping of signal, $\sim$ 2H), 4.52–4.47 (m, 1H), 4.67 (s, 1H), 3.41 (dt, $J = 14.5$, 4.1 Hz, 1H), 3.34–3.28 (m, 1H), 3.07–2.98 (m, 2H), 2.88–2.78 (m, 2H), 2.59 (ddd, $J = 16.5$, 11.3, 8.1 Hz, 1H), 2.25–1.94 (overlapping of signal, 5H).

Methyl 1*H*-indole-1-carboxylate[244]



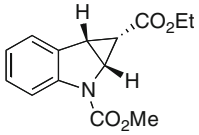
A solution of NaHMDS (1 M solution in THF; 12.69 mL, 12.69 mmol, 1.2 equiv) was added dropwise to a solution of indole (1.24 g, 10.58 mmol, 1 equiv) in THF (130 mL) at −78 °C. After 30 min, methyl chloroformate (1.07 mL, 13.15, 1.3 equiv) was added dropwise and the reaction mixture was allowed to warm to room temperature for 4 h. Then, the reaction mixture was diluted with EtOAc and washed with a sat. NH_4Cl solution. The aqueous phase was extracted 2 times with EtOAc, and finally the organic phases were washed with brine, dried over $MgSO_4$ and concentrated. After silica gel column chromatography (20:1 hexane:EtOAc), 1.43 g of the methyl 1*H*-indole-1-carboxylate was isolated (77 %).

***tert*-Butyl 1*H*-indole-1-carboxylate**[244]



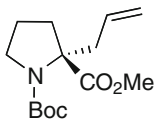
Di-*t*-butyl dicarbonate (2.05 g, 9.39 mmol, 1.05 equiv) and Et_3N (2.50 mL, 17.89 mmol,2 equiv) were added to a solution of indole (1.05 g, 8.94 mmol, 1 equiv) and DMAP (55.0 mg, 0.45 mmol, 5 mol %) in CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred overnight. Then, it was diluted with CH_2Cl_2 and washed with a sat. NH_4Cl solution. The aqueous phase was extracted 2 times with CH_2Cl_2, and finally the organic phases were washed with brine, dried over $MgSO_4$ and concentrated. After silica gel column chromatography (80:1 hexane:EtOAc), 1.92 g of the *tert*-butyl 1*H*-indole-1-carboxylate was isolated (99 %).

(1S,1aR,6bS)-1-ethyl 2-methyl 1,6b-dihydrocyclopropa[b]indole-1,2(1aH)-dicarboxylate (III-39)[65]



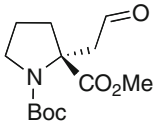
EDA (141 μL, 1.34 mmol, 7 equiv) was added dropwise to a solution of indole (33.6 mg, 0.19 mmol, 1 equiv) and $Cu(hacac)_2$ (4.6 mg, 9.59 μmol, 5 mol %) in CH_2Cl_2 (1.9 mL, 0.1 M). The reaction mixture was stitted at room temperature for14 h, was then filtered through a pad of Celite washing with CH_2Cl_2 and concentrated.

(*R*)-1-*tert*-Butyl 2-methyl 2-allylpyrrolidine-1,2-dicarboxylate (III-48)



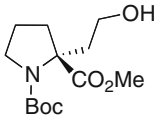
Et_3N (4.75 mL, 34.1 mmol, 2 equiv) was added to a mixture of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **III-47** (2.87 g, 17.05 mmol, 1 equiv), $(Boc)_2O$ (4.11 mL, 17.91 mmol, 1.05 equiv) and DMAP (104 mg, 0.85 mmol, 5 mol %) in dry CH_2Cl_2 (57 mL). The reaction was stirred at room temperature overnight. It was then diluted with CH_2Cl_2 and washed 3 times with a 1 M HCl solution. The organic phase was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to produce an oil, which was purified by column chromatography (7:1 to 5:1 *c*-hexane/EtOAc) to produce 15.26 g of colourless oil (72 %, 2:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.67 (m, 1H major + 1H minor), 5.11–506 (m, 2H major + 2H minor), 3.68 (br s, 3H major + 3H minor), 3.68–3.63 (m, 1H major), 3.58–3.52 (m, 1H minor), 3.38–3.27 (m, 1H major + 1H minor), 3.06 (dd, J = 13.8, 5.0 Hz, 1H minor), 2.88 (dd, J = 13.9, 5.7 Hz, 1H major), 2.59–2.54 (overlapping dd and dd, J = 13.7, 13.6, 5.2 Hz, 1H major + 1H minor), 2.13–1.94 (m, 2H major + 2H minor), 1.88–1.73 (m, 2H major + 2H minor). ^{13}C NMR (400 MHz, $CDCl_3$) δ 175.2 (C major), 175.1 (C minor), 154.0 (C minor), 153.7 (C major), 133.8 (CH minor), 133.4 (CH major), 119.1 (CH_2 major), 118.8 (CH_2 minor), 80.2 (C major), 79.6 (C minor), 67.6 (C minor), 67.1 (C major), 52.2 (CH_3 major + CH_3 minor), 48.6 (CH_2 minor), 48.5 (CH_2 major), 39.7 (CH_2 major), 38.4 (CH_2 minor), 37.1 (CH_2 major), 35.8 (CH_2 minor), 28.5 (CH_3 minor, 3C), 28.5 (CH_3 major, 3C), 23.2 (CH_2 major), 22.7 (CH_2 minor). HRMS-ESI *m/z* calcd for $C_{14}H_{23}NO_4Na$ $[M + Na]^+$ 292.1525, found 292.1522. $[\alpha]_D$ = 60.2 (c = 0.14, CH_2Cl_2).

(*R*)-1-*tert*-Butyl 2-methyl 2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (III-49)



An oven-dried flask equipped with a stir bar charged with a solution of (*R*)-1-*tert*-butyl 2-methyl 2-allylpyrrolidine-1,2-dicarboxylate **III-48** (9.86 g, 36.6 mmol, 1 equiv) in dry CH_2Cl_2 (183 mL) was cooled to −78 °C. Ozone was bubbled through the mixture until a strong blue colour persisted, at which point the solution was bubbled with oxygen to remove all excess ozone, as indicated by the disappearance of the blue colour. Dimethyl sulfide (126 mL, 1721 mmol, 47 equiv) was added, the reaction was allowed to warm to room temperature, and the mixture was stirred for 12 h. The reaction mixture was concentrated *in vacuo*, then the crude was purified using combiflash (from 10, 20 to 35 % *c*-hexane/EtOAc) to give 8.0954 g of the product as a colourless oil (78 %, 3:1 mixture of rotamers). NMR (400 MHz, $CDCl_3$) δ 9.81–9.80 (m, 1H major + 1H minor), 3.77 (s, 3H minor), 3.77 (s, 1H major), 3.75–3.72 (m, 1H major + 1H minor), 3.63–3.35 (m, 1H major + 1H minor), 3.28 (d, $J = 16.2$ Hz, 1H major), 3.23 (d, $J = 2.6$ Hz, 1H minor), 3.17 (d, $J = 16.2$ Hz, 1H major), 3.17 (d, $J = 16.0$ Hz, 1H minor), 3.05 (dd, $J = 16.1$, 1.4 Hz, 1H minor), 3.00 (d, $J = 16.0$ Hz, 1H minor), 2.61 (ddd, $J = 15.4$, 13.5, 7.5 Hz, 1H minor), 2.52 (ddd, $J = 16.1$, 13.4, 7.4 Hz, 1H major), 2.37–2.31 (m, 1H minor), 2.30–2.23 (m, 1H major + 1H minor), 2.09–1.92 (m, 2H major), 1.52 (s, 9H major), 1.50 (s, 9H minor). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 198.7 (C major), 198.3 (C minor), 174.3 (C major), 172.8 (C minor), 148.2 (C major), 147.1 (C minor), 85.2 (CH_3 major, 3C + CH_3 minor, 3C), 66.9 (C major + C minor), 53.3 (CH_3 major, CH_3 minor), 49.2 (CH_2 minor), 49.0 (CH_2 major, 2C + CH_2 minor), 48.8 (CH_2 minor), 37.6 (CH_2 major), 37.5 (CH_2 minor), 36.9 (CH_2 minor), 36.2 (CH_2 major), 27.7 (CH_3 major, 3C), 27.6 (CH_3 minor, 3C), 23.3 (CH_2 major), 22.9(CH_2 minor). HRMS-ESI *m/z* calcd for $C_{13}H_{21}NO_5Na$ $[M + Na]^+$ 294.1317, found 294.1305. $[\alpha]_D = 44.5$ (c = 0.08, CH_2Cl_2).

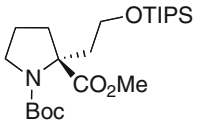
(*R*)-1-*tert*-Butyl 2-methyl 2-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate (III-50)



(*R*)-1-*tert*-butyl 2-methyl 2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate **III-49** (499.3 mg, 1.84 mmol, 1 equiv) was dissolved in anhydrous Et_2O (37 mL) under argon atmosphere at 0 °C. A solution of $Zn(BH_4)_2$ (0.5 M solution in Et_2O; 2.7 mL, 0.55 mol, 1.5 equiv) was added dropwise. The resulting solution was stirred at 0 °C for 1 h. The reaction was quenched by addition of 10 % citric acid

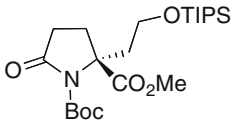
and the reaction was portioned between Et_2O and brine. The organic phase was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude was purified by column chromatography (1:1 *c*-hexane/EtOAc) to give 237.5 mg of alcohol **III-50** as a colourless oil (50 %, 1.3:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72–3.30 (overlapping of signals, (3.67, s, 3H major), (3.66, s, 3H minor), 6H major + 5H minor), 3.55–3.49 (m, 1H minor), 3.43–3.37 (m, 1H major + 1H minor), 2.97 (br s, 1H minor), 2.70 (br s, 1H major). 2.39–2.33 (dt, $J = 14.6$, 6.0 Hz, 1H minor), 2.28–2.01 (m, 4H major + 3H minor), 195–1.75 (m, 2H major + 2H minor), 1.40 (s, 9H minor), 1.36 (s, 9H major). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 175.7 (C major), 175.0 (C minor), 155.0 (C minor), 153.7 (C major), 80.4 (C major), 80.0 (C minor), 67.3 (C minor), 66.9 (C major), 59.0 (CH_2 minor), 58.2 (CH_2 major), 53.3 (CH_3 major + CH_3 minor), 48.6 (CH_2 minor), 48.2 (CH_2 major), 38.4 (CH_2 minor), 38.3 (CH_2 major, 2C), 37.8 (CH_2 minor), 28.4 (CH_3 minor, 3C), 38.3 (CH_3 major, 3C). HRMS-ESI *m/z* calcd for $C_{13}H_{23}NO_5Na$ $[M + Na]^+$ 294.1474, found 294.1496. $[\alpha]_D = 30.8$ (c = 0.08, CH_2Cl_2).

(*R*)-1-*tert*-Butyl 2-methyl 2-(2-((Triisopropylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate (III-51)



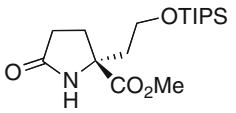
A solution of this alcohol **III-50** (444.9 mg, 1.63 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was treated with imidazole (134 mg, 1.95 mmol, 1.2 equiv), (dimethylamino)pyridine (24.1 mg, 0.20 mmol, 12 mol %), and triisopropylsilyl chloride (0.43 mL, 1.95 mmol, 1.2 equiv). The solution was stirred at room temperature for 3 h and then concentrated *in vacuo.* After column chromatography (15:1 to 1:1 *c*-hexane/EtOAc), 641.6 mg of TIPS-protected alcohol **III-51** was isolated (92 %, 1.7:1 mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84−3.80 (m, 2H major + 2 H minor), 3.76−3.70 (m, (3.73, s, 3H major), (3.72, s, 3H minor), 4H major + 3H minor), 3.65−3.59 (m, 1H minor), 3.52−3.45 (m, 1H major + 1H minor), 2.50−2.04 (m, 4H major + 4H minor), 1.94–1.86 (m, 2H major + 2H minor), 1.46 (d, $J = 2.0$ Hz, 3H major + 3H minor), 1.42 (s, 9H major), 1.42 (s, 9H minor), 1.08 (br s, 18H major + 18H minor). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 175.4 (C major), 175.2 (C minor), 154.3 (C minor), 153.9 (C major), 80.2 (C major), 79.5 (C minor), 67.3 (C minor), 66.8 (C major), 60.2 (CH_2 minor), 59.9 (CH_2 major), 52.2 (CH_3 major + CH_3 minor), 48.6 (CH_2 minor), 48.6 (CH_2 major), 38.2 (CH_2 minor), 38.1 (CH_2 major), 37.1 (CH_2 minor), 37.0 (CH_2 major), 28.5 (CH_3 minor, 3C), 28.4 (CH_3 major, 3C), 23.3 (CH_2 minor), 22.9 (CH_2 major), 18.2 (CH_3 major, 6C + CH_3 minor, 6C), 12.1 (CH major, 3C + CH minor, 3C). HRMS-ESI *m/z* calcd for $C_{22}H_{43}NO_5SiNa$ $[M + Na]^+$ 452.2808, found 452.2815. $[\alpha]_D = 40.9$ (c = 0.13, CH_2Cl_2).

(*R*)-1-*tert*-Butyl 2-methyl 5-oxo-2-(2-((Triisopropylsilyl)oxy)ethyl) pyrrolidine-1,2-dicarboxylate (III-52)



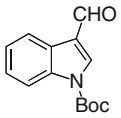
Sodium periodate (1.22 g, 5.71 mmol, 4 equiv) and ruthenium(III) chloride hydrate (59.2 mg, 0.29 mmol, 20 mol %) to a solution of pyrrolidine **III-51** (612.9 mg, 1.43 mmol, 1 equiv) in MeCN (2.9 mL), CCl_4 (2.9 mL) and H_2O (4.8 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 24 h. The solid material was filtered off and the filtrate concentrated (filtration through Celite washing with EtOAc). The residue was partitioned between EtOAc and brine and the organic phase was washed with brine and concentrated. After column chromatography (5:1 *c*-hexane/EtOAc), 355.0 mg of the pyrrolidone **III-52** was isolated (56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91–2.86 (m, 1H), 3.77 + 3.72 (overlapping signals (3.73, br s, 3H), 4H), 2.66–2.54 (m, 2H), 2.52–2.46 (m, 1H), 2.45–2.38 (m, 1H), 2.33–2.26 (m, 1H), 2.10–2.02 (m, 1H), 1.46 (br s, 9H), 1.05−1.0 (m, 18H + 3H). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 174.6 (C), 173.7 (C), 149.6 (C), 83.7 (C), 67.4 (C), 59.3 (CH_2), 52.7 (CH_3), 37.5 (CH_2), 30.9 (CH_2), 28.0 (CH_3, 3C), 27.9 (CH_2), 18.1 (CH_3, 3C), 12.0 (CH_3, 3C). HRMS-ESI *m/z* calcd for $C_{22}H_{41}NO_6SiNa$ $[M + Na]^+$ 466.2601, found 466.2602. $[\alpha]_D = 41.1$ (c = 0.12, CH_2Cl_2).

(*R*)-Methyl 5-Oxo-2-(2-((triisopropylsilyl)oxy)ethyl)pyrrolidine-2-carboxylate (III-53)



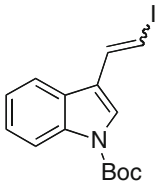
N-Boc pyrrolidone **III-53** (201.0 mg, 0.45 mmol, 1 equiv) was dissolved in CH_2Cl_2 and silica gel (500 mg SiO_2, 1 mmol/10 g) was added. The solvent was taken off and the powdered solid obtained was irradiated in the microwave (800 W) oven for 6 min. The resulting solid was thoroughly washed with methanol, and then concentrated to produce 191.2 mg of pure pyrrolidone **III-53** (quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (br s, 1H), 3.81–3.73 (overlapping signals, (3.78, ddd, J = 15.6, 10.7, 4.9 Hz, 2H), 3.73 (s, 3H), 5H), 2.41 (ddd, J = 12.6, 7.7, 5.3 Hz, 1H), 2.30 (ddd, J = 9.0, 6.6, 3.2 Hz, 2H), 2.17 (dd, J = 14.1, 9.3, 4.2 Hz, 1H), 2.13−2.06 (m, 1H), 10.9- −0.98 (m, 9H + 3H). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 176.9 (C), 174.3 (C), 65.1 (C), 60.4 (CH_2), 52.7 (CH_3), 41.2 (CH_2), 33.1 (CH_2), 29.2 (CH_2), 18.1 (CH, 3C), 11.9 (CH_3, 6C). HRMS-ESI *m/z* calcd for $C_{17}H_{33}NO_4SiNa$ $[M + Na]^+$ 366.2077, found 366.2061. $[\alpha]_D = -50.8$ (c = 0.05, CH_2Cl_2).

***tert*-Butyl 3-formyl-1*H*-indole-1-carboxylate** [241]



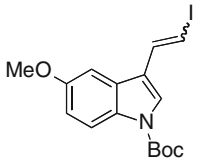
Di-*t*-butyl dicarbonate (15.92 g, 69.30 mmol, 1.2 equiv) was slowly added to a solution of 1*H*-indole-3-carbaldehyde (5.03 g, 36.40 mmol, 1 equiv) [245] and DMAP (0.43 g, 3.46 mmol, 10 mol %) in CH_2Cl_2 (69 mL) [246]. The reaction mixture was stirred for 2 h. Then, the reaction mixture was diluted with CH_2Cl_2 and washed with a sat. NH_4Cl solution. The aqueous phase was extracted 2 times with CH_2Cl_2. Finally the organic phases were washed with brine, dried over $MgSO_4$ and concentrated. 6.39 g of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate was isolated (75 %), which was used in the next step without further purification.

***tert*-Butyl 3-(2-iodovinyl)-1*H*-indole-1-carboxylate (III-55)**



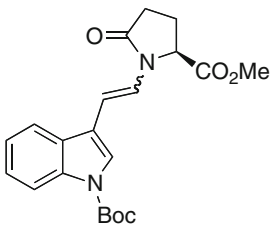
A solution of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (1.42 g, 5.85 mmol, 1 equiv), iodoform (4.57 g, 11.62 mmol, 2 equiv) in THF (29 mL) was added dropwise to a suspension of anhydrous $CrCl_2$ (0.43 g, 34.81 mmol, 6 equiv) in THF (58 mL) at 0 °C. The reaction was allowed to warm to room temperature for 2 h. Then, the reaction mixture was poured into water and extracted with ether. The combined extracts were dried over Na_2SO_4 and concentrated. After silica gel purification by combiflash (from 100 to 95 % *c*-hexane/EtOAc), 1.39 g of *tert*-butyl 3-(2-iodovinyl)-1*H*-indole-1-carboxylate was isolated (65 %, *E/Z* = 2.3:1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H minor), 8.18–8.15 (m, 1H major +1H minor), 7.71 (d, J = 6.2 Hz, 1H major), 7.61 (br s, 1H major), 7.58–7.55 (m, $1H_E + 1H_Z$), 7.51 (br s, $1H_Z$), 7.38–7.34 (m, $1H_E + 1H_Z$) 7.30–7.28 (m, 1H major +1H minor), 6.85 (d, J = 12.0 Hz, 1H major), 6.63 (d, J = 6.9 Hz, 1H minor), 1.70 (s, 9H minor), 1.67 (s, 9H major).

***tert*-Butyl 3-(2-iodovinyl)-5-methoxy-1*H*-indole-1-carboxylate (III-56)**



A solution of *tert*-butyl 3-formyl-5-methoxy-1*H*-indole-1-carboxylate (1.68 g, 6.11 mmol, 1 eqvuiv,), iodoform (4.81 g, 12.23 mmol, 2 equiv) in THF (31 mL) was added dropwised to a suspension of anhydrous $CrCl_2$ (4.51 g, 36.70 mmol, 6 equiv) in THF (61 mL) at 0 °C. The reaction was allowed to warm to room temperature for 2 h, then it was poured into water and extracted 3 times with ether. The combined extracts were dried over Na_2SO_4 and concentrated. Purification using combiflash (0–10 % EtOAc in *c*-hexane) produced 1.75 g of a red–orange oil (735, *E*/*Z* = 4.3.1.0). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H minor), 8.04−8.02 (overlapping signals (8.03, br d, J = 8.5 Hz, 1H major), (m, 1H minor)), 7.58 (br s, 1H major), 7.58−7.48 (overlapping signals (7.50, dd, J = 15.0, 0.7 Hz, 1H major), (7.51, dd, J = 8.4, 0.8 Hz, 1H minor)), 7.13 (d, J = 2.4 Hz, 1H major), 7.01 (d, J = 2.4 Hz, 1H minor), 6.98–6.94 (overlapping signals (6.97 (apparent dd, J = 9.0 Hz, 1H minor), (6.96, dd, J = 9.0, 2.5 Hz, 1H major)), 6.78 (d, J = 14.9 Hz, 1H major), 6.61 (d, J = 8.6 Hz, 1H minor), 3.88 (s, 3H major), 3.87 (s, 3H minor), 1.69 (s, 9H minor), 1.66 (s, 9H major). ^{13}C NMR (pendant; 400 MHz, $CDCl_3$) δ 156.5 (C mino +C major), 156.2 (C minor +C major), 136.6 (CH major), 129.4 (CH minor), 124.6 (CH major), 124.4 (CH minor), 119.6 (C minor + C major), 117.0 (C minor + C major), 116.3 (CH major), 116.2 (CH minor), 113.8 (CH minor), 113.6 (CH major), 102.8 (CH major), 101.4 (CH minor), 84.2 (C major), 84.2 (C minor), 79.3 (CH minor), 75.5 (CH major), 56.0 (CH_3 major), 55.9 (CH_3 minor), 28.4 (CH_3 major + CH_3 minor).

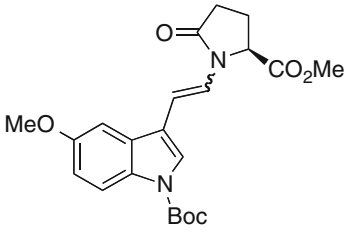
(*S*)-*tert*-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-57)



N,*N*′-Dimethylethane-1,2-diamine (2.4 μL, 0.04 mmol, 20 mol %) and a solution of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (38.0 mg, 0.23 mmol, 1.2 equiv) in THF (1 mL) were added to a soltion of *tert*-butyl 3-(2-iodovinyl)-1*H*-indole-1-carboxylate (**III-55**) (*E*/*Z* = 2.3:1.0; 81.7 mg, 0.22 mmol, 1 equiv), CuI (4.2 mg, 0.02 mmol, 10 mol %) and Cs_2CO_3 (144.0 mg, 0.44 mmol, 2 equiv) in dry THF (0.5 mL) under argon. The Schlenk tube was immersed in a preheated oil bath at 60 °C and the reaction mixture was stirred for 13 h. The resulting mixture was filtered through a silica plug eluting with EtOAc. The filtrate was concentrated to afford a brown oil (*E*-FP/*Z*-FP/*Z*-SM = 1.2:1.0:6.6), which was purified by column chromatography (50:1 to 2:1 *c*-hexane/EtOAc) yielding 61.9 mg of a mixture of both steroisomers (73 %, *E*/*Z* = 5.6:1.0). *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br d, J = 8.0 Hz, 1H), 7.70 (br d, J = 7.4 Hz, 1H),

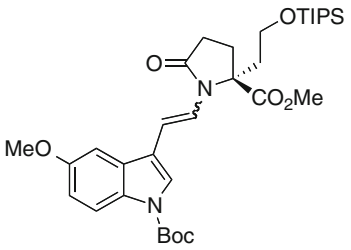
7.64 (d, $J = 15.2$ Hz, 1H), 7.58 (s, 1H), 7.34 (td, $J = 7.3$, 1.2 Hz, 1H), 7.29 (dd, $J = 7.8$, 1.2 Hz, 1H), 5.91 (d, $J = 15.1$ Hz, 1H), 4.61 (dd, $J = 9.4$, 1.9 Hz, 1H), 3.81 (s, 3H), 2.78–2.69 (apparent td, 1H), 2.59–2.44 (overlapping signals, 2H), 2.23 (apparent br t, 1H), 1.67 (s, 9H). *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $J = 8.1$ Hz, 1H), 7.41 (br d, $J = 7.9$ Hz, 1H), 7.34 (td, $J = 7.3$, 1.2 Hz, 1H), 7.26–7.22 (overlapping signals, 2H), 6.92 (d, $J = 9.8$ Hz, 1H), 5.95 (dd, $J = 9.8$, 1.4 Hz, 1H), 4.37 (dd, $J = 9.3$, 2.2 Hz, 1H), 3.36 (s, 3H), 2.49–2.43 (overlapping signals, 2H), 1.98–1.91 (m, 1H), 2.23 (apparent br t, 1H), 1.69 (s, 9H).

(*S*)-*tert*-Butyl 5-Methoxy-3-(2-(2-(methoxycarbonyl)-5-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-58)



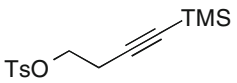
N,*N*′-Dimethylethane-1,2-diamine (3.1 μL, 0.03 mmol, 20 mol %) and a solution of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (24,9 mg, 0.17 mmol, 1.2 equiv) in THF (0.7 mL) were added to a solution of *tert*-butyl 3-(2-iodovinyl)-5-methoxy-1*H*-indole-1-carboxylate (**III-56**) (*E*/*Z* = 4.3.1.0; 57.9 mg, 0.16 mmol, 1 equiv), CuI (2.8 mg, 0.2 mmol, 10 mol %) and Cs_2CO_3 (95.0 mg, 0.32 mmol, 2 equiv) in dry THF (1 mL) under argon. The Schlenk tube was immersed in a preheated oil bath at 60 °C and the reaction mixture was stirred overnight. The resulting mixture was filtered through a silica plug eluting with EtOAc. The filtrate was concentrated to afford a brown oil (*E*/*Z* = 5.2:1.0), which was purified by column chromatography (50:1 to 2:1 *c*-hexane/EtOAc) yielding 49.5 mg of *E*-isomer (82 %, only traces of the *Z*-isomer were detected.). *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br d, $J = 8.7$ Hz, 1H), 7.60–7.56 (overlapping signals (7.58, d, $J = 15.2$ Hz, 1H), (7.56 br s, 1H)), 7.12 (d, $J = 2.4$ Hz, 1H), 6.94 (dd, $J = 9.0$, 2.5 Hz, 1H), 5.87 (d, $J = 15.1$ Hz, 1H), 4.61 (dd, $J = 9.4$, 1.9 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 2.73 (apparent dt, 1H), 2.58–2.19 (overlapping signals, apparent dt, m, 2H), 2.25−2.19 (m, 1H), 1.65 (s, 9H). ^{13}C NMR (DEPTQ; 400 MHz, $CDCl_3$) δ 173.2 (C), 172.1 (C), 156.2 (C), 129.6 (C), 123.0 (2CH), 116.8 (3C), 116.2 (CH), 113.2 (CH), 103.4 (CH), 102.7 (CH), 83.8 (C), 58.5 (CH), 56.0 (CH_3), 53.0 (CH_3), 30.0 (CH_2), 28.4 ($3CH_3$), 23.2 (CH_2). *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br d, $J = 7.9$ Hz, 1H), 7.37 (br s, 1H), 6.95–6.90 (overlapping signals (6.94, dd, $J = 9.0$, 2.5 Hz, 1H), (6.91, d, $J = 9.8$ Hz, 1H)), 6.84 (d, $J = 2.4$ Hz, 1H), 4.38 (dd, $J = 9.3$, 2.5 Hz, 1H), 3.83 (s, 3H), 3.38 (s, 3H), 2.54−2.37 (overlapping signals, 2H), 2.23−2.12 (m, 1H), 1.99–1.93 (m, 1H), 1.67 (s, 9H). HRMS-ESI *m/z* calcd for $C_{22}H_{26}N_2O_6$ $[M + Na]^+$ 437.1689, found 437.1700. $[\alpha] = -33.5$ (c = 1.0, CH_2Cl_2).

(*R*)-*tert*-Butyl 5-Methoxy-3-(2-(2-(methoxycarbonyl)-5-oxo-2-(2-((triisopropylsilyl)oxy)ethyl)pyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-60)



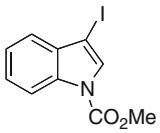
N,*N*′-Dimethylethane-1,2-diamine (2.4 μL, 0.02 mmol, 20 mol %) and a solution of (*R*)-methyl 5-oxo-2-(2-((triisopropylsilyl)oxy)ethyl)pyrrolidine-2-carboxylate (**III-53**) (41.6 mg, 0.12 mmol, 1.2 equiv) in THF (0.7 mL) were added to a solution of *tert*-butyl 3-(2-iodovinyl)-5-methoxy-1*H*-indole-1-carboxylate (**III-56**) (*E*/*Z* = 4.3.1.0; 44.0 mg, 0.11 mmol, 1 equiv), CuI (2.1 mg, 0.01 mmol, 10 mol %) and Cs_2CO_3 (71.8 mg, 0.22 mmol, 2 equiv) in dry THF (0.7 mL) under argon. The Schlenk tube was immersed in a preheated oil bath at 60 °C and the reaction mixture was stirred overnight. The resulting mixture was filtered through a silica plug eluting with EtOAc. The filtrate was concentrated to afford a brown oil (*E*-FP/*E*-SM/*Z*-SM = 1.6:2.3:1.0), which was purified by column chromatography (8:1 to 1:1 *c*-hexane/EtOAc) yielding 38.4 mg of an inseparable 1:2 mixture of the *E*-isomer and amide **III-53** (27 %). Main signal of the *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br d, J = 7.7 Hz, 1H), 7.59–7.54 (overlapping signals (7.57, d, J = 15.2 Hz, 1H), (7.54 br s, 1H), 2H), 7.06 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 9.0, 2.5 Hz, 1H), 5.86 (d, J = 15.1 Hz, 1H), 4.60 (dd, J = 9.4, 1.8 Hz, 1H), 3.87 (s, 3H).

4-(Trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate[247]



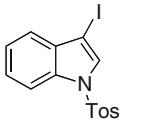
Et_3N (5.16 mL, 37.23 mmol, 1.5 equiv), DMAP (0.09 g, 0.74 mmol, 3 mol %) and tosyl chloride (5.76 g, 29.60 mmol, 1.2 equiv) were added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (5.51 g, 24.67 mmol, 1 equiv)[248] in CH_2Cl_2 (241 mL) at 0 °C. The resulting mixture was stirred for 6 h before the reaction was quenched with sat. aq. NH_4Cl. A standard extractive work up followed by flash chromatography (15:1 *c*-hexane/EtOAc) afforded 2.54 g of 4-(trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate as a pale yellow oil (35 %) [249].

Methyl 3-iodo-1*H*-indole-1-carboxylate (III-79CO_2Me)[192]



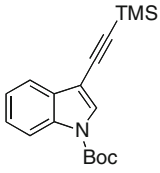
A solution of NaHMDS (1 M solution in THF; 4.90 mL, 4.90 mmol, 1.2 equiv) was added dropwise to a solution of 3-iodo-1*H*-indole [194] (0.99 g, 4.09 mmol, 1 equiv) in THF (15 mL) at −78 °C. After 1 h, methyl chloroformate (0.42 mL, 5.32 mmol, 1.3 equiv) was added dropwise and the reaction mixture was allowed to warm to room temperature for 3 h. Then, the reaction mixture was diluted with EtOAc and washed with a 10 % HCl solution. The aqueous phase was extracted 2 times with EtOAc. Finally, the organic phases were washed with brine, dried over $MgSO_4$ and concentrated. [250] 1.12 g of methyl 3-iodo-1*H*-indole-1-carboxylate was obtained (91 %), which was used in the next step without further purification.

3-Iodo-1-tosyl-1*H*-indole (III-79Tos)[194]



Tetrabutylammonium hydrogensulfate (0.10 g, 0.29 mmol, 7 mol %), potassium hydroxide (50 % aq. solution; 5 mL), and a solution of *p*-toluenesulfonyl chloride (0.97 g, 4.99 mmol, 1.2 equiv) in toluene (7 mL) were added to a solution of 3-iodo-1*H*-indole[194] (1.11 g, 4.16 mmol, 1 equiv) in toluene (4 mL). After stirring for 4 h, water was added, then the aqueous phase was washed 2 times with EtOAc. Finally, the organic phases were washed with brine, dried over $MgSO_4$ and concentrated to afford 1.43 g of 3-iodo-1-tosyl-1*H*-indole (87 %), which weas used in the next step without further purification [251].

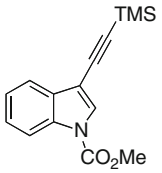
***tert*-Butyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate (III-80Boc)**[191]



[$PdCl_2(PPh_3)_2$] (62.01 mg, 0.09 mmol, 2 mol %), trimethylsilylacetylene (0.73 mL, 5.15 mmol, 1.2 equiv) and CuI (43.98 mg, 0.22 mmol, 5 mol %) were added to a solution of compound **III-79Boc** (1.47 g, 4.30 mmol, 1 equiv) in Et_3N (14 mL). The mixture was stirred at room temperature overnight. After removal of solvent under vacuum, the residue was purified by a column chromatograph on

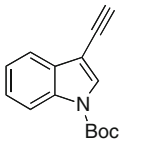
silica gel (50:1 *c*-hexanes/EtOAc) to give 1.30 g of *tert*-butyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate **(III-80Boc**) (96 %) [252].

Methyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate (III-80CO_2Me) [192]



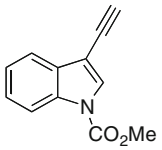
[$PdCl_2(PPh_3)_2$] (53.76 mg, 0.07 mmol, 2 mol %), trimethylsilylacetylene (0.63 mL, 4.42 mmol, 1.2 equiv) and CuI (35.68 mg, 0.18 mmol, 5 mol %) were added to a solution of compound **III-79CO_2Me** (1.02 g, 3.68 mmol, 1 equiv) in Et_3N (12 mL). The mixture was stirred at room temperature overnight. After removal of solvent under vacuum, 1.01 g of methyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate **(III-80CO_2Me**) was isolated (quant.), which was used in the next step without further purification [252].

***tert*-Butyl 3-ethynyl-1*H*-indole-1-carboxylate (III-81Boc)[253]**



KF (0.25 g, 4.24 mmol, 1.5 equiv) was added to a stirred solution of *tert*-butyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate **III-80Boc** (885.2 mg, 2.82 mmol, 1 equiv) in DMSO (10 mL) with a few drops of water at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water and dried over $MgSO_4$. After column chromatography (50:1 *c*-hexane/EtOAc), 543.5 mg of *tert*-butyl 3-ethynyl-1*H*-indole-1-carboxylate **III-81Boc** was obtained (80 %). The spectroscopic data was consistent with previously reported results.

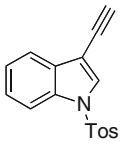
Methyl 3-ethynyl-1*H*-indole-1-carboxylate (III-81CO_2Me)[254]



KF (0.27 g, 4.64 mmol, 1.5 equiv) was added to a stirred solution of **III-80CO_2Me** (0.84 g, 3.09 mmol, 1 equiv) in DMSO (12 mL) with a few drops of water at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water and dried over $MgSO_4$. After column chromatography (25:1 *c*-hexane/EtOAc), 0.39 g of **III-81CO_2Me** was obtained (63 %) as an

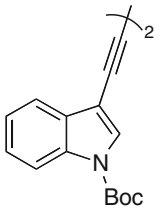
orange solid. The spectroscopic data was consistent with previously reported results.

3-Ethynyl-1-tosyl-1*H*-indole (III-81Tos)[255]



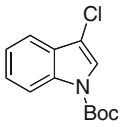
KF (0.17 g, 2.91 mmol, 1.5 equiv) was added to a stirred solution of **III-80CO$_2$Tos** (0.71 g, 1.94 mmol, 1 equiv) in DMSO (12 mL) with a few drops of water at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water and dried over $MgSO_4$, affording 0.51 g of **III-81Tos** as a white solid (89 %). The spectroscopic data was consistent with previously reported results.

Glaser-Hay product III-83



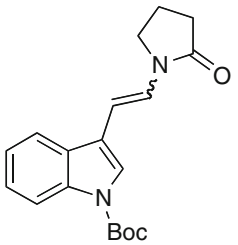
In a Slenck tube, $CuCl_2$ (115 mg, 0.86 mmol, 0.2 equiv), lactam **III-54** (307 mg, 2.15 mmol, 5 equiv), and Cs_2CO_3 (280 mg, 0.86 mmol, 2 equiv) were combined. Then reaction flask was purged with oxygen gas. After 15 min, dry DMSO (2.1 mL) was added to the reaction. A balloon filled with oxygen gas was connected to the Slenck tube via a needle, then it was placed in an oil bath and heated to 70 °C. A solution of N-Boc alkynylindole **III-81Boc** (104 mg, 0.43 mmol, 1 equiv) in dry DMSO (2.1 mL) was added over 4 h using a syringe pump. After complete addition of the alkyne, the reaction mixture was allowed to cool to room temperature. The complex mixture was extracted with 10 % HCl solution, the aqueous phase was washed 3 times with EtOAc, and the organic phase was concentrated. The reaction mixture was purified by flash chromatography on silica gel (50:1 hexane/EtOAc) affording 49 mg of the Glaser-type product **III-83** (26 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br d, $J = 8.8$ Hz, 2H), 7.90 (s, 2H), 7.75 (br d, $J = 7.1$ Hz, 2H), 7.38 (td, $J = 7.4$, 1.2 Hz, 2H), 7.33 (td, $J = 7.7$, 1.1 Hz, 2H), 1.68 (s, 18H). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 149.0 (C, 2C), 138.8(C, 2C), 131.3 (CH, 2CH), 130.7 (C, 2C), 127.6 (CH, 2C), 123.7 (CH, 2C), 120.5 (CH, 2C), 115.6 (CH, 2C), 102.4 (C, 2C), 84.8 (C, 2C), 74.3 (C, 2C), 28.3 (CH_3, 2C). LRMS-ESI *m/z* calcd for $C_{30}H_{28}N_2O_4Na$ $[M + Na]^+$ 503.947, found 503.1

***tert*-Butyl 3-chloro-1*H*-indole-1-carboxylate (III-95)**



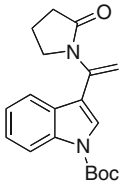
N-chlorosuccinimide (0.89 g, 6.52 mmol, 1 equiv) was added to a solution of *tert*-butyl 1*H*-indole-1-carboxylate (1.04 g, 6.52 mmol, 1 equiv) in MeCN (22 mL). The resulting micture was stirred at 100 °C for 5 h, and was washed with water, extracted with EtOAc, dried over $MgSO_4$ and concentrated. After Silica gel chromatography, 0.69 g of *tert*-butyl 3-chloro-1*H*-indole-1-carboxylate (**III-95**) (100 % to 50:1 *c*-hexane/EtOAc) was isolated (41 %). [256] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, $J = 8.4$, 0.7 Hz, 1H), 7.57 (br s, 1H), 7.53 (ddd, $J = 7.7$, 1.4, 1.0 Hz, 1H), 7.36 (td, $J = 8.1$, 1.7 Hz, 1H), 7.31 (td, $J = 7.7$, 1.2 Hz, 1H), 1.69 (s, 9H).

***tert*-Butyl 3-(2-(2-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-96)**



Cy_2MeN (74 μL, 0.34 mmol, 1.1 equiv) and *N*-vinyl pyrrolidine (51.4 μL, 0.46 mmol, 1.1 equiv) were added to a mixture of **III-95** (105.8 mg, 0.42 mmol, 1 equiv) $[Pd_2(dba)_3]$ (5.77 mg, 0.06 mmol, 15 mol %) and P(*t*-Bu)$_3$ (16.3 μL, 0.01 mmol, 3 mol %) in dioxane (1 mL). The reaction mixture, it was heated to 80 °C for 14 h. After cooling the reaction mixture was diluted with EtOAc and filtered through a pad of Silica gel. The formation of the mixture of *tert*-butyl 3-(2-(2-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (**III-96**) and *tert*-butyl 3-(1-(2-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (**III-97**) was estimated by ^{1}H-NMR of the crude using 1,3,5-trimethoxybenzene as internal standard (**III-96,** 7 % and **III-97**, 16 %). Main signal on ^{1}H NMR for *tert*-butyl 3-(2-(2-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (**III-96**): 6.37 (d, $J = 12.0$ Hz, 1H).

***tert*-Butyl 3-(1-(2-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-98)**



Cy_2MeN (74 μL, 0.34 mmol, 1.1 equiv) and *N*-vinyl pyrrolidine (37 μL, 0.34 mmol, 1.1 equiv) were added to a mixture of **III-94** (92.7 mg, 0.31 mmol, 1 equiv) $[Pd_2(dba)_3]$ (4.3 mg, 0.05 mmol, 15 mol %) and P(*t*-Bu)$_3$ (17.1 μL, 0.01 mmol, 3 mol %) in dioxane (1 mL). The reaction mixture was heated to 80 °C for 14 h. After cooling the reaction mixture, it was diluted with EtOAc and filtered through a pad of Silica gel. The reaction mixture was purified by flash chromatography on silica gel (from 50:1, 10:1 to 2:1 *c*-hexane/EtOAc) affording 9.79 mg of **III-97** (10 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $J = 7.9$ Hz, 1H), 7.60 (s, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.33 (td, $J = 7.3$, 1.2 Hz, 1H), 7.25 (td, $J = 7.3$, 1.1 Hz, 1H), 5.43 (d, $J = 3.3$. Hz, 2H), 3.57 (t, $J = 7.0$ Hz, 2H), 2.57 (t, $J = 8.0$ Hz, 2H), 2,06 (apparent quintuplet, $J = 7.2$ Hz, 2H), 1.68 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$; PENDANT) δ 191.1 (C), 174.7 (C), 136.5 (C), 128.7 (C), 127.6 (C), 125.9 (CH), 124.6 (CH), 123.4 (CH), 120.0 (CH), 118.3 (C), 115.4 (CH), 109.3 (CH_2), 85.6 (C), 49.5 (CH_2), 32.4 (CH_2), 28.4 (CH_3), 18.7 (CH_2).

References

1. Baeyer, A.: Justus Liebigs Ann. der Chem. **140**, 295–313 (1866)
2. Joule, J.A.: Science of Synthesis (Houben-Weyl, Methods of Molecular Transformations), vol 10, pp. 361–652. Georg Thieme Verlag, Stuttgart (2000)
3. Bonjoch, J., Bosch, J.: Alkaloids **48**, 75–189 (1996)
4. Sundberg, R.J.: Indoles. Academic Press, London (1996)
5. Saxton, J.E.: The Chemistry of Heterocyclic Compounds. Academic Press, New York (1994)
6. Döpp, H., Döpp, U., Langer, U., Gerding, B.: Methoden der OrganischenChemie (Houben-Weyl), vol. E6b1, pp. 546–848. Georg Thieme Verlag, Stuttgart (1994)
7. Chadwick, D.J., Jones, R.A., Sundberg, R.J.: *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford. Vol. **4**, 155–376 (1984)
8. Sharma, V., Kumar, P., Pathak, D.: J. Heterocycl. Chem. **47**, 491–502 (2010)
9. Woodward, R.B., Cava, M.P., Ollis, W.D., Hunger, A., Daeniker, H.U., Schenker, K.: J. Am. Chem. Soc. **76**, 4749–4751 (1954)
10. Steyn, P.S.: Tetrahedron Lett. **12**, 3331–3334 (1971)
11. Steyn, P.S.: Tetrahedron **29**, 107–120 (1973)
12. Sames, P.G.: Fortschr. Chem. Org. Naturst. **32**, 51–117 (1975)
13. Shiono, Y., Akiyama, K., Hayashi, H.: Biosci. Biotechnol. Biochem. **64**, 103–110 (2000)
14. Shiono, Y., Akiyama, K., Hayashi, H.: Biosci. Biotechnol. Biochem. **64**, 1519–1521 (2000)
15. Johansen, M. B., Leduc, A. B., Kerr, M. A.: Synlett 2007, 2593–2595 (2007)
16. Yang, L., Deng, G., Wang, D.-X., Huang, Z.-T., Zhu, J.-P., Wang, M.-X.: Org. Lett. **9**, 1387–1390 (2007)
17. Kam, T.-S., Yoganathan, K., Chuah, C.-H.: Tetrahedron Lett. **36**, 759–762 (1995)
18. Kam, T.-S., Lim, K.-H., Yoganathan, K., Hayashi, M., Komiyama, K.: Tetrahedron **60**, 10739–10745 (2004)
19. Joule, J. A., Monteiro, H., Durham, L. J., Gilbert, B., Djerassi, C.: J. Chem. Soc., 4773–4780 (1965)
20. Alvarez, M., Joule, J.A.: In: Cordell, A.G. (ed.) The Alkaloids, vol 57, pp 258–272. Academic Press, New York (2001)
21. Tarselli, M.A., Raehal, K.M., Brasher, A.K., Streicher, J.M., Groer, C.E., Cameron, M.D., Bohn, L.M., Micalizio, G.C.: Nature Chem. **3**, 449–453 (2011)

22. Yoneda, R., Kimura, T., Kinomoto, J., Harusawa, S., Kurihara, T.: J. Heterocycl. Chem. **33**, 1909–1913 (1996)
23. Bonjoch, J., Casamitjana, N., Gràcia, J., Ubeda, M.C., Bosch, J.: Tetrahedron Lett. **31**, 2449–2452 (1990)
24. Blechert, S., Knier, R., Schroers, H., Wirth, T.: Synthesis, 592–604 (1995)
25. Diker, K., de Maindreville, M.D., Lévy, J.: Tetrahedron Lett. **36**, 3511–3512 (1995)
26. Voskressensky, L.G., Borisova, T.N., Kulikova, L.N., Varlamov, A.V., Catto, M., Altomare, C., Carotti, A.: Eur. J. Org. Chem., 3128–3135 (2004)
27. Bennasar, M.L., Zulaica, E., Sole, D., Alonso, S.: Chem. Commun., 3372–3374 (2009)
28. Baran, P.S., Corey, E.J.: J. Am. Chem. Soc. **124**, 7904–7905 (2002)
29. Baran, P.S., Guerrero, C.A., Corey, E.J.J.: Am. Chem. Soc. **125**, 5628–5629 (2003)
30. Yang, L., Deng, G., Wang, D.-X., Huang, Z.-T., Zhu, J.-P., Wang, M.-X.: Org. Lett. **9**, 1387–1390 (2007)
31. Johansen, M.B., Leduc, A.B., Kerr, M.A.: Synlett **2007**, 2593–2595 (2007)
32. Donets, P.A., Van Hecke, K., Van Meervelt, L., Van der Eycken, E.V.: Org. Lett. **11**, 3618–3621 (2009)
33. Subramaniam, G., Kam, T.-S.: Helv. Chem. Acta **91**, 930–937 (2008)
34. Subramaniam, G., Hiraku, O., Hayashi, M., Koyano, T., Komiyama, K., Kam, T.-S.J.: Nat. Prod. **71**, 53–57 (2007)
35. Kam, T.-S., Yoganathan, K., Koyano, T., Komiyama, K.: Tetrahedron Lett. **37**, 5765–5768 (1996)
36. Awang, K., Sévenet, T., Hamid, A., Hadi, A., David, B., Païs, M.: Tetrahedron Lett. **33**, 2493–2496 (1992)
37. Orr, S.T.M., Tian, J., Niggemann, M., Martin, S.F.: Org. Lett. **13**, 5104–5107 (2011)
38. Schultz, E.E., Pujanauski, B.G., Sarpong, R.: Org. Lett. (2012). doi:10.1021/ol203302f
39. Lim, K.-H., Low, Y–.Y., Kam, T.-S.: Tetrahedron Lett. **47**, 5037–5039 (2006)
40. Lim, K.-H., Kam, T.-S.: Helv. Chem. Acta **90**, 31–35 (2007)
41. Yap, W.-S., Gan, C.-Y., Low, Y–.Y., Choo, Y.-M., Etoh, T., Hayashi, M., Komiyama, K., Kam, T.-S.J.: Nat. Prod. **74**, 1309–1312 (2011)
42. Pearson, W.H., Mi, Y., Lee, I.Y., Stoy, P.: J. Am. Chem. Soc. **123**, 6724–6725 (2001)
43. Pearson, W.H., Lee, I.Y., Mi, Y., Stoy, P.: J. Org. Chem. **69**, 9109–9122 (2004)
44. England, D.B., Padwa, A.: Org. Lett. **10**, 3631–3634 (2008)
45. Verniest, G., England, D., De Kimpe, N., Padwa, A.: Tetrahedron **66**, 1496–1502 (2010)
46. Gruit, M., Pews-Davtyan, A., Beller, M.: Org. Biomol. Chem. **9**, 1148–1159 (2011)
47. Barluenga, J., Fernández, A., Rodríguez, F., Fañanás, F.J.: J. Organomet. Chem. **694**, 546–550 (2009)
48. Yadav, J.S., Reddy, B.V.S., Padmavani, B., Gupta, M.K.: Tetrahedron Lett. **45**, 7577–7579 (2004)
49. Bhuvaneswari, S., Jeganmohan, M., Cheng, C.-H.: Chem. Eur. J. **13**, 8285–8293 (2007)
50. Zhang, L.J.: Am. Chem. Soc. **127**, 16804–16805 (2005)
51. Zhang, G., Catalano, V.J., Zhang, L.: J. Am. Chem. Soc. **129**, 11358–11359 (2007)
52. Lu, Y., Du, X., Jia, X., Liu, Y.: Adv. Synth. Catal. **351**, 1517–1522 (2009)
53. Liu, Y., Xu, W., Wang, X.: Org. Lett. **12**, 1448–1451 (2010)
54. Li, G., Liu, Y.: J. Org. Chem. **75**, 3526–3528 (2010)
55. Sanz, R., Miguel, D., Rodríguez, F.: Angew. Chem. Int. Ed. **47**, 7354–7357 (2008)
56. Hirano, K., Inaba, Y., Takahashi, N., Shimano, M., Oishi, S., Fujii, N., Ohno, H.: J. Org. Chem. **76**, 1212–1227 (2011)
57. Wang, L., Li, G., Liu, Y.: Org. Lett. **13**, 3786–3789 (2011)
58. Lebel, H., Marcoux, J.-F., Molinaro, C., Charette, A.B.: Chem. Rev. **103**, 977–1050 (2003)
59. Zhang, D., Song, H., Qin, Y.: Acc. Chem. Res. **44**, 447–457 (2011)
60. Habrant, D., Rauhala, V., Koskinen, A.M.P.: Chem. Soc. Rev. **39**, 2007–2017 (2010)
61. Joullié, M.M., Lassen, K.M.: ARKIVOC **8**, 189–250 (2010)
62. Allen, C.L., Williams, J.M.: J. Chem. Soc. Rev. **40**, 3405–3415 (2011)
63. Welstead, W.J., Stauffer, H.F., Sancilio, L.F.: J. Med. Chem. **17**, 544–547 (1974)

64. Wenkert, E., Alonso, M.E., Gottlieb, H.E., Sanchez, E.L., Pellicciari, R., Cogolli, P.: J. Org. Chem. **42**, 3945–3949 (1977)
65. Gnad, F., Poleschak, M., Reiser, O.: Tetrahedron Lett. **45**, 4277–4280 (2004)
66. Davies, H.M.L., Antoulinakis, E.G.: Intermolecular metal-catalyzed carbenoid cyclopropanations. In: Denmark S.E. et al. (eds.) Organic Reactions, vol 57, pp. 1–416. Wiley, NY (2004)
67. Song, H., Yang, J., Chen, W., Qin, Y.: Org. Lett. **8**, 6011–6014 (2006)
68. Davies, H.M.L., Hedley, S.: J. Chem. Soc. Rev. **36**, 1109–1119 (2007)
69. He, B., Song, H., Du, Y., Qin, Y.: J. Org. Chem. **74**, 298–304 (2008)
70. Magnus, P., Mugrage, B., DeLuca, M., Cain, G.A.: J. Am. Chem. Soc. **111**, 786–789 (1989)
71. Salim, M., Capretta, A.: Tetrahedron **56**, 8063–8069 (2000)
72. Jung, M.E., Slowinski, F.: Tetrahedron Lett. **42**, 6835–6838 (2001)
73. Yang, J., Song, H., Xiao, X., Wang, J., Qin, Y.: Org. Lett. **8**, 2187–2190 (2006)
74. Cuevas-Yañez, E., Muchowski, J.M., Cruz-Almanza, R.: Tetrahedron **60**, 1505–1511 (2004)
75. Yang, J., Wu, H., Shen, L., Qin, Y.: J. Am. Chem. Soc. **129**, 13794–13795 (2007)
76. Shen, L., Zhang, M., Wu, Y., Qin, Y.: Angew. Chem. Int. Ed. **47**, 3618–3621 (2008)
77. Zhang, B., Wee, A.G.H.: *Chem. Commun.,* 4837–4839 (2008)
78. Zhang, M., Huang, X., Shen, L., Qin, Y.: J. Am. Chem. Soc. **131**, 6013–6020 (2009)
79. Gagnon, D., Spino, C.: J. Org. Chem. **74**, 6035–6041 (2009)
80. Bull, J.A., Charette, A.B.: J. Am. Chem. Soc. **132**, 1895–1902 (2010)
81. Sharpless, K.B., Lauer, R.F., Teranishi, A.Y.: J. Am. Chem. Soc. **95**, 6137–6139 (1973)
82. Trost, B.M., Salzmann, T.N., Hiroi, K.: J. Am. Chem. Soc. **98**, 4887–4902 (1976)
83. Ohfune, Y., Tomita, M.: J. Am. Chem. Soc. **104**, 3511–3513 (1982)
84. Mun, J., Smith, M.B.: Synth. Commun. **37**, 813–819 (2007)
85. Fiorenza, M., Reginato, G., Ricci, A., Taddei, M., Dembech, P.: J. Org. Chem. **49**, 551–553 (1984)
86. Rassu, G., Zanardi, F., Battistini, L., Casiraghi, G.: Synlett 1999, 1333–1350 (1999)
87. Rassu, G., Zanardi, F., Battistini, L., Casiraghi, G.: Chem. Soc. Rev. **29**, 109–118 (2000)
88. Zanardi, F., Battistini, L., Rassu, G., Cornia, M., Casiraghi, G.: J. Chem. Soc. Perkin. Trans. **1** 2471–2475 (1995)
89. Davies, H.M.L., Townsend, R.J.: J. Org. Chem. **66**, 6595–6603 (2001)
90. Horwell, D.C., McKiernan, M.J., Osborne, S.: Tetrahedron Lett. **39**, 8729–8732 (1998)
91. Morales, C.L., Pagenkopf, B.L.: Org. Lett. **10**, 157–159 (2008)
92. He, B., Song, H., Du, Y., Qin, Y.J.: Org. Chem. **74**, 298–304 (2009)
93. Meng, W.-H., Wu, T.-J., Zhang, H.-K., Huang, P.-Q.: Tetrahedron Asymmetry **15**, 3899–3910 (2004)
94. Welstead, W.J., Stauffer, H.F., Sancilio, L.F.J.: Med. Chem. **17**, 544–547 (1974)
95. Feng, C.-G., Chen, J., Ye, J.-L., Ruan, Y.-P., Zheng, X., Huang, P.-Q.: Tetrahedron **62**, 7459–7465 (2006)
96. McElwee-White, L., Dougherty, D.A.: J. Am. Chem. Soc. **106**, 3466–3474 (1984)
97. Ohira, S.: Synth. Commun. **19**, 561–564 (1989)
98. Müller, S., Liepold, B., Roth, G. J., Bestmann, H. J.: Synlett 1996, 521–522 (1996)
99. Goundry, W.R.F., Baldwin, J.E., Lee, V.: Tetrahedron **59**, 1719–1729 (2003)
100. Roth, G.J., Liepold, B., Müller, S.G., Bestmann, H.J.: Synthesis, 59–62 (2004)
101. Pietruszka, J.; Witt, A. Synthesis, 4266–4268 (2006)
102. Corey, E.J., Fuchs, P.L.: Tetrahedron Lett. **13**, 3769–3772 (1972)
103. Nkosi, B., Coville, N.J., Hutchings, G.J.: J. Chem. Soc. Chem. Commun., 71–72 (1988)
104. Nkosi, B., Coville, N.J., Hutchings, G.J., Adams, M.D., Friedl, J., Wagner, F.E.J.: Catal. **128**, 366–377 (1991)
105. Conte, M., Carley, A., Hutchings, G.: Catalysis Let. **124**, 165–167 (2008)
106. Porcel, S., Echavarren, A.M.: Angew. Chem. Int. Ed. **46**, 2672–2676 (2007)
107. Morita, N., Krause, N.: Angew. Chem. Int. Ed. **45**, 1897–1899 (2006)
108. Coldham, I., Dobson, B. C., Fletcher, S. R., Franklin, A. I.: Eur. J. Org. Chem., 2676–2686 (2007)

109. Nakao, Y., Kanyiva, K.S., Oda, S., Hiyama, T.: J. Am. Chem. Soc. **128**, 8146–8147 (2006)
110. Zhang, X.-J., Liu, S.-P., Yan, M.: Chin. J. Chem. **26**, 716–720 (2008)
111. Pérez-Galán, P., Delpont, N., Herrero-Gómez, E., Maseras, F., Echavarren, A.M.: Chem. Eur. J. **16**, 5324–5332
112. Fructos, M.R., Belderrain, T.R., Nicasio, M.C., Nolan, S.P., Kaur, H., Díaz-Requejo, M.M., Pérez, P.J.: J. Am. Chem. Soc. **126**, 10846–10847 (2004)
113. Mairena, M.A., Urbano, J., Carbajo, J., Maraver, J.J., Alvarez, E., Díaz-Requejo, M.M., Pérez, P.: J. Inorg. Chem. **46**, 7428–7435 (2007)
114. Caballero, A., Sabater, M., Morilla, M.E., Nicasio, M.C., Belderraín, T.R., Díaz-Requejo, M.M., Pérez, P.: J. Inorg. Chem. Acta **362**, 4599–4602 (2009)
115. Moser, W.R.: J. Am. Chem. Soc. **91**, 1135–1140 (1969)
116. Fructos, M.R., Belderrain, T.R., de Frémont, P., Scott, N.M., Nolan, S.P., Díaz-Requejo, M.M., Pérez, P.J.: Angew. Chem. Int. Ed. **44**, 5284–5288 (2005)
117. Prieto, A., Fructos, M.R.: Mar Díaz-Requejo, M.; Pérez, P. J.; Pérrez-Galán, P.; Delpont, N.; Echavarren, A. M. Tetrahedron **65**, 1790–1793 (2009)
118. Wang, H.; Germanas, J. P. Synlett 1999, 33–36 (1999)
119. Seebach, D., Boes, M., Naef, R., Schweizer, W.B.: J. Am. Chem. Soc. **105**, 5390–5398 (1983)
120. Orsini, F., Pelizzoni, F., Forte, M., Sisti, M., Bombieri, G., Benetollo, F.J.: Heterocycl. Chem. **26**, 837–841 (1989)
121. Artman III, G., Williams, R.M.: Org. Synth. **86**, 262–273 (2009)
122. Dikshit, D.K., Maheshwari, A., Panday, S.K.: Tetrahedron Lett. **36**, 6131–6134 (1995)
123. Wu, G.G.,; Werne, G., Fu, X.; Orr, R.K., Chen, F.X., Cui, J., Sprague, V.M., Zhang, F., Xie, J., Zeng, L., Castellanos, L.P., Chen, Y., Poirier, M., Mergelsberg, I: PCT Int. Appl. WO 2010/028232 (2010)
124. Amedjkouh, M.: Ahlberg. P. Tetrahedron: Asymmetry **13**, 2229–2234 (2002)
125. Köhn, U., Schramm, A., Klofl, F., Görls, H., Arnold, E.: Anders. E. Tetrahedron: Asymmetry **18**, 1735–1741 (2007)
126. Kazmaier, U., Mues, H., Krebs, A.: Chem. Eur. J. **8**, 1850–1855 (2002)
127. Chandan, N., Moloney, M.G.: Org. Biomol. Chem. **6**, 3664–3666 (2008)
128. Moriyama, K., Sakai, H., Kawabata, T.: Org. Lett. **10**, 3883–3886 (2008)
129. Raheem, I.T., Goodman, S.N., Jacobsen, E.N.: J. Am. Chem. Soc. **126**, 706–707 (2003)
130. Chu, W., Perlman, J.H., Gershengorn, M.C., Moeller, K.D.: Bioorg. Med. Chem. Lett. **8**, 3093–3096 (1998)
131. Gao, F., Chen, Q.-H., Wang, F.-P.: Tetrahedron Lett. **50**, 5270–5273 (2009)
132. Narasimhan, S., Balakumar, R.: Aldrichimica Acta **31**, 19–26 (1998)
133. Våbenø, J., Brisander, M., Lejon, T., Luthman, K.: J. Org. Chem. **67**, 9186–9191 (2002)
134. Wipf, P., Kim, Y., Goldstein, D.M.: J. Am. Chem. Soc. **117**, 11106–11112 (1995)
135. Carlsen, P.H.J., Katsuki, T., Martin, V.S., Sharpless, K.B.: J. Org. Chem. **46**, 3936–3938 (1981)
136. Sheehan, J.C., Tulis, R.W.: J. Org. Chem. **39**, 2264–2267 (1974)
137. Yoshifuji, S., Tanaka, K.-I., Kawai, T., Nitta, Y.: Chem. Pharm. Bull. **33**, 5515–5521 (1985)
138. Yoshifuji, S., Tanaka, K.-I., Kawai, T., Nitta, Y.: Chem. Pharm. Bull. **34**, 3873–3878 (1986)
139. Tanaka, K.-I., Yoshifuji, S., Nitta, Y.: Chem. Pharm. Bull. **34**, 3879–3884 (1986)
140. Penning, T.D., Zhu, G.-D., Gandhi, V.B., Gong, J., Liu, X., Shi, Y., Klinghofer, V., Johnson, E.F., Donawho, C.K., Frost, D.J., Bontcheva-Díaz, V., Bouska, J.J., Osterling, D.J., Olson, A.M., Marsh, K.C., Luo, Y., Giranda, V.L.: J. Med. Chem. **52**, 514–523 (2008)
141. Siro, J.G., Martín, J., García-Navío, J.L., Remuiñan, M.J., Vaquero, J.J.: Synlett, 147–148 (1998)
142. Dehli, J.R., Legros, J., Bolm, C.: Chem. Commun., 973–986 (2005)
143. Evano, G., Blanchard, N., Toumi, M.: Chem. Rev. **108**, 3054–3131 (2008)
144. Shen, R., Porco, J.A.: Org. Lett. **2**, 1333–1336 (2000)
145. Shen, R., Lin, C.T., Bowman, E.J., Bowman, B.J., Porco, J.A.: J. Am. Chem. Soc. **125**, 7889–7901 (2003)

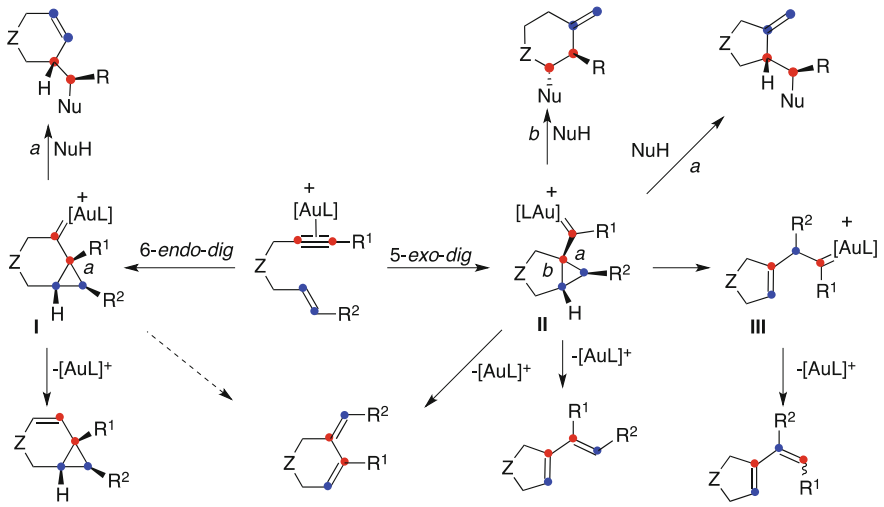
146. Jiang, L., Job, G.E., Klapars, A., Buchwald, S.L.: Org. Lett. **5**, 3667–3669 (2003)
147. Wallace, D.J., Klauber, D.J., Chen, C.-Y., Volante, R.P.: Org. Lett. **5**, 4749–4752 (2003)
148. Klapars, A., Campos, K.R., Chen, C.-Y., Volante, R.P.: Org. Lett. **7**, 1185–1188 (2005)
149. Hesse, S. P., Kirsch, G.: Synthesis 2007, 1571–1575 (2007)
150. Ogawa, T., Kiji, T., Hayami, K., Suzuki, H.: Chem. Lett. **20**, 1443–1446 (1991)
151. Han, C., Shen, R., Su, S., Porco, J.A.: Org. Lett. **6**, 27–30 (2003)
152. Pan, X., Cai, Q., Ma, D.: Org. Lett. **6**, 1809–1812 (2004)
153. Lam, P.Y.S., Vincent, G., Bonne, D., Clark, C.G.: Tetrahedron Lett. **44**, 4927–4931 (2003)
154. Bolshan, Y., Batey, R.A.: Angew. Chem. Int. Ed. **47**, 2109–2112 (2008)
155. Sun, C., Camp, J.E., Weinreb, S.M.: Org. Lett. **8**, 1779–1781 (2006)
156. Meketa, M.L., Weinreb, S.M.: Org. Lett. **9**, 853–855 (2007)
157. Meketa, M.L., Weinreb, S.M.: Tetrahedron **63**, 9112–9119 (2007)
158. Yang, L., Deng, G., Wang, D.-X., Huang, Z.-T., Zhu, J.-P., Wang, M.-X.: Org. Lett. **9**, 1387–1390 (2007)
159. Vaswani, R.G., Chamberlin, A.R.: J. Org. Chem. **73**, 1661–1681 (2008)
160. Takai, K., Nitta, K., Utimoto, K.: J. Am. Chem. Soc. **108**, 7408–7410 (1986)
161. Takai, K.., Ichiguchi, T., Hikasa, S.: Synlett 1999, 1268–1270 (1999)
162. Coleman, R.S., Liu, P.-H.: Org. Lett. **6**, 577–580 (2004)
163. Chu, W., Perlman, J.H., Gershengorn, M.C., Moeller, K.D.: Bioorg. Med. Chem. Lett. **8**, 3093–3096 (1998)
164. Moeller, K.D., Rutledge, L.D.: J. Org. Chem. **57**, 6360–6363 (1992)
165. Simpson, J.C., Ho, C., Berkley Shands, E.F., Gershengorn, M.C., Marshall, G.R., Moeller, K.D.: Biorg. Med. Chem. **10**, 291–302 (2002)
166. Reported results in the Doctoral Thesis of Catalina Ferrer Llabrés (Prof. Echavarren group, January 2008)
167. Johansen, J.E., Christie, B.D., Rapoport, H.J.: Org. Chem. **46**, 4914–4920 (1981)
168. Chianelli, D., Kim, Y.-C., Lvovskiy, D., Webb, T.R.: Bioorg. Med. Chem. **11**, 5059–5068 (2003)
169. Rigo, B.; Gautret, P.; Legrand, A.; Hénichart, J.-P.; Couturier, D. *Synlett*, 998–1000 (1997)
170. Hwang, D.-Y., Chen, S.-G., Gu, J.-T.J.: Chinese Chem. Soc. **26**, 49–52 (1979)
171. Abel, E., Maguire, G.E.M., Murillo, O., Suzuki, I., De Wall, S.L., Gokel, G.W.: J. Am. Chem. Soc. **121**, 9043–9052 (1999)
172. Staffel, W.; Kaeshammer, S.; Kessinger, R.; Vogelsang, R.; Paul, A.; Tuttelberg, M. PCT Int. Appl. WO 2009071479 2009, CAN 151:56717
173. Lögers, M., Overman, L.E., Welmaker, G.S.: J. Am. Chem. Soc. **117**, 9139–9150 (1995)
174. Sutou, N., Kato, K.: Akita., H.: Tetrahedron.: Asymmetry **19**, 1833–1838 (2008)
175. Cacchi, S., Fabrizi, G.: Chem. Rev. **105**, 2873–2920 (2005)
176. Humphrey, G.R., Kuethe, J.T.: Chem. Rev. **106**, 2875–2911 (2006)
177. Gathergood, N., Scammells, P.J.: Org. Lett. **5**, 921–923 (2003)
178. Rudler, H., Parlier, A., Bezennine-Lafollée, S., Vaissermann, J.: Eur. J. Org. Chem. **1999**, 2825–2833 (1999)
179. Bélanger, G., Larouche-Gauthier, R., Ménard, F., Nantel, M., Barabé, F.: Org. Lett. **7**, 4431–4434 (2005)
180. Simandan, T., Smith, M.B.: Synth. Commun. **26**, 1827–1838 (1996)
181. Honda, T., Matsukawa, T., Takahashi, K.: Org. Biomol. Chem. **9**, 673–675 (2011)
182. Mukherjee, A., Liu, R.-S.: Org. Lett. **13**, 660–663 (2011)
183. Ikemoto, T., Ito, T., Nishiguchi, A., Miura, S., Tomimatsu, K.: Org. Process Res. Dev. **9**, 168–173 (2005)
184. Ceccon, J., Greene, A.E., Poisson, J.-F.: Org. Lett. **8**, 4739–4742 (2006)
185. Heider, M., Henkelmann, J., Ruehl, T.: EP 646571 1995. Chem. Abstr. **123**, 229254 (1995)
186. Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y.: *J. Chem. Soc., Chem. Commun.* **1995**, 413–414
187. Arndt, M., Salih, K.S.M., Fromm, A., Gooßen, L.J., Menges, F., Niedner-Schatteburg, G.: J. Am. Chem. Soc. **133**, 7428–7449 (2011)

188. Gooßen, L.J., Rauhaus, J.E., Deng, G.: Angew. Chem. Int. Ed. **44**, 4042–4045 (2005)
189. Gooßen, L.J., Arndt, M., Blanchot, M., Rudolphi, F., Menges, F., Niedner-Schatteburg, G.: Adv. Synth. Catal. **350**, 2701–2707 (2008)
190. Yudha, S.: S.; Kuninobu, Y.; Takai, K.: Org. Lett. **9**, 5609–5611 (2007)
191. R = Boc, He, W.; Li, C.; Zhang, L.: *J. Am. Chem. Soc.* **133**, 8482–8485 (2011)
192. R = CO_2Me, Oakdale, J. S.; Boger, D. L.: *Org. Lett.* **12**, 1132–1134 (2010)
193. R = Tos, Li, Y.; Zou, H.; Gong, J.; Xiang, J.; Luo, T.; Quan, J.; Wang, G.; Yang, Z.: *Org. Lett.* **9**, 4057–4060 (2007)
194. R = Boc: Witulski, B.; Buschmann, N.; Bergsträsser, U.: *Tetrahedron* **56**, 8473–8480 (2000)
195. Möhrle, H., Kilian, R.: Tetrahedron **25**, 5745–5753 (1969)
196. DeKorver, K.A., Li, H., Lohse, A.G., Hayashi, R., Lu, Z., Zhang, Y., Hsung, R.P.: Chem. Rev. **110**, 5064–5106 (2010)
197. Jouvin, K., Couty, F., Evano, G.: Org. Lett. **12**, 3272–3275 (2010)
198. Coste, A., Karthikeyan, G., Couty, F., Evano, G.: Angew. Chem. Int. Ed. **48**, 4381–4385 (2009)
199. Jia, W., Jiao, N.: Org. Lett. **12**, 2000–2003 (2010)
200. Hamada, T., Ye, X., Stahl, S.S.: J. Am. Chem. Soc. **130**, 833–835 (2008)
201. Zhang, Y., Hsung, R.P., Tracey, M.R., Kurtz, K.C.M., Vera, E.L.: Org. Lett. **6**, 1151–1154 (2004)
202. Yao, B., Liang, Z., Niu, T., Zhang, Y.: J. Org. Chem. **74**, 4630–4633 (2009)
203. Coste, A., Karthikeyan, G., Couty, F., Evano, G.: Angew. Chem. Int. Ed. **48**, 4381–4385 (2009)
204. Villa, M.V.J., Targett, S.M., Barnes, J.C., Whittingham, W.G., Marquez, R.: Org. Lett. **9**, 1631–1633 (2007)
205. Mathieson, J.E., Crawford, J.J., Schmidtmann, M., Marquez, R.: Org. Biomol. Chem. **7**, 2170–2175 (2009)
206. Del Valle, J.R., Goodman, M.: J. Org. Chem. **68**, 3923–3931 (2003)
207. Li, Q., Lu, L., Zhong, C., Shi, J., Huang, Q., Jin, X., Peng, T., Qin, J., Li, Z.J.: Phys. Chem. B. **113**, 14588–14595 (2009)
208. Li, Z.; Li, Q.; Shi, J.; Lu, L.; Peng, T.; Qin, J.: *Patent No.* CN 101602759, **2009**
209. Beletskaya, I.P., Cheprakov, A.V.: Chem. Rev. **100**, 3009–3066 (2000)
210. Cabri, W., Candiani, I.: Acc. Chem. Res. **28**, 2–7 (1995)
211. Wucher, P., Caporaso, L., Roesle, P., Ragone, F., Cavallo, L., Mecking, S., Göttker-Schnetmann, I.: Proc. Natl. Acad. Sci. U. S. A. **108**, 8955–8959 (2011)
212. Ziegler, C.B., Heck, R.F.: J. Org. Chem. **43**, 2949–2952 (1978)
213. Ruan, J., Xiao, J.: Acc. Chem. Res. **44**, 614–626 (2011)
214. Andersson, C.M., Hallberg, A.: J. Org. Chem. **53**, 235–239 (1988)
215. Andersson, C.M., Hallberg, A.: J. Org. Chem. **53**, 2112–2114 (1988)
216. Littke, A.F., Fu, G.C.: J. Am. Chem. Soc. **123**, 6989–7000 (2001)
217. Littke, A.F., Fu, G.C.: Angew. Chem. Int. Ed. **41**, 4176–4211 (2002)
218. Littke, A.F., Fu, G.C.: J. Org. Chem. **64**, 10–11 (1999)
219. Schnyder, A., Aemmer, T., Indolese, A.F., Pittelkow, U., Studer, M.: Adv. Synth. Catal. **344**, 495–498 (2002)
220. Chandrasekhar, S., Narsihmulu, C., Sultana, S.S., Reddy, N.R.: Org. Lett. **4**, 4399–4401 (2002)
221. Herrmann, W.A., Böhm, V.P.W., Reisinger, C.-P.: J. Organomet. Chem. **576**, 23–41 (1999)
222. Datta, G.K., von Schenck, H., Hallberg, A., Larhed, M.: J. Org. Chem. **71**, 3896–3903 (2006)
223. Colbon, P., Ruan, J., Purdie, M., Xiao, J.: Org. Lett. **12**, 3670–3673 (2010)
224. Cabri, W., Candiani, I., Bedeschi, A., Santi, R.: J. Org. Chem. **57**, 3558–3563 (1992)
225. Vallin, K.S.A., Zhang, Q., Larhed, M., Curran, D.P., Hallberg, A.: J. Org. Chem. **68**, 6639–6645 (2003)
226. Mo, J., Xu, L., Xiao, J.: J. Am. Chem. Soc. **127**, 751–760 (2004)

227. Mo, J., Xiao, J.: Angew. Chem. Int. Ed. **45**, 4152–4157 (2006)
228. Hyder, Z., Ruan, J., Xiao, J.: Chem. Eur. J. **14**, 5555–5566 (2008)
229. Calò, V., Nacci, A., Monopoli, A., Cotugno, P.: Angew. Chem. Int. Ed. **48**, 6101–6103 (2009)
230. Brice, J.L., Meerdink, J.E., Stahl, S.S.: Org. Lett. **6**, 1845–1848 (2004)
231. Yue, D., Larock, R.C.: Org. Lett. **6**, 1037–1040 (2004)
232. Yue, D., Yao, T., Larock, R.C.: J. Org. Chem. **71**, 62–69 (2005)
233. Putey, A., Fournet, G., Joseph, B.: Synlett 2006, 2755–2758 (2006)
234. Mitsudo, K., Thansandote, P., Wilhelm, T., Mariampillai, B., Lautens, M.: Org. Lett. **8**, 3939–3942 (2006)
235. Della Sala, G.; Izzo, I.; Spinella, A. Synlett 2006, 1319–1322 (2006)
236. Busacca, C.A., Dong, Y.: Tetrahedron Lett. **37**, 3947–3950 (1996)
237. Omura, K., Choshi, T., Watanabe, S., Satoh, Y., Nobuhiro, J., Hibino, S.: Chem. Pharm. Bull. **56**, 237–238 (2008)
238. Hussain, M.; Tang, D. T.; Langer, P. Synlett 2009, 1822–1826 (2009)
239. James, C.A., Coelho, A.L., Gevaert, M., Forgione, P., Snieckus, V.J.: Org. Chem. **74**, 4094–4103 (2009)
240. Cabri, W., Candiani, I.: Acc. Chem. Res. **28**, 2–7 (1995)
241. Oliveira, D.: d. J.; Coelho, F. Synth. Commun. **30**, 2143–2159 (2000)
242. Dutheuil, G., Webster, M.P., Worthington, P.A., Aggarwal, V.K.: Angew. Chem. Int. Ed. **48**, 6317–6319 (2009)
243. Procedure reported in the Catalina Ferrer Llabrés Doctoral Thesis (Prof. Antonio Echavarren, January 2008)
244. Jacquemard, U., Bénéteau, V., Lefoix, M., Routier, S., Mérour, J.-Y., Coudert, G.: Tetrahedron **60**, 10039–10047 (2004)
245. Coowar, D., Bouissac, J., Hanbali, M., Paschaki, M., Mohier, E., Luu, B.: J. Med. Chem. **47**, 6270–6282 (2004)
246. Bringmann, G., Tasler, S., Endress, H., Peters, K., Peters, E.-M.: Synthesis 1998, 1501–1505 (1998)
247. Negishi, E., Boardman, L.D., Sawada, H., Bagheri, V., Stoll, A.T., Tour, J.M., Rand, C.L.J.: Am. Chem. Soc. **110**, 5383–5396 (1988)
248. Dieter, R.K., Chen, N.: J. Org. Chem. **71**, 5674–5678 (2006)
249. Fürstner, A., Bouchez, L.C., Morency, L., Funel, J.-A., Liepins, V., Porée, F.-H., Gilmour, R., Laurich, D., Beaufils, F., Tamiya, M.: Chem. Eur. J. **15**, 3983–4010 (2009)
250. Coldham, I., Dobson, B.C., Fletcher, S.R., Franklin, A.I.: Eur. J. Org. Chem., 2676–2686 (2007)
251. Wang, K., Liu, Z.: Synth. Commun. **40**, 144–150 (2009)
252. Pérez-Serrano, L., Domínguez, G., Pérez-Castells, J.J.: Org. Chem. **69**, 5413–5418 (2004)
253. Trost, B.M., Dyker, G., Kulawiec, R.J.J.: Am. Chem. Soc. **112**, 7809–7811 (1990)
254. Oakdale, J.S., Boger, D.L.: Org. Lett. **12**, 1132–1134 (2010)
255. Wada, A., Babu, G., Shimomoto, S., Ito, M: Synlett 2011, 1759–1762 (2011)
256. Liégault, B.T., Petrov, I.. Gorelsky, S.I., Fagnou, K.: J. Org. Chem., **75**, 1047–1060 (2010)
257. Optimizing results from the Doctoral Thesis of Catalina Ferrer Llabrés (ICIQ/URV, Tarragona, January 2008).

Chapter 5
Summary and Outlook

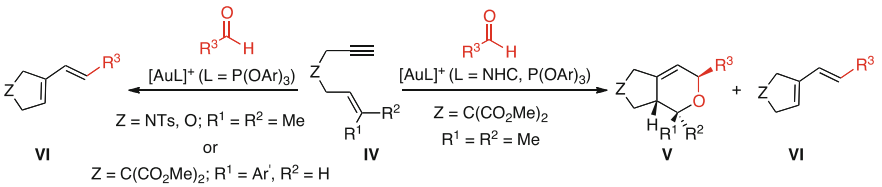
After many years in the shadow of palladium and rhodium, gold has become one of the most widely used late transition metals in homogeneous and heterogeneous catalysis [1]. Over the last few years, the Echavarren group developed new gold-based transformations mostly aimed at the activation of alkynes [2, 3]. Numerous methodologies have been developed that favour the attack of different nucleophiles, like olefins, indoles or aryls, to alkynes [2, 3]. In the case of 1,6-enynes, where the alkene has the role of nucleophile, experimental and theoretical results show that the cyclization takes place through the activation of the alkyne via coordination of the gold and subsequent, nucleophilic attack of the olefin (Scheme 5.1).



Scheme 5.1 Involved intermediates in the gold-catalyzed cyclization of 1,6-enynes

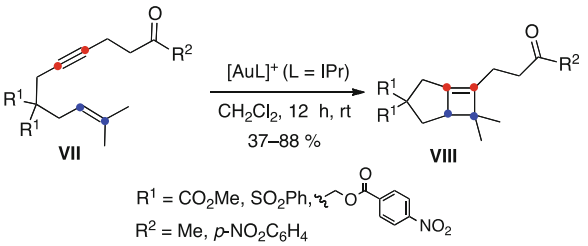
A. Escribano Cuesta, *New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids*, Springer Theses, DOI: 10.1007/978-3-319-00702-1_5,

The different gold carbenes (**I**, **II**, or **III**, Scheme 5.1) can be trapped depending on the nucleophile present in the medium [3]. For example, carbonyl compounds can act as nucleophiles in the intra- [4] and inter-molecular [5, 6] reaction of 1,6-enynes. Thus, we decided to study the *intermolecular gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes of type **IV*** possessing a tri-substituted olefinic group (Scheme 5.2) [7]. Products of [2 + 2 + 2] cycloaddition **V** and/or 1,3-dienes **VI** were synthesized selectively, depending on the substitution pattern of the alkene, the heteroatom in the tether (Z) or the ligand in the gold complex (L).



Scheme 5.2 Gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes of type **IV**

As an extension of this project, we wanted to obtain a clearer picture of the intertwined reaction pathways at play in the gold(I)-catalyzed addition of carbonyl compounds. Therefore, we investigated the reactivity of 1,6-enynes of type **VII** bearing a carbonyl group at the alkyne moiety (Scheme 5.3) [8], and observed the unexpected formation of cyclobutene compounds of type **VIII**.

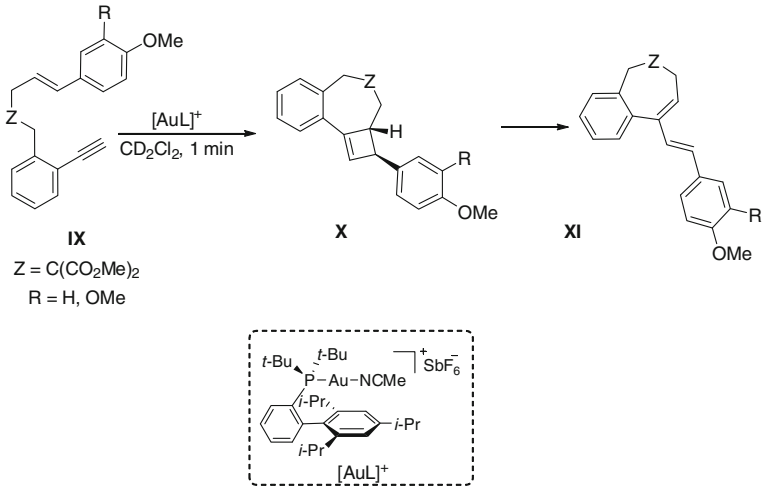


Scheme 5.3 Gold(I)-catalyzed cycloisomerization of 1,6-enynes **VII**

In order to unambiguously confirm the presence of the cyclobutene subunit and overcome the unstability problems, the corresponding hydrazone derivative was synthesized and characterized by X-Ray diffraction.

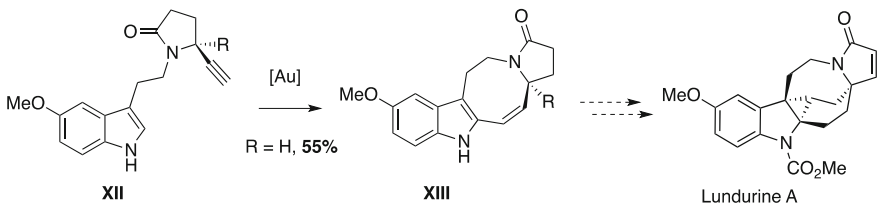
Due to the high importance of the cyclobutene motif and the intrinsic difficulties of its synthesis, we decided to study the formation of cyclobutene-containing compounds form 1,8-enynes [9]. Cyclobutenes of type **X** were synthesized via isomerization of 1,8-enynes of type **IX** using gold complexes (Scheme 5.4).

However, the isolation of these cyclobutene-containing compounds was unsatisfactory in all the cases. In conclusion, with this work we have confirmed that in the case of 1,8-enynes of type **IX**, cyclobutene-containing compounds **X** are reactive intermediates in the formation of the correspondent 1,3-dienes **XI** ("Unpublished" results).



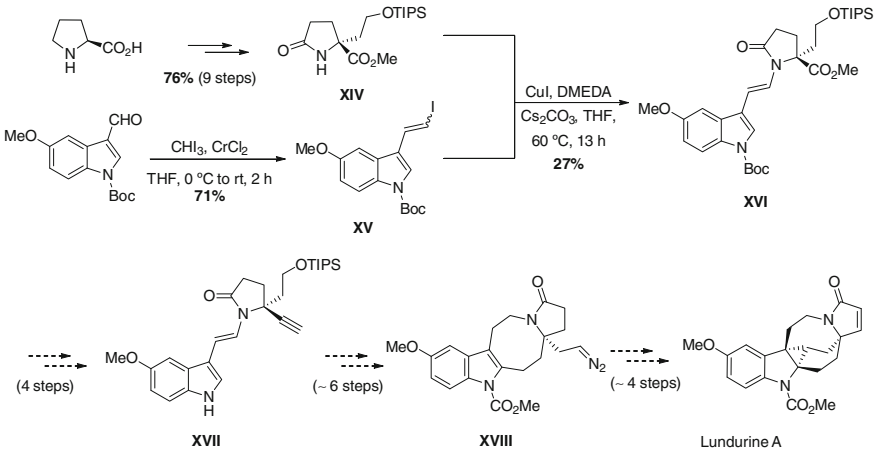
Scheme 5.4 Synthesis of cyclobutene-containing compounds of type **X**

In addition, we applied the methodology developed in the group for the gold(I)-catalyzed cyclization of indoles with alkynes in the total synthesis of lundurines [10, 11]. Lundurines A–D are a new type of alkaloids characterized by a cyclopropylic fragment embedded within a hexacyclic ring system that includes a 1*H*–azocine [5,4–*b*] indole ring unit [12, 13]. Interestingly, lundurines B and D display significant cytoxicity in vitro toward B16 melanoma cells. The key step in the total synthesis of lundurine A is a 8–*endo*–*dig* cyclization of the alkynyl indole **XII** catalyzed by $AuCl_3$, which affords exclusively the desired azocine[5,4–*b*]indole derivative **XIII** (Scheme 5.5) [14].



Scheme 5.5 Proposed synthesis of the main core of Lundurine A

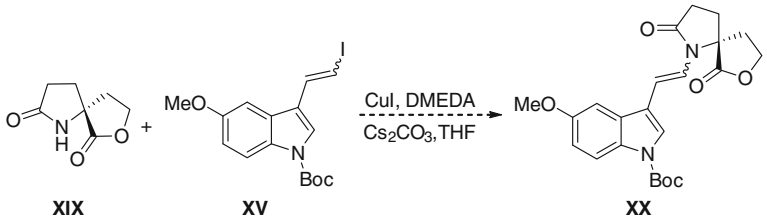
As a result, a general protocol toward the total synthesis has been elaborated, including an efficient preparation of the corresponding building blocks (Scheme 5.6). Moreover, the coupling of the key system has been solved (several methodologies were tested, e.g. nucleophilic substitution, hydroamination of alkynes, Wittig reaction or Heck cross-coupling). Finally, alkenyl indole **XVI** was obtained using a copper-catalyzed cross-coupling of enantiomerically pure lactam **XIV** with vinyl iodide derivative **XV** [15]. However, the desired alkenylindole **XVI** was obtained in low yield (27 %), due to steric hindrande.



Scheme 5.6 Summary of the approach toward the total synthesis of Lundurine A

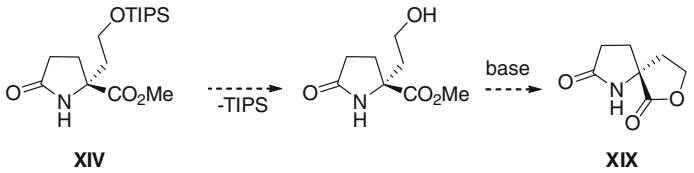
The next step toward the completion of the preparation of Lundurine A would involve the synthesis of alkynylindole **XVII** and the subsequent cyclization via a gold-catalyzed reaction. The intermediate reactions have already been identified and optimized on a model system. The key steps in the synthesis will be the conversion of alkynylindole **XVII** into **XVIII** and a subsequent intramolecular cyclopropanation to obtain Lunderine A [16–26].

In order to increase the yield of the copper-catalyzed cross-coupling reaction, the synthesis of a less bulky lactam is proposed (Scheme 5.7). This new lactone-lactama **XIX** is characterized by a less steric hindrace around the quaternary center.



Scheme 5.7 Copper-catalyzed coupling of lactam **XIX** and alkenylindole **XV**

Lactama **XIX** can readily be synthesized from lactama **XIV**, through the removing of the protecting group and subsequent lactonization (Scheme 5.8).



Scheme 5.8 Proposed synthesis of latone-lactma **XIX**

References

1. Hashmi, A.S.K.: Gold Bull. **37**, 1–2 (2004)
2. Jiménez-Núñez, E., Molawi, K., Echavarren, A.M.: Chem. Commun. 7327–7329 (2009)
3. Jiménez-Núñez, E., Echavarren, A.M.: Chem. Rev. **108**, 3326–3350 (2008)
4. Jiménez-Núñez, E., Claverie, C.K., Nieto-Oberhuber, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **45**, 5452–5455 (2006)
5. Schelwies, M., Dempwolff, A.L., Rominger, F., Helmchen, G.: Angew. Chem. Int. Ed. **46**, 5598–5601 (2007)
6. Schelwies, M., Moser, R., Dempwolff, A.L., Rominger, F., Helmchen, G.: Chem. Eur. J. **15**, 10888–10900 (2009)
7. Escribano-Cuesta, A., López-Carrillo, V., Janssen, D., Echavarren, A.M.: Chem. Eur. J. **15**, 5646–5650 (2009)
8. Escribano-Cuesta, A., Pérez-Galán, P., Herrero-Gómez, E., Sekine, M., Braga, A.A.C., Maseras, F., Echavarren, A.M.: Org. Biomol. Chem. **10**, 6105–6111 (2012)
9. Odabachin, Y., Gagosz, F.: Adv. Synth. Catal. **351**, 379–386 (2009)
10. Ferrer, C., Echavarren, A.M.: Angew. Chem. Int. Ed. **45**, 1105–1109 (2006)
11. Ferrer, C., Amijs, C.H.M., Echavarren, A.M.: Chem. Eur. J. **13**, 1358–1373 (2007)
12. Kam, T.-S., Yoganathan, K., Chuah, C.-H.: Tetrahedron Lett. **36**, 759–762 (1995)
13. Kam, T.-S., Yoganathan, K., Koyano, T., Komiyama, K.: Tetrahedron Lett. **37**, 5765–5768 (1996)
14. Ferrer, C., Escribano-Cuesta, A., Echavarren, A.M.: Tetrahedron **65**, 9015–9020 (2009)
15. Jiang, L., Job, G.E., Klapars, A., Buchwald, S.L.: Org. Lett. **5**, 3667–3669 (2003)
16. Magnus, P., Mugrage, B., DeLuca, M., Cain, G.A.: J. Am. Chem. Soc. **111**, 786–789 (1989)
17. Salim, M., Capretta, A.: Tetrahedron **56**, 8063–8069 (2000)
18. Jung, M.E., Slowinski, F.: Tetrahedron Lett. **42**, 6835–6838 (2001)
19. Yang, J., Song, H., Xiao, X., Wang, J., Qin, Y.: Org. Lett. **8**, 2187–2190 (2006)
20. Cuevas-Yañez, E., Muchowski, J.M., Cruz-Almanza, R.: Tetrahedron **60**, 1505–1511 (2004)
21. Yang, J., Wu, H., Shen, L., Qin, Y.: J. Am. Chem. Soc. **129**, 13794–13795 (2007)
22. Shen, L., Zhang, M., Wu, Y., Qin, Y.: Angew. Chem. Int. Ed. **47**, 3618–3621 (2008)
23. Zhang, B., Wee, A.G.H.: Chem. Commun. 4837–4839 (2008)
24. Zhang, M., Huang, X., Shen, L., Qin, Y.: J. Am. Chem. Soc. **131**, 6013–6020 (2009)
25. Gagnon, D., Spino, C.: J. Org. Chem. **74**, 6035–6041 (2009)
26. Bull, J.A., Charette, A.B.: J. Am. Chem. Soc. **132**, 1895–1902 (2010)