NEW GOLD-CATALYZED REACTIONS AND APPLICATIONS FOR THE SYNTHESIS OF ALKALOIDS

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Dipòsit Legal: T.1297-2013

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

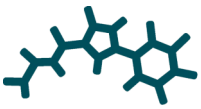
DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institut Català d'Investigació Química

UNIVERSITAT ROVIRA I VIRGILI

Tarragona
2012



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FAIG CONSTAR que aquest treball, titulat "New Gold-Catalyzed Reactions and Applications for the Synthesis of Alkaloids", que presenta Ana Escribano Cuesta per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Analítica i Química Orgánica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, Febrer de 2012

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

A mi familia

"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

.

Agradecimientos

Este trabajo de Tesis Doctoral se ha realizado en el Institut Català d'Investigació Química (ICIQ) en Tarragona (mayo 2007-abril 2011) bajo la dirección del Profesor Antonio M. Echavarren, a quien quiero agradecer toda su dedicación, entusiasmo e ilusión por la química, por la confianza depositada en mí y por saber sacar lo mejor de cada uno de nosotros.

El trabajo recogido en esta memoria se ha llevado a cabo gracias a la financiación del Institut Català d'Investigació Química y una beca de Formación del Profesorado Universitario del Ministerio de Educación y Ciencia (FPU).

Durante mi Tesis Doctoral, he realizado una estancia breve, gracias a la beca FPU del Ministerio de Educación y Ciencia, en el grupo de investigación del Profesor James L. Leighton (Columbia University, New York City, US, septiembre-noviembre 2009). También he realizado una segunda estancia de seis meses en BASF SE (Ludwigshafen, Alemania, septiembre 2011-febrero 2012) bajo la supervisión del Dr. Klaas Lohmann. Me gustaría agradecer a ambos la oportunidad de haber podido formar parte de sus grupo.

Por supuesto me gustaría agradecer el apoyo de Sònia Gavaldà y Vanessa Martínez. No solo por su dedicación y hacernos la vida más fácil a todos, sino también por todas las risas y lágrimas derramadas en estos casi cinco años.

Me gustaría expresar mi agradecimiento a la Dra. Noemí Cabello y Alba González de espectrometría de masas; al Dr. Gabriel González, Kerman Gómez e Israel Macho de servicio de RMN; al Dr. Jordi Benet-Buchholz y Eduardo Escudero del servicio de rayos-X; a las Dra. Marta Giménez, Dra. Yvette A. Mate y Mariona Urtasun de la unidad de Tecnología de las reacciones químicas y finalmente a Mario Endara, Ángel Mosquera, Álvaro Virga y David Pena de tecnología informática. Sin su ayuda este trabajo me hubiera llevado unos cuantos años más.

No puedo olvidarme de todos los compañeros del laboratorio P2.2, P2.3 y fase II, a los que me gustaría hacer una pequeña mención aquí: Dra. Almudena Díaz, Dra. Christelle Claverie, Dar. Susana Porcel, Dr. Antonio Rosellón, Dar. Eloísa Jiménez-Núñez, Dra. Catelijne Amijs, Dra. Noemí Cabello, Dr. Dominic Janssen, Dr. Christophe Bour, Dr. Sergio Pascual, Dra. Elena Herrero-Gómez (mi mentora), Dra. Catalina Ferrer, Dr. Thorsten Lauterbach, Dr. Dirk Spiegel, Dra. Patricia Pérez-Galán, Dra. Paula de Mendoza, Dr. Francesco Camponovo, Dr. Nicolas Delpont, Dr. Mihai Raducan, Dra. López-Carillo, Dr. Julian Ceccon, Dra. Nolwenn Martin (mi consejera), Dr. César Rogelio

Solorio, Dr. Kian Molawi, Madeleine Livendahl (mi sueca favorita), Masha Kirillova, Núria Huguet (gracias por esa energía desbordante), Dra. Lorena Riesgo, Morgane Gaydou, Dr. Riccardo Sinisi, Claudia de León (del Sol), Anthony Pitaval, Carla Obradors, Anna Homs (gracias por todo tu ilusión), Dr. Paul McGonigal, Katya Smirnova, Dra. María Moreno, Pilar Calleja, Yahui Wang y al Dr. Juhanes Aydin. Gracias por toda la ayuda y los momentos que hemos compartido.

También quiero agradecer de forma especial a todos los que durante estos años me han brindado su amistad: Mickaël Gicquel (gracias por tu ayuda con la portada), Pere Miro, Lucas Montero de Espinosa, Olivier Diebolt, Silvia Díez, Serena Fantasía, Lora Farjon, Simona Curreli, Nora Planas, Xacobe Couso, Cristina Gracía, Ramón Amat, Masaki Sekine, Olesya Tomashenko, Julian Valero, Judith Martínez, Torstein Fjermestad, James Ryan, Abel Locati, Edu Tous y Xisco Caldentey. Ich möchte auch allen danken, die mich in Deutschland unterstützt und aufgeheitert haben: Maria Böhm, Jelena Širić, Alison Scott (thank you for your English corrections), Amanda Loo, Anna Gärtner, Rosa Corberán, Simon Ruppenthal, Chantalle Lee, Elisabeth Bank, Jens Willwacker, Markus Nett, Petra Faber, Simone Weis and Yannick Roux. Un especial reconocimiento es para Nicolas Marion al que agradezco su apoyo y consejos. Tampoco me puedo olvidar de mis amigos de Asturias, a los que añoro en la distancia, como Bea, Rubén, David, Marcos, Paola, y Laura. Y por supuesto a Giovanni, "grazie per quest'anno e mezzo".

Y, como no, a familia: en especial a mi madre y a mi padre por estar siempre orgullosos de mi y animarme a seguir mis sueños. Gracias por todo el amor y la confianza.

Hasta el momento de redactar esta memoria, los resultados aquí descritos han dado lugar a las siguientes publicaciones:

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

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Esta memoria del trabajo de Tesis Doctoral se ha dividido en siete partes: un resumen en castellano, una introducción general, unos objetivos generales y tres capítulos de resultados. Los capítulos se dividen a su vez en cuatro secciones, una introdución específica para cada una de ellos, una descripción de los objetivos del capítulo, un apartado de resultados y discusión, las conclusiones del capítulo y finalmente la parte experimental correspondiente a cada capítulo.

En el apartado *Introduction* se recogen los principios básicos sobre catálisis homogénea de oro en las activaciones de alquinos, centrada principalmente en las reacciones de adición de nucleófilos a alquinos y las ciclaciones de eninos.

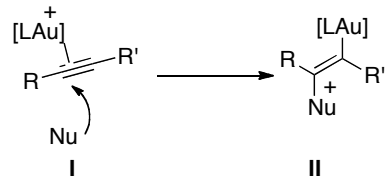
El trabajo recogido en el *Chapter 1. Gold(I)-Catalyzed Reactions of 1,6-Enynes with Aldehydes: Cycloaddition versus Metathesis-Type Reactions* se ha realizado en colaboración con la Dr. Dominic Janssen. Algunos de sus resultados se han incluido en forma de esquemas para asegurar la coherencia en el desarrollo de la discursión.

En el trabajo recogido en el apartado *2.3.1 Synthesis of cyclobutene compounds via gold(I)-catalyzed intramolecular addition of carbonyl compounds to 1,6-enynes* ha colaborado Masaki Sekine durante una estancia de cuatro meses. Algunos de los resultados se han incluido en forma de esquema para facilitar el desarrollo de la discursión.

El trabajo discutido en el apartado *3.3.1 Intermolecular Approach* se ha basado en el resultados previos recogidos en la tesis doctoral de la Dra. Catalina Ferrer Llabrés (ICIQ/URV, Tarragona, Enero 2008).

Resumen

Dentro del campo de la catálisis organometálica, el oro es finalmente considerado, después de muchos años pasados a la sombra del paladio o del rodio, como uno de los metales de mayor importancia: hoy en día, es uno de los catalizadores más usados, tanto en catálisis homogénea como en catálisis heterogénea.[1] Durante los últimos años, dentro del grupo del Profesor Echavarren, se han desarrollado nuevos complejos de oro(I) que han sido aplicados de forma satisfactoria en la activación de alquinos.[2] La coordinación del oro al alquino permite el ataque nucleofílico debido a la formación de un complejo-π **I** que, a continuación da lugar a la formación del complejo *E*-alquenil oro **II** como intermedio (Esquema 1).[2]



Esquema 1. *Activación de alquinos por complejos de oro(I)*

En el grupo se han desarrollado diferentes metodologías usando oro como catalizador que favorecen el ataque de distintos núcleofilos a alquinos, tales como olefinas, indoles o arilos.[2] Una gran parte de los esfuerzos han sido enfocados en el aislamiento de diferentes intermedios de reacción, elucidando de este modo el mecanismo a través del cual la catálisis ocurre.

Dentro del caso particular de 1,6-eninos, donde el alqueno tiene el papel de nucleófilo, resultados experimentales y teóricos muestran que la ciclación tiene lugar mediante la activación del alquino al coordinarse el oro y el consecuente, ataque nucleófilo de la olefina. Diferentes intermedios pueden estar involucrados en el transcurso de la reacción, dependiendo de si la ciclación es 5-*exo*-*dig* o 6-*endo*-*dig* (Esquema 2). A su vez, el tipo de intermedio puede variar con la sustitución en el alquino (R), el grupo puente entre la parte acetilénica y la olefínica (Z) o el ligando presente en la esfera de coordinación del oro (L).

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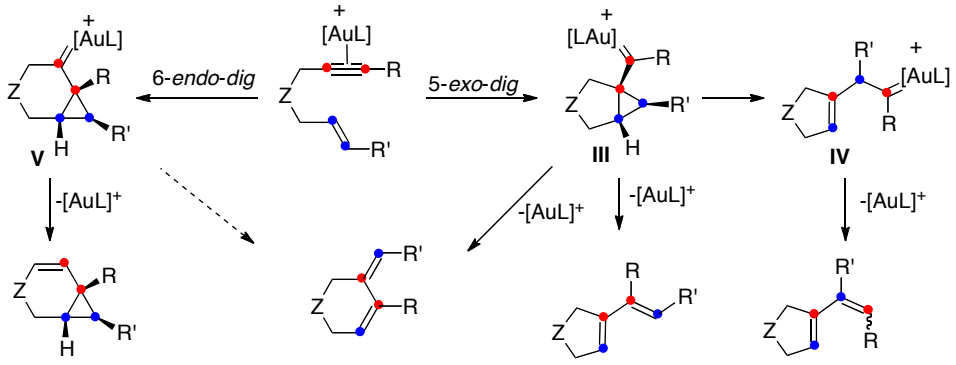
1 Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 1–2.

2 (a) Jiménez-Núnez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350.

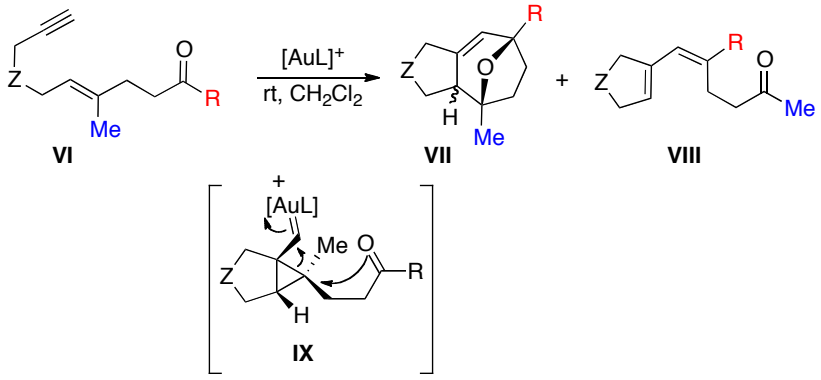


Esquema 2. *Intermedios presentes en la ciclación de 1,6-eninos catalizada por complejos de oro(I)*

Los diferentes ciclopropil carbeno de oro (**III**, **IV**, o **V**, Esquema 2) pueden ser atrapados dependiendo del nucleófilo presente en el medio de reacción.[2b] De este modo, compuestos carbonílicos pueden actuar como nucleófilos en la reacción intra-[3] e intermolecular[4] de 1,6-eninos. En 2006, en el grupo se observó que eninos del tipo **VI**, dotados de una unidad carbonílica en la cadena olefínica, se ciclaban en presencia de complejos de oro(I) formando derivados oxatetracíclicos **VII** y cetonas transpuestas **VIII** a través de intermedios ciclopropil carbeno de oro de tipo **IX** (Esquema 3).[3]

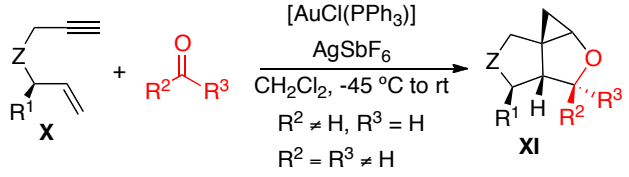
3 Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455.

4 (a) Schelwies, M.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5598–5601. (b) Schelwies, M.; Moser, R.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10888–10900.



Esquema 3. *Ciclación de 1,6-eninos de tipo* ***VI*** *catalizada por complejos de oro(I)*

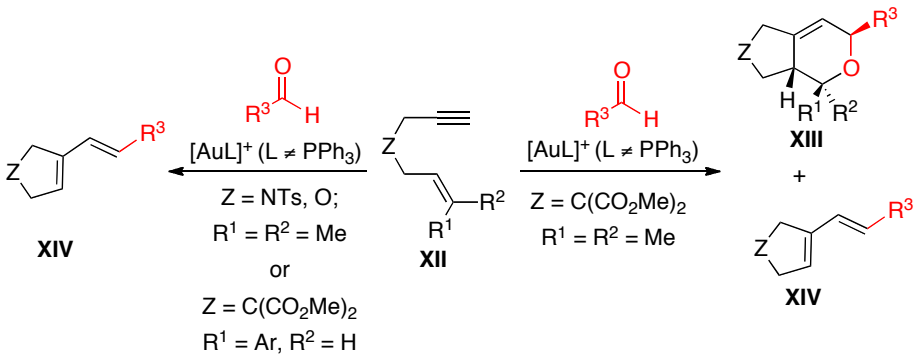
En 2007, el grupo del Profesor Helmchen desarrolló la versión intermolecular de esta reacción con 1,6-eninos del tipo **X,** caracterizados por tener una olefina terminal (Esquema 4).[4a] La reacción da lugar a la formación de compuestos tríciclicos **XI**, mediante el ataque nucleófilo del grupo carbonílico a un intermedio ciclopropil carbeno de oro de tipo **IV** (Esquema 2).



Esquema 4. *Adición intermolecular de compuesto carbonílicos a 1,6-eninos* ***X***

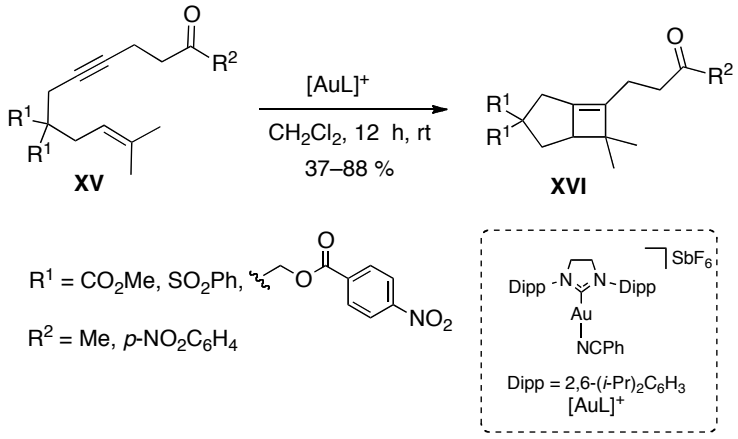
A la vista de estos resultados, nos planteamos estudiar la adición intermolecular de compuestos carbonílicos a 1,6-eninos caracterizados por tener una olefina trisustituida (**XII**) (Esquema 5).[5] Productos de [2+2+2] cicloadición **XIII** o 1,3-dienos **XIV** son sintetizados de forma selectiva, dependiendo del grupo puente entre la parte acetilénica y la olefínica (Z) o del ligando presente en la esfera de coordinación del oro (L). En este caso la reacción transcurre a través de un intermedio ciclopropil carbeno de oro de tipo **III** (Esquema 2).

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



Esquema 5. *Adición intermolecular de compuesto carbonílicos a 1,6-eninos* ***XII***

Como extensión de este proyecto, nos propusimos continuar con el estudio de la reacción intramolecular de 1,6-eninos con compuestos carbonílicos. En esta Tesis Doctoral se describe la cicloisomerización catalizada por complejos de oro(I) de 1,6-eninos de tipo **XV**, donde la unidad carbonílica se encuentra unida a la cadena acetilénica, observándose la formación de un nuevo tipo de estructura, ciclobutenos **XVI** (Esquema 6). La estructura ciclobuténica fue caracterizada de forma inequívoca mediante difracción de rayos X, tras la formación de un derivado de hidrazona con uno de los compuestos.

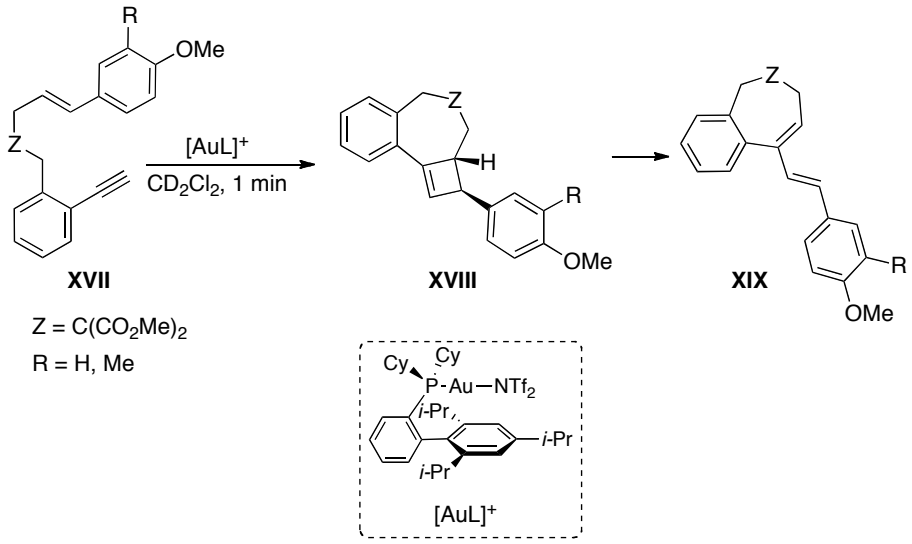


Esquema 6. *Ciclación de 1,6-eninos de tipo* ***XV*** *catalizada por complejos de oro(I)*

Dada la importancia y la dificultad de sintetizar compuestos que contengan la subunidad biciclo[3.2.0]hept-5-eno, nos planteamos estudiar la formación de ciclubutenos a partir de 1,8-eninos.[6] Ciclobutenos de tipo **XVIII** fueron sintetizados mediante cicloisomerización de

6 Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386.

1,8-eninos **XVII** catalizada por complejos de oro (I) (Esquema 7). Aunque el aislamiento de los compuestos ciclobuténicos fue insatisfactorio en todos los casos, hemos confirmado que en el caso de 1,8-eninos de tipo **XVII**, ciclobutenos **XVIII** son intermedios reactivos en la formación de los correspondientes 1,3-dienos **XIX**.



Esquema 7. *Síntesis de ciclobutenos de tipo* ***XVII*** *mediante cicloadición [2+2] catalizada por oro(I)*

En el último capítulo de esta Tesis Doctoral, se ha aplicado la metodología desarrollada en el grupo para la ciclación de indoles con alquinos catalizada con oro en la síntesis total de las lundurinas.[7] Las lundurinas son un nuevo tipo del alcaloides indólicos que se caracterizan por poseer un fragmento ciclopropílico que incluye una unidad principal 1*H*-azocino[5,4-*b*]indol (Figura 1).[8] Cabe destacar la citotoxicidad in vitro contra células de melanoma B16 mostrada por lundurinas B y D.

7 (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373.

8 (a) Kam, T.-S.; Yoganathan, K.; Chuah, C.-H. *Tetrahedron Lett.* **1995**, *36*, 759–762. (b) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765–5768.

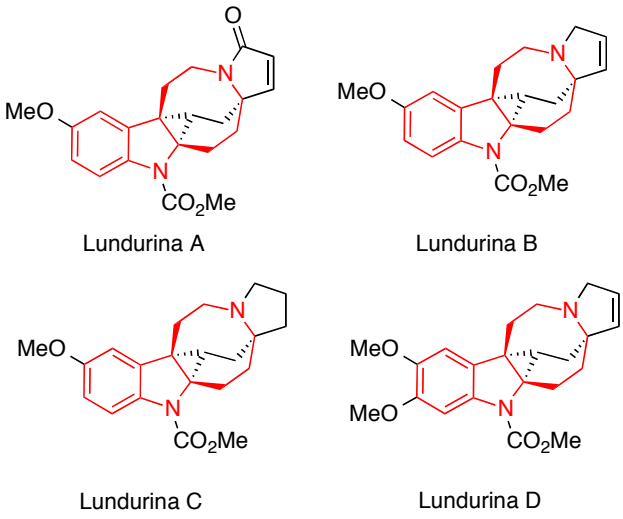
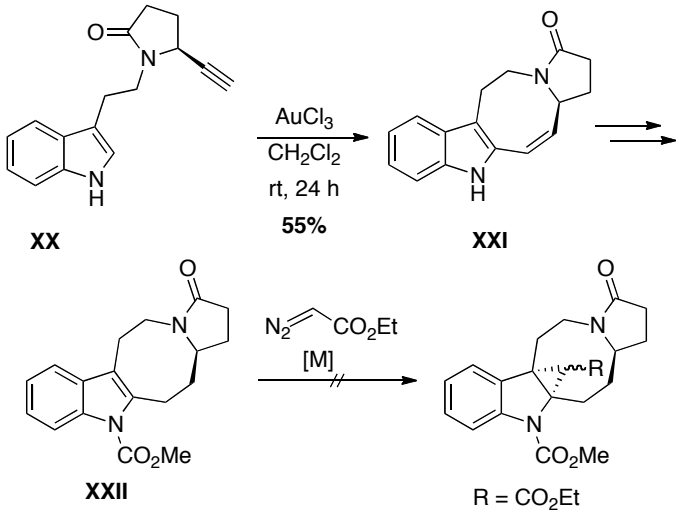


Figura 1. *Estructura de las lundurinas*

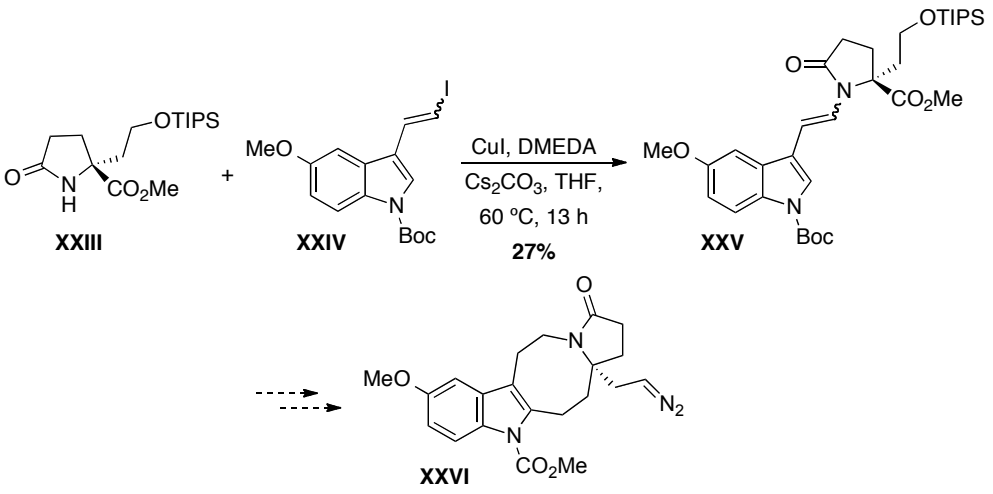
En la primera parte del capítulo se describe la aproximación intermolecular hacia la síntesis de lundurina A. El paso principal está basado en una ciclación 8-*endo-dig* del alquinil indol **XX** en presencia de $AuCl_3$ que da lugar a la formación exclusiva del derivado azocino[5,4-*b*]indol **XXI** (Esquema 8).[9] Alquinil indol **XX** es sintetizado a partir del compuesto 3-indoloacetonitrilo mediante una secuencia de 7 pasos. Desafortunadamente, la ciclopropanación intermolecular del indoloazocino **XXII** no tuvo lugar bajo todas las condiciones probadas, demostrando de este modo la no viabilidad de esta aproximación hacía la síntesis de la lundurina A.

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



Esquema 8. *Aproximación intermolecular hacía la síntesis de la lundurina A*

Por ello en la segunda parte del capítulo, la aproximación intramolecular es revisada. Se describe la metodología adecuada que permite unir la parte lactámica **XXII** y la indólica **XXIV**, obteniéndose de este modo un intermedio avanzado en la síntesis, **XXV** (Esquema 9). Después de varias modificaciones, el compuesto alquinil indol **XXV** daría lugar a la formación del indoloazocino **XXVI**, y éste a su vez a la lundurina A, tras una ciclopropanación intramolecular de la subunidad indol con del fragmento diazo.



Esquema 9. *Aproximación intramolecular hacía la síntesis de la lundurina A*

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.

Additional abbreviations and acronyms used in this manuscript are referenced in the list below:

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

Introduction

Transition metal catalysis is one of the most important tools in organic synthesis, which has made possible new transformation with high efficiency and selectivity. In this context, the electrophilic activation of alkynes by π-Lewis acids[10] has become a broadly used transformation for the synthesis of highly functionalized carbo- and heterocycles.

I.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.[11] When an alkyne behaves as a ligand, there are four orbitals that can participate in the bonding (Figure 1).[11c] The in-plane orbitals, $\pi_{\parallel}$ and $\pi^*_{\parallel}$, are responsible for a σ-donor interaction (M←L donation) and a π-acceptor interaction (M→L back-donation) respectively. The orthogonal, out-of-plane orbitals, $\pi_{\perp}$ and $\pi^*_{\perp}$, are engaged in the M←L π donation and the δ symmetry M→L back-donation respectively. This latter interaction can be neglected, due to the weak overlap of the orbitals.

10 Lewis, G.N., *Valence and the Structure of Atoms and Molecules* (1923) p. 142.

11 (a) Hashmi, A. *Gold Bulletin* **2003**, *36*, 3–9. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (d) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (g) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

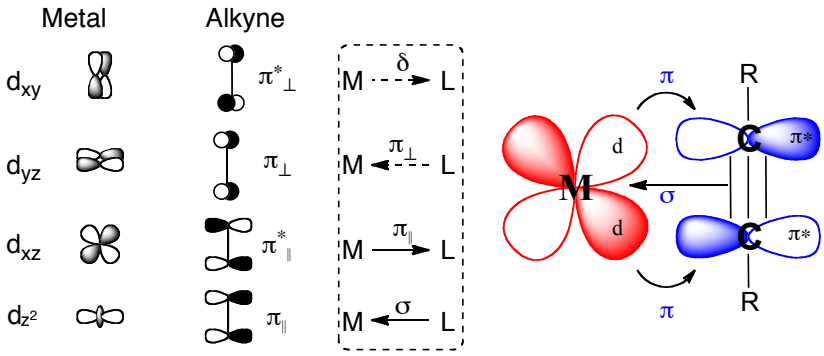


Figure 1. *Qualitative orbital diagram*

In the case of $[Au(alkyne)]^+$ complexes, the contributions of the individual σ and π terms have been analyzed by high level computational methods quantitively.[12] 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 Figure 1). Thus, alkynes are strong-electron σ donor, but fairly weak π acceptors toward gold(I). Consequently, for $[Au(alkyne)]^+$ complexes the Dewar-Chatt-Duncanson model[13] predicts an elongation of the triple bond, due to the net shift of electron density form the bonding π into the antibonding π^* orbital. Furthermore, the coordination withdraws electron density form the alkyne. Thus, the alkyne is more electrophilic, and hence more susceptible to nucleophilic attack.

The addition of water to alkynes catalyzed by Brønsted acid 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[14] character of this large and polarizable cation has a

12 Nechaev, M. S.; Rayón, V. M.; Frenking, G. *J. Phys. Chem. A* **2004**, *108*, 3134–3142.

13 (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71–C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939-2947. (c) Nelson, J. H.; Wheelock, K. S.; Cusachs, L. C.; Jonassen, H. B. *J. Am. Chem. Soc.* **1969**, *91*, 7005–7008.

14 Jolly, W. L. (1984). *Modern Inorganic Chemistry*. New York: McGraw-Hill. Additional references: (a) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561–567. (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

much greater affinity to the substrate, leading reactions that proceed under mild conditions.[11d] However, the use of stoichiometric amounts of toxic mercury salts is inconvenient. This problem was solved by the used 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] in which the main contribution to the substantial shortening and strengthening of the $[Au{=}CH_2]^+$ bond is due to relativistic effects.[16] These properties make gold an excellent soft Lewis acid for the activation of C–C multiple bonds[11d] under mild reaction conditions. As a result, gold complexes have been successfully applied to nucleophilic additions (using heteroatom- or carbon nucleophiles), Friedel-Crafts reactions, C–H activation, hydrogenations, and oxidations.[11]

I.2 Gold Properties

Gold is a metal characterized by a high electronegativity.[17] 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. Theses 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

15 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. (b) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510–2513. (c) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat Chem* **2009**, *1*, 482–486. (d) Casanova, J.; Kent, D. R.; Goddard, W. A.; Roberts, J. D. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 15–19.

16 (a) Heinemann, C.; Hertwig, R. H.; Wesendrup, R.; Knoch, W.; Schwarz, H. *J. Am. Chem. Soc.* **1995**, *117*, 495-500. (b) Irikura, K. K.; Goddard, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 8733–8740.

17 (a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573–3578. (b) Schwarz, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4442–4454. (c) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

ligand present in the coordination sphere of the gold. This fact has a high impact in the catalyst properties, because it implies the possibility to modulate 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.

I.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. As a result, in most cases gold is stabilized by donor ligands. The reactivity of the complexes can be modulated changing the ligand in the coordination sphere of gold. Thus, an increase in the electron-density of the metal is clearly observed by moving from electron-withdrawing to electron-donating ligands (Figure 2).

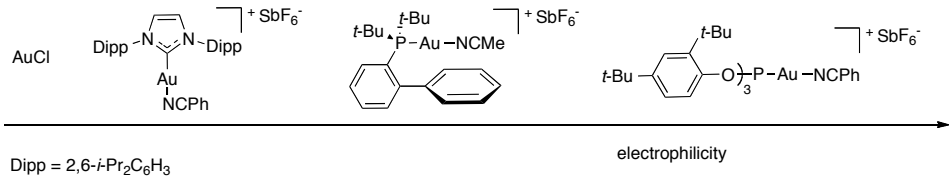


Figure 2. *Ligand modulation of the reactivity of gold(I) complexes*

Gold(I) preferentially coordinates in a linear bicoordinative geometry. This limited coordination requires the abstraction of one ligand from a neutral bicoordiante 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.[18] Similarly, cationic gold(I) complexes can be formed *in situ* by chloride abstraction form [AuLCl] complexes using one equivalent of a silver(I) salt with a non-coordinating anion.[19] The cationic version of these complexes with a weakly

18 (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.

19 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677–1693. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316.

coordinated ligand (acetonitrile or benzonitrile in most cases) instead of the chloride have 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.[20] The analogous cationic version, complexes **5-8** are more convenient catalyst[15a,21] since reactions can be carried out in the absence of silver(I) salts.[19b] Related complexes **9** and **10** with a weakly coordinated bis(trifluoromethanesulfonyl)amide NTf_2 have been also reported.[22]

20 Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

21 (a) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029–6032. (b) Partyka, D. V.; Robilotto, T. J.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2007**, *27*, 28–32.

22 Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

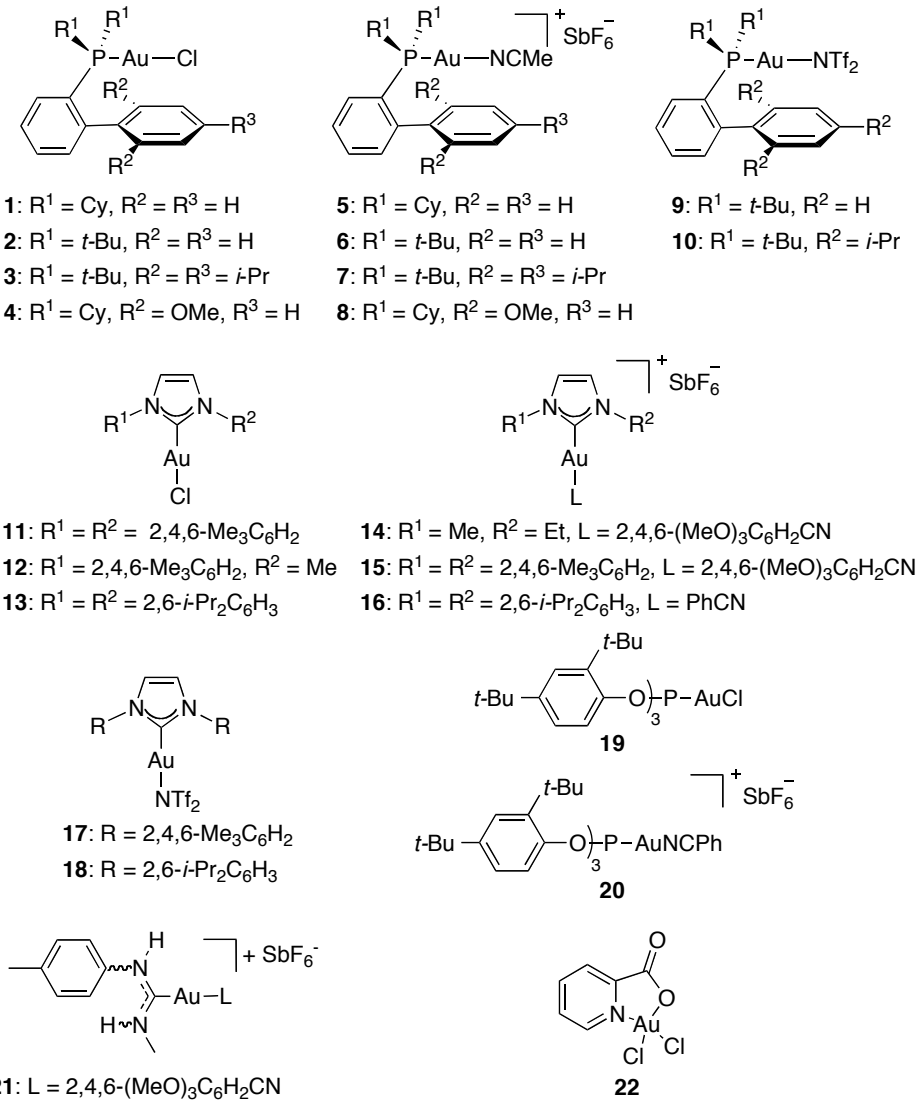


Figure 3. *Gold complexes*

Complexes with N-heterocyclic carbenes (NHC),[23] such as **11-13**,[15b,20,24] cationic **14-16**[25] as well as neutral **17** and **18**,[26] usually afford more selective catalysts, due to the more donating

23 (a) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782. (b) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676. (c) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542–2546. (d) Nolan, S. P. *Acc. Chem. Res.* **2011**, *44*, 91–100.

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.[27] Acyclic carbenes,[28] such as **21**, and other related carbenes[29] also give rise to selective catalysts of moderate electrophilicity.

Gold(I) complexes with phosphites as ligands showed to be more active catalysts, due to their more electron-withdrawing character. Complexes **19**[21a] and its cationic derivative

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24 (a) Deetlefs, M.; Raubenheimer, H. G.; Esterhuysen, M. W. *Cat. Today* **2002**, *72*, 29–41. (b) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363–2370. (c) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411–2418. (d) de Frémont, P.; Singh, R.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2007**, *26*, 1376–1385. (e) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721–7730.

25 (a) de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045–2047. (b) de Frémont, P.; Marion, N.; Nolan, S. P. *J. Organomet. Chem.* **2009**, *694*, 551–560.

26 (a) Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156–5159. (b) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.

27 (a) Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 2742–2744. (b) Gaillard, S.; Bosson, J.; Ramón, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J.* **2010**, *16*, 13729–13740.

28 (a) Bartolomé, C.; Carrasco-Rando, M.; Coco, S.; Cordovilla, C.; Martín-Alvarez, J. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 1616–1624. (b) Bartolomé, C.; Ramiro, Z.; Pérez-Galán, P.; Bour, C.; Raducan, M.; Echavarren, A. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 11391–11397. (c) Bartolomé, C.; Ramiro, Z.; García-Cuadrado, D.; Pérez-Galán, P.; Raducan, M.; Bour, C.; Echavarren, A. M.; Espinet, P. *Organometallics* **2010**, *29*, 951–956. (d) Bartolomé, C.; García-Cuadrado, D.; Ramiro, Z.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758–9764. (e) Hashmi, A. S. K.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal.* **2010**, *352*, 1315–1337.

29 (a) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 2779–2782. (b) Frey, G. D.; Dewhurst, R. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *J. Organomet. Chem.* **2008**, *693*, 1674–1682. (c) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166–3169. (d) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem. Eur. J.* **2009**, *15*, 3056–3060. (e) Kilpin, K. J.; Paul, U. S. D.; Lee, A.-L.; Crowley, J. D. *Chem. Commun.* **2011**, *47*, 328–330.

20,[24e,30] bearing tris(2,6-di-*tert*-butylphenyl)phosphite are one the most electrophilic cationic gold(I) catalysts reported to date.

In general gold(III) complexes, characterized by a square-planar geometry, are less used than gold(I) complexes. The use of pyridinecarboxylic acid as ligand, like in complex **22**,[31] allows the stabilization of the catalyst. It is worth mentioning that higher oxidation states also increases the affinity to hard donor sites. Therefore, gold(III) complexes are more oxophilic, whereas gold(I) complexes are more carbophilic.

I.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 more thermodynamically favored. In the context of 1,6-enynes, the $[AuL]^+$ species indifferently coordinates to both π -systems. However, the addition occurs exclusively to the $[Au(alkyne)]^+$ complex, which has a lower LUMO than the analogous $[Au(alkene)]^+$ complex.[32]

The coordination of the $[AuL]^+$ fragment to the alkyne moiety allows the *anti* attack of a nucleophiles due to the formation of a π-complex **I** and, consequently, the formation of *(E)*-alkenyl-gold complex **II** as intermediate (Figure 4).

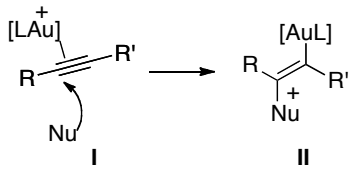


Figure 4. *Gold(I)-catalyzed addition of nucleophiles to alkynes*

30 (a) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949–1953. (b) Fortman, G. C.; Nolan, S. P. *Organometallics* **2010**, *29*, 4579–4583.

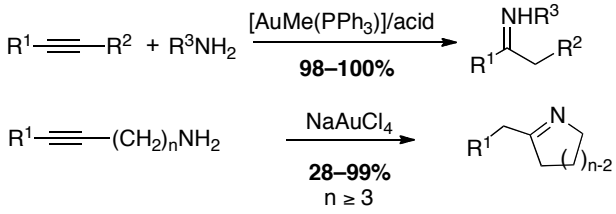
31 (a) Annibale, G.; Canovese, L.; Cattalini, L.; Marangoni, G.; Michelon, G.; Tobe, M. L. *J. Chem. Soc., Dalton Trans.* **1984**, 1641–1646. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejović, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547.

32 García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; Lopez, N. *ChemPhysChem* **2008**, *9*, 1624–1629.

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

I.4.1 Gold-Catalyzed Addition of Carbo- and Heteronucleophiles to alkynes

The gold-catalyzed inter- and intramolecular addition of carbon- and heteronucleophiles to alkynes lead to a wide variety of products.[11e] In the case of nitrogen nucleophiles, the addition of amines,[33] anilines,[34] imines,[35] pyridines[36] and azides[37] is possible (Scheme 1).



Scheme 1. *Selected examples for the addition of nitrogen nucleophiles*

Alcohols,[38] carboxylic acids,[39] carbonyl compounds,[40] carboxamides,[41] epoxides,[42] sulfoxides[43] and thiols[44] can also participate as nucleophiles (Scheme 2).

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33 Selected examples: (a) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **1999**, *19*, 170–183. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352. (c) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184.

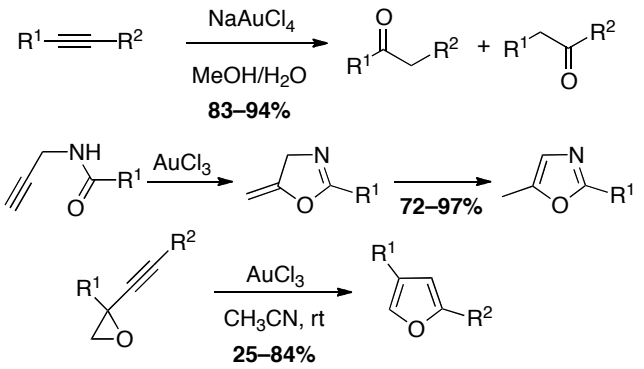
34 Selected examples: (a) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627–630. (b) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2005**, *8*, 289–292.

35 Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537–3540.

36 Selected examples: (a) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433–3436. (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050–12051.

37 Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.

38 Selected examples: (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729–3731. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412. (d) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489–4492. (e) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2091–2093. (f) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.



Scheme 2. *Selected examples for the addition of oxygen nucleophiles*

The hydrochlorination[45] and hydrofluorination[46] of alkynes catalyzed by gold complexes have also been reported (Scheme 3).

39 Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113.

40 Selected examples: (a) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515–518. (b) Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539–3542. (c) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, *2007*, 1763–1766. (c) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262.

41 Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394.

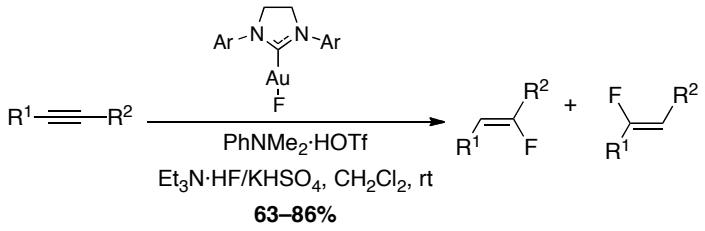
42 Selected examples: (a) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432–438. (b) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191–3194. (c) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Qi, C.-Z.; Liang, Y.-M. *Adv. Synth. Catal.* **2007**, *349*, 2493–2498.

43 Selected examples: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161. (b) Davies, P. W.; Albrecht, S. J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 8372–8375.

44 Selected examples: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473–4475. (b) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081–4083.

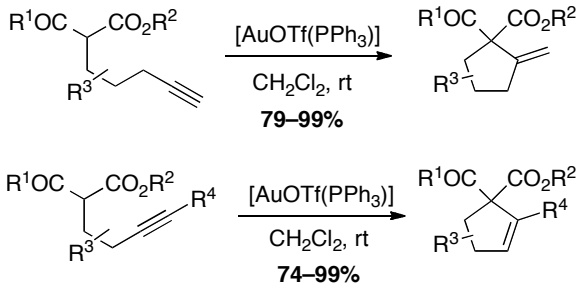
45 Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin. Trans. 1* **1976**, 1983–1987.

46 Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737.



Scheme 3. *Gold(I)-catalyzed hydrofluorination of alkynes*

Two types of carbon nucleophiles are commonly utilized in gold catalysis: electron-rich (hetero)arenes[11b,11e] and 1,3-carbonyl compounds.[47] The first will be discussed latter in a separate section. The addition of 1,3-carbonyl compounds to alkynes, known as the Conia-ene cyclization,[47] takes place via the corresponding enol tautomer or the corresponding silyl enol ether (Scheme 4).



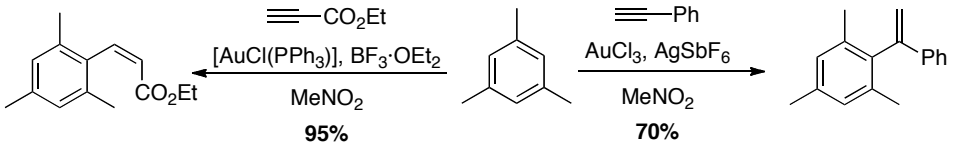
Scheme 4. *Gold(I)-catalyzed intramolecular addition of 1,3-carbonyl compounds*

47 (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350–5352. (c) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487. (d) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991–5994. (e) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673. (f) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287–6289. (g) Pan, J.-H.; Yang, M.; Gao, Q.; Zhu, N.-Y.; Yang, D. *Synthesis* **2007**, *2007*, 2539–2544. (h) Ito, H.; Makida, Y.; Ochida, A.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2008**, *10*, 5051–5054. (i) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025–1028. (j) Barabé, F.; Bétournay, G. V.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236–4238. (k) Davies, P. W.; Detty-Mambo, C. *Org. Biomol. Chem.* **2010**, *8*, 2918–2922.

I.4.2 Gold-Catalyzed Friedel-Crafts-Type Reactions

The gold-catalyzed reaction of alkynes with aromatic units has been extensively studied.[48] 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;[49] 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.[50] The inverse regioselectivity in favor the 1,2-disubstituted alkenes is observed for alkynes with electron-withdrawing groups (Scheme 5).[51]



Scheme 5. *Gold-catalyzed hydroarylation of alkynes*

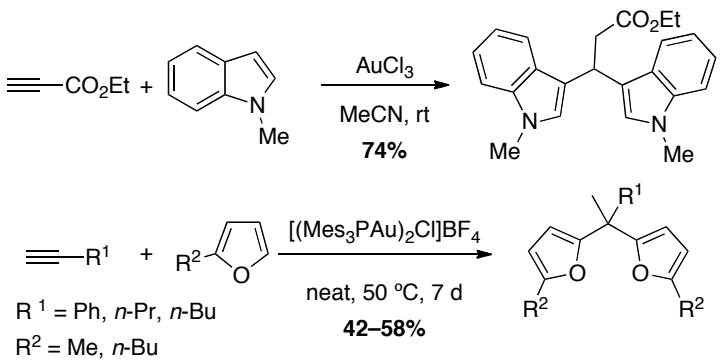
48 (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (b) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075–5087. (c) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801–820.

49 Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053–3059. Selected examples for the direct auration of arenes and heteroarenes: (a) Porter, K. A.; Schier, A.; Schmidbaur, H. *Organometallics* **2003**, *22*, 4922–4927. (b) Fuchita, Y.; Ieda, H.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2000**, 271–274. (c) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330–2334. (d) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058–12059. (e) Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2028–2032. (f) Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. *J. Am. Chem. Soc.* **2010**, *132*, 5580–5581. (g) ref 27a. (h) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910–1925.

50 Reetz, Manfred T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, *2003*, 3485–3496.

51 Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.

In contrast, the intermolecular reaction of heteroarenes, such as indoles,[52b] 2,3-benzofurans,[52a] and furanes,[53,54] generally results in a double addition to the alkyne (Scheme 6).



Scheme 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,[55] cinnoline derivatives,[56] phenantrenes,[57] coumarines,[51] and pyrrolo[1,2-a]quinilines[58] (Scheme 7).

52 (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049–5054. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373.

53 Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem*. **2006**, 4340–4342.

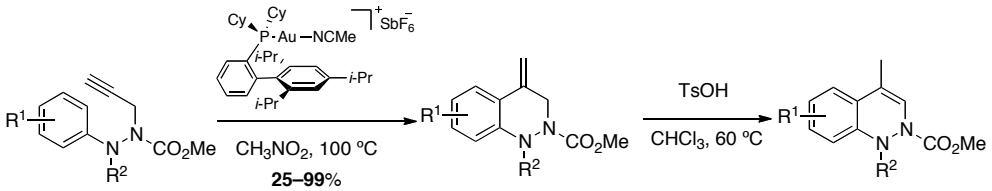
54 In contrast, the gold(I)-catalyzed reaction of phenylacetylene and 2,5-disubstituted furane delivers the product of mono-addition and a phenol derivative. Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709–713.

55 Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901–8903.

56 Jurberg, I. D.; Gagosz, F. *J. Organomet. Chem*. **2011**, *696*, 37–41.

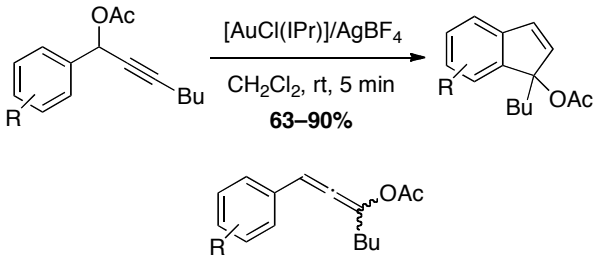
57 Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556–4575.

58 (a) Liu, X.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3805–3810. (b) Zhou, Y.; Feng, E.; Liu, G.; Ye, D.; Li, J.; Jiang, H.; Liu, H. *J. Org. Chem*. **2009**, *74*, 7344–7348.



Scheme 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.[59] The formation of the indenes proceeds by 1,3-shift to form an allene, followed by the hydroarylation (Scheme 8). Notably, this reaction requires strictly anhydrous conditions, since in the presence of water, conjugated enones and enals are isolated.[60] Related transformations are the reaction with propagyl sulfide, dithioacetals, which allows the synthesis of indenes,[61] or the synthesis of naphthalenes via double migration cascade reactions.[62]



Scheme 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

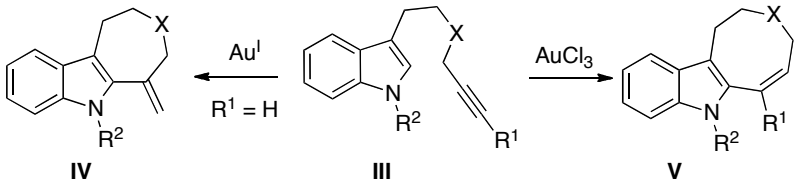
59 (a) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3647–3650. (b) Nun, P.; Gaillard, S.; Poater, A.; Cavallo, L.; Nolan, S. P. *Org. Biomol. Chem.* **2011**, *9*, 101–104.

60 Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437–6451.

61 Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192–1197.

62 (a) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 1465–1468. (b) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Tetrahedron* **2009**, *65*, 1859–1870.

derivatives **IV**, via 7-*exo-dig* cyclization, or indoloazocine **V**, via 8-*endo-dig* cyclization (Scheme 9).[52b,63]

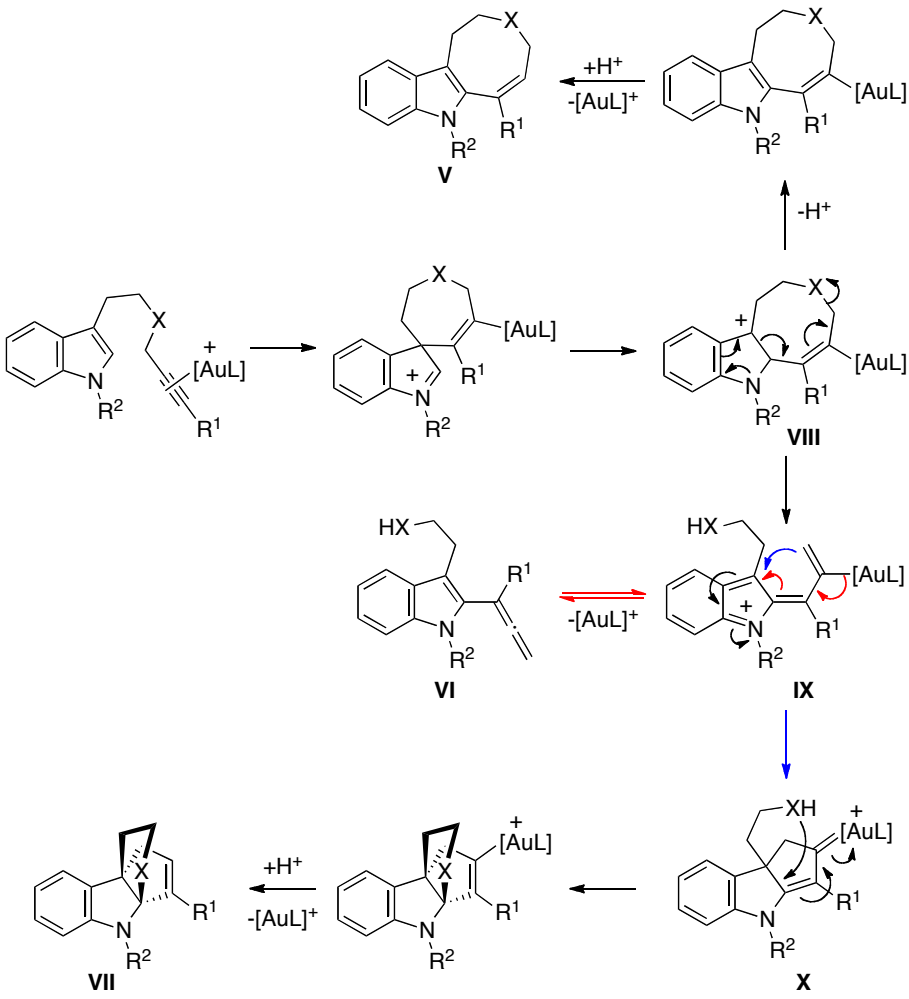


Scheme 9. *Intramolecular gold(I)-catalyzed reaction of indoles and alkynes*

Cationic gold(I) complexes favor the formation of six- and seven-membered ring 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 10). In Scheme 10 the proposed mechanism for the formation of the different products is shown. Nucleophilic attack of the indole to 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**.

This methodology and its application on total synthesis will be discussed in more details in Chapter 3.

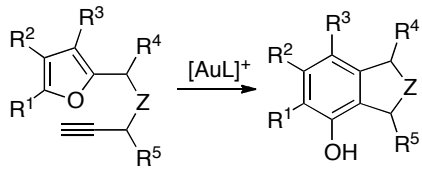
63 (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020.



Scheme 10. *Mechanism for the intramolecular reaction of indoles and alkynes*

Generally the intramolecular reaction of furanes with alkynes forms phenols in good to excellent yields using gold(I),[64] $AuCl_3$,[31b,65] or heterogeneous gold[66] as catalysts (Scheme 11).

64 Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Rivas Nass, A.; Frey, W. *Chem. Eur. J.* **2006**, *12*, 5376–5382.



Scheme 11. *Synthesis of phenols via gold-catalyzed intramolecular reaction of furanes and alkynes*

The mechanistic proposal depicted in Scheme 12 is based on experimental and theoretical studies using gold and platinum as catalysts.[65d,66f,66,67] 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. However, 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**.[68] Finally, intermediate **XV** aromatizes to give the final phenol.

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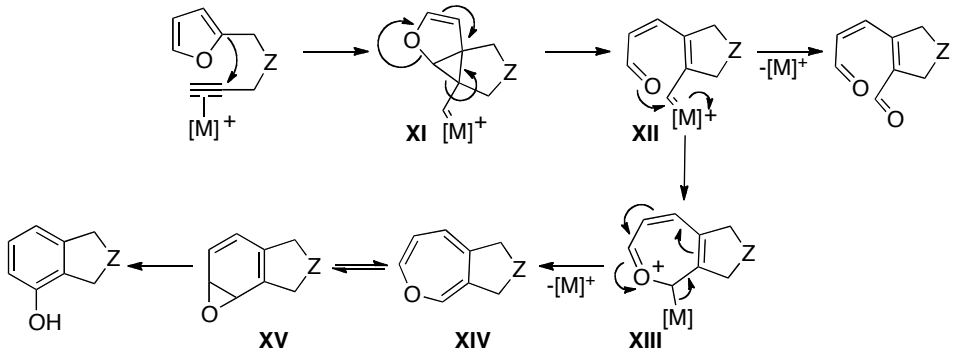
65 (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771. (c) Shmi, A. S. K.; Frost, T. M.; Bats, J. W. *Cat. Today* **2002**, *72*, 19–27. (d) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejović, E.; Frost, T. M.; Miehlich, B.; Frey, W.; Bats, J. W. *Chem. Eur. J.* **2006**, *12*, 5806–5814. (e) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Chem. Eur. J.* **2006**, *12*, 6991–6996. (f) Hashmi, A. S. K.; Kurpejović, E.; Frey, W.; Bats, J. W. *Tetrahedron* **2007**, *63*, 5879–5885. (g) Hashmi, A.; Ata, F.; Kurpejovic, E.; Huck, J.; Rudolph, M. *Top. Catal.* **2007**, *44*, 245–251. (h) Hashmi, A. S. K.; Schäfer, S.; Bats, J. W.; Frey, W.; Rominger, F. *Eur. J. Org. Chem.* **2008**, **2008**, 4891–4899. (i) Hashmi, A. S. K.; Ata, F.; Haufe, P.; Rominger, F. *Tetrahedron* **2009**, *65*, 1919–1927.

66 Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2006**, *348*, 1283–1288.

67 Hashmi, A. S. K.; Rudolph, M.; Siehl, H.-U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem. Eur. J.* **2008**, *14*, 3703–3708.

68 The intermediate arene oxide **XV** was trapped by reaction with *N*-phenyltriazolinedione. Hashmi, A. S. K.; Kurpejović, E.; Wölfle, M.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2007**, *349*, 1743–1750.



Scheme 12. *Proposed mechanism for the formation of phenols*

Others application of this methodology allow the synthesis of benzofurans,[69] chromans,[70] dihydrobenzofurans,[70] dihydroindoles,[70] tetrahydroquilones[70] or complex tetracyclic products[71] in a highly selective manner.

I.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 compounds. This versatile transformation can be promoted by a large array of transition metals.[72]

With regard to the mechanism, three pathways are possible depending on the type of coordination of the metal to the enyne (Scheme 13). In the first pathway, the simultaneous coordination of the metal to the alkyne and the alkene leads to the formation of 1,3- and 1,4-

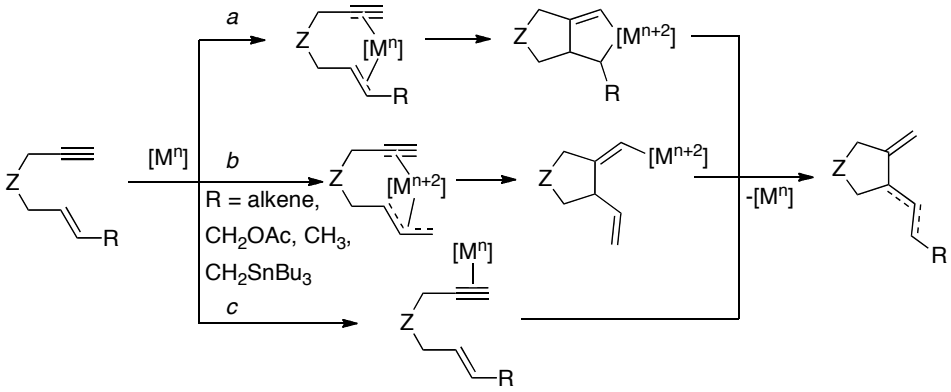
69 Hashmi, A. S. K.; Enns, E.; Frost, T. M.; Schäfer, S.; Frey, W.; Rominger, F. *Synthesis* **2008**, 2707–2718.

70 Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672–6678.

71 Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzić, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 5848–5852.

72 General reviews for the behavior of 1,n-enynes in the presence of transition metals: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813–834. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215–236. (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Echavarren, A.; Jiménez-Núñez, E. *Top. Catal.* **2010**, *53*, 924–930.

dienes through metallacyclopentene intermediates (pathway a, Scheme 13). In this process, a two-electron oxidation of the metal takes places, 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 has a functional group that promotes the formation of π-allylmetal intermediates (pathway b, Scheme 13). Finally, the third pathway is based on the selective activation of the alkyne moiety by the metal (pathway c, Scheme 13).



Scheme 13. *Different pathways for the metal-catalyzed cycloisomerization of 1,n-enynes*

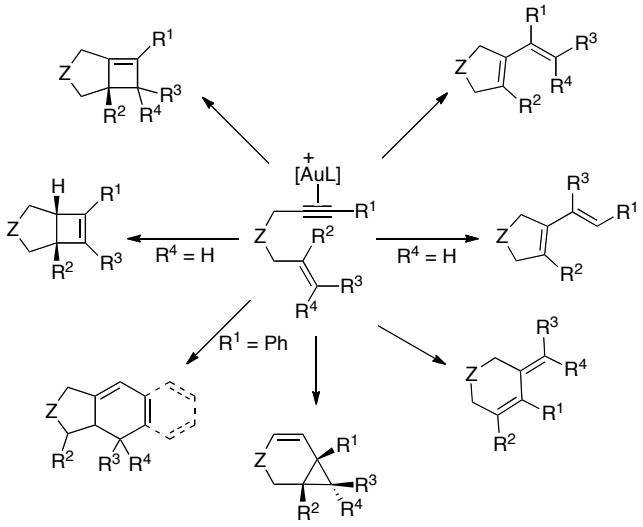
In the cycloisomerization of 1,n-enynes using gold complexes as catalysts, only the third pathway takes place. This high selectivity is due to two main reasons: (i) the fragment $[AuL]^+$ has only one vacant site, thus it can not coordinate simultaneously the alkyne or the alkene moieties, (ii) oxidative addition processes are not facile for gold complexes.[17d,73] In general, gold(I) complexes surpass the reactivity shown by platinum(II) and other electrophilic metals for the reaction of enynes.[72d,74]

73 (a) Nakanishi, W.; Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 1446–1453. (b) Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006–3009.

74 Selected reviews: (a) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431–436. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (c) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328–2334. (d) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296. (e) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916–5923. (f) Abu Sohel, S. M.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269–2281.

I.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 reactions within gold catalysis. In the absence of nucleophiles a variety of products can be obtained, some examples are highlighted in Scheme 14.[11g,74]

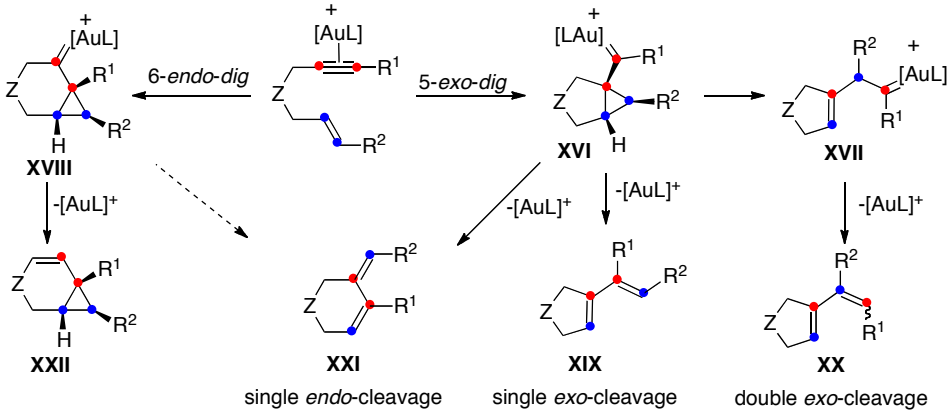


Scheme 14. *Selected products in the gold-catalyzed cyclization of 1,6-enynes*

The mechanism of this reaction starts with the activation of the alkyne moiety by the gold complexes, followed by the *anti* attack of the alkene via 5-*exo*-*dig* or 6-*endo*-*dig* pathway (Scheme 15).[72d] In the absence of nucleophiles, 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).[75] On the other hand, bicyclic compound **XXII** is obtained by e*ndo*-cyclization via carbene **XVIII**.[19b,74e,76]

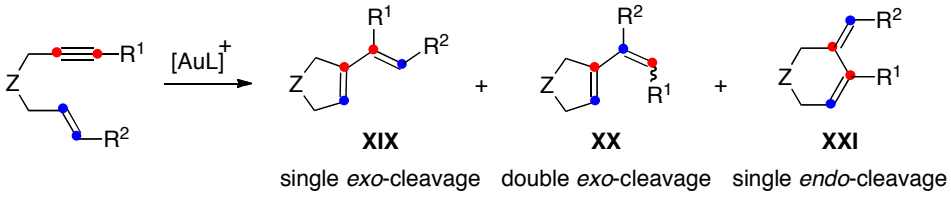
75 Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, *2007*, 4217–4223.

76 (a) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, *71*, 9366–9372. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988–6990.



Scheme 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 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.[77]



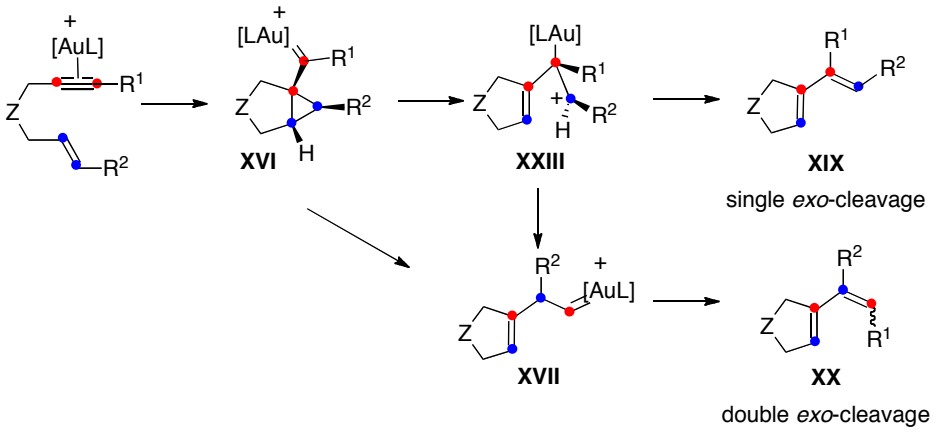
Scheme 16. *Dienes of single and double cleavage rearrangement*

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 17). The single *exo*-cleavage is akin to the metathesis of enynes,[74b,78] although the mechanism is completely different. Nevertheless, the double cleavage rearrangement take places through cyclopropyl gold carbene **XVII**, which can be formed by diotropic rearrangement from

77 Ota, K.; Chatani, N. *Chem. Commun.* **2008**, 2906–2907.

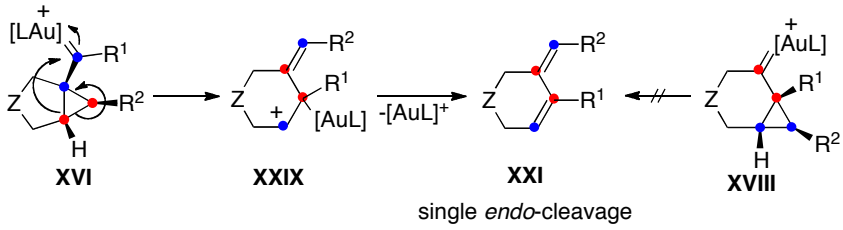
78 Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121–135.

carbene **XVI**[79] or by carbocation 1,2-shift of the cyclic alkenyl group in **XXIII**.[15a] Formation of the diene **XX**, form carbene **XVII**, involves loss of a α-proton, followed by protodemetallation.



Scheme 17. *Single- and double-cleavage exocyclic skeletal rearrangement*

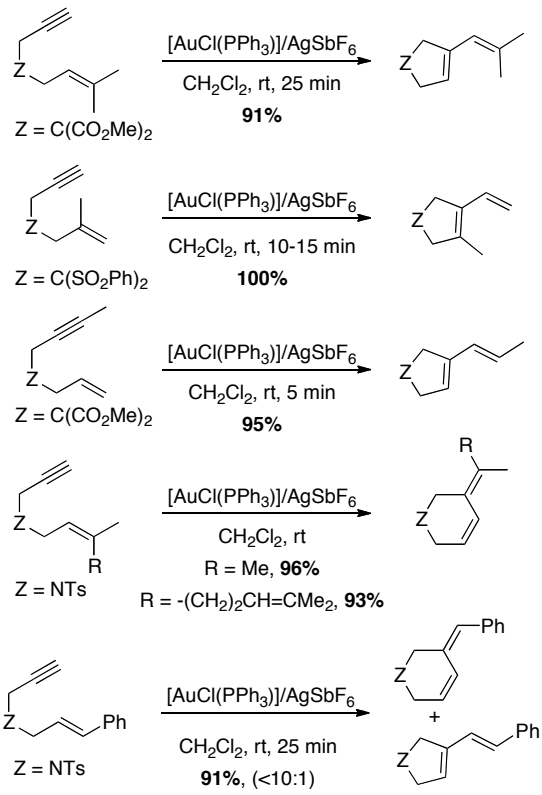
The formation of the six-membered ring **XXI** was initially proposed to take place through cyclopropyl gold carbene **XVIII** via 6-*endo-dig* cyclization (Scheme 18).[19a] However, DFT calculations support a mechanism in wich cyclopropyl gold carbene **XVI** rearranges to cation **XXIX**, followed by protodemetallation.[75]



Scheme 18. *Endocyclic rearrangement of 1,6-enynes*

Selected examples of single *exo*-, double *exo*- and single *endo*-cleavage products are shown in Scheme 19.[15a,75]

79 (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129–130. (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 130–131. (c) Nouri, D. H.; Tantillo, D. J. *J. Org. Chem.* **2006**, *71*, 3686–3695.



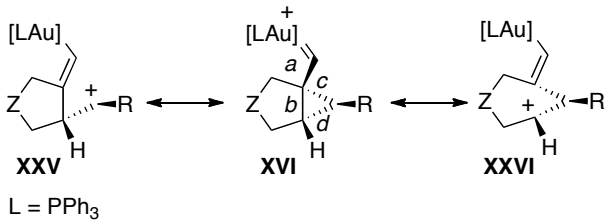
Scheme 19. *Selected examples of gold-catalyzed cycloisomerization of 1,6-enynes*

Intermediates **XVI**, **XVII** and **XVIII** (Scheme 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 dependent of the substitution pattern of the enyne and the nature of the ligand (Table 1).[15a,15d,75,80,81] 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.

80 Pérez-Galán, P.; Martin, N. J. A.; Campaña, A. G.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Asian. J.* **2011**, *6*, 482–486.

81 Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895.

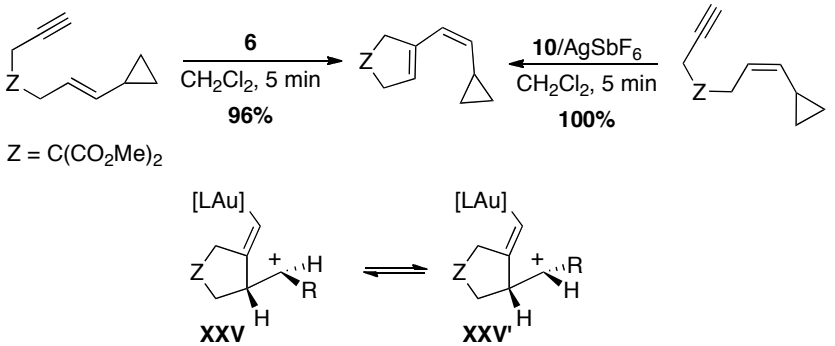
Table 1. *Bond distances for cyclopropyl gold carbene* ***XVI*** *determined by DFT calculations*



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 20).[81] 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 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,[82] the carbenic character of the carbene intermediates have been confirmed by trapping of the cyclopropyl gold carbenes **XVI** and **XVII** via intra-[19a,83] and intermolecular[21a,84] cyclopropanation of alkenes (Scheme 21), as well as by formation of the corresponding aldehydes when the reaction is carried out in the presence of Ph_2SO.[85] Interestingly, a gold carbene has been generated in gas phase showing the reactivity expected for these species.[86]

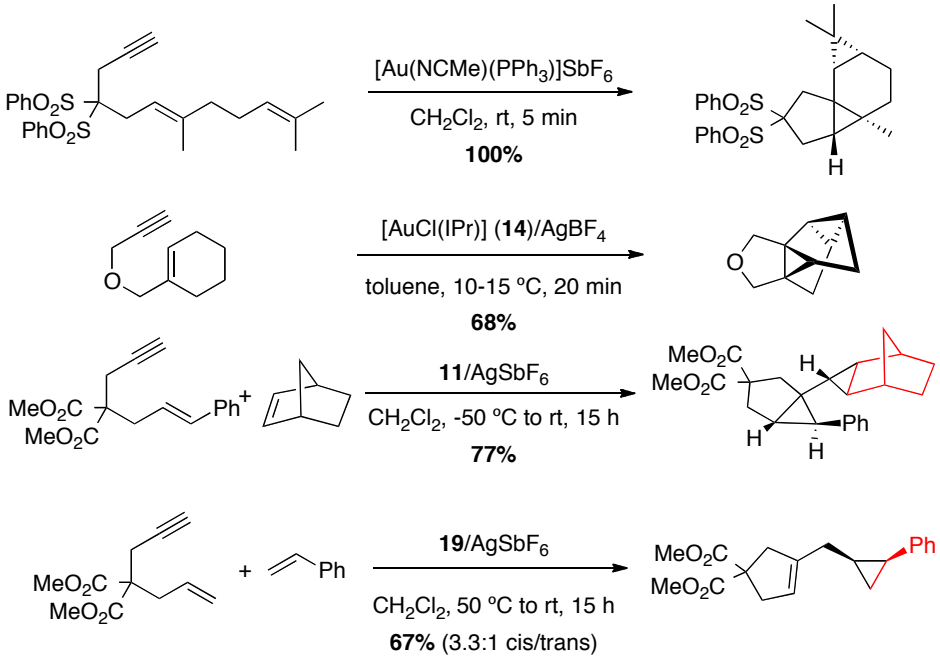
82 Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241.

83 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1694–1702. (b) Kim, S. M.; Park, J. H.; Choi, S. Y.; Chung, Y. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 6172–6175.

84 Pérez-Galán, P.; Herrero-Gómez, E.; Hog, D. T.; Martin, N. J. A.; Maseras, F.; Echavarren, A. M. *Chem. Sci.* **2011**, *2*, 141–149.

85 Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

86 (a) Fedorov, A.; Moret, M.-E.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 8880–8881. (b) Fedorov, A.; Chen, P. *Organometallics* **2009**, *28*, 1278–1281. (c) Batiste, L.; Fedorov, A.; Chen, P. *Chem. Commun.* **2010**, *46*, 3899–3901. (d) Fedorov, A.; Chen, P. *Organometallics* **2010**, *29*, 2994–3000.

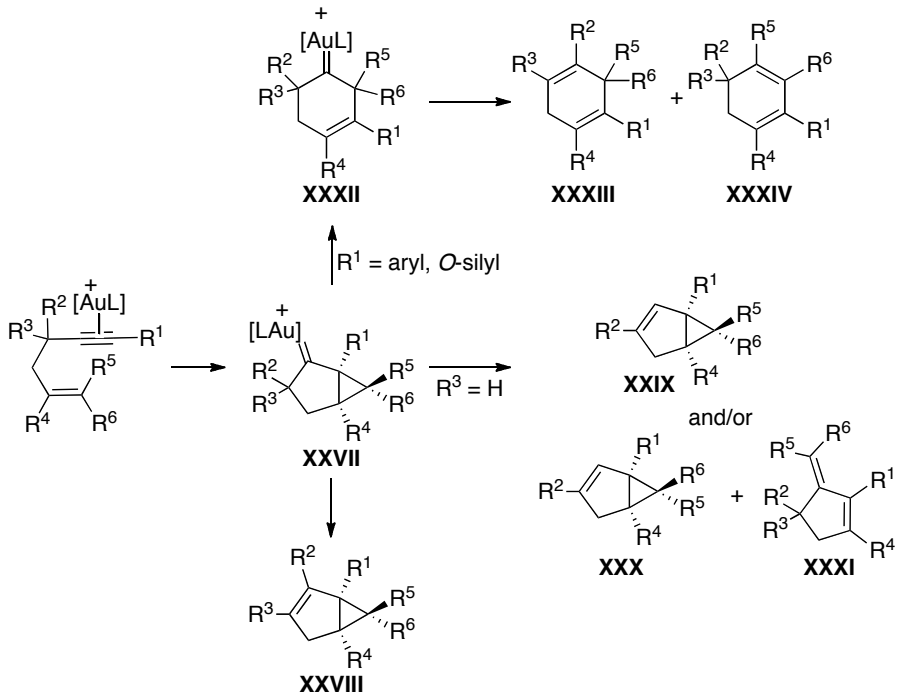


Scheme 21. *Selected examples for the gold-catalyzed reaction of 1,6-enynes with olefins*

I.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 product (Scheme 22),[17d,74b] in which the mechanistic proposal resembles the one of 1,6-enynes. In most cases, 1,5-enynes cyclize through an endocyclic pathway. However, the *exo*-pathway is more favorable when terminal alkynes or iodoalkynes are used.[87]

87 Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 4411–4414.



Scheme 22. *General overview for the gold-catalyzed cyclization of 1,5-enynes*

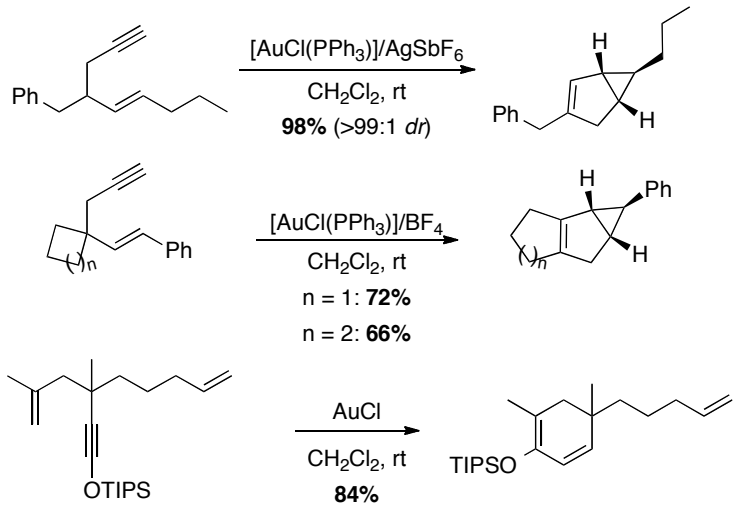
1,5-Enyne cycloisomerization gives bicyclo[3.1.0]hexanes **XXVIII**, **XXIX** and/or **XXX** in a stereoespecific transformation. The proposed mechanism starts by 5-*endo-dig* cyclization to give an internal cyclopropyl gold carbene **XXVII**, which undergoes hydride 1,2-shift to give **XXVIII**.[22,88] 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**.[88c] Stereoisomer **XXX** is the one expected for the *Z* isomer of the starting 1,5-enynes. Double cleavage products **XXXIII** and **XXXIV**

88 (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (c) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129–4132. (d) Fürstner, A.; Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181–9191. (e) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811. (f) Liu, Y.; Zhang, D.; Zhou, J.; Liu, C. *J. Phys. Chem. A* **2010**, *114*, 6164–6170.

are obtained from aryl- and silyloxy-1,5-enynes.[89] 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.[90]

Selected examples for the gold-catalyzed cyclization of 1,5-enynes are shown in Scheme 23.[88a,88c]



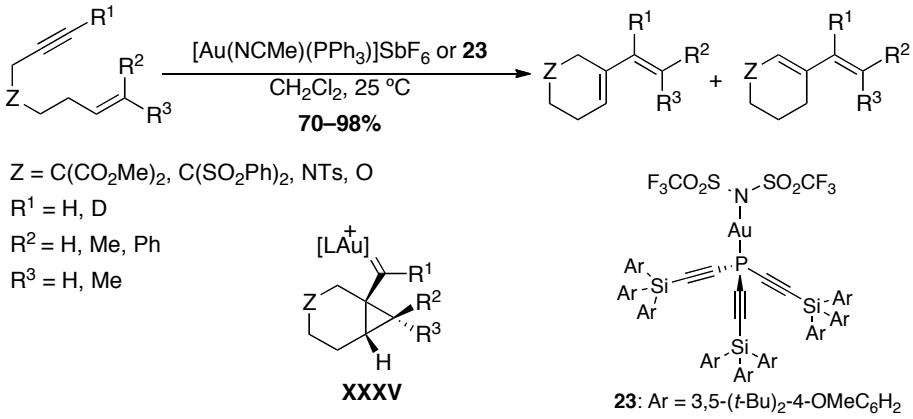
Scheme 23. *Selected examples of gold-catalyzed cycloisomerization of 1,5-enynes*

89 (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807. (b) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710.

90 López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972–10978.

I.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 24).[47c,91] 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.[92]



Scheme 24. *Single cleavage rearrangement of 1,7-enynes*

In the special case of 1,7- and 1,8-enynes when the alkene moiety is a silylenolether, seven-membered rings are obtained by a 7-*exo-dig* cyclization.[93]

Gold(I)-catalyzed cyclization of 1,8-enynes give cyclobutene compounds as the main product (Scheme 25).[66,94] 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-

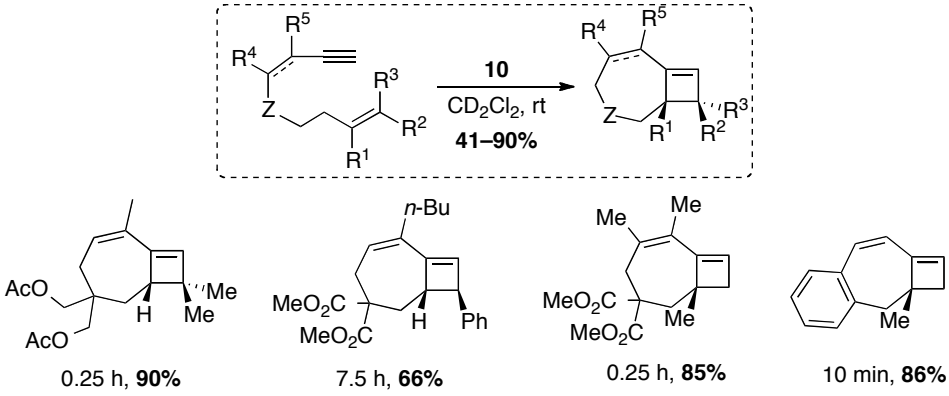
91 Cabello, N.; Rodríguez, C.; Echavarren, A. M. *Synlett.* **2007**, 1753–1758.

92 Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203–15211.

93 Ito, H.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 4380–4383.

94 Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386.

enynes.[15a] The formation of cyclobutene compounds by gold-catalyzed cycloisomerization of 1,n-enynes will be discussed in Chapter 2.



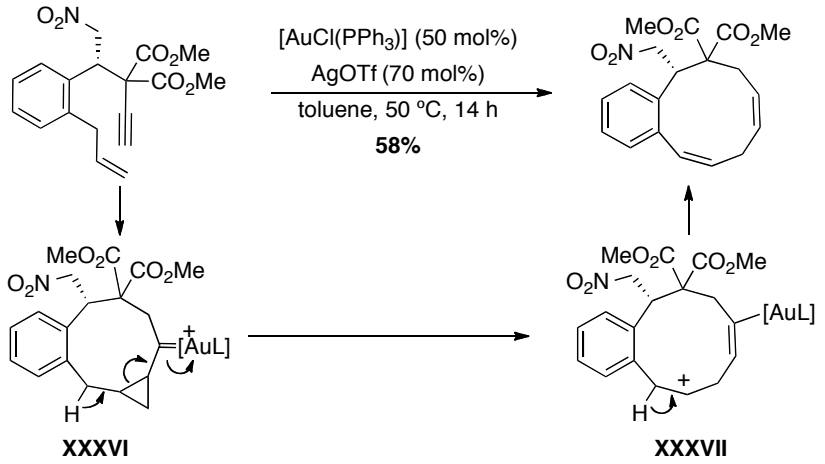
Scheme 25. *Formation of cyclobutene compounds by gold(I)-catalyzed cyclization of 1,8-enynes*

Alternatively, in the case of 1,7- and 1,8-enynes bearing a propargyl acetate group, cyclopropyl compounds are isolated in good yields.[95]

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 26).[96] The cycloisomerization presumably occurs via cyclopropyl gold carbene **XXXVI**, which can open to carbocation **XXXVII** or give directly the 10-membered ring.

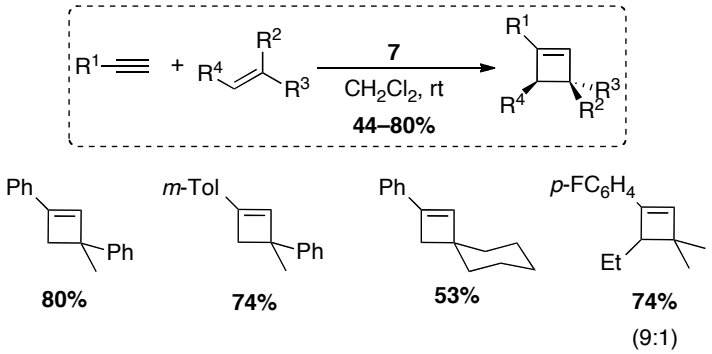
95 (a) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43–48. (b) Boyer, F.-D.; Le Goff, X.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163–5166.

96 Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. *Org. Lett.* **2007**, *9*, 2123–2126.



Scheme 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 27).[97] This transformation shows that in the absence of the constrains imposed by the tethers in the intramolecular processes, a [2+2] cycloaddition is the predominant mechanism.



Scheme 27. *Gold(I)-catalyzed intermolecular reaction of alkynes with alkenes*

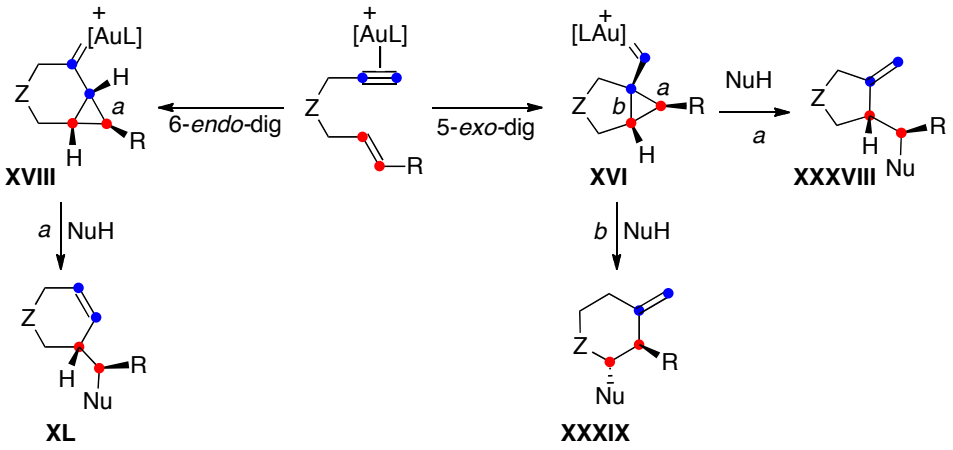
I.4.4 Gold-Catalyzed Nucleophilic Additions to 1,n-Enynes

One of the most emblematic reactions is the trapping of different intermediates of 1,n-enynes with different nucleophiles, which allows the formation of complicated structures from readily simple starting materials.[72f]

97 López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.

I.4.4.1 Hydroxy-, Alkoxy-cyclization 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.[72f] This process involves an opening of the cyclopropyl gold carbene intermediate **XVI** or **XVIII**, which results in a formal nucleophilic 1,4-addition (Scheme 28). Two different products can be synthesized by 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 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-[98] and intermolecular[99] reaction with 1,6-enynes. The asymmetric version of the reaction proceeds

98 For 1,6-enynes: (a) ref 19b. (b) ref 28b (d) ref 28 (e) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030–5033. For 1,5-enynes: (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963.

99 For 1,6-enyes: (a) ref 19b. (b) ref 26f. (c) Chao, C.-M.; Toullec, P. Y.; Michelet, V. *Tetrahedron Lett.* **2009**, *50*, 3719–3722. For 1,5-enynes: (f) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141–1144.

with good to excellent enantioselectivity using chiral gold complexes.[100] The hydroxy- and alkoxycyclization of 1,7-enynes takes place in a similar way.[91b] Furthermore, this methodology has been extended to other nucleophiles, like amines,[101] carbamates,[101a] carboxylic acids,[19b,102] and phenols.[103]

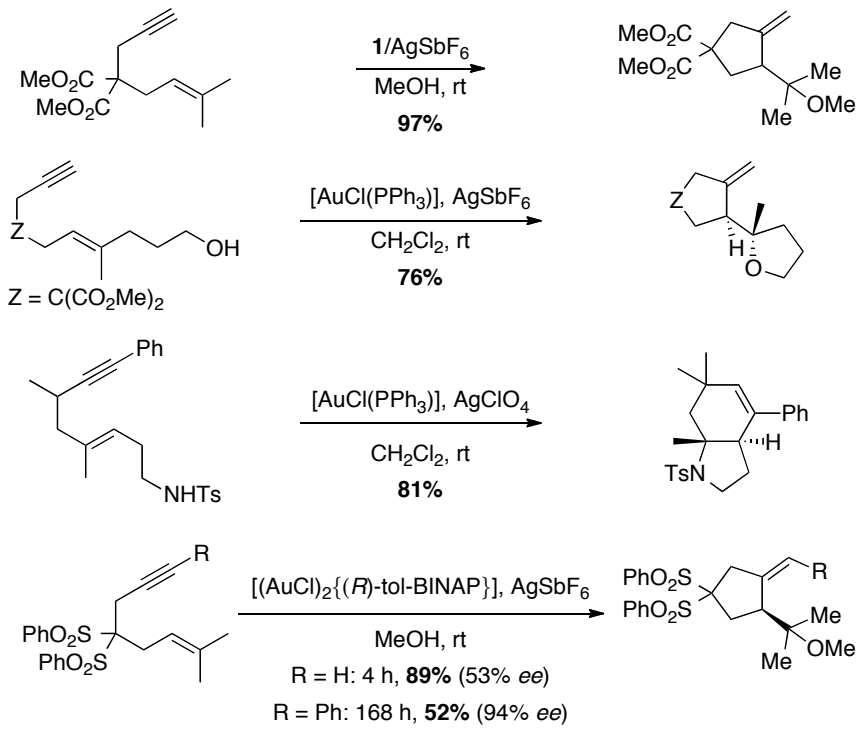
Selected examples for the gold-catalyzed addition of nucleophiles to 1,5 and 1,6-enynes are shown in Scheme 29.[19b,100b,101b]

100 (a) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300. (b) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391. (c) Sengupta, S.; Shi, X. *ChemCatChem.* **2010**, *2*, 609–619.

101 For the intramolecular reaction of 1,5-enynes with amines: (a) ref 98b. For the intramolecular reaction of 1,6-enynes with carbamates: (b) Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Org. Lett.* **2007**, *9*, 4049–4052.

102 For the intramolecular reaction of 1,6-enynes with carboxylic acids,; Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276-8277.

103 For the intramolecular reaction of 1,5-enynes with phenols: Toullec, P. Y.; Blarre, T.; Michelet, V. R. *Org. Lett.* **2009**, *11*, 2888–2891.



Scheme 29. *Selected examples for the hydroxy-, alkoxy- and aminocyclization of enynes*

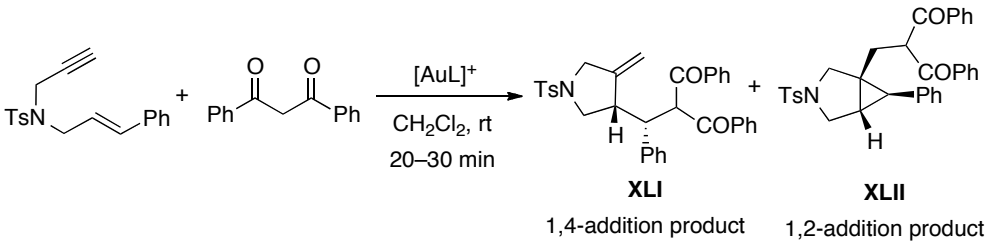
I.4.4.2 Addition of Carbon Nucleophiles to 1,n-Enynes

Electron-rich arenes,[104] indoles,[24e] 1,3-dicarbonyl compounds[24e] and allyl silanes[24e] 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. In the addition of indole and 1,3-dicarbonyl compounds a strong effect of the ligand present in the gold complex was detected (Table 2). In this reaction, the product of 1,2-addition is favored with a more electron-donating ligands, like NHC gold(I) complexes (Table 2, entries 5 and 6), as a result of the direct trapping of the gold(I) carbene by the nucleophile. On the other hand, catalysts with a more electrophilic ligands (such as phosphates) led to 1,4-addition

104 (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem. Int. Ed.* **2006**, *45*, 7427–7430. (b) Leseurre, L.; Chao, C.-M.; Seki, T.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Tetrahedron* **2009**, *65*, 1911–1918. (c) Seo, H.; Roberts, B. P.; Abboud, K. A.; Merz, K. M.; Hong, S. *Org. Lett.* **2010**, *12*, 4860–4863.

products (Table 2, entries 2 and 3).[24e,28c,104c] In addition, the asymmetric versions of the reaction with electron-rich arenes and 1,3-dicarbonyl compounds have been reported.[102,105]

Table 2. *Ligand effect in the addition of 1,3-dicarbonyl compounds to 1,6-enynes*



XLI 1,4-addition product

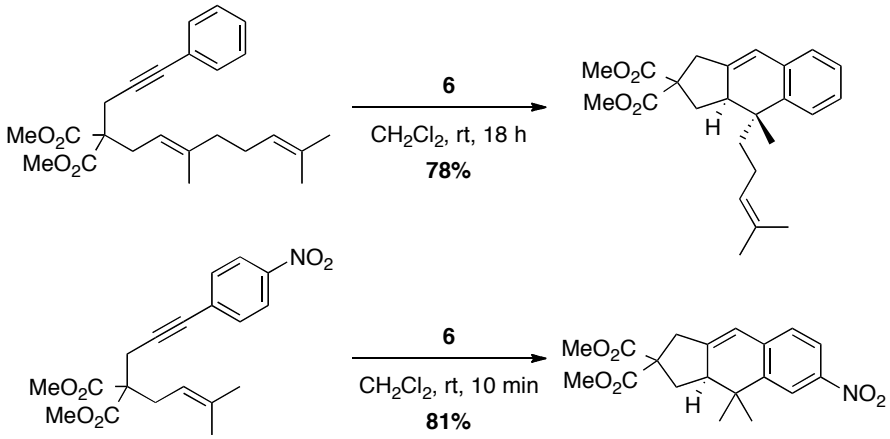
XLII 1,2-addition product

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 to yield tricyclic compound (Scheme 30).[20,106] Generally, the reaction is stereospecific and tolerates electron-donating and electron-withdrawing groups at several positions of the aryl moiety. However, olefin substituted with electron-releasing group leads to a lack of stereospecicity of the reaction.[81]

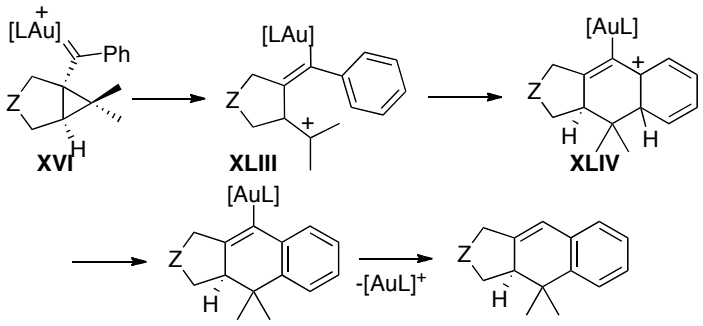
105 Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319–1323.

106 (a) 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.* **2007**, *130*, 269–279. (b) M.-C. P.; Tsao, W.-C.; Lee, B.-J.; Lin, T.-L. *Organometallics* **2008**, *27*, 5326–5332.



Scheme 30. *Selected examples for [4+2]-cycloaddition of arylenynes*

The reaction proceeds by the formation of cationic intermediate **XLIII** from *anti*-cyclopropyl gold carbene **XVI**. Intermediate **XLIII** is stabilized by a π-interaction with the aryl ring. Friedel-Crafts-type reaction forms cationic **XLIV**, which evolves by aromatization and protodemetallation to form the tricyclic compound (Scheme 31).

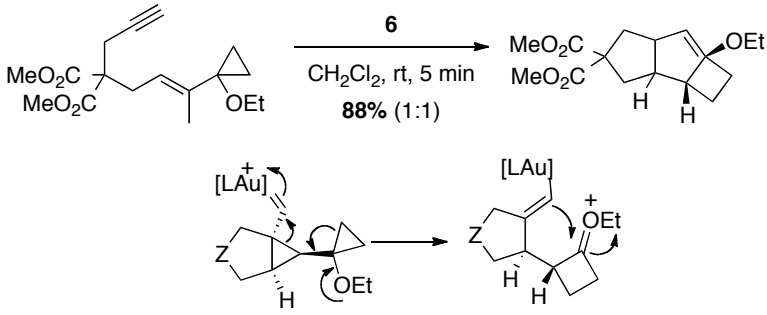


Scheme 31. *Proposed mechanism for [4+2] cycloaddition of arylenynes*

The *endo*-cyclization takes place as a minor pathway in certain cases, which is the favored one in platinum- and gold-catalyzed cycloaddition of related arylenynes with enesulfonamides or enamines.[107] Analogous tricylic products can be synthesized via gold-catalyzed [4+2] cycloaddition reaction of benzyl-substituted 1,5-enynes.[90]

107 (a) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367–370. (b) Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929–6935. (c) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585–8590.

In addition, hydrindanes are synthesized from 1,8-dien-3-ynes by [4+2] cycloaddition.[20,80b,106a] However, 1,3-dien-8-ynes undergo intramolecular Diels-Alder reaction to give formal [4+2] products or hexahydropentalene compounds.[108] The reaction of cyclopropylenynes gives pentalenes via Prins cyclization (Scheme 32).[81] 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 32. *Gold-catalyzed reaction of cyclopropylenynes*

I.4.4.3 Other Nucleophilic Additions to 1,n-Enynes

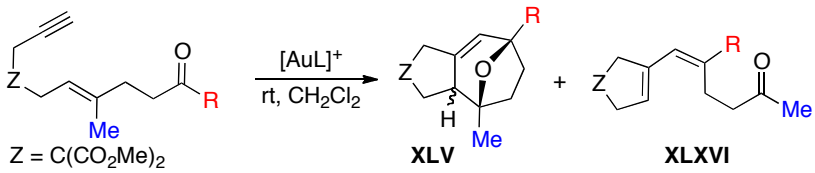
Aldehydes and ketones can act as nucleophiles in the gold-catalyzed reaction of 1,6-enynes. Only a general view of this reactivity will be discussed in this general introduction, since it will be presented deeply in Chapter 1.

1,6-Enynes bearing a carbonyl group at the alkenyl side chain led to oxatricyclic compounds in the presence of AuCl as catalyst (Table 3).[109] The reaction proceeds through a formal [2+2+2] cycloaddition, where two C–C and one C–O bonds are formed.

108 (a) Fürstner, A.; Stimson, C. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8845–8849. (b) Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 4269–4272.

109 Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455.

Table 3. *Gold(I)-catalyzed cyclization of carbonyl 1,6-enynes*



Entry	*R*	*[AuL]*$^+$	*Yield* ***XLV*** *(syn/anti)*	*Yield* ***XLVI***
1	H	[AuCl(PPh$_3$)]/AgSbF$_6$	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%

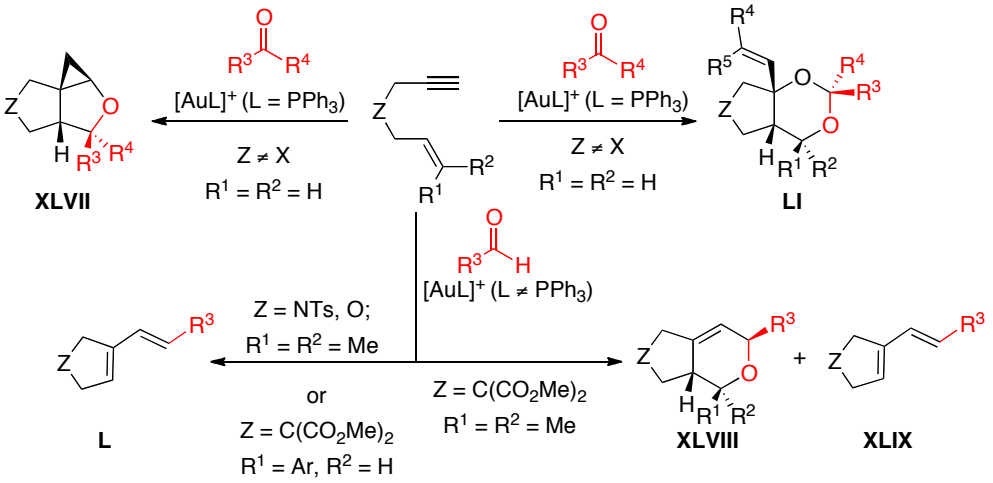
This valuable transformation has been successfully applied in the total synthesis of natural compounds like like (±)-pubinernoid B,[110] (+)-orientalol F,[110] and (-)-englerin A and B.[111]

The gold-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes is also feasible. This methodology led to a wide range of compounds (Scheme 33).[112] 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 been also reported.[112b]

110 Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327–7329.

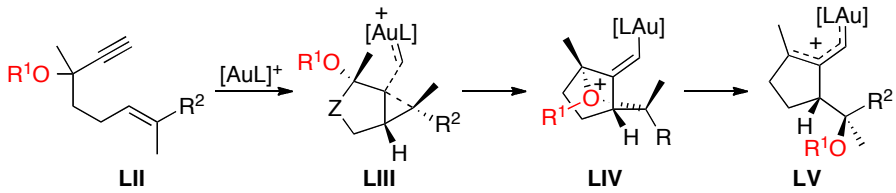
111 Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517–3519.

112 (a) Schelwies, M.; Dempwolff, A. L.; Rominger, F.; Helmchen, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5598–5601. (b) Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J.* **2009**, *15*, 5646–5650. (c) Schelwies, M.; Moser, R.; Dempwolff, A. L., Rominger, F., Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10888–10900.



Scheme 33. *General overview of the gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes*

In this context is worth to mention 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 34).[113] The reaction proceeds through an intermediate **LIII** and then, the OR group migrates in intermediate **LIII** to form **LV**, which then opens to give allylgold cation **LIV**.

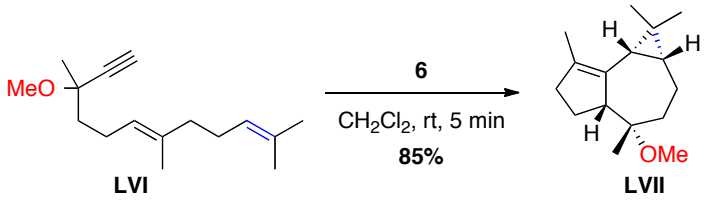


Scheme 34. *Gold-catalyzed 1,5-migration of 1,6-enynes of type* ***LII***

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 a 85% yield (Scheme 35).[113a] Interestingly, this

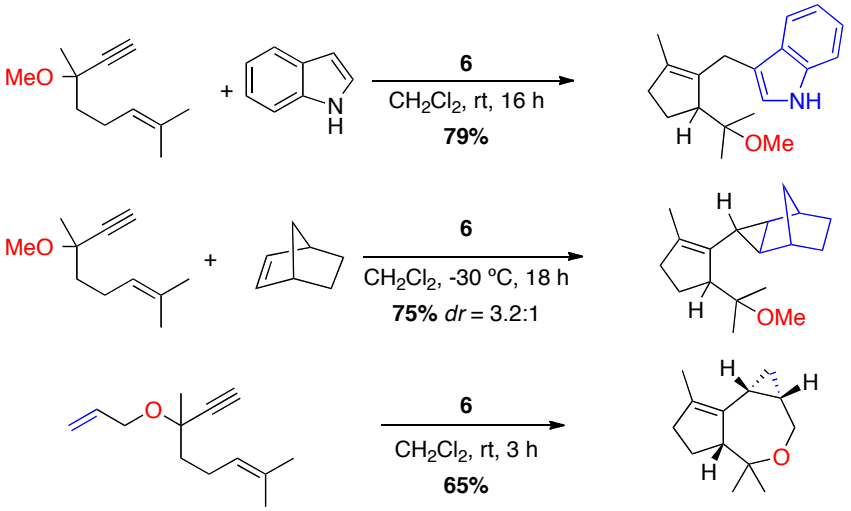
113 (a) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152–6155. (b) Solorio-Alvarado, C. s. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883.

reaction leads to tricyclic compounds that are structurally related with globulol,[114] epiglobulol[114] and halichonadin F.[115]



Scheme 35. *Gold-catalyzed 1,5-migration of dienyne* ***LVI***

In addition, intermediate **LIII** can react with indoles, alkenes, or dienes to form products with a remarkable increase of molecular complexity (Scheme 36).[113]

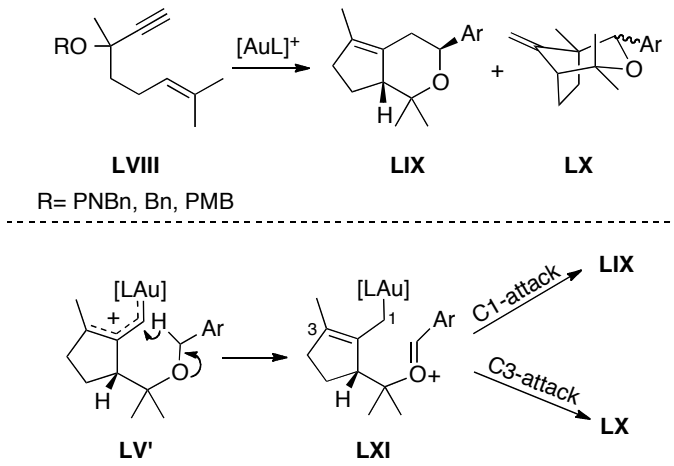


Scheme 36. *Selected examples for the 1,5-migration of the enynes of type* ***LII***

On the other hand, 3-benzyloxy-1,6-enynes of type **LVIII** lead to **LIX** and **LX** compounds via formal C–H insertion on intermediate **LV'** (Scheme 37). The reaction proceeds via proton abstraction from the CH_2Ar' group in **LV'** to form a η^1-allyl gold intermediate **LXI**, which reacts at C1 or C3 with the oxonium cation to give **LIX** or **LX**, respectively.

114 Caine, D. S.; Gupton, J. T. *J. Org. Chem.* **1975**, *40*, 809–810.

115 Ishiyama, H.; Kozawa, S.; Aoyama, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. i. *J. Nat. Prod.* **2008**, *71*, 1301–1303.



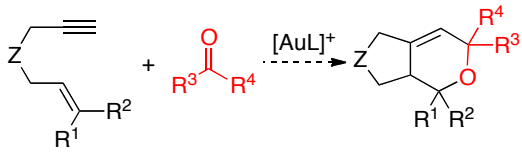
Scheme 37. *1,5-Migration of 3-benzyloxy-1,6-enynes followed by formal C–H insertion*

Another example of cascade reaction is the cycloisomerization of 3-silyloxy1,5-enynes, which gives carbonyl compounds through a pinacol rearrangement.[116]

116 (a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2310–2313. (b) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 2605–2607. (c) Menz, H.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Kirsch, S. F.; Klahn, P.; Liébert, C. *Tetrahedron* **2009**, *65*, 1880–1888.

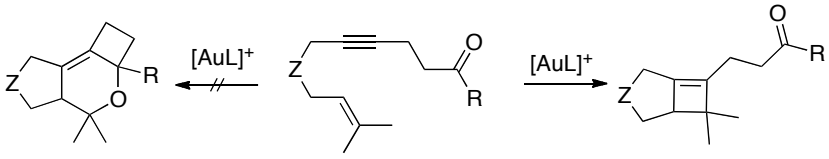
General Objectives

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.[11] Over the last few years, the Echavarren group reported new gold-based transformations mostly aimed at the activation of alkynes.[11b,72d] Numerous methodologies have been developed that favor the attack of different nucleophiles, like olefins, indoles or aryls, to alkynes.[11b,72d] For example, carbonyl compounds can act as nucleophiles in the intra-[109] and intermolecular[112] 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).



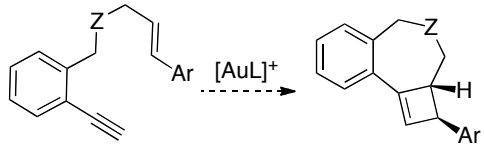
Scheme 1. *Proposal for the study of the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes*

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 2). Unexpectedly, this type of 1,6-enynes promoted the formation of cyclobutene compounds.



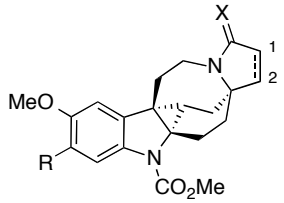
Scheme 2. *Gold(I)-catalyzed cycloisomerization of 1,6-enynes bearing a carbonyl group at the alkyne side chain*

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 3).



Scheme 3. *Formation of cyclobutenes via gold(I)-catalyzed [2+2] cycloaddition*

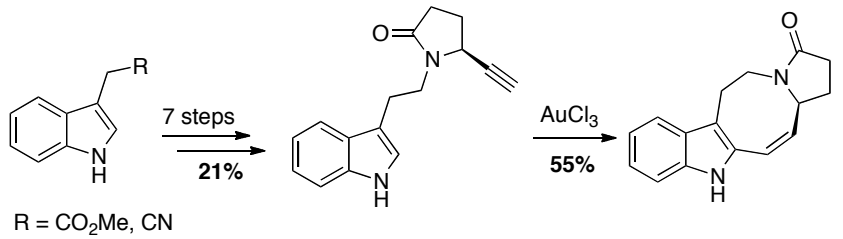
The last objective of this Doctoral Thesis was the application of the methodology developed in the group for the total synthesis of lundurines.[63] Lundurines A–D are a new type of alkaloids characterized by a cyclopropylic fragment embedded within a hexacyclic ring system that includes a 1*H*–azocine[5,4–*b*]indole ring unit (Figure 1). Importantly, lundurines B and D display significant cytoxicity *in vitro* toward B16 melanoma cells.



Lundurine A: R = H, X = O, $\Delta^{1,2}$
Lundurine B: R = H, X = H, $\Delta^{1,2}$
Lundurine C: R = H, X = H
Lundurine D: R = OMe, X = H, $\Delta^{1,2}$

Figure 1. *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 4).[63c] Thus, based on previously reported results, our objective was to develop an efficient approach toward the total synthesis of lundurines.



R = CO_2Me, CN

Scheme 4. *Previous results for the synthesis of the tetracyclic core of lundurines*

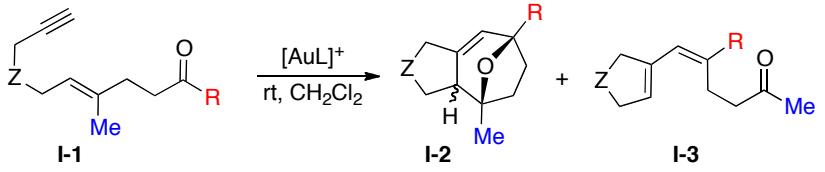
Chapter 1: Gold(I)-Catalyzed Reactions of 1,6-Enynes with Aldehydes: Cycloaddition versus Metathesis-Type Reactions

The intermolecular gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes of type **I-15** possessing a tri-substituted olefinic group has been studied. Products of [2+2+2] cycloaddition **I-16** and/or 1,3-dienes **I-17** were obtained selectively, depending on the substitution pattern of the alkene, the heteroatom in the tether (Z) or the ligand in the gold complex (L).

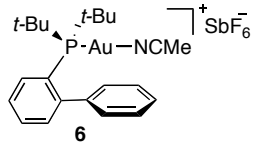
Part of these results have been published in: Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem. Eur. J.* **2009**, *15*, 5646–5650.

1.1 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).[72d] 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 1).[109] Fragmentation products **I-3** are also obtained as minor products.

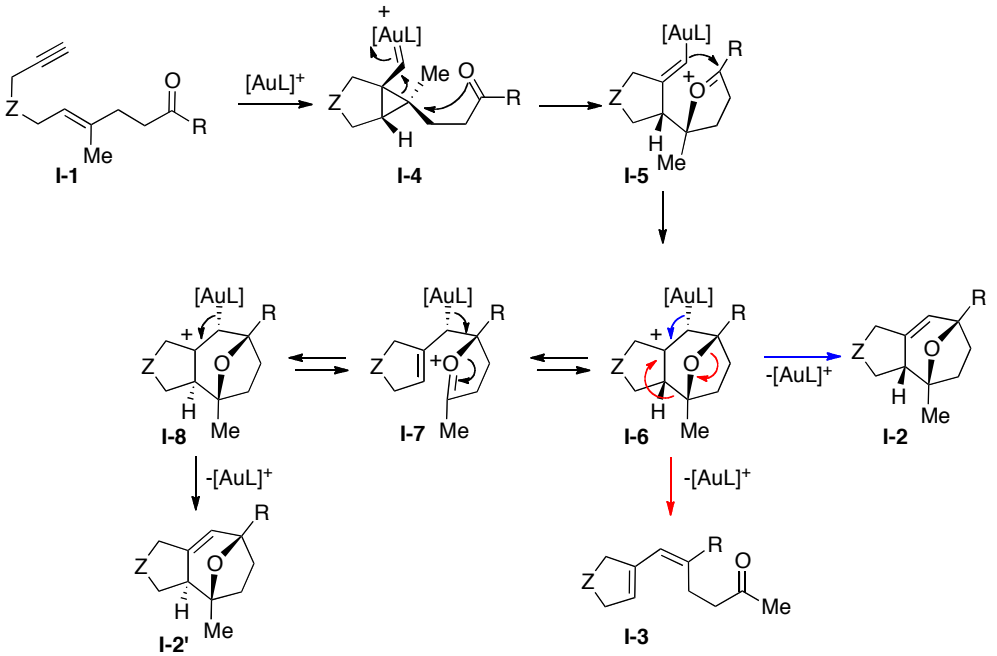


Z	R	[AuL]+	I-2 (*syn*/*anti*)	I-3
$C(CO_2Me)_2$	Me	AuCl	79 (50:1)	10
$C(CO_2Me)_2$	*i*-Pr	**6**	44 (26.1)	39



Scheme 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**. 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). 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.[11c,11g,72g,72d,117]



Scheme 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,[110] (+)-orientalol F,[110] and (-)-englerin A and B[111] (Figure 1).

117 Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

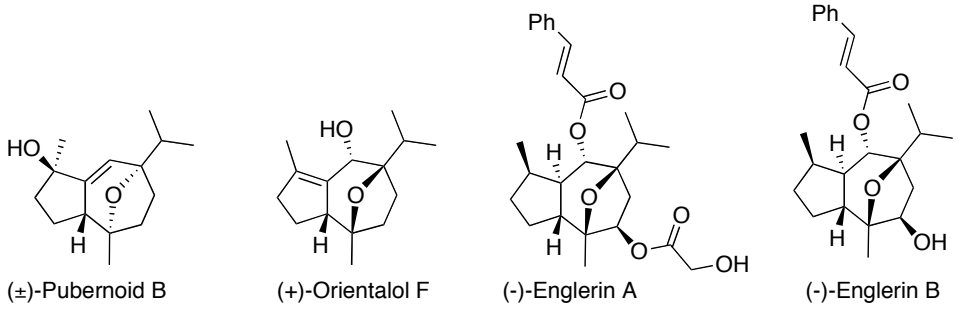
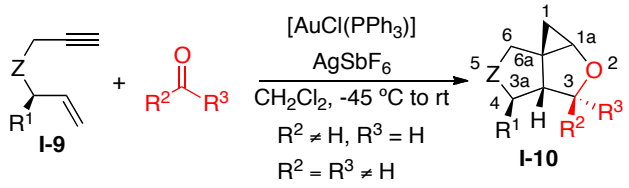


Figure 1. *Structures of (±)-pubernoid B, (+)-orientalol F, (-)-englerin A and (-)-englerin B*

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 3).[112a] The reaction proceeds with complete diastereoselectivity with respect to the stereogenic centers C1a, C3, C3a, and C6a.



Scheme 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 Figure 2.

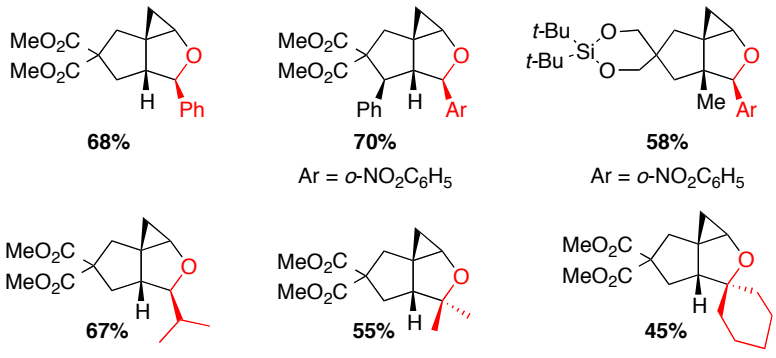
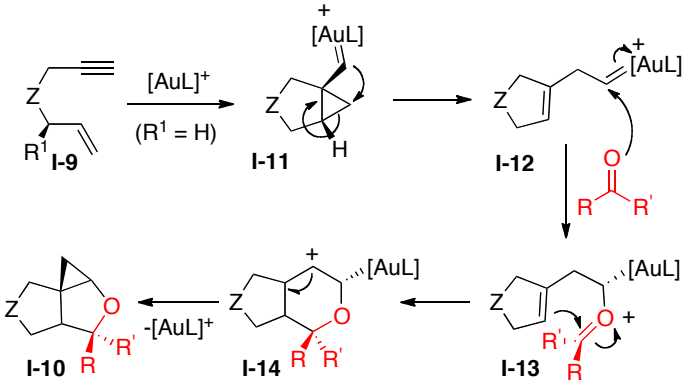


Figure 2. *Products of the intermolecular addition of different aldehydes and ketones to 1,6-enynes* ***I-9***

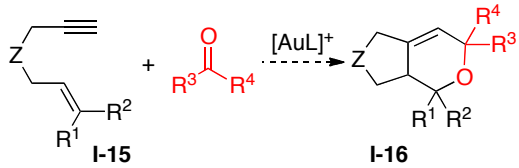
The gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enyne **I-9** presumably proceeds by trapping rearranged gold carbene intermediate **I-12** with the carbonyl compounds (Scheme 4). Thereby forming the oxonium cation **I-13**, which undergoes a Prins-type reaction to give **I-10**, probably via intermediate **I-14**.



Scheme 4. *Proposed mechanism for the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes* ***I-9***

1.2 Objective

The precedent results shown in Scheme 3 suggested that aldehydes could react intermolecularly with 1,6-enynes possessing a terminal alkene moiety through cyclopropyl carbene **I-12** (see Scheme 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 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 5).



Scheme 5. *Proposal for the study of the gold(I)-catalyzed intermolecular addition of carbonyl compounds to 1,6-enynes* ***I-15***

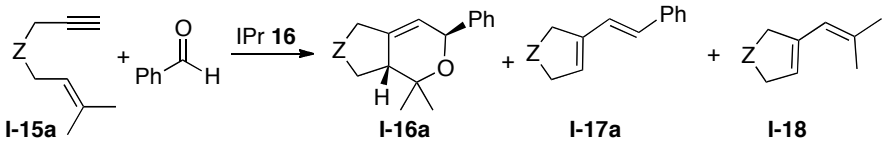
Therefore, the aim of the research was to study the intermolecular addition of carbonyl compounds to 1,6-enynes bearing a tri-substituted alkene (**I-15**) catalyzed by gold(I) complexes. This would provide a new methodology for the synthesis of bicyclic compounds of type **I-16**.

1.3 Results and Discussion

1.3.1 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 1). Using the standard conditions for the intermolecular trapping of 1,6-enynes with nucleophiles,[21a] 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 1, entry 1). Interestingly, we were able to decrease the yield of **I-18** by increasing the reaction time to 12 h at -40 ºC (Table 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 1. *Gold(I)-catalyzed intermolecular reaction of enyne* ***I-15a*** *and benzaldehyde*

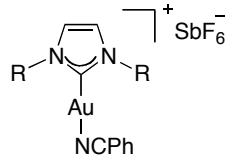


I-15a **I-16a** **I-17a** **I-18**

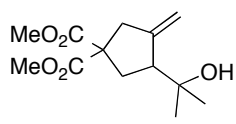
Z = $C(CO_2Me)_2$

Entry	*Equiv aldehyde*	*Conditions*	*Conv. (%)*	***I-16a*:*I-17a*:*I-18*** *Ratio*[a]
1	2	-40 ºC (2 h) to rt (10 h)	100	28:18:55
2	5	-40 ºC (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 ºC (12 h) to rt (10 h). [a] Ratios determined by ^{1}H-NMR. [b] Traces of hydroxycyclization **I-19** were observed.



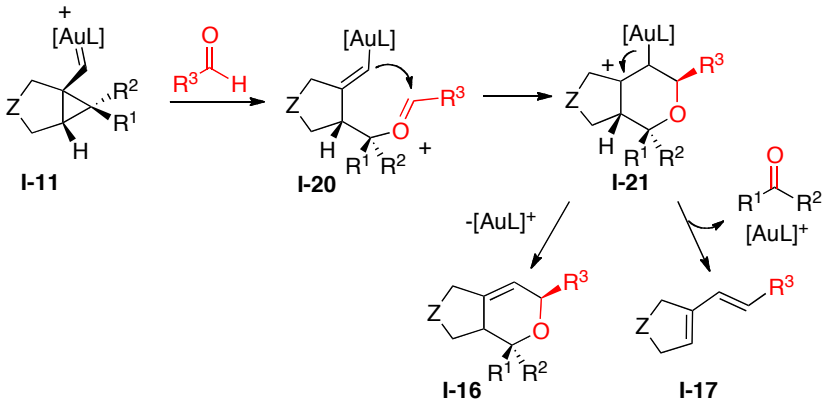
16: R = 2,6-*i*-$Pr_2C_6H_3$



I-19

The mechanism for this reaction is analogous to its intramolecular version,[109] and starts with the formation of the cyclopropyl carbene **I-11** (Scheme 6). Direct attack of the aldehyde to

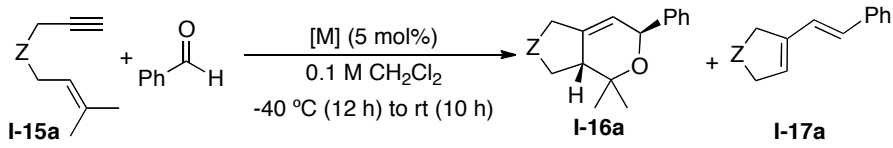
the cyclopropyl gold(I) intermediate **I-11** leads to the oxonium cation **I-20**, which suffers Prins-type cyclization to give tetrahydropyranyl cation **I-21**. Intermediate **I-21** can undergo metalation to yield bicycle **I-16** or can evolve by a fragmentation reaction to form 1,3-diene **I-17**.



Scheme 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). The best ratios were obtained with cationic gold(I) complexes (Table 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, 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, entries 2-3). No difference between the results with the cationic phosphite gold(I) **20** and the *in situ* form **19**/$AgSbF_6$ were found (Table 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, entries 4-6).

Table 2. *Screening of catalysts for the gold(I)-catalyzed intermolecular reaction of enyne* ***I-15a*** *with benzaldehyde*

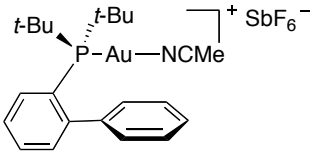


I-15a **I-16a** **I-17a**

Z = $C(CO_2Me)_2$

Entry	*[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 ºC (12 h) to rt (10 h). [a] Ratios determined by ^{1}H-NMR. [b] Traces of hydroxycyclization product **I-19** were observed.



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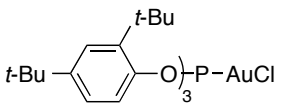

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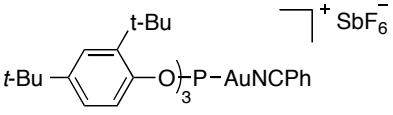

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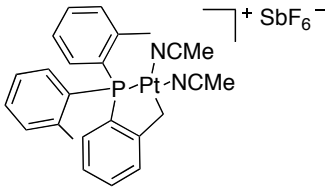

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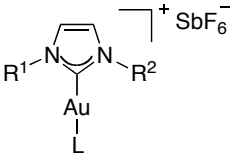


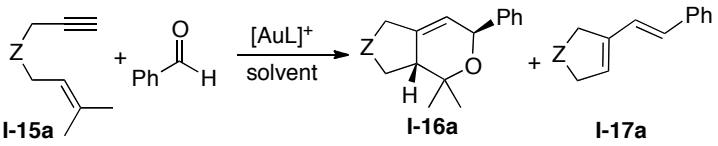
14: R^1 = Me, R^2 = Et, L = 2,4,6-$(MeO)_3C_6H_2CN$
15: $R^1 = R^2$ = 2,4,6-$Me_3C_6H_2$, L = 2,4,6-$(MeO)_3C_6H_2CN$
16: $R^1 = R^2$ = 2,6-*i*-$Pr_2C_6H_3$, L = PhCN

In the reaction catalyzed by AuCl and platinacycle **24**[19c] the rearranged product **I-18** was observed as the major product (Table 2, entries 7 and 10), whereas very low conversions (≤ 7%) were obtained when using $PtCl_2$, $PtCl_4$, $PdCl_2$, $AgSbF_6$, $InCl_3$, or $GaCl_3$ as catalysts (Table 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 3). In CH_2Cl_2, phosphine complex **6** gave a similar ratio to phosphite complex **20** (Table 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 3, entry 2). DMF completely inhibited the reaction of all the complexes (Table 3, entries 4, 9, and 13).

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 3, entries 6-8), whereas low conversion of **I-15a** was observed in Et_2O (Table 3, entry 7).

Table 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 ºC (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**.

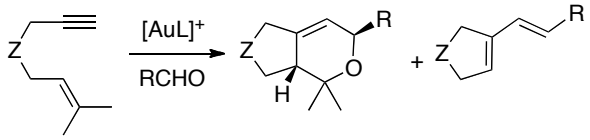
1.3.2 Scope of the Reaction

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 4). The reaction proceeded readily with electron-rich aldehydes. Conversely, in the reaction of **I-15a** with *o*-nitrobenzaldehyde, no adduct was formed (Table 4, entry 17), which is in contrast with the previously reported results for 1,6-enynes bearing a terminal alkene moiety **I-9**.[112a,c]

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-trimethoxybenzaldehyde using phosphite complex **20** as catalyst (Table 4, entries 3, 5, 7, and 16). In contrast, with 2,4-dimethylbenzaldehyde, 2,4,6-trimethylbenzaldehyde, 4-methoxybenzaldehyde, and 2,4-dimethoxybenzaldehyde, the major products were the dihydropyran **I-16c-f** using IPr NHC complex **16** (Table 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 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 4, entries 3, 5, 7 and 16).

Table 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)

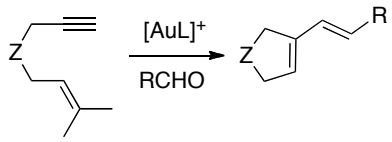
Reaction conditions: Aldehyde (2 equiv) and $[AuL]SbF_6$ (2 mol%) in 0.1 M CH_2Cl_2 at -40 ºC, 12 h. [a] 9:1–1:1 mixture of **I-16** and its $\Delta^{[4a,5]}$ isomer. [b] Yield determined by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as standard). [c] Skeletal rearrangement product was also formed (10–50% yield).

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 5).[118] 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**[19a,19b,72d,119] in moderate to good yields (Table 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 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 ºC gave prenyl pyrenyl diene **I-17o** in 76% yield (Table 5, entry 5).

118 Results carried out in collaboration with Dr. D. Janssen.

119 Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627–2635.

Table 5. *Study of the gold(I)-catalyzed intermolecular reaction of enyne* ***I-15b-c*** *with different aldehydes*



I-15b Z = NTs
I-15c Z = O

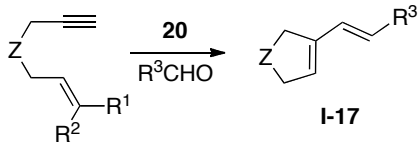
I-17

Entry	***I-15***	*[AuL]*$^+$	*R*	***I-17*** *Yield (%)*
1		**20**	Ph	**I-17i** (65)
2		**20**	4-MeC_6H_4	**I-17j** (63)
3	**b**	**20**	2,4,6-$Me_3C_6H_2$	**I-17k** (91)
4		**20**	4-BrC_6H_4	**I-17l** (67)
5		**6**	1-pyrenyl	**I-17m** (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 ºC, 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 6, entries 1-6).[81] Surprisingly, electron-rich aldehydes, such as 4-methoxybenzaldehyde or 3,4-dimethoxybenzaldehyde, only led to decomposition or low yield using enynes with an aryl substituent at the alkene **I-15b-f** (Tables 5 and 6).

Table 6. *Study of the gold(I)-catalyzed intermolecular reaction of enyne* ***I-15d-f*** *with different aldehydes*

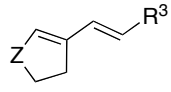


I-17

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		4-MeC_6H_4	**I-17b** (78)[a]
2	**d**	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 ºC, 12 h. [a] 1:1 mixture of **I-17** and **1-22** isomer. [b] 1:5 mixture of **I-17** and **1-22** isomer.

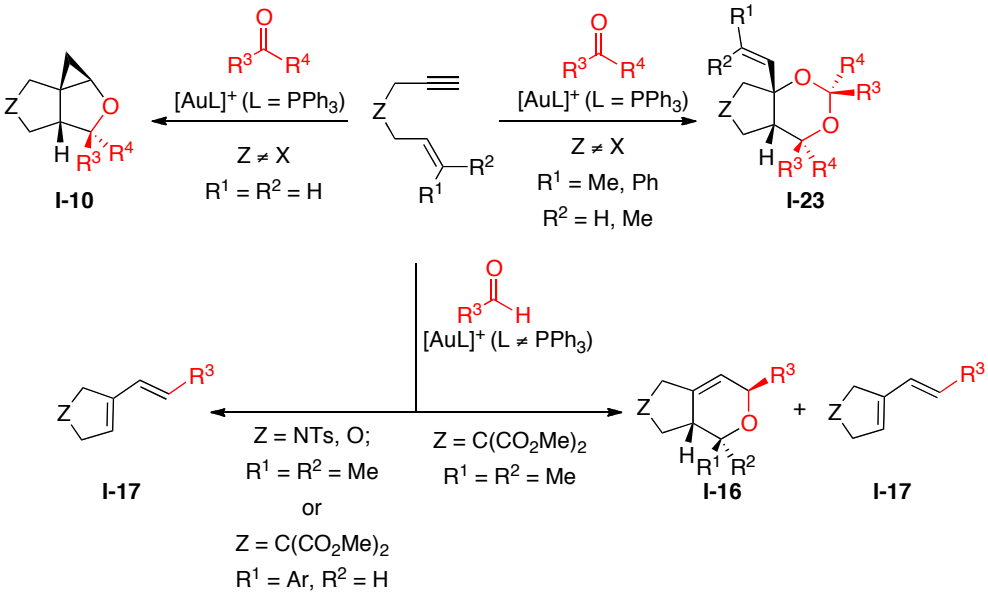


I-22

1.4 Conclusions

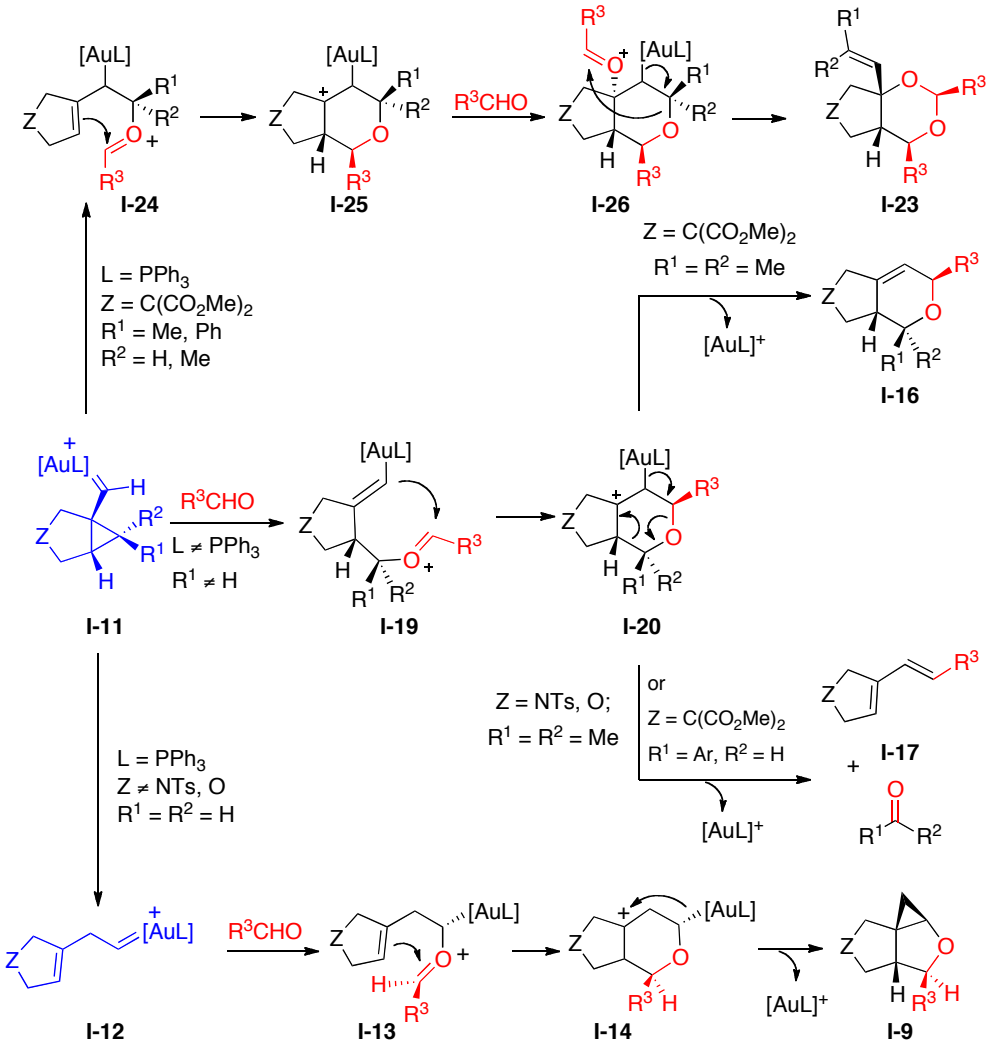
In summary, a clearer picture of the intertwined reaction pathways at play in the intermolecular gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes has emerged from this study. Ultimately, this work complements the investigations leading to tricyclic compound **I-10** and 1,3-dioxolanes **I-23** reported by the Helmchen group (Scheme 7).[112a,112c]

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**.[112]



Scheme 7. *General overview of the gold(I)-catalyzed addition of carbonyl compounds to 1,6-enynes*

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 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**.



Scheme 8. *Mechanism hypothesis concerning the formation of the different products from 1,6-enynes and carbonyl compounds*

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.

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.

1.5 Experimental Section

1.5.1 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.

1.5.2 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**,[25] IMes gold(I) **15**,[25] IPr gold(I) **16**,[25] phosphite gold(I) **19**,[21a] cationic phosphite gold(I) **20**,[24e] platinacycle **24**[19c] were prepared according to the reported procedure.

The starting 1,6-enynes were synthesized following the literature procedures: **I-15a**,[120] **I-15b**,[121] **I-15c**,[122] **I-15d**,[123] **I-15e**,[81] and **I-15d**.[81]

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120 Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, *29*, 1231–1234.

121 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2002**, *124*, 5025–5036.

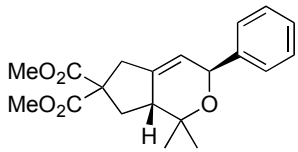
122 Kataoka, T.; Yoshimatsu, M.; Noda, Y.; Sato, T.; Shimizu, H.; Hori, M. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 121–129.

1.5.3 Cyclization products

General procedure for the reaction of 1,6-enynes with aldehydes (Table 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 -40ºC and the gold complex **6**, **16** or **20** (2 mol%) was added after 15 min. The solution was kept at -40ºC 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**,[124] **I-17c**,[81] **I-17e**,[19b] **I-17f**,[81] **I-17g**,[81] and **I-17h**.[81]

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.

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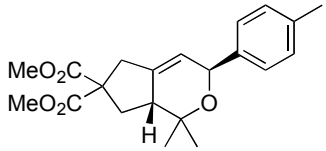
123 Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050.

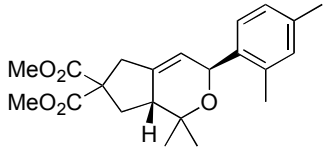
124 Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837–2847.

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.

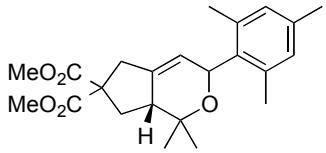
Dimethyl 3-(2,4-dimethylphenyl)-1,1-dimethyl-3,5,7,7a-tetrahydro-cyclopenta[c]pyran-6,6(1H)-dicarboxylate (I-16c)



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

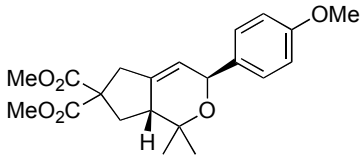
NMR (125 MHz, $CDCl_3$; PENDANT) δ 172.5 (C), 172.4 (C), 137.3 (C), 137.3 (C), 136.3 (C), 136.2 (C), 131.6 (CH), 128.0 (CH), 126.9 (CH), 119.4 (CH), 74.4 (C), 70.5 (CH), 58.1 (C), 53.1 (CH_3), 53.0 (CH_3), 47.4 (CH), 38.8 (CH_2), 36.2 (CH_2), 29.6 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 19.0 (CH_3). HRMS-ESI *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)



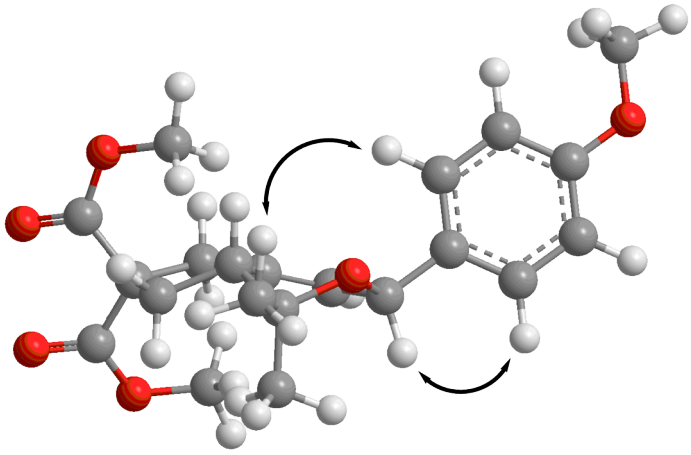
Compound **I-16d** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (84.6 mg, 0.36 mmol) and mesitaldehyde (0.11 mL, 0.71 mmol) with catalyst **16**. The residue was purified by column chromatography (15:1 hexane/EtOAc) to give 116.2 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)



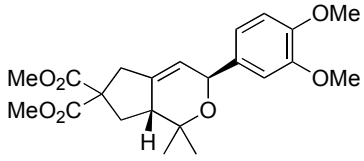
Compound **3ae** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (92.5 mg, 0.39 mmol) and *p*-methoxybenzaldehyde (0.10 mL, 0.78 mmol) with catalyst **16**. The residue was purified by

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).

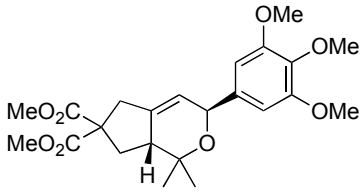
Dimethyl 3-(3,4-dimethoxyphenyl)-1,1-dimethyl-3,5,7,7a-tetrahydro-cyclopenta[c]pyran-6,6(1H)-dicarboxylate (I-16f)



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

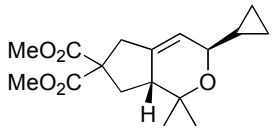
I-16f (63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-6.80 (m, 3H), 5.50 (br s, 1H), 4.95 (br s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.76 (d, J = 0.9 Hz, 3H), 3.74 (d, J = 0.8 Hz,, 3H), 3.14 (d, J = 17.5 Hz, 1H), 2.96 (d, J = 17.4, 1H), 2.68-2.63 (m, 1H), 2.53 (dd, J = 12.7, 7.8 Hz, 1H), 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**)



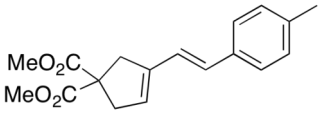
Compound **I-16g** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (96.4 mg, 0.40 mmol) and 3,4,5-trimethoxybenzaldehyde (0.16 g, 0.81 mmol) with catalyst **20**. The residue was purified by column chromatography (from 4:1 to 3:1 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.

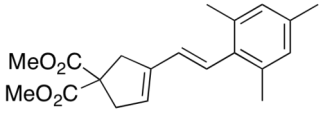
(*E*)-Dimethyl 3-(4-methylstyryl)cyclopent-3-ene-1,1-dicarboxylate (I-17b)



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 $C_{18}H_{20}O_4Na$

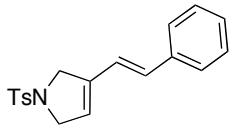
[*M*+Na**[**$^+$ 323.1259, found 323.1265. The structure was confirmed by HMBC, HSQC and COSY experiments.

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



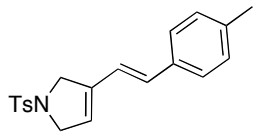
Compound **I-17d** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15a** (84.6 mg, 0.36 mmol) and mesitaldehyde (0.11 mL, 0.71 mmol) with catalyst **16**. The residue was purified by column chromatography (15:1 hexane/EtOAc) to give 9.9 mg of the compound **I-17d** (9%) as a colorless white solid: mp 126-127 ºC. ^{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)



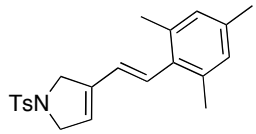
Compound **I-17i** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.4 mg, 0.30 mmol) and benzaldehyde (64.3 mg, 0.60 mmol) with catalyst **20**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 63.5 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)



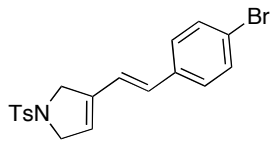
Compound **I-17j** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.4 mg, 0.30 mmol) and *p*-tolualdehyde (72.1 mg, 0.60 mmol) with catalyst **20**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 64.6 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)



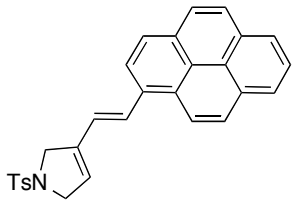
Compound **I-17k** was synthesized following the general procedure for the reaction of 1,6-enynes with aldehydes, starting from **I-15b** (83.9 mg, 0.30 mmol) and mesitaldehyde (89.8 mg, 0.60 mmol) with catalyst **6**. The residue was purified by column chromatography (5:1 hexane/EtOAc) to give 100.3 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.

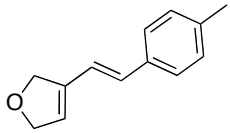
(*E*)-3-(2-(pyren-1-yl)vinyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole (I-17m)



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 ºC. ^{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),

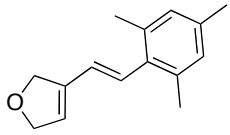
125.2 (CH), 125.1 (C), 125.0 (C), 124.4 (CH), 124.0 (CH), 123.4 (CH), 122.7 (CH), 55.4 (CH2), 54.0 (CH2), 21.7 (CH3). HRMS-ESI *m/z* calcd for $C_{29}H_{23}NNaO_2S$ $[M+Na]^+$ 472.1347, found 472.1346. UV-Vis (CH_2Cl_2) λ_{max} (ε_{max}) 388 nm (28830), 371 (31780), 289 (23470), 237 (34990). Fluorescence (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.

Chapter 2: Formation of Cyclobutene Compounds via Gold(I)-Catalyzed Cycloisomerization of 1,n-Enynes

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As an extension of chapter 1 and, in order to obtain a clearer picture of the intertwined reaction pathways at play in the gold(I)-catalyzed addition of carbonyl compounds. The gold-catalyzed cycloisomerization of 1,6-enynes of type **II-22** bearing a carbonyl group at the alkyne moiety was examinazed. The reaction led to the unexpected formation of cyclobutene compounds of type **II-23**. As a further development of cyclobutene synthesis, two more examples presenting the cyclobutene motif (**II-24**) were obtained via gold(I)-catalyzed cyclization of 1,8-enynes.

2.1 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.[125] 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[74e] or postulated as intermediates.[74e] 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

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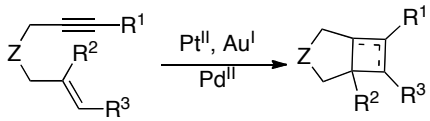
125 (a) Dembitsky, V. M. *J. Nat. Med.* **2008**, *62*, 1–33. (b) Sergeiko, A.; Poroikov, V. V.; Hanu, L. O.; Dembitsky, V. M. *The Open Medicinal Chemistry Journal* **2008**, 26–37. (c) Hansen, T. V.; Stenstrøm Y. "Organic Synthesis: Theory and Applications" Vol. *5*, Elsevier, Amsterdam, **1996**, 1–38.

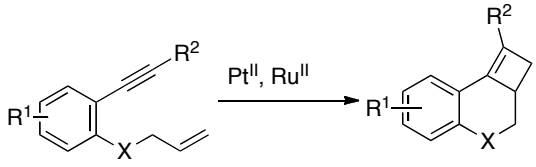
alkene and/or alkyne takes place and disfavors the skeletal rearrangement. It is not easy to formulate a general rule for the formation of cyclobutene compounds starting from 1,6- and 1,7-enynes. Certain 1,6-enynes possessing an acyclic alkene and an aryl- or esteralkyne moiety, as in **II-1**, can be transformed into the corresponding cyclobutenes in the presence of palladium(II),[126a] platinum(II),[126b] or gold(I)[20,74e] as catalysts (Scheme 1).



II-1 R^1 = ester, aryl
R^2, R^3 = H, Me
Z = $C(CO_2Me)_2$

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

In addition, 1,7-enynes possessing an acyclic alkene and a haloalkyne moiety **II-2** produce cyclobutene compounds via platinum(II)-[127a] or ruthenium(II)-catalyzed[127b] cycloisomerization (Scheme 2).



II-2 R^2 = *n*-Pr, I, Br, Cl
X = O, NTs, NAc, CH_2, CH(OMe)

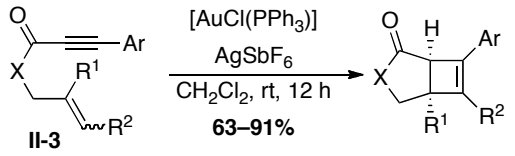
Scheme 2. *Metal-catalyzed synthesis of cyclobutenes from 1,7-enynes* ***II-2***

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).[128]

126 (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638. (b) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245.

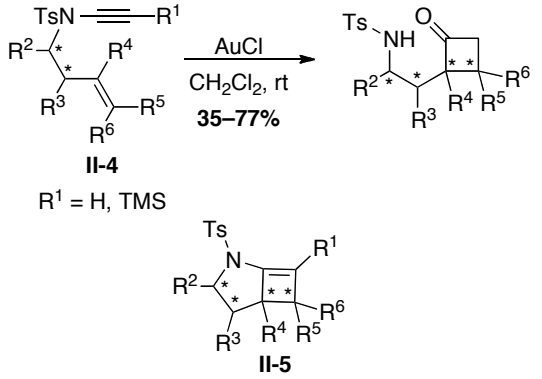
127 (a) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892–897. (b) Fürstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277–4279.

128 Lee, Y. T.; Kang, Y. K.; Chung, Y. K. *J. Org. Chem.* **2009**, *74*, 7922–7934.



Scheme 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-ene-ynamides **II-4** (Scheme 4).[129] 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.[130]

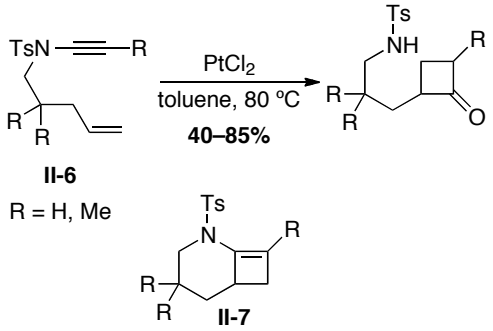


Scheme 4. *Synthesis of cyclobutanones via gold(I)-catalyzed cycloisomerization of 1,6-ene-ynamides* ***II-4***

In addition, cyclobutanones are synthesized via platinum(II)-catalyzed cyclization of 1,7-ene-ynamides **II-6** (Scheme 5). The cyclobutanones are formed after hydrolysis of the corresponding bicycle[4.2.0] compounds **II-7.**

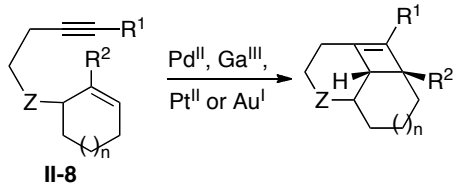
129 (a) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726–6730. (b) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 1809–1832.

130 (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509–1511. (b) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856–3871.



Scheme 5. *Synthesis of cyclobutanones via platinum(II)-catalyzed cycloisomerization of 1,7-ene-ynamides* ***II-6***

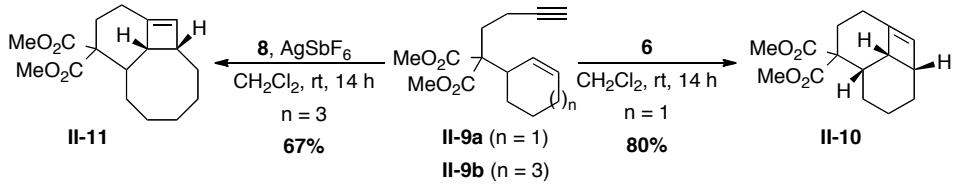
In the particular case of 1,7-enynes bearing an endocyclic alkene moiety **II-8**, cyclobutenes are obtained in a general way using palladium(II),[131a] gallium(III),[131b] platinum(II),[131c] or gold(I)[15a] as catalysts (Scheme 6). Other cyclobutene compounds have also been isolated from 1,6-enynes bearing an endocyclic alkene moiety via platinum(II)-[127b] or gold(I)-catalyzed[76a] [2+2] cycloaddition.



Scheme 6. *Formation of cyclobutene compounds from 1,7-enynes* ***II-8***

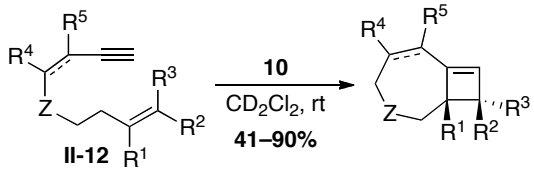
By using cationic gold(I) complexes, bicyclo[4.2.0]oct-6-ene **II-10** or **II-11** are obtained starting from 1,7-enynes **II-9a** or **II-9b** (Scheme 7).[15a] Ring opening to form 1,3-dienes does not occur even after heating at 120–150 ºC.

131 (a) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295. (b) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295. (c) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.



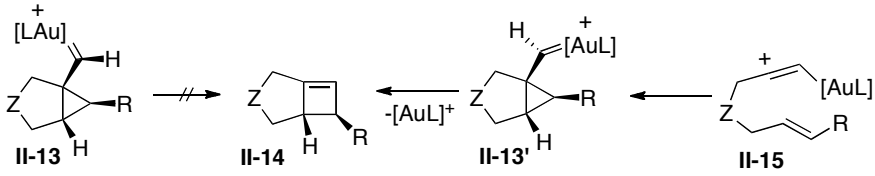
Scheme 7. *Gold(I)-catalyzed cyclization of 1,7-enynes* ***II-9***

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 8).[94] The formation of 1,3-dienes was observed after prolonged reaction times and in the presence of trace acids.



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

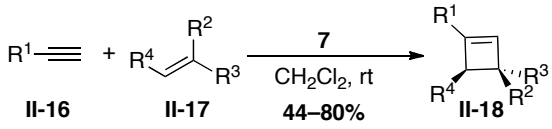
DFT calculations have been carried out to shed some light on the mechanism for cyclobutene formation. No direct pathway for the formation of cyclobutene **II-14** from *anti-exo*-cyclopropyl gold carbene **II-13** was found (Scheme 9). In contrast, *syn-exo*-cyclopropyl gold carbene **II-13'** forms 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 substituion at the alkene and/or the alkyne does not favor the skeletal rearrangement.[15a]



Scheme 9. *Mechanism for gold(I)-catalyzed formation of cyclobutenes* ***II-14***

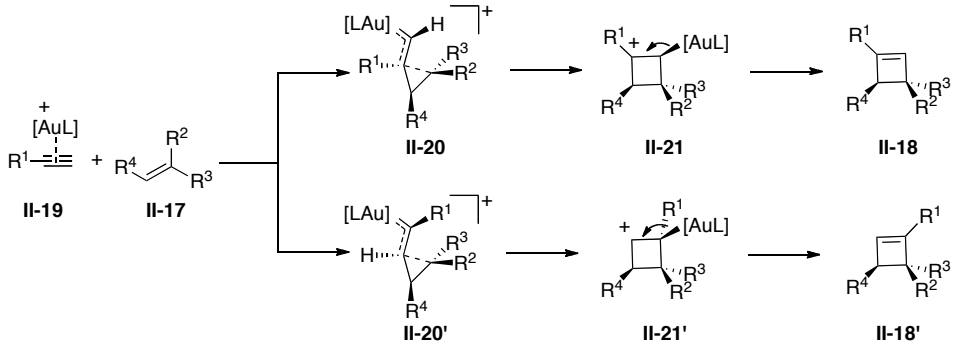
The intermolecular reaction of alkynes **II-16** with alkenes **II-17** catalyzed by gold(I) leads to cyclobutenes **II-18** with complete regio- and diastereoselectivity. Moderate to good yields are obtained when gold(I) complex **7** with a very bulky phosphine ligand is used (Scheme 10).[90] This 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 10. *Gold(I)-catalyzed intermolecular [2+2] cycloaddition of alkynes and alkenes*

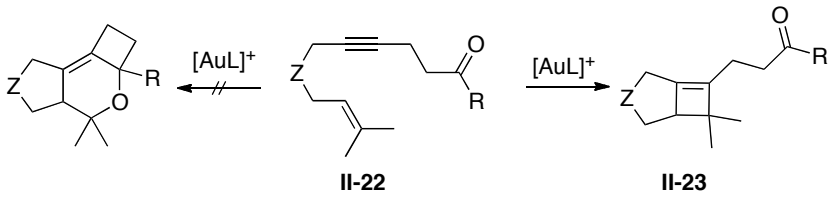
Based on the general reactivity of 1,n-enynes with gold(I), it is assumed that the reaction proceeds through similar cyclopropyl gold(I) carbenes **II-20**/**II-20'**. These intermediates are formed via the nucleophilic attack of alkenes **II-17** to cationic gold(I)-alkyne complexes **II-19**. Intermediates **II-20**/**II-20'**evolve toward cyclobutenes **II-18**/**II-18'** via carbocations **II-21**/**II-21'** (Scheme 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 11*. Mechanism for the gold(I)-catalyzed intermolecular [2+2] cycloaddition of alkynes and alkenes*

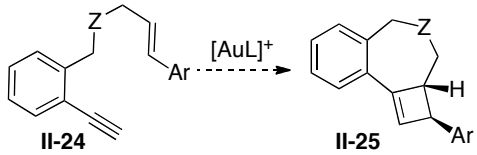
2.2 Objectives

Based on the results shown for the intermolecular gold(I)-catalyzed reaction of 1,6-enynes with carbonyl compounds (Chapter 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 12). Unexpectedly, the cyclization of these types of 1,6-enynes **II-22** led to the isolation of cyclobutenes **II-23**.



Scheme 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,[125] we decided to develop methodologies leading to cyclobutene-containing compounds via gold(I)-catalyzed cyclization of type **II-24** 1,8-enynes (Scheme 13).

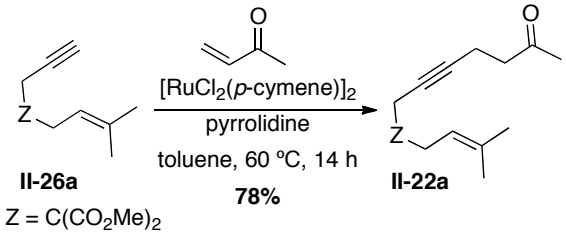


Scheme 13. *Formation of cyclobutenes* ***II-25*** *via gold(I)-catalyzed [2+2] cycloaddition*

2.3 Results and Discussion

2.3.1 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 14).[132]

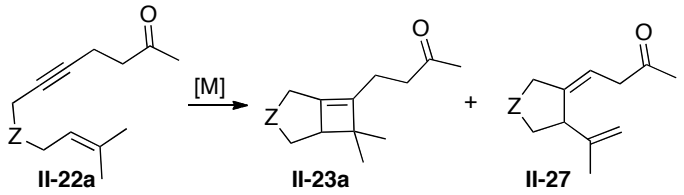


Scheme 14. *Synthesis of 1,6-enyne* ***II-22a***

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 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 1, entry 2). Unfortunately, the most active complex, phosphite gold(I) **20**, only resulted in decomposition of the starting material (Table 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 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 1, entries 5-13). A new product, 1,3-diene **II-27** of a single cleavaged rearrangement was isolated using platinacycle **24**[19c] in a 41% yield (Table 1, entry 14).

132 Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089–2091.

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

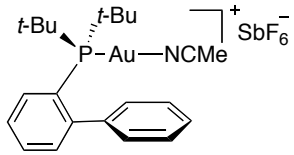


II-22a **II-23a** **II-27**

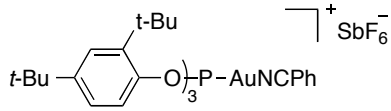
Z = $C(CO_2Me)_2$

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]

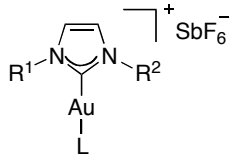
Reaction conditions: [M] (5 mol%) in 0.1 M CH_2Cl_2 at rt. [a] Yield determined by ^{1}H-NMR crude analysis using 1,3,5-trimethoxybenzene as internal standard. [b] Complex mixture. [c] Isolated yield.

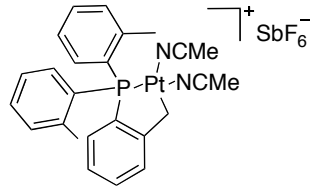


6



20

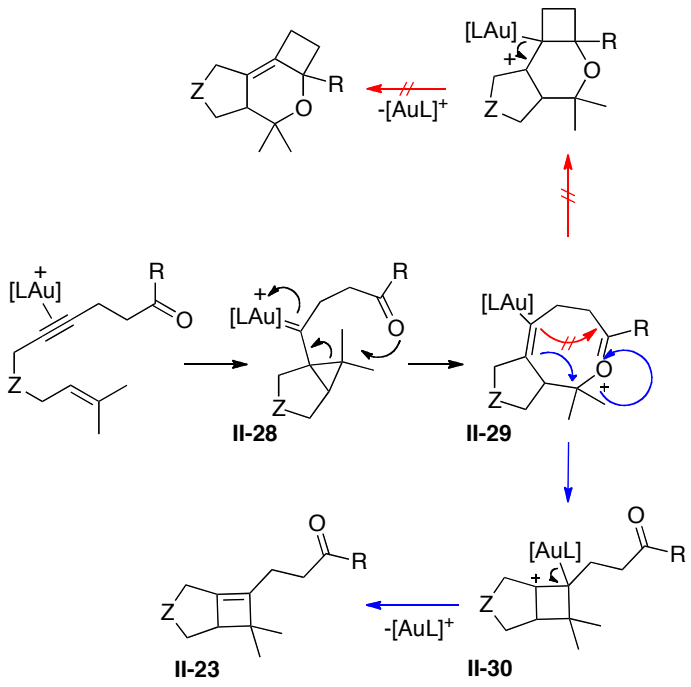




24

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

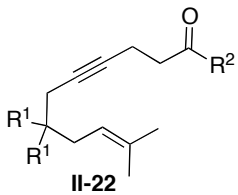
Scheme 15 shows a possible mechanism for the formation of cyclobutene **II-23**. In analogy with the intramolecular cycloisomerization of 1,6-enynes bearing the carbonyl function at the alkene moiety **I-1** (Chapter 1, Scheme 1), this [2+2] cycloaddition proceeds via the opening of cyclopropyl gold 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 15, red arrow), but at the quaternary *gem*-dimethyl carbon (Scheme 15, blue arrow), allowing the formation of cyclobutane intermediate **II-30**, which finally evolves via metal loss to give cyclobutene **II-23**.



Scheme 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 (Figure 1).[133]

133 Results obtained in collaboration with Masaki Sekine (visiting PhD student from the group of Prof. Eiichi Nakamura, Tokyo University, Japan).



II-22

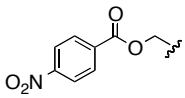
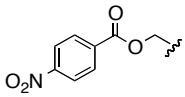
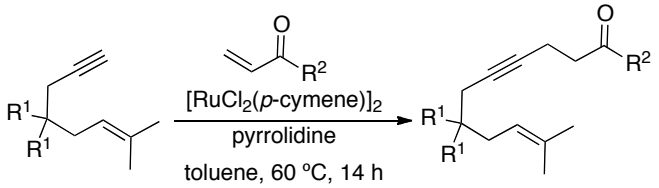
	R^1	R^2		R^1	R^2
II-22b		p-$NO_2C_6H_4$	**II-22d**	CO_2Me	p-$NO_2C_6H_4$
II-22c		CH_3	**II-22e**	SO_2Ph	p-$NO_2C_6H_4$

Figure 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 16).[132]



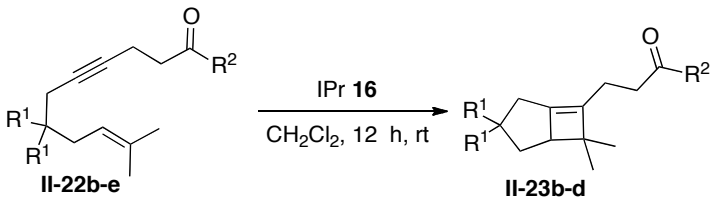
II-26a ($R^1 = CO_2Me$)
II-26b ($R^1 = CH_2OCO(p\text{-}NO_2C_6H_4)$)
II-26c ($R^1 = SO_2Ph$)

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

Scheme 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 2, entries 1-3). The only exception was the case of 1,6-enyne **II-22e**, where a complex mixture was detected (Table 2, entry 4).

Table 2. *Gold(I)-catalyzed cycloisomerization of 1,6-enynes* ***II-22b-d***



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** (Figure 2). Therefore, the formation of a cyclobutene compound was unanmbigously confirmed.

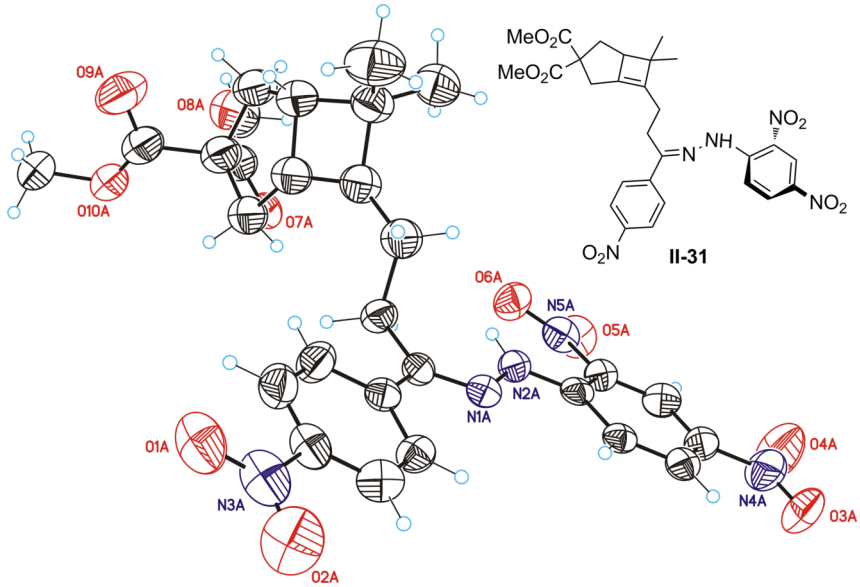
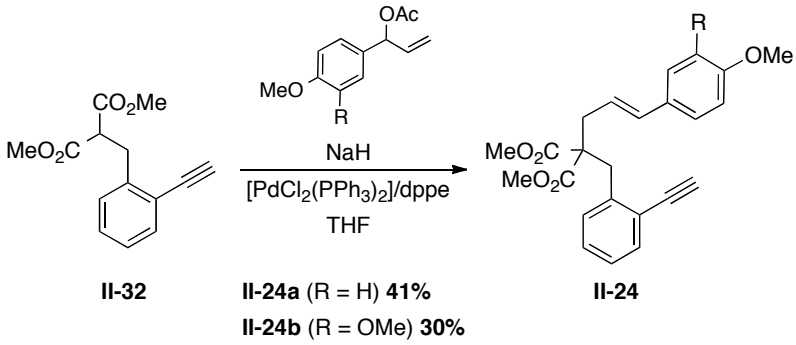


Figure 2. *X-Ray structure of hydrazone* ***II-31***

2.3.2 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 17).[81]

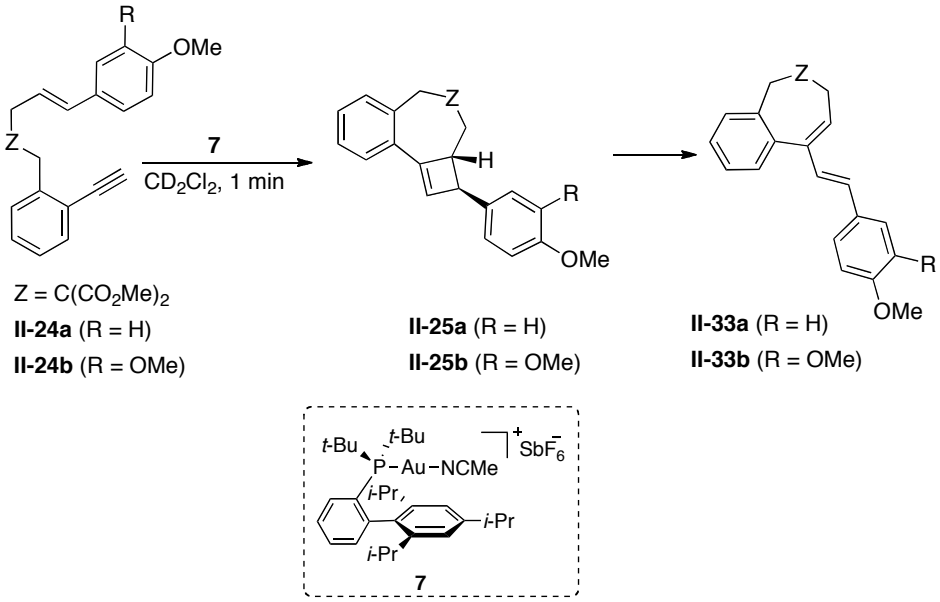


II-32 **II-24a** (R = H) **41%** **II-24b** (R = OMe) **30%** **II-24**

Scheme 17. *Synthesis of 1,8-enynes* ***II-24a-b***

Appling the Gagosz conditions for the cyclization of 1,8-enynes,[94] we observed the complete conversion toward cyclobutenes **II-25** after 1 minute, which rearranged to 1,3-dienes **II-33** in 14 or 17 h (Scheme 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,[134] a mixture of **II-25a**/**II-33a** = 1.3:1.0 was isolated.

134 PPh_3-bound polymer was added before purification to completely remove the gold(I) complex.



Scheme 18. *Gold(I)-catalyzed cycloisomerization of 1,8-enynes* ***II-24***

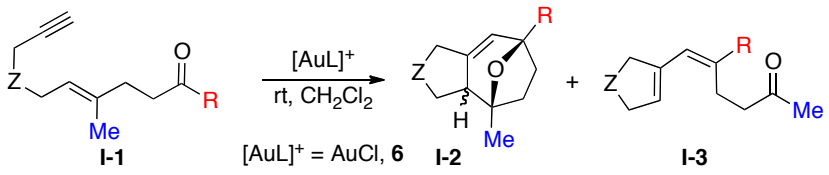
It was observed that cyclobutenes **II-25** rearranged to 1,3-dienes **II-33** in 17 h, even in the absence of gold complex.[135] Furthermore, after only 14 h 1,3-diene **II-33a** was detected by ^{1}H-NMR in the presence of proton sponge or 2,6-di(*t*-butyl)pyridine, which indicates that the opening 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 19, Introduction).[81]

135 A 1M solution of Et_3N in cyclohexane was added, folloed by filtration through a plug of Celite to quench the gold(I) complex.

2.4 Conclusions

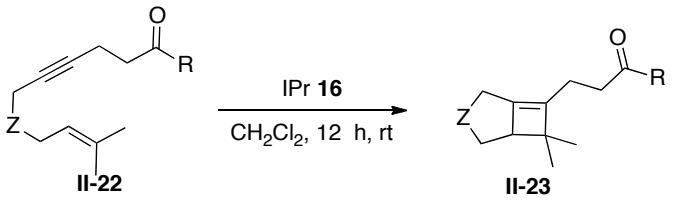
As an extension of the previous chapter, we decided to clarify the picture for the gold(I)-catalyzed intramolecular addition of carbonyl compounds to 1,6-enynes.

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 19).[109]



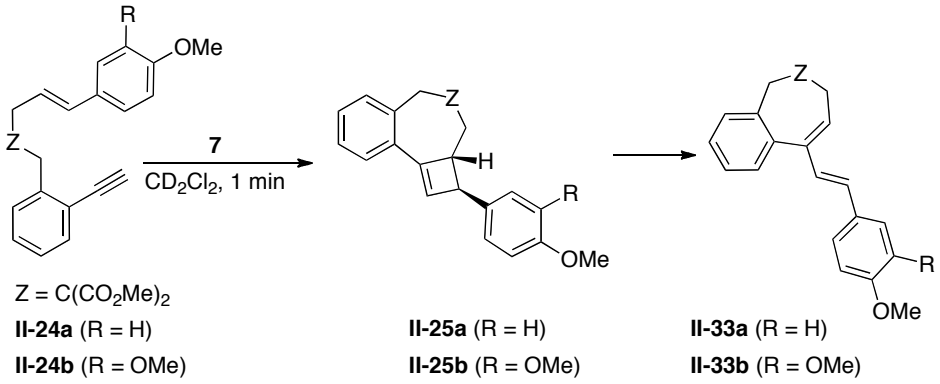
Scheme 19. *Gold(I)-catalyzed cyclization of **I-1** enynes*

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 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 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 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**.



Z = $C(CO_2Me)_2$

II-24a (R = H) **II-25a** (R = H) **II-33a** (R = H)

II-24b (R = OMe) **II-25b** (R = OMe) **II-33b** (R = OMe)

Scheme 21. *Synthesis of intermediates* ***II-25*** *via gold(I)-catalyzed reaction of 1,8-enynes*

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.

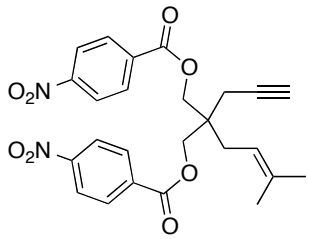
2.5.2 Preparation of Substrates

The metal salts AuCl (Strem), $AuCl_3$ (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**,[25] IMes gold(I) **15**,[25] IPr gold(I) **16**,[25] cationic phosphite gold(I) **20**,[24e] and platinacycle **24**[19c] were prepared according to the reported procedure.

The strating 1,6-enynes were synthesized following the literature procedures: **I-26a**,[136] and **II-26c**.[136]

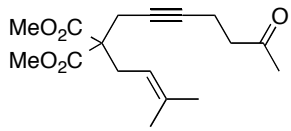
136 Muñoz, M. P.; Méndez, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Synthesis* **2003**, 2898–2902.

2-(3-Methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diyl bis(4-nitrobenzoate) (II-26b)[137]



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 ºC. 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.

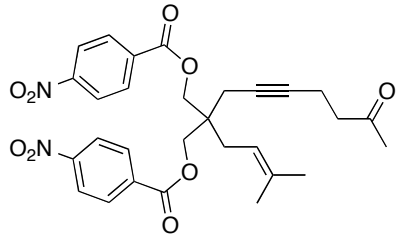
Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(6-oxohept-2-yn-1-yl)malonate (II-22a)



137 Blaszykowski, C.; Harrak, Y.; Brancour, C.; Nakama, K.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Synthesis* **2007**, 2037–2049.

Pyrrolidine (0.07 mL, 0.84 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 (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 ºC, 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.

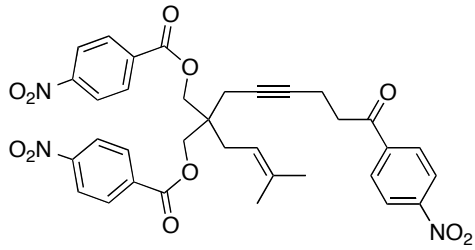
2-(3-Methylbut-2-en-1-yl)-2-(6-oxohept-2-yn-1-yl)propane-1,3-diyl bis(4-nitrobenzoate) (II-22b)



Pyrrolidine (0.03 mL, 0.38 mmol, 0.2 equiv) was added to a stirred solution of [$RuCl_2$(*p*-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 (0.780mL, 9.37 mmol, 5 equiv). The mixture was stirred at 60 ºC 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).

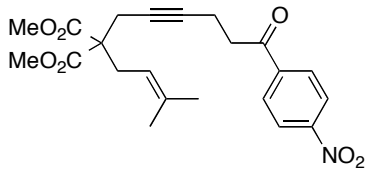
^{13}C (400MHz, $CDCl_3$) δ 205.5 (C), 164.5 (2C), 150.9 (2C), 136.7 (2C), 135.4 (C), 130.9 (4CH), 123.9 (4CH), 117.3 (CH), 82.5 (C), 75.4 (C), 67.3 ($2CH_2$), 42.8 (C), 41.8 (CH_2), 30.8 (CH_2), 30.0 (CH_3), 26.4 (CH_3), 23.1 (CH_2), 18.2 (CH_3), 13.5 (CH_2). HRMS-ESI Caldc for $C_{29}H_{30}N_2O_9$ [*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)



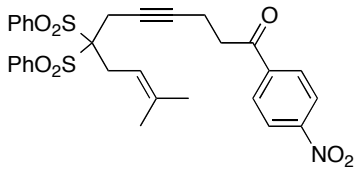
Pyrrolidine (0.03 mL, 0.38 mmol, 0.2 equiv) was added to a stirred solution of [$RuCl_2$(*p*-cymene)$_2$] (59.03 mg, 0.09 mmol,) in toluene (8 mL). The resulting mixture was stirred for 10 min at room temperature, which was followed by the addition of 1,6-enyne **II-26b** (908.09 mg, 1.89 mmol, 1 equiv) 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 ºC 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 ($CDCl_3$, 400MHz) 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*-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 ºC. 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).

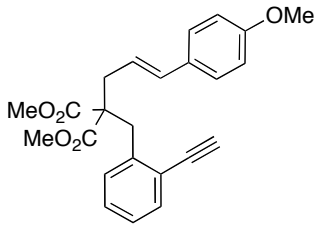
10-Methyl-1-(4-nitrophenyl)-7,7-bis(phenylsulfonyl)undec-9-en-4-yn-1-one (II-22e)



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 ºC 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[81] (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[138] (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 ºC. 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).

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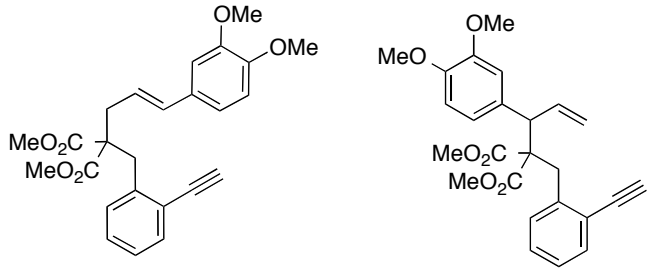
(*E*)-Dimethyl 2-(3-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (II-24b) and dimethyl 2-(1-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (II-24b')



A solution of 1-(3,4-dimethoxyphenyl)allyl acetate[81] (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 ºC. 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 to 5:1, c-Hex/EtOAc) to afford **II-24b** (112.5 mg, 30%) and **II-24b'** (52.4 mg, 14%).

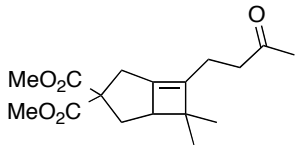
(*E*)-Dimethyl 2-(3-(3,4-dimethoxyphenyl)allyl)-2-(2-ethynylbenzyl)malonate (**II-24b**): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.59 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.37 (td, *J* = 7.5, 1.5 Hz, 1H), 7.22-7.16 (overlapping signals, 2H), 6.87-6.85 (overlapping signals (dd, 1H), (6.85, br s, 1H), 2H), 6.79 (br d, *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).

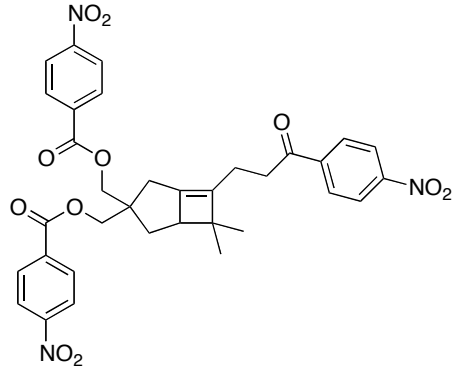
2.5.3 Cyclization Products

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



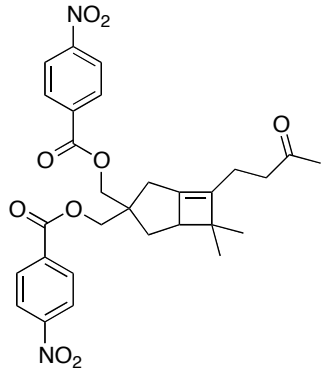
IPr gold(I) **16** (0.02 g, 0.03 mmol, 5 mol%) was added to a solution of **II-22a** (0.15 g, 0.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After 1.5 h, the reaction was quenched with Et_3N/*c*-Hex (0.1 M; 1 mL), and the resulting mixture was passed through a membrane filter. The solvent was removed under 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)



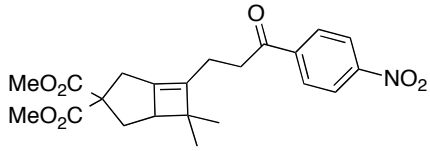
IPr gold (I) **16** (23.11 mg, 0.025 mmol, 5 mol%) was added to a solution of **II-22b** (329.87 mg, 0.50 mmol, 1 equiv) in CH_2Cl_2 (3 mL). After 12 h, the reaction was quenched by the addition of a Et_3N/*c*-Hex (0.1 M; 1 mL) solution. The resulting mixture was separated through membrane filter. The 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; 1mL). 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 chromatograhy (10:1 to 5:1, *c*-Hex/EtOAc) to give **II-23c** (144.27 mg, 64 %) as a pale yellow solid (trace amout 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.

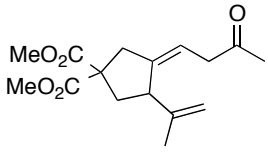
Dimethyl 7,7-dimethyl-6-(3-(4-nitrophenyl)-3-oxopropyl)bicyclo[3.2.0]hept-5-ene-3,3-dicarboxylate (II-23d)



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

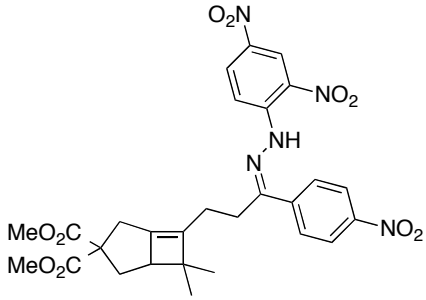
mixture was filtered through a membrane filter. The filtrate was concentrated under reduced pressure to obtain a crude mixture. The target product was isolated by silica gel column chromatography (10:1 to 4:1, *c*-Hex/EtOAc) to give **II-23d** (182.03 mg, 88 %) as a sticky yellow oil. ^{1}H-NMR (400 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.

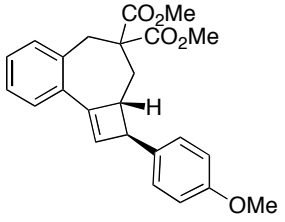
(*Z*)-Dimethyl 6-(3-(2-(2,4-Dinitrophenyl)hydrazono)-3-(4-nitrophenyl)propyl)-7,7-dimethylbicyclo[3.2.0]hept-5-ene-3,3-dicarboxylate (II-31)

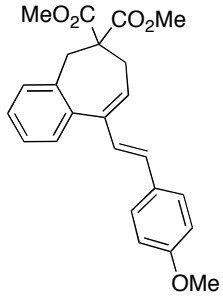


A solution of 2,4-2,dinitrophenylhydrazine (1.03 g, 3.38 mmol, 0.97 equiv) in sulfuric acid (3.31 ml, 60.9 mmol, 18 equiv) was added to a mixture of H_2O (5 mL) and EtOH (17 mL) and stirred for 10 min at room temperature. This reaction mixture was added to a solution of **II-23d** (147 mg, 0.35 mmol, 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.).

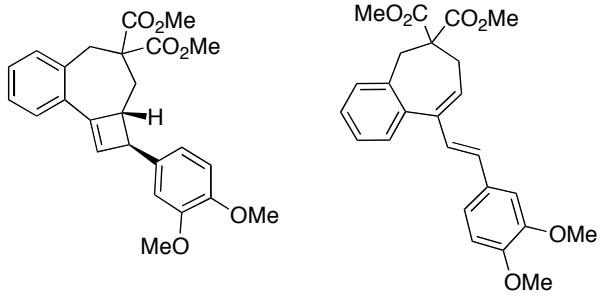
(2*S*,2a*R*)-dimethyl 2-(4-methoxyphenyl)-2a,3-dihydro-2*H*-benzo[*a*]cyclobuta[*c*]

[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 (0.1M; 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.

2.5.4 Crystallographic Data

Crystallographic data for compound II-31

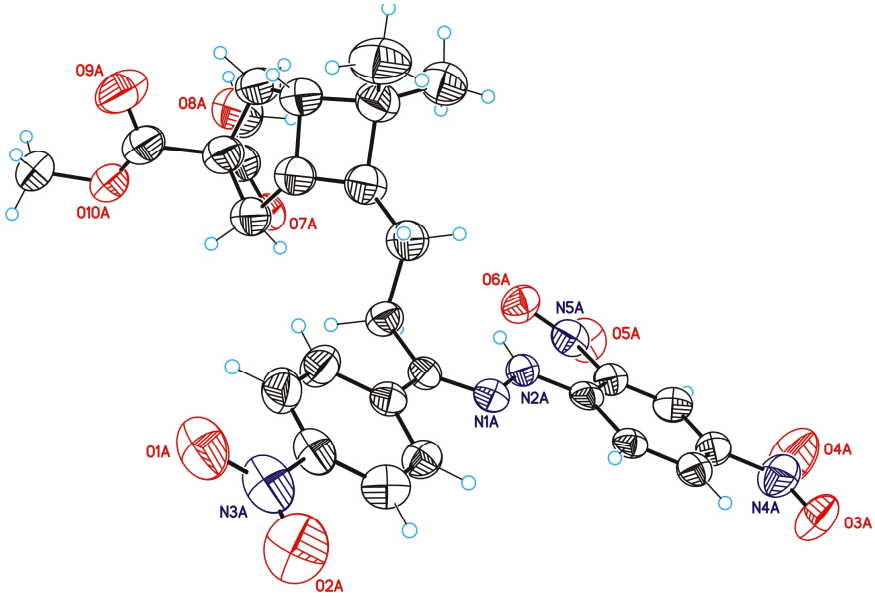


Table 1. **Crystal data and structure refinement for II-31**

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	α= 87.116(7) °.
	b = 13.6978(16) Å	β = 76.553(7) °.
	c = 20.614(2) Å	γ = 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 x 0.20 x 0.04 mm^3	
Theta range for data collection	3.48 to 67	
Index ranges	-12 <=h<=13 ,-13 <=k<=13 ,0 <=l<=23	
Reflections collected	7193	
Independent reflections	7193 [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 2. **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)
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)
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)
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)
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)
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)
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)
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. **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)
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)
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)
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)
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)
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)
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)
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)
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)

Chapter 3: Approach Toward the Total Synthesis of Lundurines

The methodology developed in the group for the gold-catalyzed cyclization of indoles with alkynes was applied in the total synthesis of lundurines. Lundurines A–D are a new type of alkaloids characterized by a cyclopropyl fragment embedded within a hexacyclic ring system that includes a 1*H*–azocine[5,4–*b*]indole ring unit. The key step in the total synthesis of lundurine A is a 8–*endo*–*dig* cyclization of the alkynylindole catalyzed by $AuCl_3$, which affords exclusively the desired azocine[5,4–*b*]indole derivative.

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

3.1 Introduction

3.1.1 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.[139] Since then, the indole scaffold is probably one of the most commonly occurring structural

139 Baeyer, A. *Justus Liebigs Ann. der Chem*. **1866**, 140, 295–313.

subunits among natural products and pharmaceutically important compounds, and is crucial for the discovery of new drugs.[140]

The importance of the indole ring lies in its presence in many alkaloids. Indole alkaloids are presenced in more than 4100 different known compounds (Figure 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).[141] 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.

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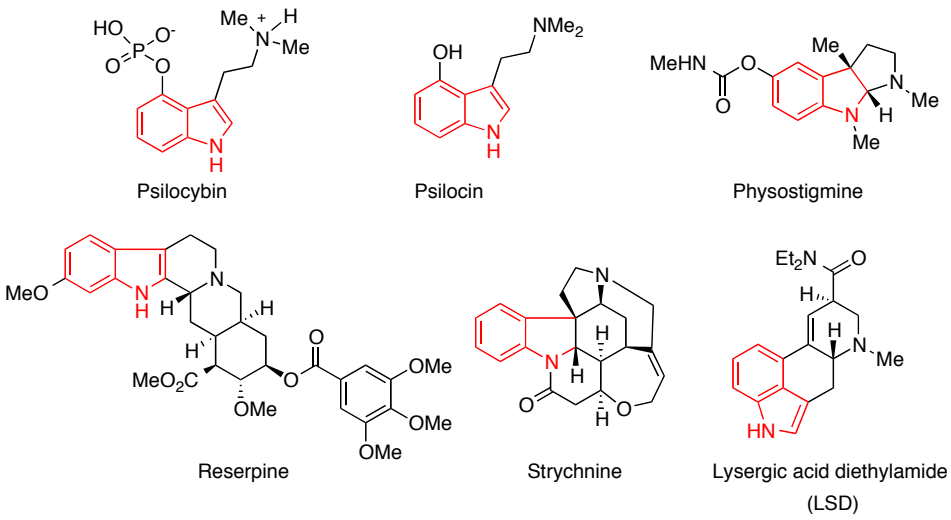


Figure 1. *Several examples of indole and indoline alkaloids*

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.[142] 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.

3.1.2 Indoloazocine Framework: Important Indole Alkaloids

Indoloazocine core is formed by the fusion of an eight-membered *N*-containing azocine ring with the indole nucleus (Figure 2).

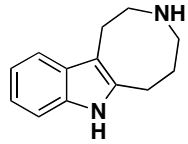
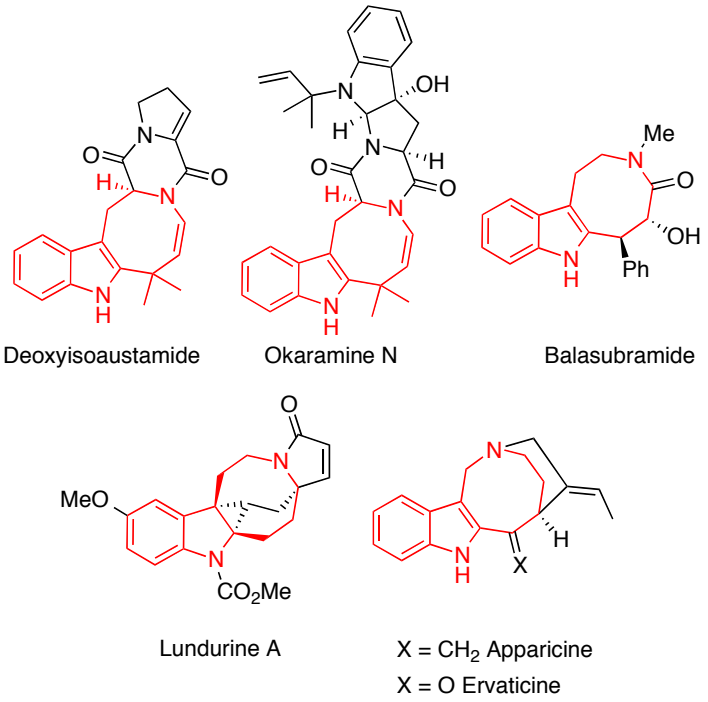


Figure 2. *Indoloazocine skeleton*

142 Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751.

This ring system is present in some indole alkaloids such as deoxyisoaustamide,[143] okarimine N,[144] balasubramide,[145] lundurines,[146] appericine,[147] and ervaticine (or conolidine) (Figure 3).[148]



143 (a) Steyn, P. S. *Tetrahedron Lett.* **1971**, *12*, 3331–3334. (b) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107–120. (c) Sames, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51–117.

144 (a) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 103–110. (b) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1519–1521.

145 (a) Johansen, M. B.; Leduc, A. B.; Kerr, M. A. *Synlett* **2007**, *2007*, 2593–2595. (b) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387–1390.

146 (a) Kam, T.-S.; Yoganathan, K.; Chuah, C.-H. *Tetrahedron Lett.* **1995**, *36*, 759–762. (b) Kam, T.-S.; Lim, K.-H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745.

147 Joule, J. A.; Monteiro, H.; Durham, L. J.; Gilbert, B.; Djerassi, C. *J. Chem. Soc.* **1965**, 4773–4780.

148 (a) Alvarez, M; Joule, J. A. *The Alkaloids*, ed. A. G. Cordell, Academic Press, New York, **2001**, *57*, 258–272. (b) 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.* **2011**, *3*, 449–453.

Figure 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.[149] More recent approaches include tandem cleavage of hydrogenated β-and α-carbolines,[150] ring closing metathesis,[151] and metal-catalyzed Friedel-Crafts-type reactions of indole derivatives with several electrophiles (such as alkynes, alkenes or epoxides).[52b,63a,152]

3.1.3 Lundurines A-D

Lundurines A-D[146] 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 (Figure 4).

149 (a) Yoneda, R.; Kimura, T.; Kinomoto, J.; Harusawa, S.; Kurihara, T. *J. Heterocycl. Chem.* **1996**, *33*, 1909–1913. (b) Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Ubeda, M. C.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 2449–2452. (c) Blechert, S.; Knier, R.; Schroers, H.; Wirth, T. *Synthesis* **1995**, 592–604. (d) Diker, K.; de Maindreville, M. D.; Lévy, J. *Tetrahedron Lett.* **1995**, *36*, 3511–3512.

150 Voskressensky, L. G.; Borisova, T. N.; Kulikova, L. N.; Varlamov, A. V.; Catto, M.; Altomare, C.; Carotti, A. *Eur. J. Org. Chem.* **2004**, *2004*, 3128–3135.

151 Bennasar, M. L.; Zulaica, E.; Sole, D.; Alonso, S. *Chem. Commun.* **2009**, 3372–3374.

152 (a) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628–5629. (c) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387–1390. (d) Johansen, M. B.; Leduc, A. B.; Kerr, M. A. *Synlett* **2007**, *2007*, 2593–2595. (e) Donets, P. A.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Org. Lett.* **2009**, *11*, 3618–3621.

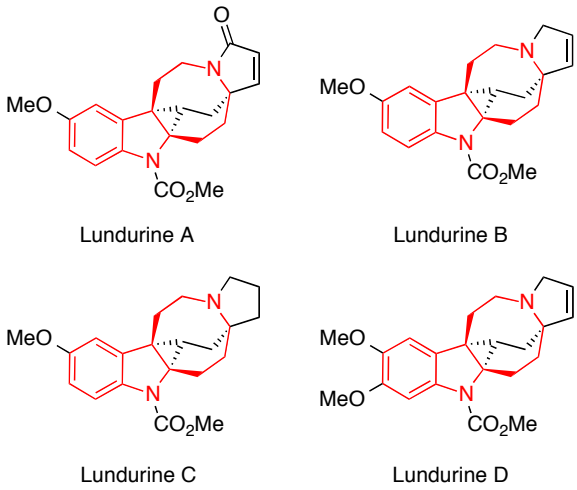


Figure 4. *Structures of lundurines*

These novel dihydroindole derivatives have been isolated from plants of the genus *Kopsia* (Figure 5), and have proven to be rich sources of novel alkaloids with intriguing carbon skeletons that display a wide variety of interesting activities.[153]

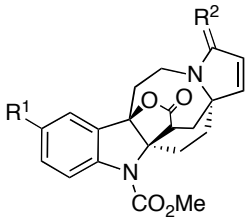
Figure 5. *Kopsia fructicosa*

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-

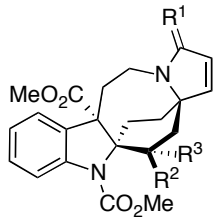
153 Lead references on indole alkaloids form genus *Kopsia*: (a) Subramaniam, G.; Kam, T.-S. *Helv. Chem. Acta* **2008**, *91*, 930–937.(b) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *71*, 53–57. (c) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765–5768. (d) Awang, K.; Sévenet, T.; Hamid, A.; Hadi, A.; David, B.; Païs, M. *Tetrahedron Lett.* **1992**, *33*, 2493–2496.

resistant KB cells. To date only three approaches toward the total synthesis of lundurines A-D have been reported.[63a,154] Furthermore, various approaches toward related indoloazocine compounds have been published (in the next section, these syntheses will be briefly reviewed).

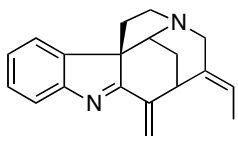
In Figure 6, other examples of indole alkaloids isolated from the genus *Kopsia* are depicted.[153d,155] In particular, the indoloazocine derivative lapideilectine B has been synthetized by Pearson and coworkers in 23 linear steps. [156]



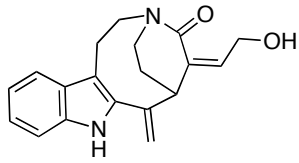
R^1 = OMe, R^2= O: Tenuisine C
R^1 = H, R^2 = H_2: Lapidilectine B
R^1 = H, R^2 = O: Grandilodine C



R^1 = H_2, R^2 = CO_2Me, R^3 = H: Lapilectine A
R^1 = H_2, R^2 = H, R^3 = CO_2Me: Isolapidelectine A
R^1 = O, R^2 = CO_2Me, R^3 = H: Lapidilectam
R^1 = O, R^2 = H, R^3 = CO_2Me: Grandilodine B



Valparicine



Pericidine

Figure 6. *Structures of indole alkaloids present in plants of genus Kopsia*

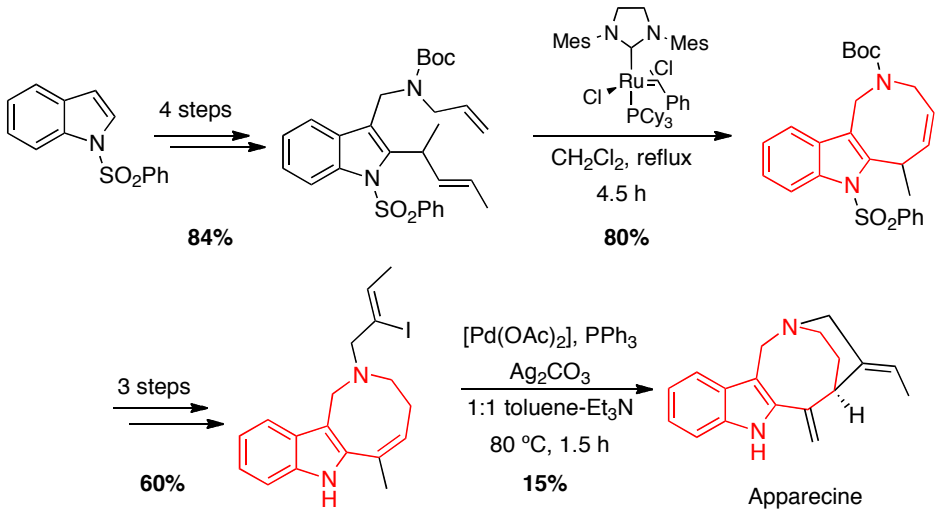
154 (a) Orr, S. T. M.; Tian, J.; Niggemann, M.; Martin, S. F. *Org. Lett.* **2011**, *13*, 5104–5107. (b) Schultz, E. E.; Pujanauski, B. G.; Sarpong, R. *Org. Lett.* **2012**, doi: 10.1021/ol203302f.

155 (a) Lim, K.-H.; Low, Y.-Y.; Kam, T.-S. *Tetrahedron Lett.* **2006**, *47*, 5037–5039. (b) Lim, K.-H.; Kam, T.-S. *Helv. Chem. Acta* **2007**, *90*, 31–35. (c) Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2011**, *74*, 1309–1312.

156 (a) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724–6725. (b) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109–9122.

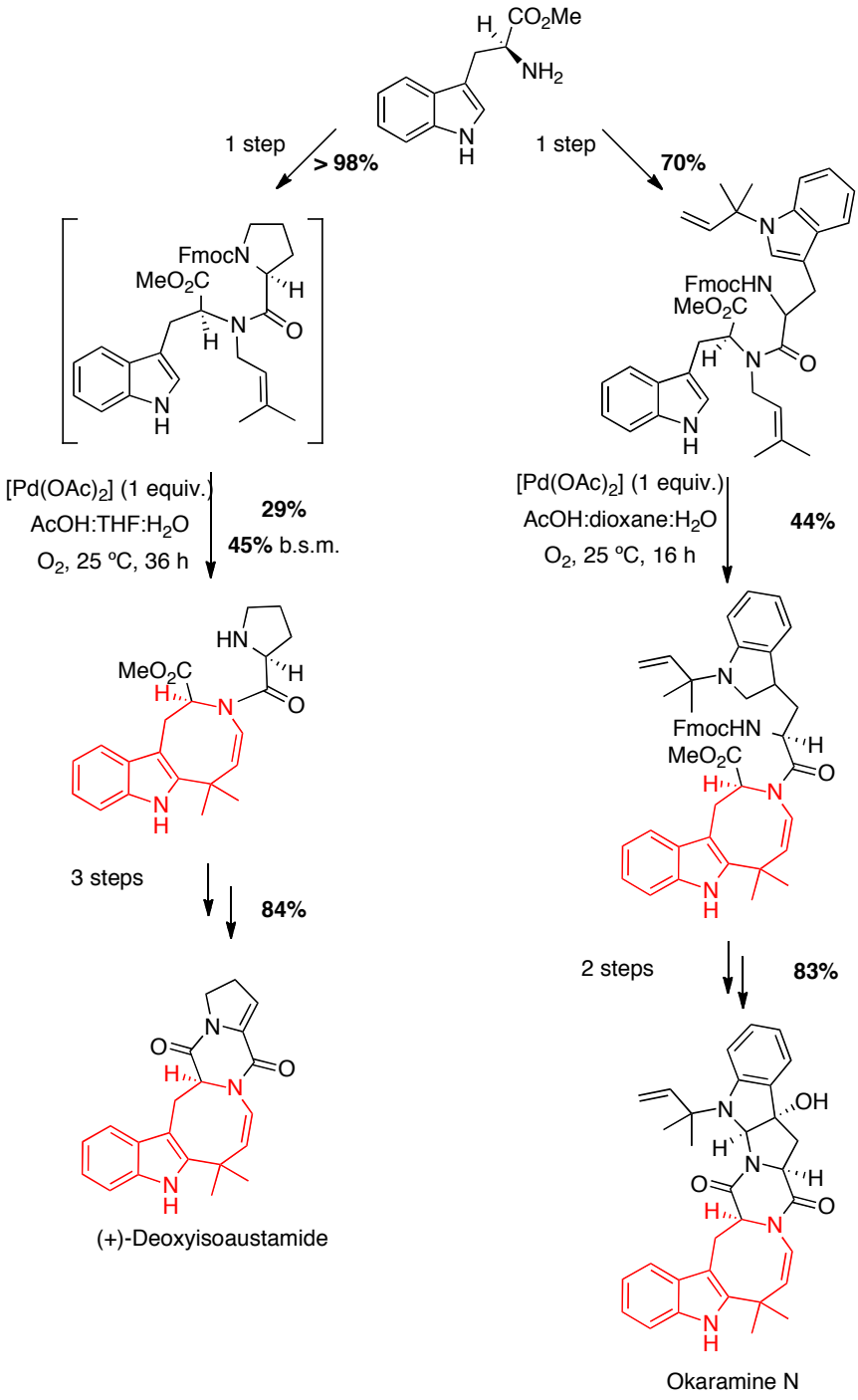
3.1.4 Synthesis of other Indoloazocine Derivatives

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 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.[151]



Scheme 1. *Total synthesis of (±)-apparicine*

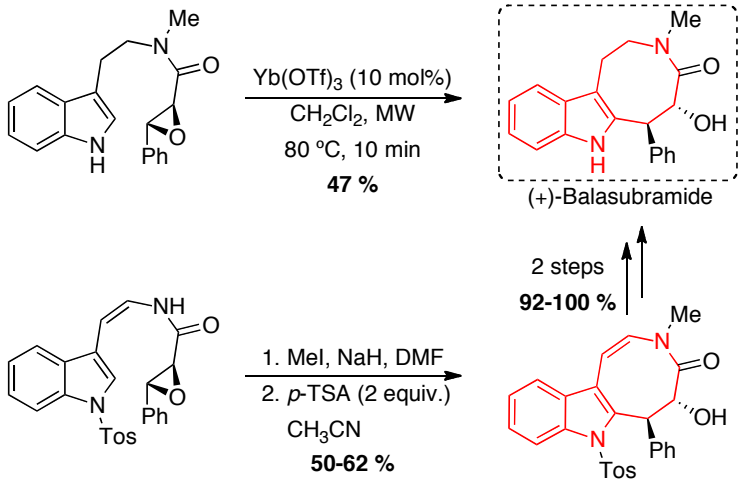
A major contribution toward the synthesis of indoloazocine skeletons is based on metal-mediated Friedel-Crafts-type reaction of indole derivates with several electrophiles. In this context, Baran and Corey developed an impressive palladium-mediated transformation of *N*-prenylated tryptophan derivatives allowing the synthesis of the dihydroindoloazocine tricycle in one step. This straightforward methodology was applied to the total synthesis of (+)-deoxyisoaustamide[152a] and okaramine N[152b] in a remarkably short synthetic route (Scheme 2).



Scheme 2. *Total synthesis of (+)-dexoxyisoaustamide and okaramine N*

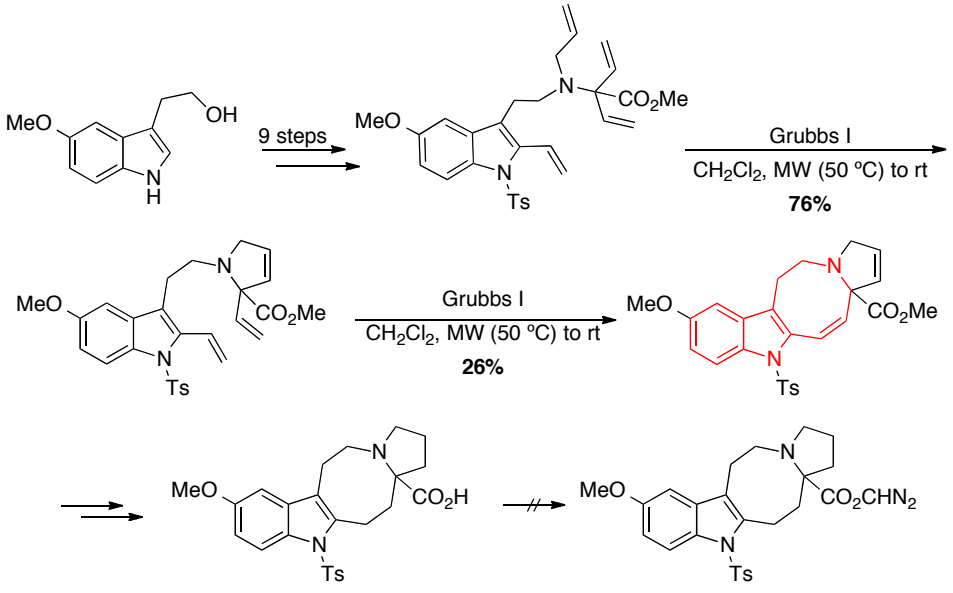
Another possibility is based on a biomimetic approach, a stereoselective 8-*endo*-epoxide-indole cyclization. Using this methodology, the Kerr group has reported the synthesis of (-)

or (+)-balasubramide using ytterbium triflate as the catalyst,[145a] while the Zhang group used *p*-toluenesulfonic acid (*p*-TSA).[145b]



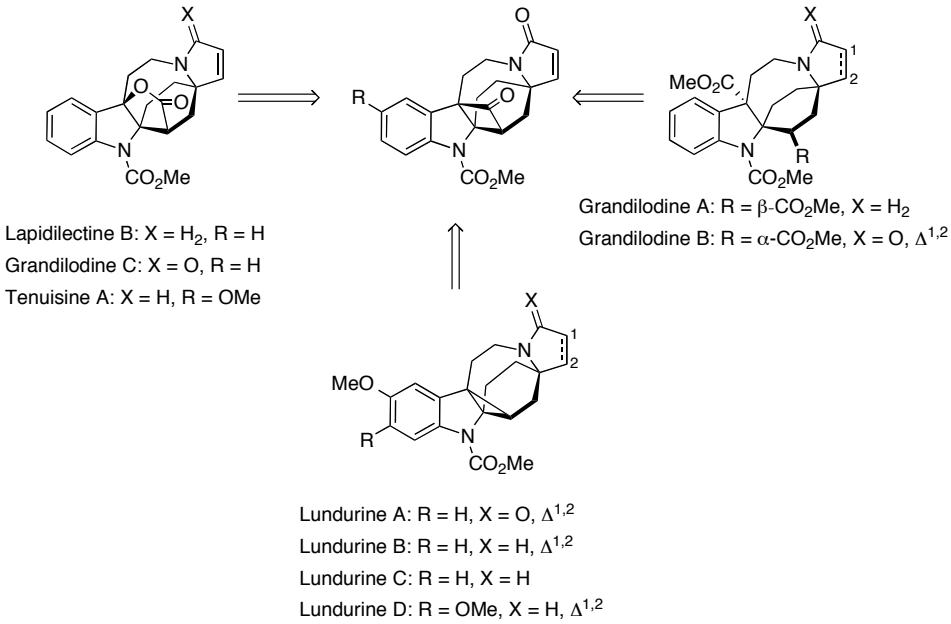
Scheme 3. *Synthesis of balasubramide*

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).[154a] 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.



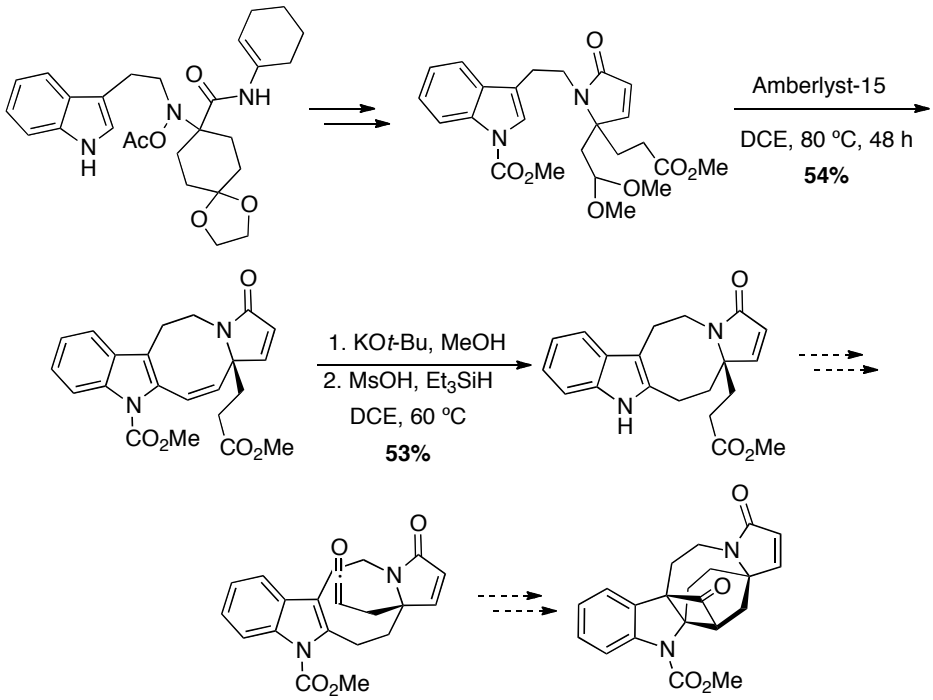
Scheme 4. *Synthesis of the tetracyclic framework of lundurine B*

Very recently, synthetic studies toward lapidilectine-type *Kopsia* alkaloids have been developed by Sarpong and co-workers.[154b] 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 5).



Scheme 5. *Common intermediate for the synthesis of Kopsia alkaloids*

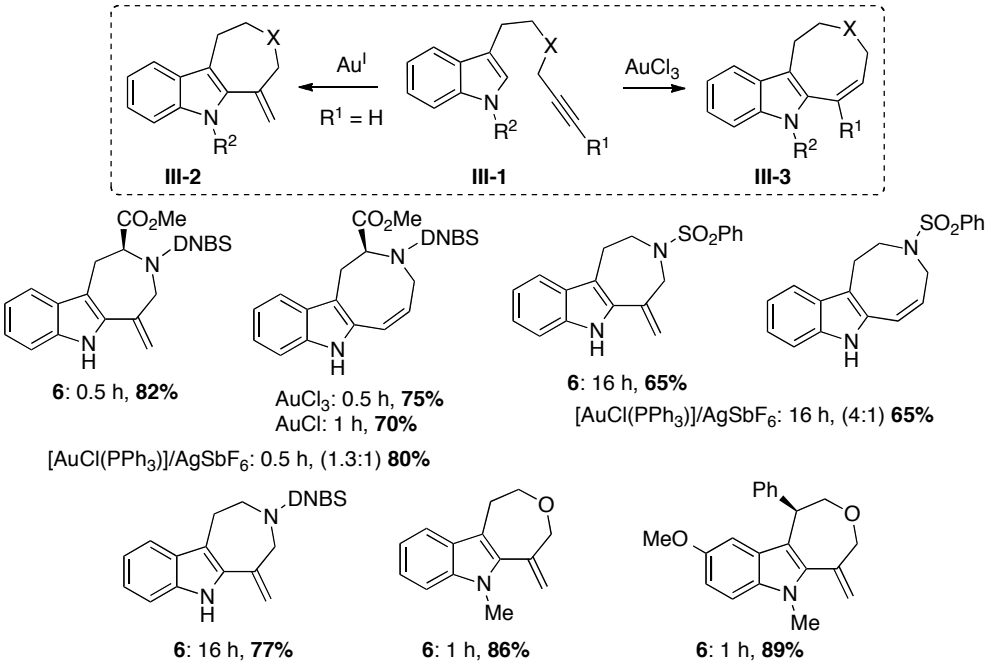
In Scheme 6 is shown the syntesis of the tetracyclic core of *Kopsia* alkaloids, which are related to lapidilectine. An Ugi four-component coupling allowed the synthesis of the β-aminoamide adduct from simple starting material. After several steps, a Fridel-Crafts-type transformation of dimethyl acetal 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 6. *Key step of the synthetic studies toward lapidilectine-type alkaloids*

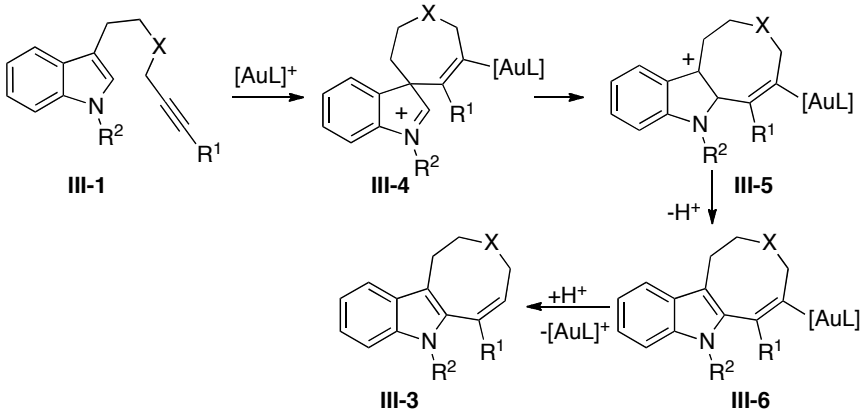
3.1.5 Gold-Catalyzed Reaction of Indoles with Alkynes

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.[52b,63a] 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 7). Under certain forcing conditions, allenes and tetracyclic compounds were also obtained.[52b,63a]



Scheme 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 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 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*.

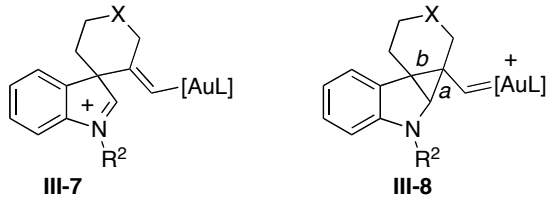
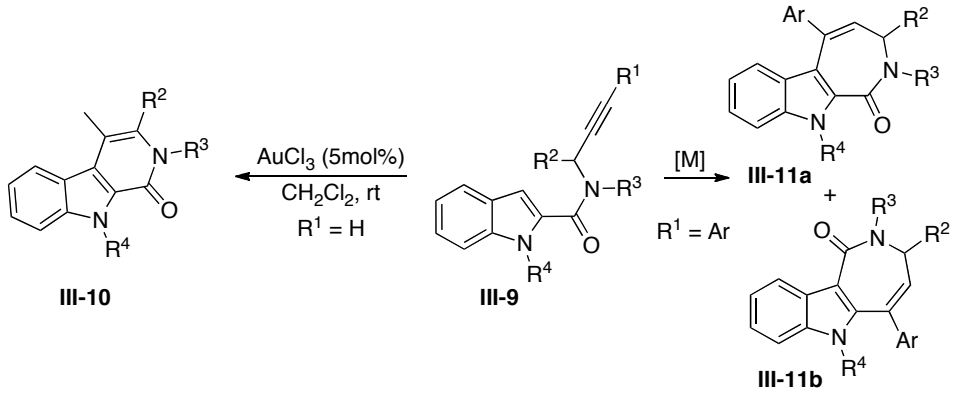


Figure 7. *Proposed intermediates in the 7-exo-dig cyclization of alkynylindole* ***III-1***

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 9).[157] 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 $PtCl_2$.[158]



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

157 (a) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631–3634. (b) Verniest, G.; England, D.; De Kimpe, N.; Padwa, A. *Tetrahedron* **2010**, *66*, 1496–1502.

158 Gruit, M.; Pews-Davtyan, A.; Beller, M. *Org. Biomol. Chem.* **2011**, *9*, 1148–1159.

The intermolecular reaction of indoles with alkynes and alkynyl alcohols takes place with gold(I),[52b,159] gallium(III),[160] or platinum(II)[161] 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.[162] Gold-catalyzed cascade and tandem cyclization of indole derivatives with alkynes have been applied to the formation of dihydrocyclohepta[*b*]indole,[163] teracyclic indolines,[164] 3-allenylindole derivatives,[165] and indene-containing indole scaffolds through a new 1,2-indole migration.[166] 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.[167] Recently, the synthesis of functionalized carbazoles was achieved through gold-catalyzed deacylative cycloisomerization of 3-indolynes.[168]

159 Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *J. Organomet. Chem.* **2009**, *694*, 546–550.

160 Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 7577–7579.

161 Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2007**, *13*, 8285–8293.

162 (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805. (b) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358–11359.

163 Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517–1522.

164 Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448–1451.

165 Li, G.; Liu, Y. *J. Org. Chem.* **2010**, *75*, 3526–3528.

166 Sanz, R.; Miguel, D.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 7354–7357.

167 Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212–1227.

168 Wang, L.; Li, G.; Liu, Y. *Org. Lett.* **2011**, *13*, 3786–3789.

3.2 Objective

Lundurines are a new type of indole alkaloids, which are characterized by an unusual carbon skeleton (Figure 4).[146] 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.

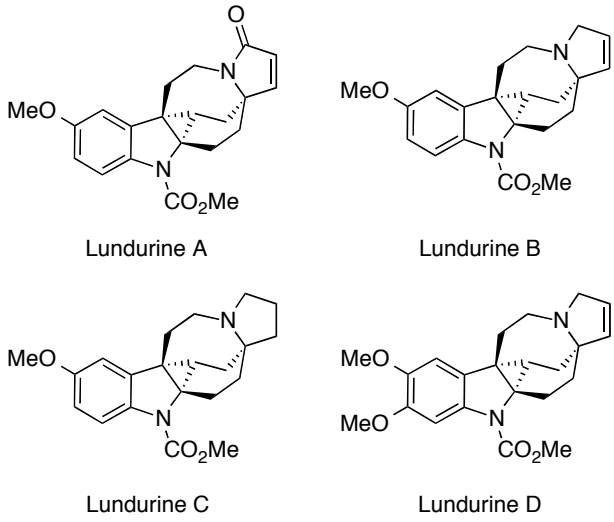
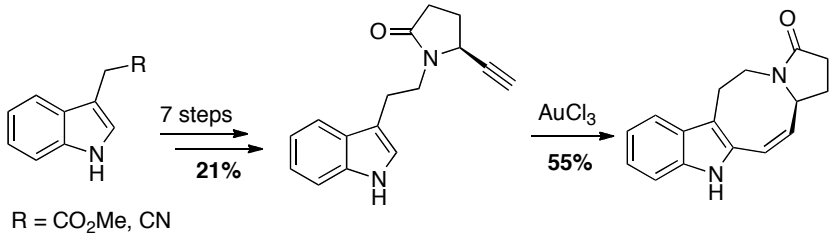


Figure 4. *Structures of lundurines A-D*

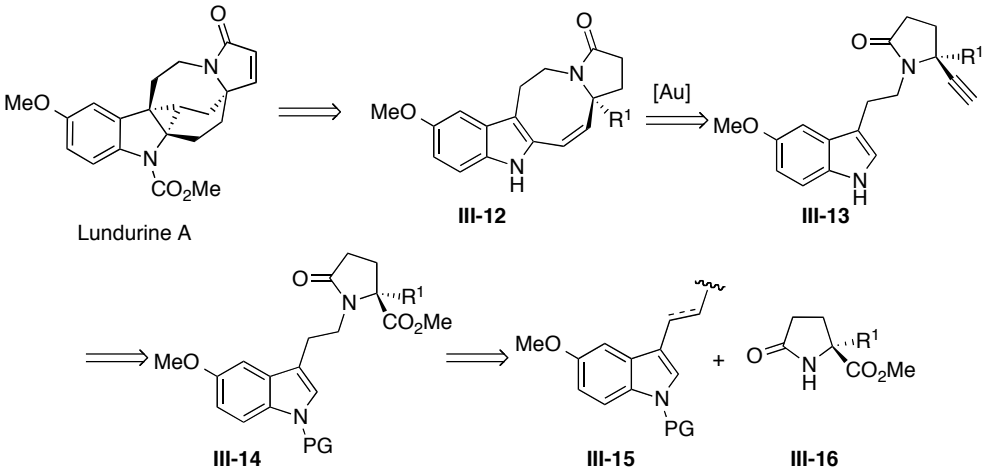
The main tetracyclic core of these alkaloid compounds has been synthesized by applying the methodology developed in the group for the intramolecular reaction of indoles with alkynes catalyzed by gold complexes (Scheme 10).[52b,63a] Thus, based on previously reported results, our objective was to develop an efficient approach toward the total synthesis of lundurines.



Scheme 10. *Previous results for the synthesis of the tetracyclic core of lundurines*

3.3 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 11.



Scheme 11. *Retrosynthetic analysis of the synthesis of lundurine A*

Lundurine A could be synthesized from indoloazocine **III-12** after cyclopropanation of the indole ring.[169,170] The intermediate **III-12** would be formed by gold(III)-catalyzed cyclization of the alkynylindole **III-13**,[52b,63a] which arises from **III-14** upon conversion of the ester group into a homologated alkyne.[171] Compound **III-14** would be assembled from an enantiomerically pure pyroglutamic ester derivative **III-16** and an indole derivative **III-15**.[172]

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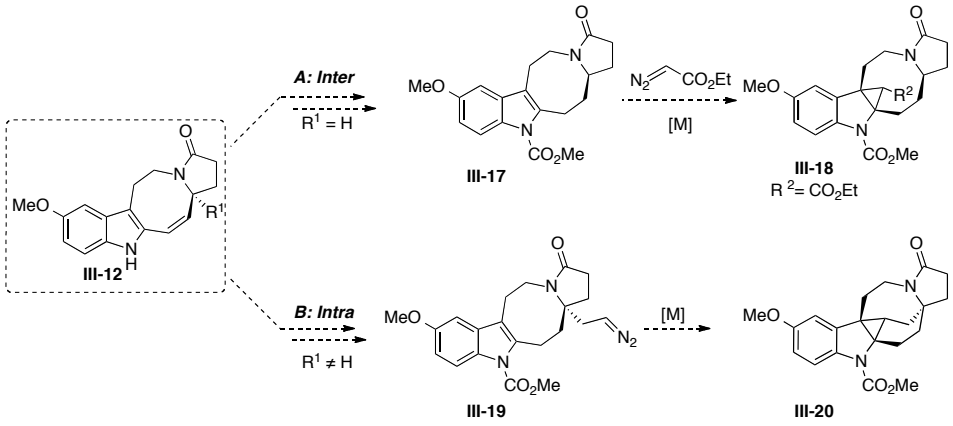
169 General review about cyclopropanation: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.

170 General review about indole cyclopropanation: Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447–457.

171 General review about conversion of carbonyl compounds to alkynes: Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007–2017.

172 General reviews about metal-catalyzed approaches to amide bond formation: (a) Joullié, M. M.; Lassen, K. M. ARKIVOC **2010**, *8*, 189–250. (b) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405–3415.

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



Scheme 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).[173] In the intramolecular approach, cyclopropylindole **III-20** would be obtained from the diazoindole **III-19**.[174]

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173 (a) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544–547. (b) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945–3949. (c) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277–4280. (d) Davies, H. M. L.; Antoulinakis, E. G., Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. In *Organic Reactions*, John Wiley & Sons, Inc.: 2004; Vol. 57, pp 1–416. (e) Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011–6014. (f) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109–1119. (g) He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2008**, *74*, 298–304.

174 (a) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 786–789. (b) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063–8069. (c) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835–6838. (d) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187–2190. (e) Cuevas-Yañez, E.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron* **2004**, *60*, 1505–1511. (f) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794–13795. (f) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618–3621. (g) Zhang, B.; Wee, A. G. H. *Chem. Commun.* **2008**, 4837–4839. (h) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020. (i) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035–6041. (j) Bull, J. A.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1895–1902.

3.3.1 Intermolecular Approach

In this strategy toward the total synthesis of lundurine A (Scheme 13), the key steps involved are:

i. The condensation of **III-22** with dimethyl (*L*)-glutamate by reductive amination, followed by *in situ* lactamization to give **III-14H.**

ii. Transformation of the remaining methyl ester group into the alkyne **III-13H** via the corresponding aldehyde.[171]

iii. Gold-catalyzed 8-*endo*-*dig*-cyclization to give **III-12H**.[52b,63a]

iv. 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**.[173]

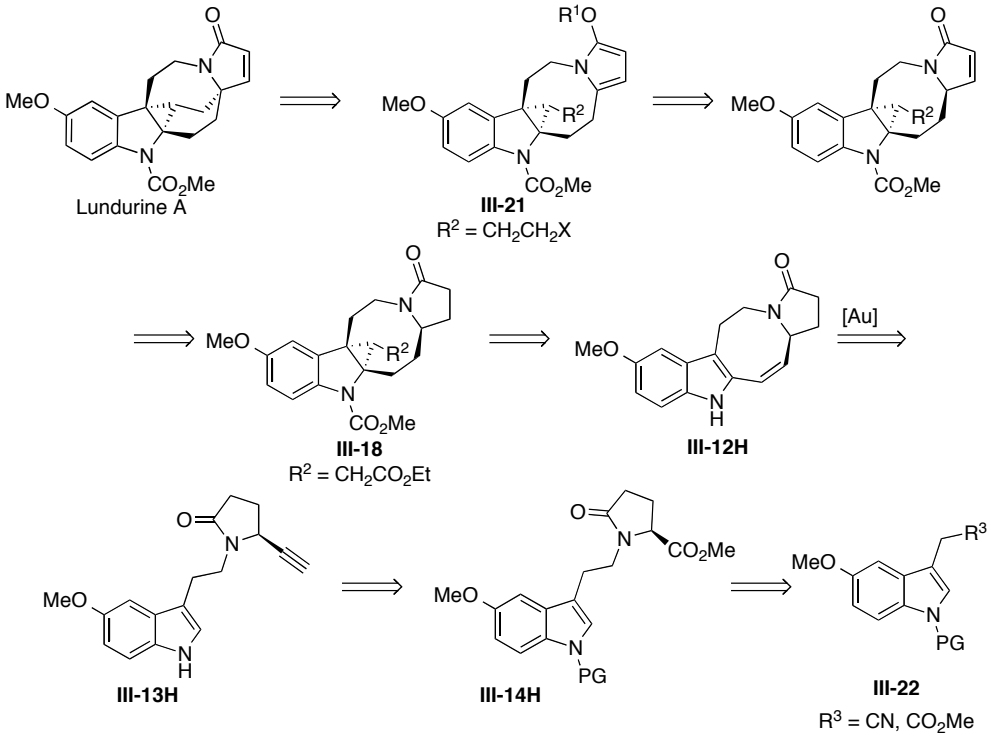
v. Reduction of the ester to the alcohol (R^2), installation of the double bond in the lactam ring,[175] and formation of the pyrrole-based silyl dienol ether **III-21**.[176,177,178] The final C–C bond in the lundurine A could be formed by intramolecular regioselective γ-alkylation of the pyrrole **III-21**in the presence of a Lewis acid.[178]

175 (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139. (b) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902. (c) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511–3513. (d) Mun, J.; Smith, M. B. *Synth. Commun.* **2007**, *37*, 813–819.

176 First example of synthesis and reactivity of pyrrole-based silyl dienol ether: Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M.; Dembech, P. *J. Org. Chem.* **1984**, *49*, 551–553.

177 Selected reviews: (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, *1999*, 1333–1350. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109–118.

178 Synthesis and γ-alkylation of pyrrole-based silyl dienol ether: Zanardi, F.; Battistini, L.; Rassu, G.; Cornia, M.; Casiraghi, G. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 2471–2475.



Scheme 13. *Retrosynthetic analysis of the intermolecular strategy*

3.3.1.1 Synthesis of alkynylindole[63b]

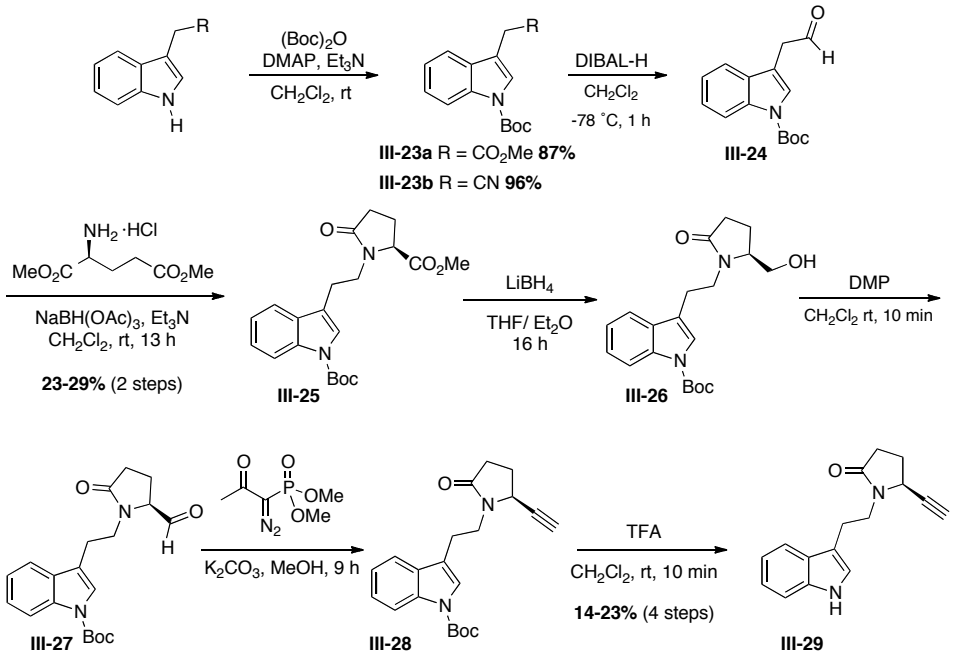
In order to obtain a suitable enantiomerically pure precursor for the synthesis of lundurine A, we started with the preparation of alkynylindole **III-29** following synthetic sequence shown in Scheme 14.[179] Methyl 2-(1*H*-indol-3-yl)acetate was protected as a Boc-carbamate,[180] which was reduced 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

179 Optimizing results from the Doctoral Thesis of Catalina Ferrer Llabrés (ICIQ/URV, Tarragona, January 2008).

180 Davies, H. M. L.; Townsend, R. J. *J. Org. Chem*. **2001**, *66*, 6595–6603.

yield, by *in situ* lactamization. Alternatively, aldehyde **III-24** could also be prepared from 2-(1*H*-indol-3-yl)acetonitrile.[181]

Ester **III-25** was reduced to alcohol **III-26** using lithium borohydride.[182] Alternatively, alcohol **III-26** could also be prepared using sodium borohydride and calcium chloride, but a with longer reaction time (1-2 days).[183] When lithium aluminium hydride was used, competitive reduction of the lactam was also observed, even at low temperatures.



Scheme 14. *Synthesis of alkynylindole* ***III-29***

181 (a) Horwell, D. C.; McKiernan, M. J.; Osborne, S. *Tetrahedron Lett.* **1998**, *39*, 8729–8732. (b) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159.

182 He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298–304.

183 (a) Meng, W.-H.; Wu, T.-J.; Zhang, H.-K.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 3899–3910. (b) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544–547. (c) Feng, C.-G.; Chen, J.; Ye, J.-L.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2006**, *62*, 7459–7465.

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[184] 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.[185]

3.3.1.2 Gold-catalyzed Cyclization of Alkynylindole[63b]

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 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,[186] were also observed using $AuCl_3$.

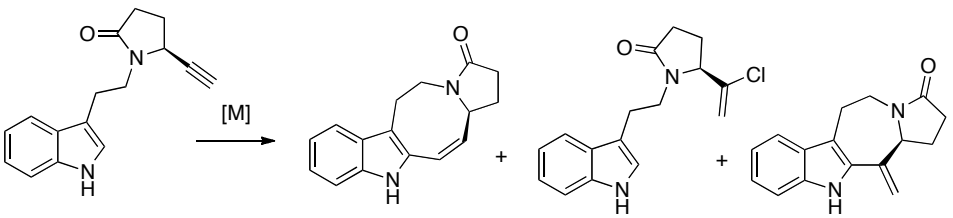
The cyclization was less efficient using gold(III) complex **22** or $HAuCl_4$ as catalyst (Table 1, entries 2 and 3). In the case of $NaAuCl_4$, formation of a complex mixture was observed (Table 1, entry 4). Surprisingly, complex **21** and $[Au(NCMe)(PPh_3)]SbF_6$ (**25**) also favored the 8-*exo-dig* cyclization leading to indoloazocine **III-30** as the major product (Table 1, entry 5 and 6)**.**

184 (a) McElwee-White, L.; Dougherty, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 3466–3474. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (c) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521–522. (d) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrahedron* **2003**, *59*, 1719–1729. (e) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, *2004*, 59–62. (f) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266–4268.

185 Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

186 (a) Nkosi, B.; Coville, N. J.; Hutchings, G. J. *J. Chem. Soc., Chem. Commun.* **1988**, 71–72. (b) Nkosi, B.; Coville, N. J.; Hutchings, G. J.; Adams, M. D.; Friedl, J.; Wagner, F. E. *J. Catal.* **1991**, *128*, 366–377. (c) Conte, M.; Carley, A.; Hutchings, G. *Catalysis Let.* **2008**, *124*, 165–167.

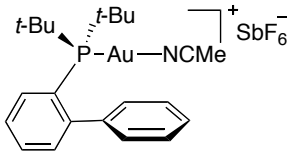
Table 1. *Gold-catalyzed cyclization of alkynylindole* ***III-29***



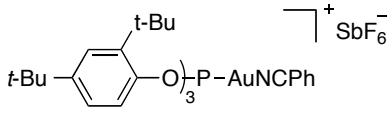
III-29 **III-30** **III-31** **III-32**

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**	-
12	$AgSbF_6$	100	**III-30**	17
13	AgOTf	29	**III-30**	-
14	$GaCl_3$	-[c]	-	-
15	$InCl_3$	-[c]	-[d]	-
16	TfOH	-[c]	-	-

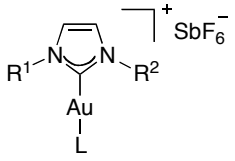
Reaction carried out with 5 mol% [M] in CH_2Cl_2 at room temperature for 24 h. [a] Determined by NMR using 1,3,5-trimethoxybenzene as standard. [b] Complex mixture. [c] Conversion <5%. [d] Traces of **III-30** were observed.



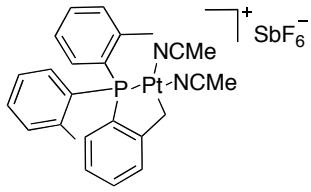
6



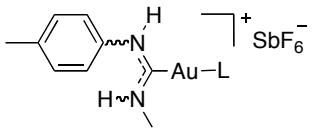
20



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-$(MeO)_3C_6H_2CN$

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 1, entries 7 and 8). Similar selectivity was observed using phosphite gold(I) **20** (Table 1, entry 9). As expected, higher conversions were observed with the gold(III) complexes and phosphite gold(I) complex **20**, both more electrophilic (Table 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 1, entry 10).[52b] On the other hand, only low conversion was achieved with cationic platinacycle **24**[19c] (Table 1, entry 11). Low yields of indoloazocine **III-30** were obtained using silver(I) salts such as $AgSbF_6$ and AgOTf[187] whereas, $GaCl_3$, $InCl_3$, and Brønsted acid (TfOH) were not effective (Table 1, entries 12-16).

187 Porcel, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2672–2676.

The fact that very similar results were obtained using $AuCl_3$ and AuCl (Table 1, entries 1 and 10) suggests that gold(III) might be reduced to gold(I) under the reaction conditions.[188] 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 1, entries 1-5 and 10-13).

3.3.1.3 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 15):

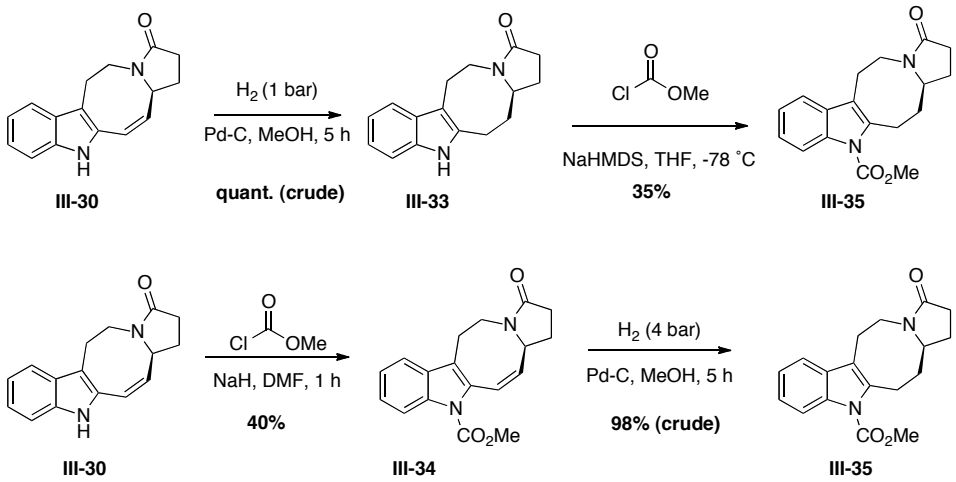
i. First, hydrogenolysis of indoloazocine **III-30**, followed by protection as methyl carbamate **III-35** using methyl cloroformate and NaHMDS, as base, in THF.[189]

ii. Protection as methyl carbamate **III-34** using methyl chloroformate and sodium hydride,[190] and subsequent hydrogenolysis. In this case, a higher hydrogen pressure (4 bar) was needed to afford complete conversion.

188 Morita, N.; Krause, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1897–1899.

189 Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, *2007*, 2676–2686.

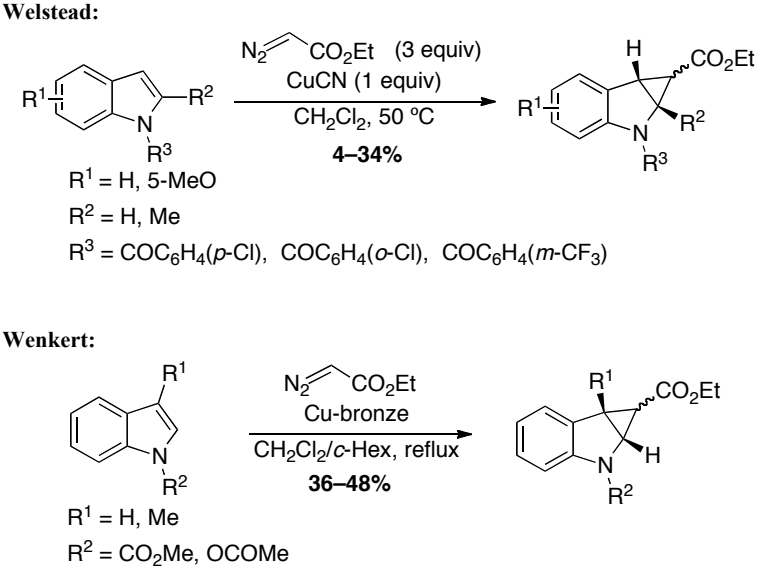
190 Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147.



Scheme 15. *Synthesis of precursor* ***III-35***

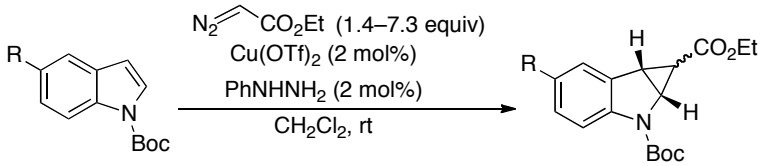
3.3.1.4 Study of cyclopropanation reaction

For the study of the cyclopropanation reaction of indoles with diethyl diazoacetate (EDA), we were inspired by the pioneering work of Welstead[173a] and Wenkert.[173b] 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 16).



Scheme 16. *Welstead and Wenkert results*

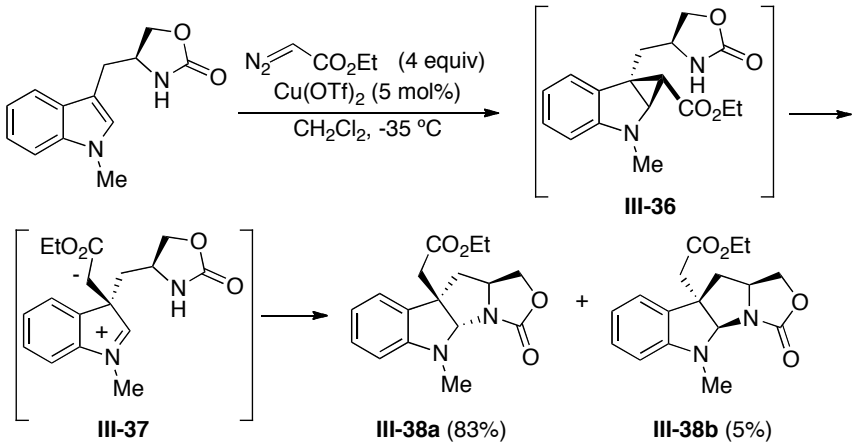
In 1993, Reiser improved the yield toward the cyclopropanated adducts using copper(I) complex and Boc-protected indoles (Scheme 17).[173c]



R = H: *exo* = **30%**, *endo* = **10%**
R = OMe : *exo* = **68%**, *endo* = **22%**

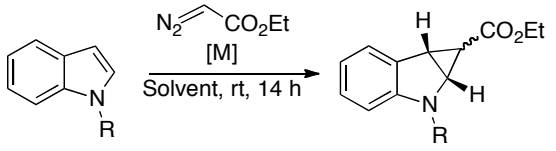
Scheme 17. *Reiser results*

More recently, Qin has developed a new cascade reaction to afford 3-substituted hexahydropyrroloindole **III-38**.[173e] 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 18). This methodology has been applied for the total synthesis of (-)-ardeemin.[173g]



Scheme 18. *Qin results*

We first decided to optimize the reaction conditions using simple indoles as a models (Scheme 19).



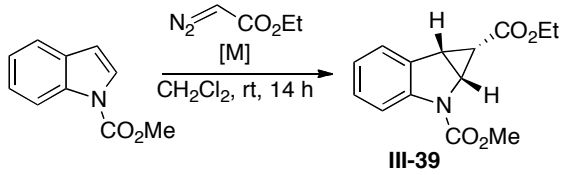
Scheme 19. *Screening of conditions for the cyclopropanation reaction*

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.[173f,191]

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.[173f] Thus, for the cyclopropanation of methyl 1*H*-indole-1-carboxylate with EDA (Table 2), the best yield was observed using 5 mol% of $[Cu(hacac)_2]$ (hfacac = hexafluoroacetylacetonato)[191] as catalyst in CH_2Cl_2 at room temperature, affording the desired cyclopropanated product **III-39** in 72% yield (Table 2, entry 1). The reaction was less efficient with $[Rh_2(OAc)_4]$, $Cu(OTf)_2$ and CuOTf (Table 2, entries 2-4).

191 Zhang, X.-J.; Liu, S.-P.; Yan, M. *Chin. J. Chem.* **2008**, *26*, 716–720.

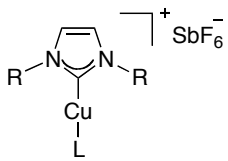
Table 2. *Cyclopropanation of indole* ***III-39*** *with diethyl diazoacetate*



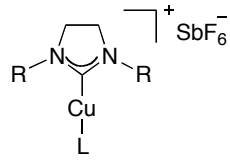
III-39

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

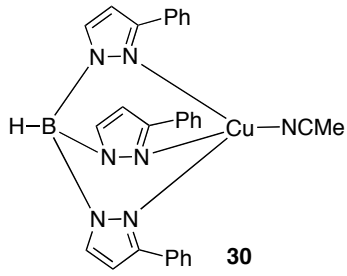
Reaction carried out with 7 equiv of EDA, 5 mol% [M] in CH_2Cl_2 at room temperature for 14 h. [a] Determined by NMR using 1,3,5-trimethoxybenzene as internal standard.



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[192] (Table 2, entries 5-8), which are less reactive but more stable.[193] Furthermore, no conversion was observed using hydrotrispyrazolylborate (Tp^{Ph}) complex **30**,[194] 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.[195] 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.[196] Nonetheless, better yields were obtained with copper(II) compared to copper(I) complexes (Table 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 3). $[Cu(hfacac)_2]$, which gave the best yield with methyl 1*H*-indole-1-carboxylate, was ineffective with indole **III-35** (Table 3, entry 1). Also, $[Rh_2(OAc)_4]$ was unproductive in this transformation (Table 3, entry 2).

192 Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* *16*, 5324–5332.

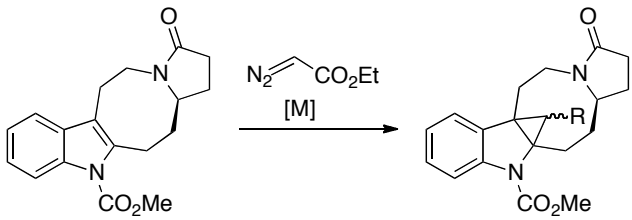
193 (a) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846–10847.

194 Mairena, M. A.; Urbano, J.; Carbajo, J.; Maraver, J. J.; Alvarez, E.; Díaz-Requejo, M. M.; Pérez, P. J. *Inorg. Chem.* **2007**, *46*, 7428–7435.

195 Caballero, A.; Sabater, M.; Morilla, M. E.; Nicasio, M. C.; Belderraín, T. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Inorg. Chem. Acta* **2009**, *362*, 4599–4602.

196 Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135–1140.

Table 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 ºC, 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 ºC, 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 3, entry 3).[173c,g] Furthermore, no conversion was observed using $Cu(OTf)_2$, CuOTf, IME copper(I) **27** or IMes gold(I) **15** complexes as catalysts (Table 3, entries 3-7).[197] 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.

197 (a) 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.* **2005**, *44*, 5284–5288. (b) Prieto, A.; Fructos, M. R.; Mar Díaz-Requejo, M.; Pérez, P. J.; Pérrez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790–1793.

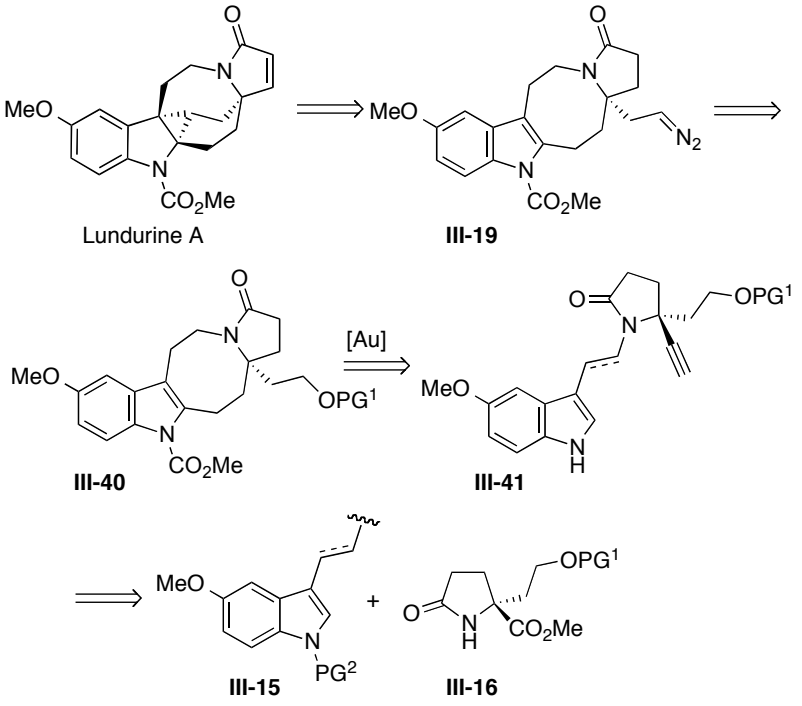
3.3.2 Intramolecular Approach

For this strategy, the key steps are described in Scheme 20:

i. The assembly of indole derivative **III-15** with an enantiomerically pure pyroglutamic ester derivative **III-16**,[172] followed by transformation of the ester moiety into an alkyne to afford alkynylindole **III-41**.[171]

ii. Gold-catalyzed 8-*endo-dig* cyclization,[52b,63a] catalytic hydrogenation of the alkene and formation of the methyl carbamate to give indoloazocine **III-40**.

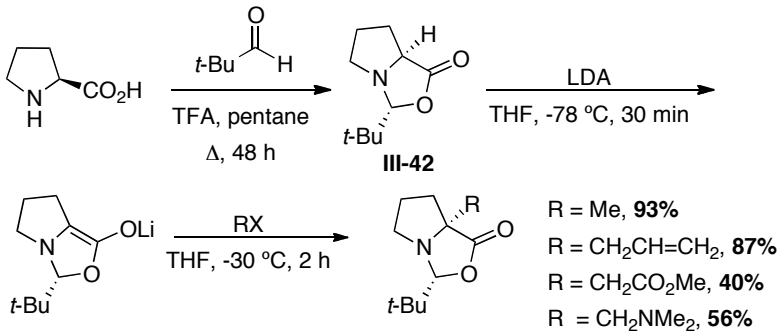
iii. Finally, intramolecular cyclopropanation of diazo compound **III-19**[174] and formation of the α,β-unsaturated lactam to form lundurine A.[175]



Scheme 20. *Retrosynthetic analysis of the intramolecular strategy*

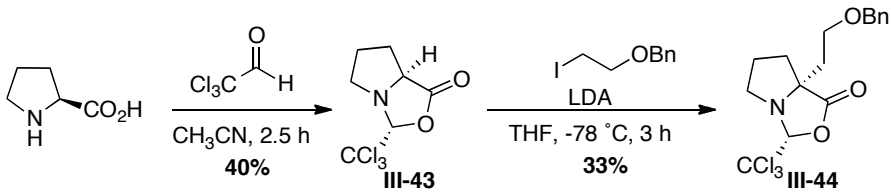
3.3.2.1 Synthesis of substituted 2-pyrrolidone

For the synthesis of 2-pyrrolidone **III-16**, we followed the procedure described by Germanas and coworkers for the enantioselective alkylation of proline.[198] This procedure was based on a method reported by Seebach,[199] 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**,[200] which is deprotonated with LDA to give a chiral enolate that can be alkylated with an electrophile (Scheme 21).



Scheme 21. *Synthesis of α-substituted proline derivatives*[199]

Germanas described the condensation of proline with chloral instead of pivaldehyde to give a more stable oxazolidinone **III-43** (Scheme 20). Thus, they reported the alkylation of **III-43** using LDA and ((2-iodoethoxy)methyl)benzene in 33% yield.[179]



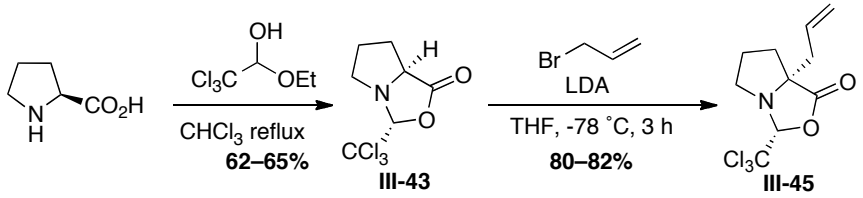
Scheme 22. *Alkylation of 2-trichloromethyloxazolidin-5-ones*[179]

198 Wang, H.; Germanas, J. P. *Synlett* **1999**, 33–36.

199 Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.

200 Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Bombieri, G.; Benetollo, F. *J. Heterocycl. Chem.* **1989**, *26*, 837–841.

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 23). Proline/chloral **III-43** was synthesized using 2,2,2-trichloro-1-ethoxyethanol.[201] The use of chloral was avoided, since it is a regulated substance, which greatly limits its commercial availability even in small quantities.



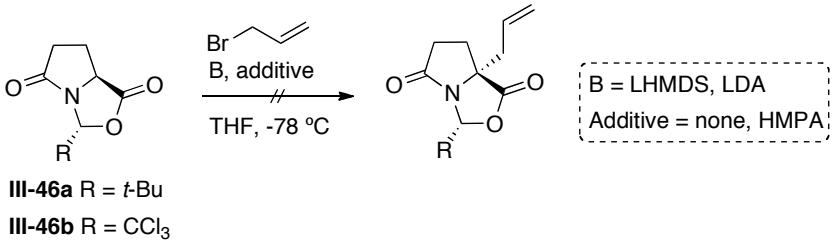
Scheme 23. *Allylation of 2-trichloromethyloxazolidin-5-ones*[201]

In addition, the analogous 2-*t*-butyloxazolidin-4-one **III-46a**[202] and 2-trichloromethyloxazolidin-4-one **III-46b**[203] precursor, derived from *S*-pyroglutamic acid, were also synthesized (Scheme 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**.

201 Artman III, G.; Williams, R. M. *Org. Synth*. **2009**, *86*, 262–273.

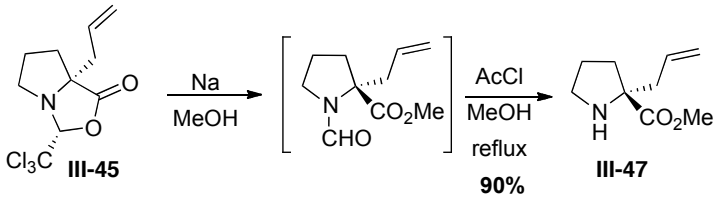
202 (a) Dikshit, D. K.; Maheshwari, A.; Panday, S. K. *Tetrahedron Lett.* **1995**, *36*, 6131–6134. (b) Wu, G. G.; Werne, G.; Fu, X.; Orr, R. K.; Chen, F. X.; Cui, J.; Sprague, V. M.; Zhang, F.; Xie, J.; Zeng, L.; Castellanos, L. P.; Chen, Y.; Poirier, M.; Mergelsberg, I. PCT Int. Appl. WO 2010/028232, 2010.

203 (a) Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229–2234. (b) Köhn, U.; Schramm, A.; Klofl, F.; Görls, H.; Arnold, E.; Anders, E. *Tetrahedron: Asymmetry* **2007**, *18*, 1735–1741.



Scheme 24. *Alkylation of oxazolidin-4-one precursors*

Optically active α-branched proline derivative **III-47** was obtained by a one-pot procedure (Scheme 25).[201] 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.[204,205]



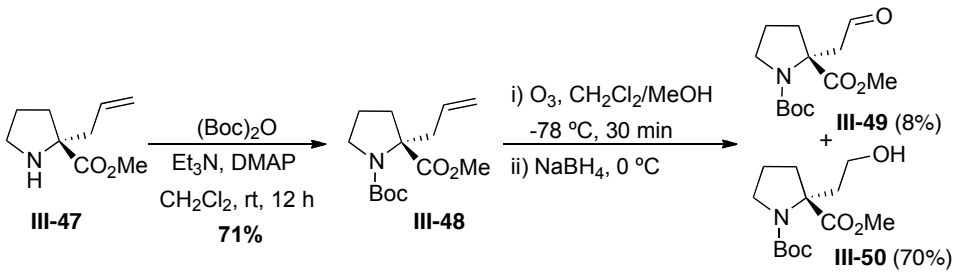
Scheme 25. *Cleavage of the trichloro auxiliary*[201]

Pyrrolidine **III-47** was protected as a Boc carbamate (Scheme 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%), [206] which were separated by column chromatography.

204 **III-47** can be synthesized by Ireland-Claisen ester rearrangement but only on small scale: (a) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850–1855. (b) Chandan, N.; Moloney, M. G. *Org. Biomol. Chem.* **2008**, *6*, 3664–3666.

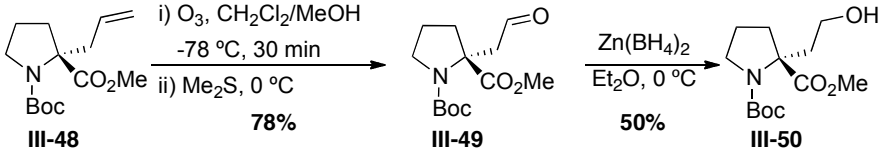
205 The reported *ee* of **III-47** was determined via conversion of the final product to the Mosher amide under Schotten-Bauman conditions.[201] The desired product was observed as a single peak, >99% diasteromerically pure.

206 Moriyama, K.; Sakai, H.; Kawabata, T. *Org. Lett.* **2008**, *10*, 3883–3886.



Scheme 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 27).[207] After an extensive screening of reducing agents ($NaBH_4$, DIBALH, H_2/PtO_2),[208] solvents, and conditions, we obtained alcohol **III-50** using zinc borohydride in ether[209] with 84% yield without purification and 50% after column chromatography.



Scheme 27. *Optimized conditions for the synthesis alcohol* ***III-50***

Finally, the desired lactam **III-53** was synthesized following the sequence shown in Scheme 28. Thus, triisopropylsilyl ether-protection (TIPS) of alcohol **III-50**,[210] oxidative of

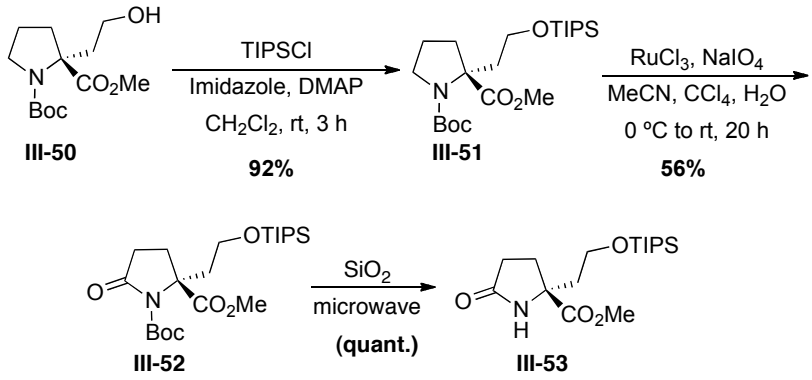
207 Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *126*, 706–707.

208 (a) Chu, W.; Perlman, J. H.; Gershengorn, M. C.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3093–3096. (b) Gao, F.; Chen, Q.-H.; Wang, F.-P. *Tetrahedron Lett.* **2009**, *50*, 5270–5273.

209 (a) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19–26. (b) Våbenø, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186–9191.

210 Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106–11112.

pyrrolidine **III-51**, using the Sharpless and Katsuki conditions,[211] afforded 2-pyrrolidone **III-52**,[212,213] which was subsequently deprotected to give the lactam **III-53**.[214]



Scheme 28. *Synthesis toward lactam* ***III-53***

3.3.2.2 Connection of 2-pyrrolidine III-53 and the indole part[215]

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

211 Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

212 First example for the oxidation of cyclic amines with ruthenium tetraoxide: (a) Sheehan, J. C.; Tulis, R. W. *J. Org. Chem.* **1974**, *39*, 2264–2267. (b) Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5515–5521. (c) Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873–3878. (d) Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3879–3884.

213 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.* **2008**, *52*, 514–523.

214 Siro, J. G.; Martín, J.; García-Navío, J. L.; Remuiñan, M. J.; Vaquero, J. J. *Synlett* **1998**, 147–148.

215 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.

enamides.[216] 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.[217]

Although palladium-[218] 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,[219] 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 29).[217a,217b,220] Under these conditions, the coupling of 2-pyrrolidine and (*E*)-1-iodohept-1-ene takes place in 99% yield.

---

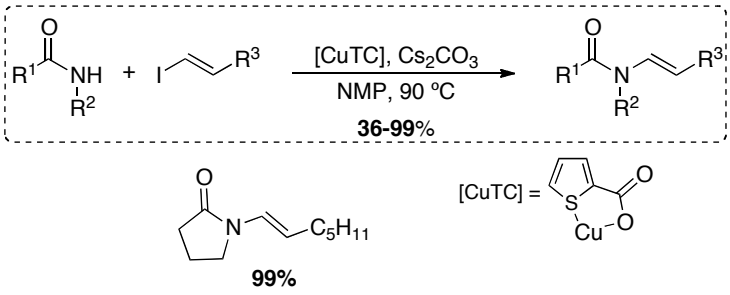
216 Reviews about metal-catalyzed coupling reaction: (a) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–986. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

217 (a) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333–1336. (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901. (c) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.

218 Synthesis of enamides starting from 2-pyrrolidine and vinyl triflates: (a) Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749–4752. (b) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185–1188. From vinyl chlorides: Hesse, S. P.; Kirsch, G. *Synthesis* **2007**, 1571–1575.

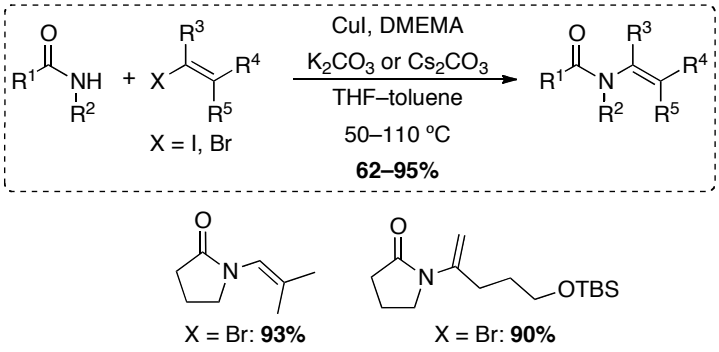
219 Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, *20*, 1443–1446.

220 For the synthesis of *N*-acyl vinylogous carbamic acids and ureas see: Han, C.; Shen, R.; Su, S.; Porco, J. A. *Org. Lett.* **2003**, *6*, 27–30.



Scheme 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 30).[217c] The coupling required Cs_2CO_3 in THF at temperatures ranging from 50 to 70 ºC using vinyl iodides, whereas vinyl bromides required the use of K_2CO_3 in toluene at 110 ºC.

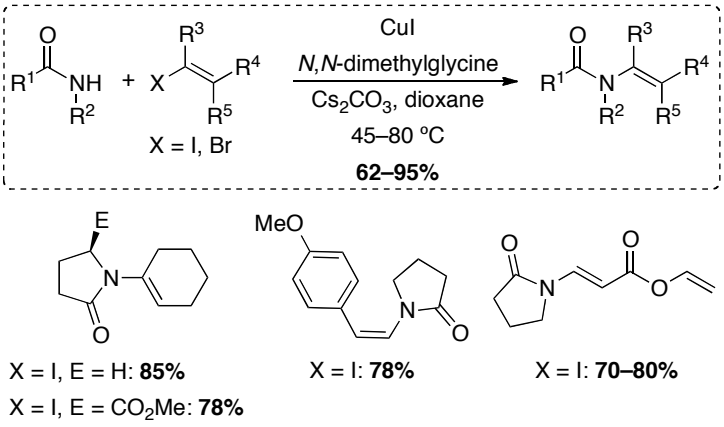


Scheme 30. *CuI/diamine-catalyzed synthesis of enamides*

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 ºC (Scheme 31).[221]

221 Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812.



Scheme 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.[222] 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 alkenyltrilfluoroborates, which allows the copper-catalyzed cross-coupling of amides and oxazolidines under base free conditions at 40 ºC.[223]

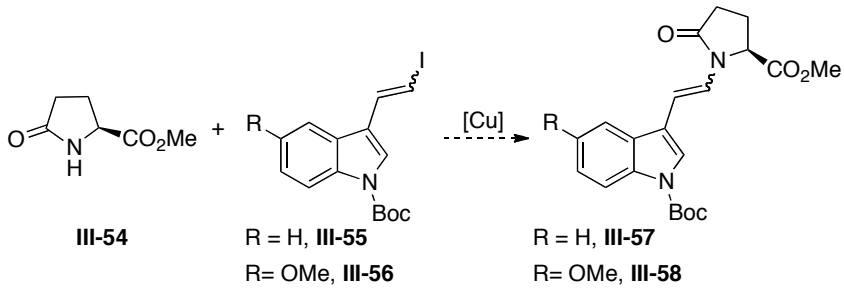
Encouraged by the previously reported results for the copper-catalyzed coupling of amides and heteroaryl vinyl halides,[224] we decided to study of the reaction with the model lactam **III-54**[225] and indolylvinyl iodide **III-55** (R = H) and **III-56** (R = OMe) (Scheme 32).

222 Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927–4931.

223 Bolshan, Y.; Batey, R. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2109–2112.

224 Selected examples for the copper-catalyzed cross-coupling of lactam and heteroaryl vinyl halides: (a) Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779–1781. (b) Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2007**, *9*, 853–855. (c) Meketa, M. L.; Weinreb, S. M. *Tetrahedron* **2007**, *63*, 9112–9119. (d) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387–1390.

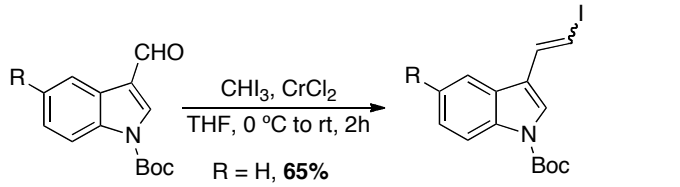
225 Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, *73*, 1661–1681.



III-54 R = H, **III-55** R= OMe, **III-56** R = H, **III-57** R= OMe, **III-58**

Scheme 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,[226] starting from the corresponding aldehydes, in moderate to high yields (Scheme 33). Unfortunately, when we tried this reaction catalylitic, only traces of the iodides were detected.[227]



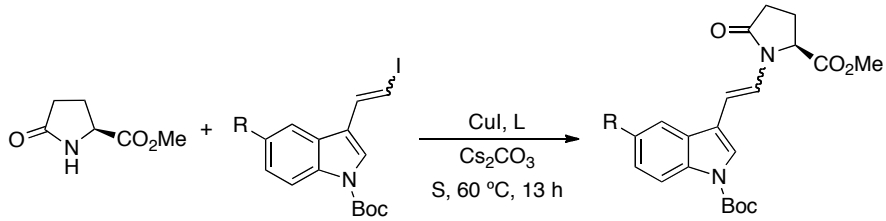
Scheme 33. *Synthesis of indolylvinyl iodides*

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,[221] no reaction was observed (Table 4, entry 1). Nevertheless, enamides **III-57** and **III-58** were obtained in high yields using the Buchwald conditions[217c] (Table 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.

226 Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

227 Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268–1270.

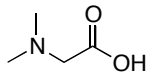
Table 4. *Study of the copper-catalyzed cross-coupling of lactam* ***III-54*** *and indolylvinyl iodides*



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.

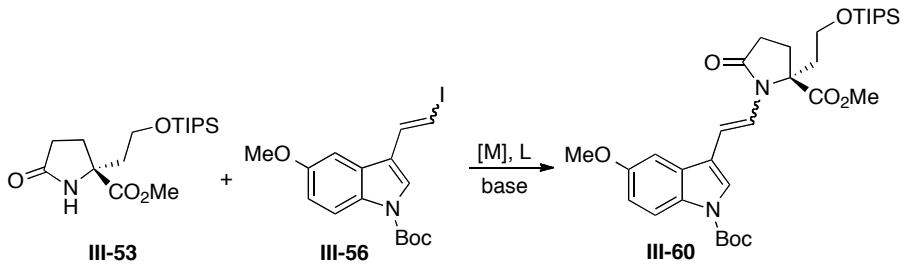


III-59

Although a systematic screening of the metal, ligand, base and the solvent was done, only selected conditions are shown in Table 5 using amide **III-53**. Unfortunately, only traces of the desired enamide **III-60** were detected when we applied the Buchwald conditions[217c] for the copper-catalyzed cross-coupling of more complex lactam **III-53** and indolyl vinyl iodide **III-56** (Table 5, entry 1). Under more forcing conditions, only decomposition of the iodide was observed (Table 5, entry 2). The same result was achieved using the Porco conditions (Table 5, entry 3),[217a,217b] the modified version using diamine **III-61** (Table 5, entry 4),[228] and palladium as catalyst (Table 5, entry 5).

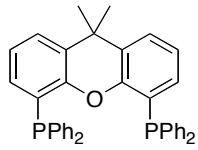
228 Optimizated conditions for the copper-catalyzed cross-coupling of protected maleimide hemianals: Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577–580.

Table 5. *Study of the metal-catalyzed cross-coupling of lactam* ***III-53*** *and indolylvinyl iodide* ***III-56***

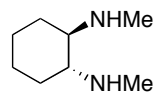


Entry	*[M]*	*L*	*base*	*S*	*Cond.*	*Yield. (%)*
1	CuI	DMEDA	Cs_2CO_3	THF	60 ºC, 13 h	27[a]
2	CuI	DMEDA	Cs_2CO_3	THF	MW, 110 ºC, 12 h	-
3	[CuTC]	-	Cs_2CO_3	NMP	90 ºC, 1 d	-
4	[CuTC]	**III-61**	K_3PO_4	dioxane	90 ºC, 1 d	-
5	$[Pd_2(dba)_3]$	xantphos	Cs_2CO_3	dioxane	110 ºC, 1d	-

[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 (Figure 8).

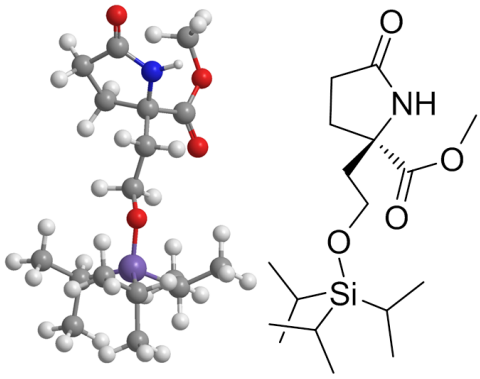
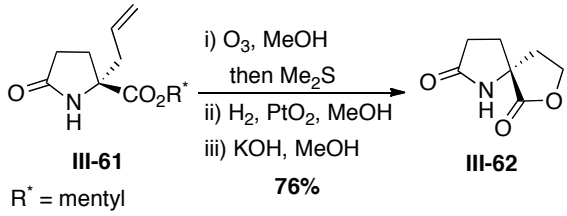


Figure 8. *Optimized structure of lactam* ***III-53*** *using MM2*

3.3.2.3 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 34).[229]

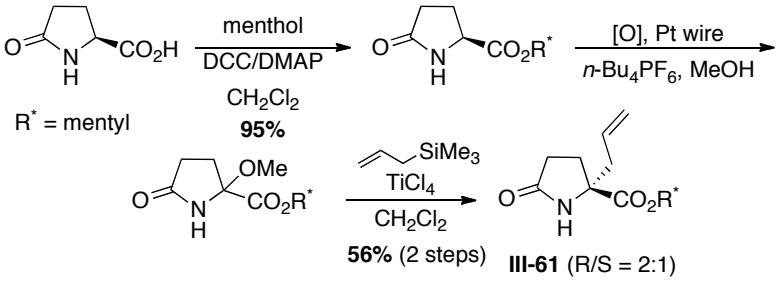


Scheme 34. *Reported synthesis of spiro lactama* ***III-62***

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

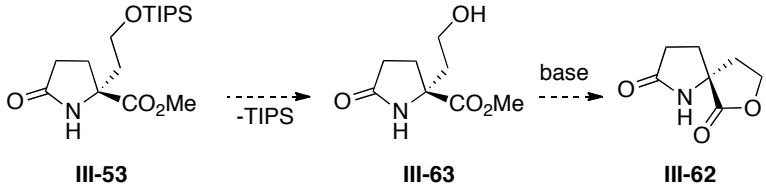
229 Chu, W.; Perlman, J. H.; Gershengorn, M. C.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3093–3096.

treatment of the correspondening methoxylethers amide with allyltrimethylsilane and titanium tetrachloride (Scheme 35).[230]



Scheme 35. *Synthesis of lactam* ***III-61***[230]

Based on this strategy, Scheme 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 36. *Synthetic approach toward lactona-lactma* ***III-61***

This spiro lactam **III-62** is characterized by less hindrance around the quaternary carbon (Figure 9), which should allow the C–N coupling reaction to go to completion.

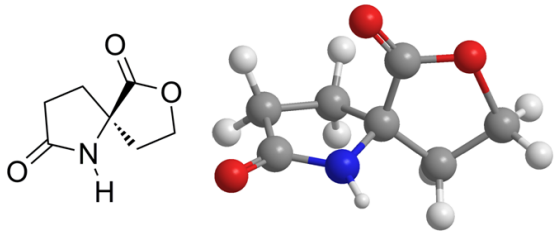


Figure 9. *Optimized structure of lactam* ***III-62*** *using MM2*

230 (a) Moeller, K. D.; Rutledge, L. D. *J. Org. Chem.* **1992**, *57*, 6360–6363. (b) Simpson, J. C.; Ho, C.; Berkley Shands, E. F.; Gershengorn, M. C.; Marshall, G. R.; Moeller, K. D. *Biorg. Med. Chem.* **2002**, *10*, 291–302.

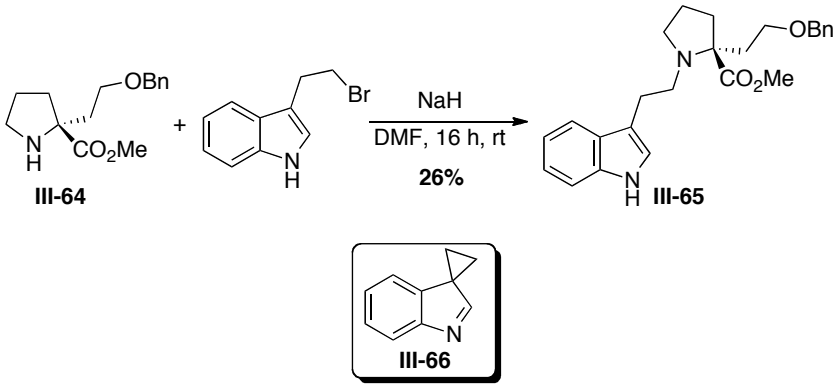
3.3.2.4 Annex: other methodologies tested for the connection of 2-pyrrolidine III-53 and the indole part

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.

3.3.2.4.1 Nucleophilic substitution (S_N2)

Following the precedents reported for the alkylation of proline and pyroglutamic derivatives,[231] 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 37),[231] 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.[232]



Scheme 37. *Alkylation of proline derivative* ***III-64*** *with 3-(2-bromoethyl)-1H-indole*[231]

In the work of Rapoport,[232] 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.

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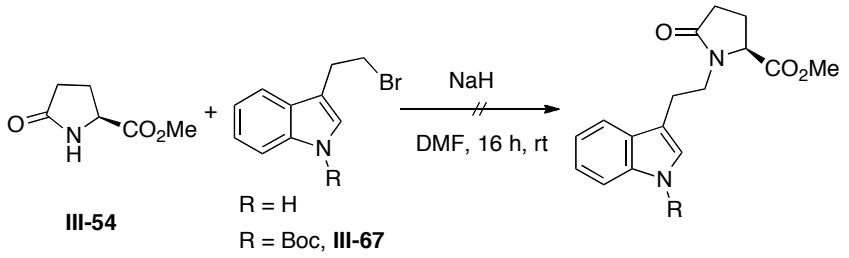
231 Reported results in the Doctoral Thesis of Catalina Ferrer Llabrés (Prof. Echavarren group, January 2008).

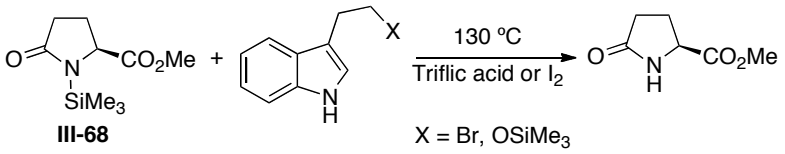
232 Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914–4920.

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**)[233] (Scheme 38), the desired alkylated product was not detected.



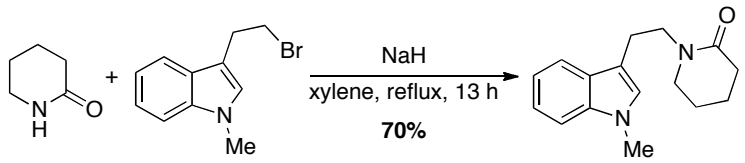
Scheme 38. *Alkylation of lactam* ***III-54*** *with different N-protected bromoindoles*

The Rigo methodology[234] 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 39).[231] Under these conditions, only (*L*)-methyl pyroglutamate was formed.



Scheme 39. *Alkylation of pyroglutamate derivative* ***III-68*** *with several electrophiles*[231]

Given these unsuccessful alkylation attempts, we decided to examine the methodology developed by Hwang and coworkers[235] in which 2-piperidone is alkylated with 1-methyltryptophylbromide using sodium hydride under reflux conditions (Scheme 40).



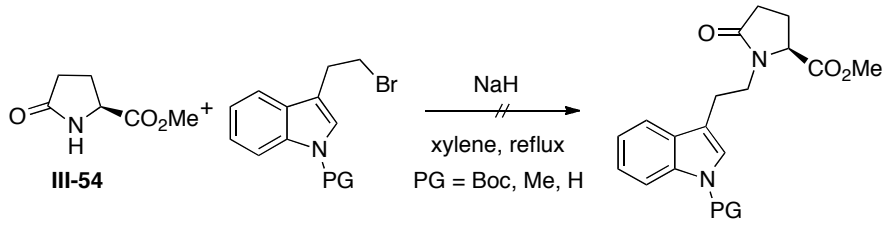
Scheme 40. *Alkylation of 2-piperidone*[235]

233 Chianelli, D.; Kim, Y.-C.; Lvovskiy, D.; Webb, T. R. *Bioorg. Med. Chem.* **2003**, *11*, 5059–5068.

234 Rigo, B.; Gautret, P.; Legrand, A.; Hénichart, J.-P.; Couturier, D. *Synlett* **1997**, 998–1000.

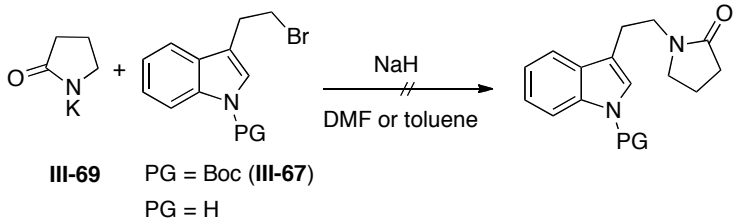
235 Hwang, D.-Y.; Chen, S.-G.; Gu, J.-T. *J. Chinese Chem. Soc.* **1979**, *26*, 49–52.

The reaction of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) with different 3-(2-bromoethyl)indole derivatives (PG = H, Boc, Me[236]) only provided a complex mixture of products (Scheme 41).



Scheme 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**.[237] Unfortunately, no alkylated product was detected in the reaction of **III-69** with *N*-Boc indole **III-67** in DMF (Scheme 42).[238] 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 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 43).

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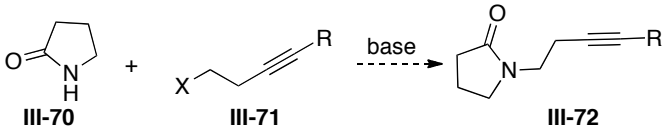
236 Abel, E.; Maguire, G. E. M.; Murillo, O.; Suzuki, I.; De Wall, S. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 9043–9052.

237 Staffel, W.; Kaeshammer, S.; Kessinger, R.; Vogelsang, R.; Paul, A.; Tuttelberg, M. PCT Int. Appl. WO 2009071479 2009, CAN 151:56717.

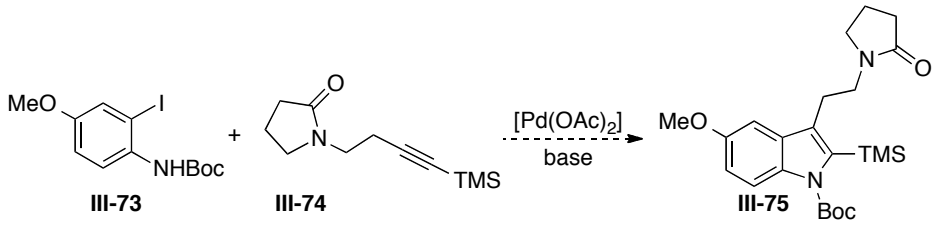
238 Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150.



III-70 III-71 III-72

Scheme 43. *Strategy for the synthesis of lactam* ***III-72***

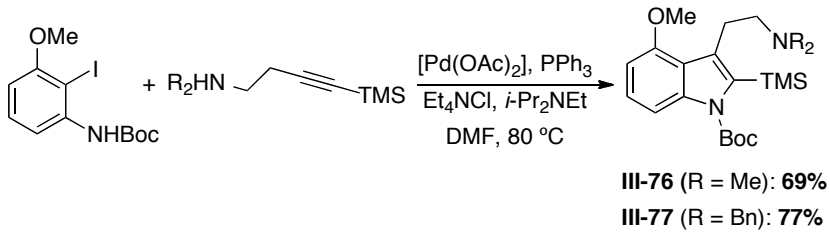
Finally, lactam **III-74** could react with *o*-iodoaniline **III-73**,[239] leading to indole **III-75** by the Larock indole synthesis (Scheme 44). [240]



III-73 III-74 III-75

Scheme 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 45).[241]



III-76 (R = Me): **69%**
III-77 (R = Bn): **77%**

Scheme 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-

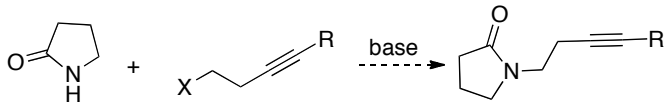
239 Sutou, N.; Kato, K.; Akita, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1833–1838.

240 (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.

241 Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921–923.

yl)trimethylsilane and KH in THF,[242] no reaction was observed (Table 6, entries 1 and 2). The same result was also obtained using (4-iodobut-1-yn-1-yl)trimethylsilane and NaH in THF (Table 6, entry 3).[243] Unfortunately, no nucleophilic subsitution was detected with 4-(iodobut-1-yn-1-yl)trimethylsilane or 4-iodobut-1-yne and NaHMDS in DMF (Table 6, entries 4 and 5).[244] In the case of 4-iodobut-1-yne[245] and KOH in THF,[242,243,246] or NaOH in biphasic conditions,[247] only starting material was detected (Table 6, entries 6 and 7).

Table 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

242 (a) Rudler, H.; Parlier, A., Bezennine-Lafollée, S.; Vaissermann, J. *Eur. J. Org. Chem.* **1999**, *1999*, 2825–2833. (b) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *Org. Lett.* **2005**, *7*, 4431–4434.

243 Simandan, T.; Smith, M. B. *Synth. Commun.* **1996**, *26*, 1827–1838.

244 Honda, T.; Matsukawa, T.; Takahashi, K. *Org. Biomol. Chem.* **2011**, *9*, 673–675.

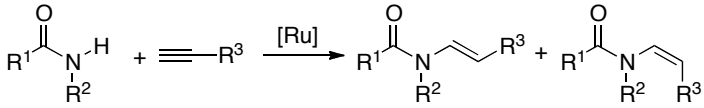
245 Mukherjee, A.; Liu, R.-S. *Org. Lett.* **2011**, *13*, 660–663.

246 Ikemoto, T.; Ito, T.; Nishiguchi, A.; Miura, S.; Tomimatsu, K. *Org. Process Res. Dev.* **2005**, *9*, 168–173.

247 Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 4739–4742.

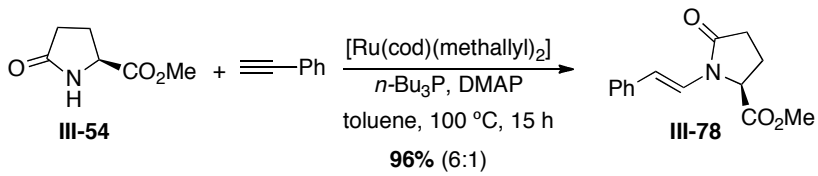
3.3.2.4.2 Synthesis of enamides by hydroamidation

The transition metal catalyzed addition of amides to alkynes provides a useful approach to the preparation of enamides.[248] In this context, Gooβen and coworkers have developed efficient ruthenium catalysts, which allow the anti-Markovnikov addition of amide to terminal alkynes (Scheme 46).[249]



Scheme 46. *Ruthenium-catalyzed anti-Markovnikov addition of amides to alkynes*[249]

The Gooβen group has identified bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II) [Ru(methallyl)$_2$(cod)] with *n*-Bu$_3$P and DMAP as an efficient catalyst for the selective formation of (*E*)-enamides.[250] 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 47).



Scheme 47. *Anti-Markovnikov addition of lactam **III-54** to phenylacetylene*[250]

Recently, Gooβen 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

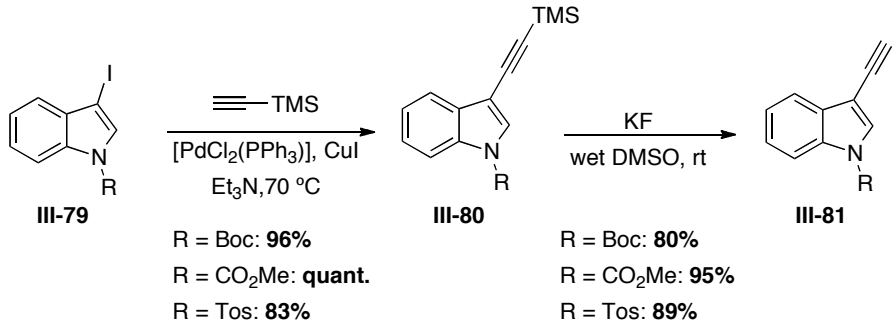
248 Pioneer examples of ruthenium complexes, which mediate the addion of certain amides to terminal alkynes: (a) Heider, M.; Henkelmann, J.; Ruehl, T. EP 646571 1995, Chem. Abstr. **1995**, *123*, 229254. (b) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413–414.

249 Arndt, M.; Salih, K. S. M.; Fromm, A.; Gooßen, L. J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428–7449.

250 Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4042–4045.

[Ru(cod)(methallyl)$_2$].[251] 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.[252] 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 48. Trimethylsilyl derivatives **III-80**[253] were obtained by Sonogashira cross-coupling of *N*-protected iodoindoles **III-79**,[254] and ethynyltrimethylsilane with high yield in all the cases. Then, TMS-removal afforded the desired *N*–protected alkynylindole derivatives **III-81**.



Scheme 48. *Synthesis of alkynylindoles derivatives*

Unfortunately, when lactam **III-54** was allowed to react with *N*-Boc alkynylindole **III-81** using the Gooβen conditions with [Ru(cod)(methallyl)$_2$] (Table 7, entry 1) or $RuCl_3$ (Table 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 7, entry 3).

---

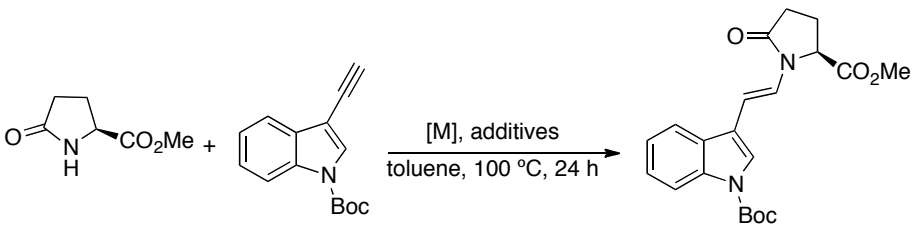
251 Gooßen, L. J.; Arndt, M.; Blanchot, M.; Rudolphi, F.; Menges, F.; Niedner-Schatteburg, G. *Adv. Synth. Catal.* **2008**, *350*, 2701–2707.

252 Yudha S., S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611.

253 (a) R = Boc, He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485. (b) R = CO_2Me, Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132–1134. (c) R = Tos, Li, Y.; Zou, H.; Gong, J.; Xiang, J.; Luo, T.; Quan, J.; Wang, G.; Yang, Z. *Org. Lett.* **2007**, *9*, 4057–4060.

254 R = Boc: Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473–8480.

Table 7. *Study of the addition of lactam* ***III-54*** *to alkyne* ***III-81Boc***



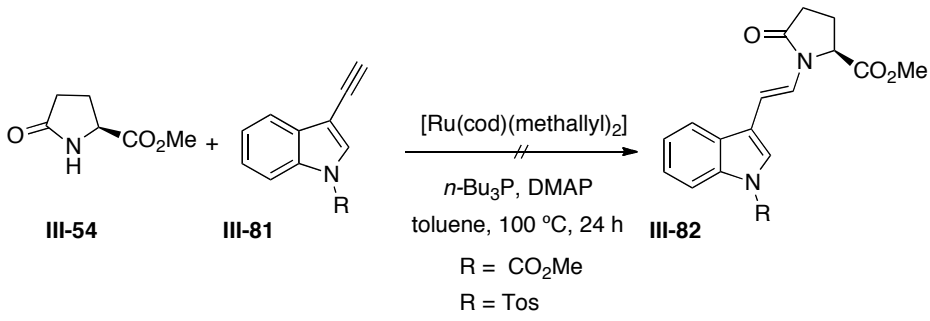
III-54 **III-81Boc** **III-82Boc**

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.[255] As before, no alkylated product was detected.

Finally, we tested the Gooβen conditions with the other *N*-protected alkynylindole derivatives **III-81** (R = CO_2Me or Tos) (Scheme 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**.



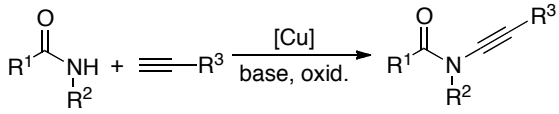
III-54 **III-81** **III-82**

Scheme 49. *Study of the addition of lactam* ***III-54*** *to alkynes* ***III-81***

255 Möhrle, H.; Kilian, R. *Tetrahedron* **1969**, *25*, 5745–5753.

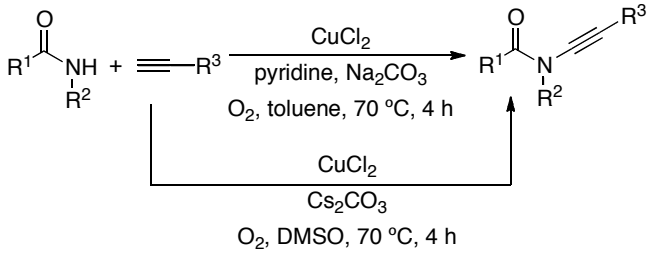
3.3.2.4.3 Synthesis of ynamides: amidative cross-coupling of terminal alkynes

Ynamides can be easily synthesized by metal-catalyzed amidative cross-coupling of alkynes (Scheme 50).[256] Other alternatives employ lithiated amides with alkynyliodonium salts,[256] or metal-catalyzed coupling of amides with alkynyl bromides,[256] potassium alkynyltrifluoroborates,[257] 1,1-dihalo-1-alkenes,[258] or propylic acids.[259]



Scheme 50. *Copper-catalyzed amidative cross-coupling of alkynes*

In 2008, the Stahl group published the first copper-catalyzed aerobic oxidative amidation of terminal alkynes.[260] An extensive screening of various copper sources, Brønsted bases, and solvents led to the optimal conditions shown in Scheme 51.



Scheme 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

256 See general review: DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064–5106.

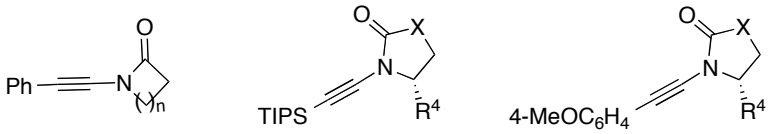
257 Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272–3275.

258 Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381–4385.

259 Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000–2003.

260 Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

yields. Figure 10 highlights the most relevant examples for the copper-catalyzed aerobic oxidative amidation of terminal alkynes using 2-pyrrolidone derivatives.



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

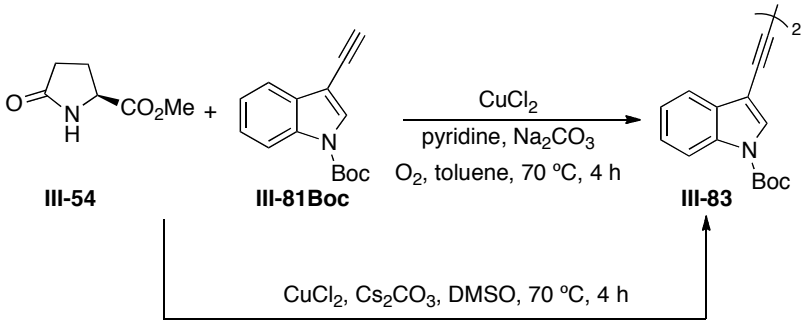
X = O, R^4 = H: **83%**
X = O, R^4 = Bn: **78%**
X = CH_2, R^4 = H: **95%**
X = NMe, R^4 = H: **70%**

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

Figure 10. *Selected examples*

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.

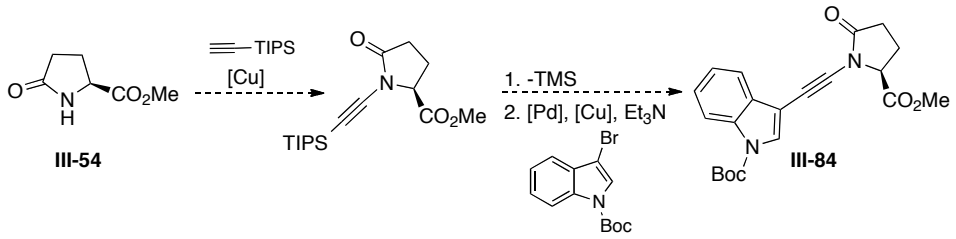
When we applied the Stahl conditions to the copper-catalyzed coupling of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**III-54**) and *N*-Boc ethynylindole derivate **III-81Boc**, only the Glaser-Hay product **III-83** was isolated together with starting material (Scheme 52). This result did not surprise us, since Stahl had reported the same problem during the coupling of 2-pyrrolidone and phenylacetylene (Figure 10).



III-54 **III-81Boc** **III-83**

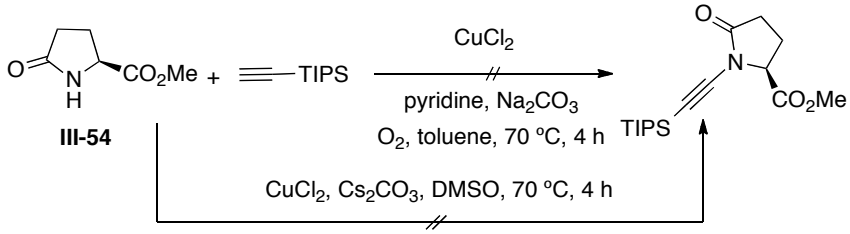
Scheme 52. *Copper-catalyzed coupling of lactam* ***III-54*** *and alkynylindole* ***III-81Boc***

Since Stahl has reported a good yield (95%) for the coupling of 2-pyrrolidine and ethynyltriisopropylsilane (Figure 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 53).



Scheme 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 54).

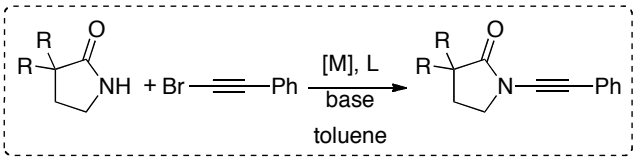


Scheme 54. *Copper-catalyzed coupling of lactam* ***III-54*** *and ethynyltriisopropylsilane*

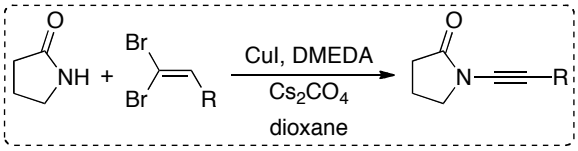
Another plausible alternative is the metal-catalyzed coupling of amides with alkynyl bromides or 1,1-dibromo-1-alkene.[256] Scheme 55 shows the more significant reported results with 2-pyrrolidine derivatives.[261,262]

261 For alkynyl bromides: (a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154. (b) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem*. **2009**, *74*, 4630–4633.

262 For 1,1-dibromo-1-alkene: Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381–4385.



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



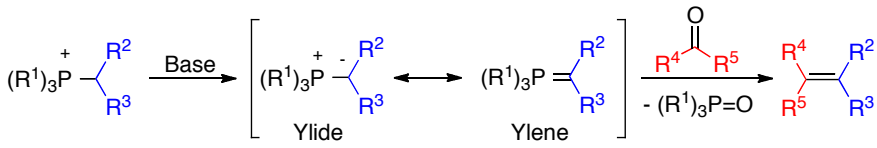
R	*Yield (%)*
Ph	80
p-$MeOC_6H_4$	66
t-Bu	34
Cy	43

Scheme 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.

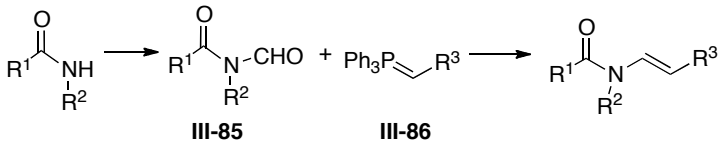
3.3.2.4.4 Synthesis of enamides by Wittig reaction

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 56). The geometry of the resulting alkene depends on the reactivity of the ylide.



Scheme 56. *Wittig reaction*

The Wittig reaction can be modified to allow the synthesis of enamides. In Scheme 57, the Wittig olefination of *N*-formyl imide precursor **III-85**[263] (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 57. *Imide olefination*

In 2007, the group of Marquez reported the first synthesis of enamides through the use of *N*-formyl imides.[263] These *N*-formyl imides behave as carbonyls due to the presence of a second carbonyl unit, which effectively ties up the nitrogen lone pair (Figure 11).

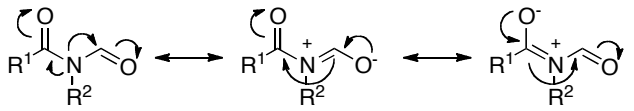
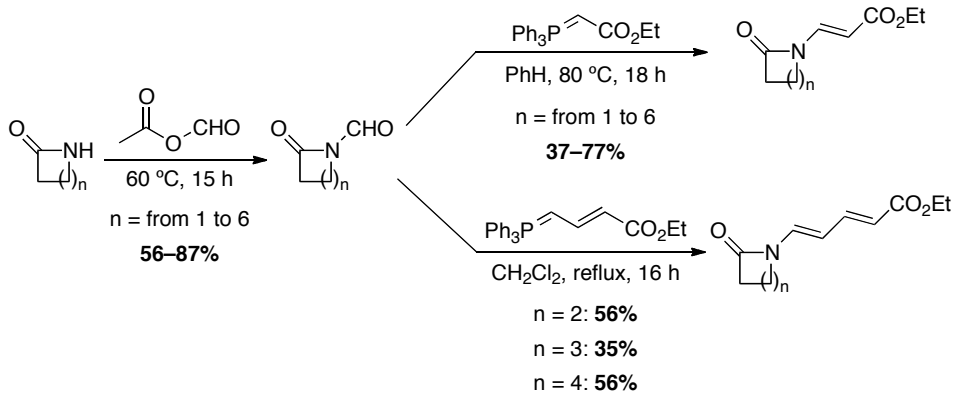


Figure 11. *Delocalization of the N-lone pair of the imide*

In Scheme 56, the most relevant results with cyclic *N*-formyl imides are shown.[263,264] Unfortunately, the scope of the phosphonium ylide is not very broad, since good yields are only reported when R^3 = -CO_2R' or –CH=$CHCO_2$Me (Scheme 58).

263 Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. *Org. Lett.* **2007**, *9*, 1631–1633.

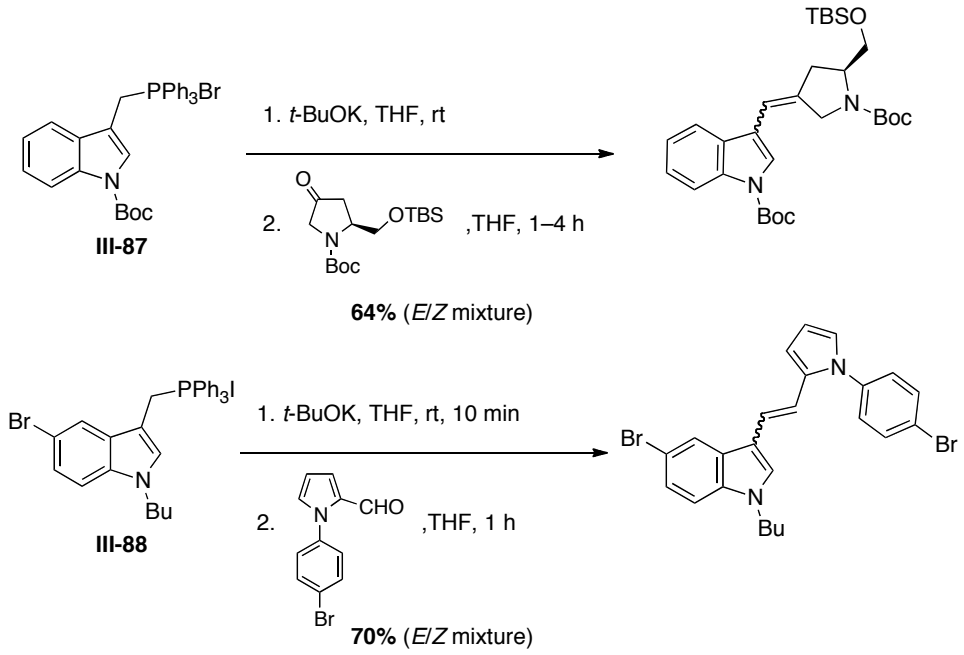
264 Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R. *Org. Biomol. Chem.* **2009**, *7*, 2170–2175.



Scheme 58. *Most relevant results for the cyclic N-formyl imide olefination*

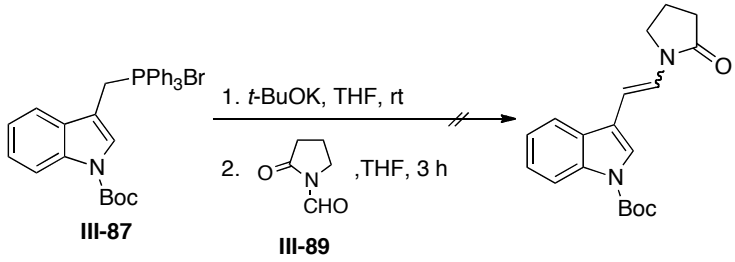
Regarding the phosphonium ylide derivative **III-86**, there are three publications of the Wittig olefination of carbonyl compounds with indolylmethyl phosphonium ylide derivatives.[265] In Scheme 59, two examples are highlighted: the reaction of *tert*-butyl 3-((bromotriphenylphosphoranyl)methyl)-1*H*-indole-1-carboxylate (**III-87**) with a ketone,[265a] and the reaction of 5-bromo-1-butyl-3-((iodotriphenylphosphoranyl)methyl)-1*H*-indole (**III-88**) with an aldehyde.[265b]

265 (a) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923–3931. (b) Li, Q.; Lu, L.; Zhong, C.; Shi, J.; Huang, Q.; Jin, X.; Peng, T.; Qin, J.; Li, Z. *J. Phys. Chem. B.* **2009**, *113*, 14588–14595. (c) Li, Z.; Li, Q.; Shi, J.; Lu, L.; Peng, T.; Qin, J. *Patent No.* CN 101602759, **2009**.



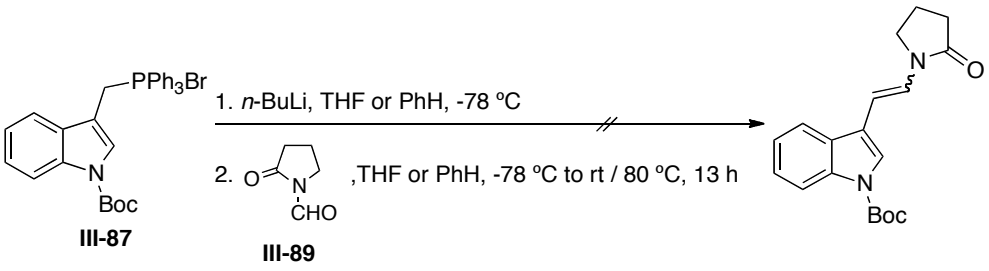
Scheme 59. *Most relevant results of Wittig reaction using indolylmethyl phosphonium ylide derivatives*[264]

The Wittig olefination of cyclic *N*-formyl imides and simple phosphonium ylide derivatives is possible (Scheme 56). Furthermore, the reaction of carbonyl compounds with indolylmethyl phosphonium ylide derivatives is also feasible (Scheme 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 60). The reaction was repeated under reflux, but the formation of the olefin was not observed.



Scheme 60*. Study of the Wittig reaction with N-formyl imide* ***III-89*** *and ylide* ***III-87***

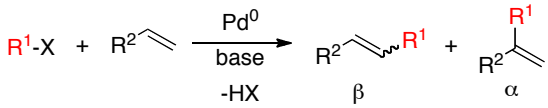
No improvement of the Wittig olefination was observed in changing the base to *n*-BuLi, whether in THF or in benzene, at room temperature or at 80 ºC (Scheme 61).



Scheme 61. *Witting reaction of N-formyl imide* ***III-89*** *and phosphinium bromide* ***III-87***

3.3.2.4.5 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 62).[266] 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.



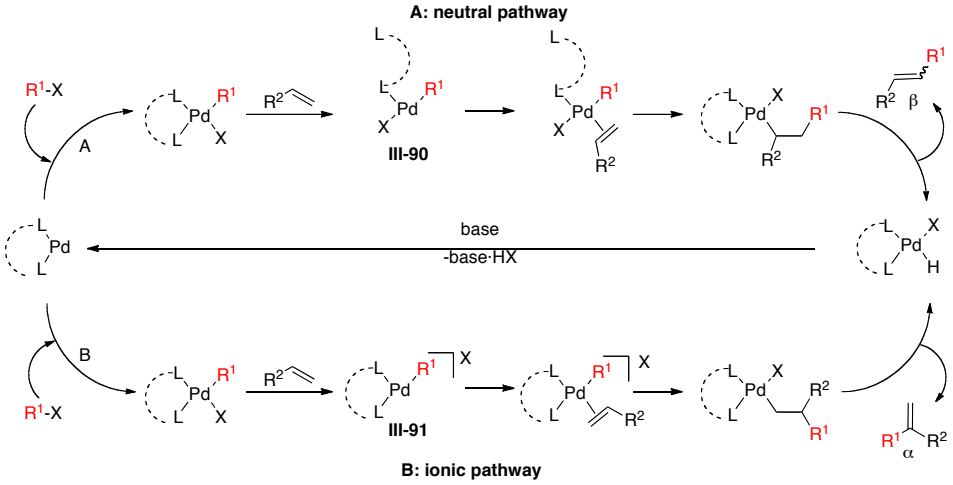
Scheme 62. *Mizoroki-Heck reaction*

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 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

266 Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

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 63. *Two competing pathways in the Heck reaction*

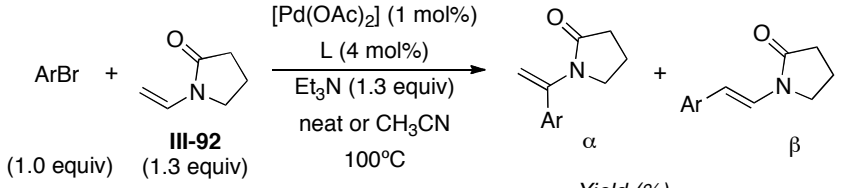
The Heck reaction can give rise to two regioisomeric products. It is now generally accepted that the regioselectivity issue exists due to the two competing reaction pathways. The neutral pathway (Scheme 63, pathway A) yields the β-alkene, whereas the ionic pathway (Scheme 63, pathway B) produces the α-alkene.[267] 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.[268] The regioselectivity of methyl acrylate insertion into Pd-methyl and -phenyl bonds is inverted to yield the opposite "regioirregular" olefin in stochiometric reactions.

267 Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

268 Wucher, P.; Caporaso, L.; Roesle, P.; Ragone, F.; Cavallo, L.; Mecking, S.; Göttker-Schnetmann, I. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 8955–8959.

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 64).[269] 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*-Tol)$_3$	8 h	40	60
Ph	P(2,5-*i*-Pr$_2$C$_6$H$_3$)$_3$	9.5 h	44	55
p-Me$_2$NC$_6$H$_4$	P(*o*-Tol)$_3$	2 d	57[a]	0

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

Scheme 64. *Vinylic substitution of N-vinylpyrrolidone* ***III-92***

At present, due to extensive research by the groups of Cabri, Hallberg, and Larhed,[270] 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.

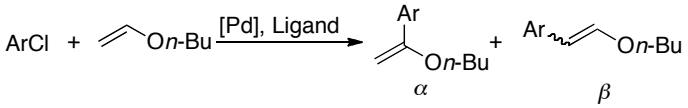
The use of silver and thallium salts, as halide scavengers, promotes the ionic pathway (Scheme 61, pathway B). Similarly, the lability of the Pd–OTf bond facilitates the formation of the cationic [Pd(alkene)]$^{+2}$ species **III-91**. More recently, the Xiao group has reported the α-arylation of electron-rich alkenes with aryl halides using alcohols (such as ethylene

269 Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949–2952.

270 General review about α-arylation of electron-rich olefins: Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614–626.

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

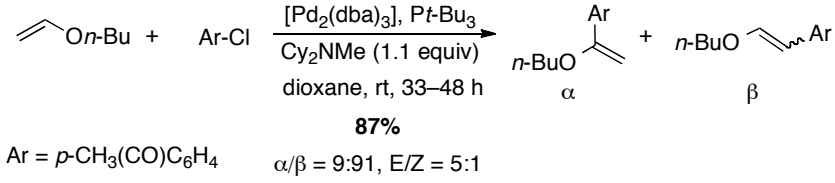
Favoring the β-regioselectivity of the Heck reaction with electron-rich alkenes is not so simple. In 1988, Andersson and Hallberg observed that the type of halide coordinating to the metal center had a profound influence on the regioselectivity, chloride favoring the formation of the β-alkene when using vinyl ethers.[271] Scheme 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 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 66). The reaction proceeded at room temperature, furnishing a high α/β selectivity of 9:91.[272]



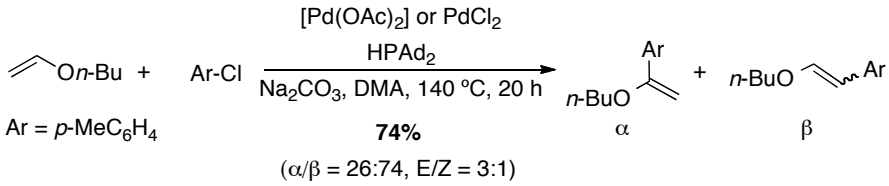
Scheme 66. *Heck coupling of aryl halides at room temperature*

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.[273,274] These conditions are also very efficient when using aryl bromides.

271 (a) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 235–239. (b) Andersson, C. M.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 2112–2114.

272 Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

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 67).[275] The reaction afforded α/β selectivity of 26:74.



Scheme 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.[276] 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[277] and [*t*-Bu_3PH]BF_4,[278] favoring the formation of the *β*-arylated alkenes in moderate yields.[279] A regioselective tendency is observed in the selected results shown in Scheme 68, where aryl chlorides with electron-withdrawing

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273 General review about palladium-catalyzed coupling reactions of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.

274 First example of the Heck reaction using aryl chlorides and P(*t*-Bu)$_3$ as ligand: Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

275 Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495–498.

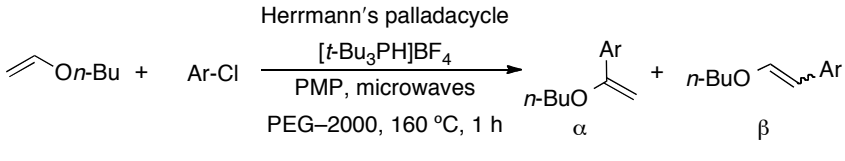
276 Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399–4401.

277 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, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23–41.

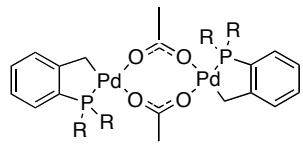
278 [(*t*-Bu_3)PH]BF_4 is used as an air-stable preligand of P(*t*-Bu)$_3$.

279 Datta, G. K.; von Schenck, H.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 3896–3903.

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.

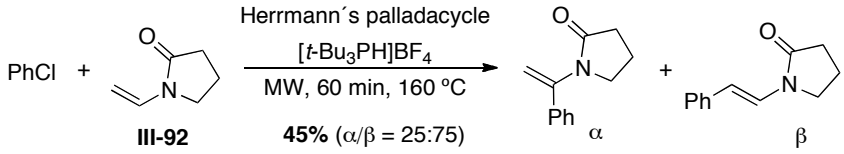


Ar	*Yield (%)*	*ratio* α/β
p-$NO_2C_6H_4$	60	2:98
p-$CF_3C_6H_4$	65	2:98
p-$CHOC_6H_4$	62	2:98
p-AcC_6H_4	70	2:98
o-Naphtyl	60	8:92
Ph	59	7:93
p-$CF_3C_6H_4$	52	17:83
o-$CF_3C_6H_4$	54	18:82
p-$MeOC_6H_4$	46	22:78



Scheme 68. *Heck coupling of n-butyl vinyl ether with aryl chlorides*

In Scheme 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.

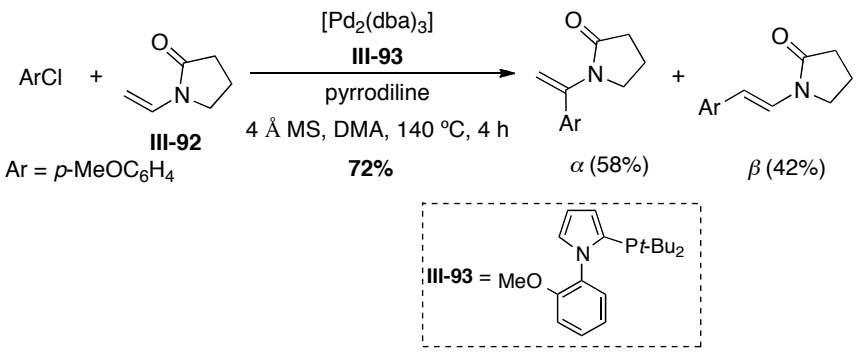


Scheme 69. *Heck coupling of phenyl chloride and N-vinylpyrrolidone* ***III-92***

Recently, the Xiao group has reported the Heck arylation of vinyl pyrrolidine **III-92** with 1-chloro-4-methoxybenzene (Scheme 70).[280] Despite the use of a bulky electron-rich monophosphine **III-93**, the α-arylated alkene is the major product. Alternatevely, when a

280 Colbon, P.; Ruan, J.; Purdie, M.; Xiao, J. *Org. Lett.* **2010**, *12*, 3670–3673.

bidentate ligand is used under ionizing conditions, the α-product can be exclusively obtained from **III-92**.[281]



Scheme 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.[282] An α/β selectivity of 20:80 was detected in both cases. Unfortunately a low yield (25%) was obtained with the unactivated chlorobenzene.

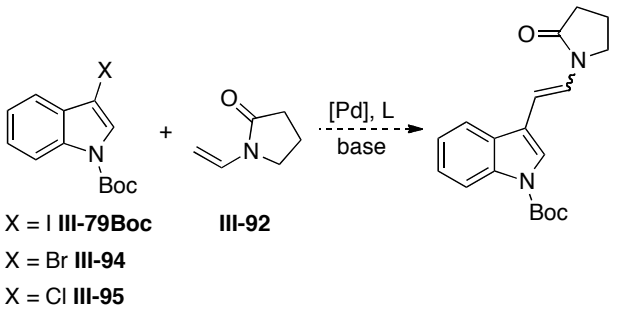
With all of these precedents, it was clear that controlling the β-regioselectivity heteroarylation of *N*-vinyl pyrrolidine (**III-92**)[283] would not be easy. Despite these previous results, we decided to test the Heck reaction with different *N*-Boc 3-haloindoles. We started

281 (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645. (c) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2004**, *127*, 751–760. (g) Mo, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4152–4157. (h) Hyder, Z.; Ruan, J.; Xiao, J. *Chem. Eur. J.* **2008**, *14*, 5555–5566.

282 Calò, V.; Nacci, A.; Monopoli, A.; Cotugno, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 6101–6103.

283 The analogous *N*-vinyl pyrrolidine of lactam **III-53** could be synthesized by palladium(II)-catalyzed vinyl tranfer from vinyl ethers: Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.

the study with *N*-Boc 3-iodo indole **III-79Boc**[284] and *N*-Boc 3-bromo indole **III-94**[285,286] (Scheme 71).



Scheme 71.*General overview of the indol-functionalization of N-vinyl pyrrolidone*

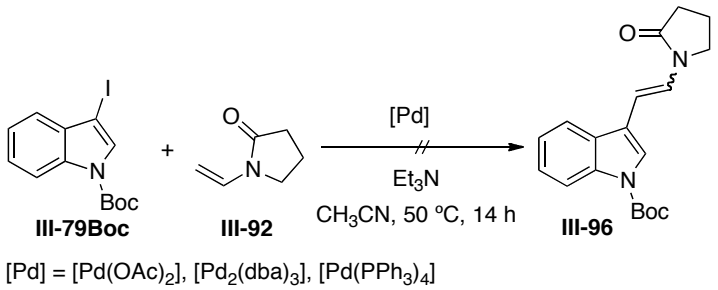
Starting with *N*-Boc iodo indole **III-79Boc**, only decomposition was observed using $[Pd(OAc)_2]$, $[Pd_2(dba)_3]$ or $[Pd(PPh_3)_4]$ as catalysts, without the addition of any ligand (Scheme 72). It should be noted that it has been reported that the presence of a ligand is not necessary when using aryl iodides.[287]

284 Complete *β*-regioselective Heck reaction has been reported using *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate (**III-62Boc**) with electron-poor alkenes: (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037–1040. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *71*, 62–69. (c) Putey, A.; Fournet, G.; Joseph, B. *Synlett* **2006**, *2006*, 2755–2758. (d) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939–3942. (e) Della Sala, G.; Izzo, I.; Spinella, A. *Synlett* **2006**, 1319–1322.

285 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: (a) Busacca, C. A.; Dong, Y. *Tetrahedron Lett.* **1996**, *37*, 3947–3950. (b) Omura, K.; Choshi, T.; Watanabe, S.; Satoh, Y.; Nobuhiro, J.; Hibino, S. *Chem. Pharm. Bull.* **2008**, *56*, 237–238. (c) Hussain, M.; Tang, D. T.; Langer, P. *Synlett* **2009**, 1822–1826.

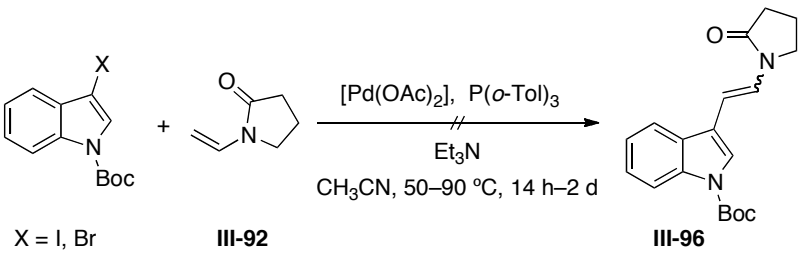
286 James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4094–4103.

287 Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.



Scheme 72. *Heck reaction of vinyl pyrrolidone* ***III-92*** *and iodo indole* ***III-79Boc***

When we tested the Heck conditions[269] with iodo indole **III-79Boc**, only complex mixture of product was observed and no traces of the desired enamide **III-96** were present (Scheme 73). On the other hand, in the case of bromo indole **III-93**, almost no reaction was observed. Furthermore, under the same conditions, no improvement was achieved by changing the solvent to DMF.



Scheme 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** (Figure 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.

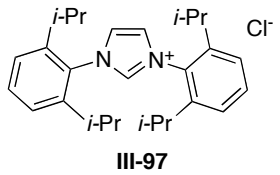
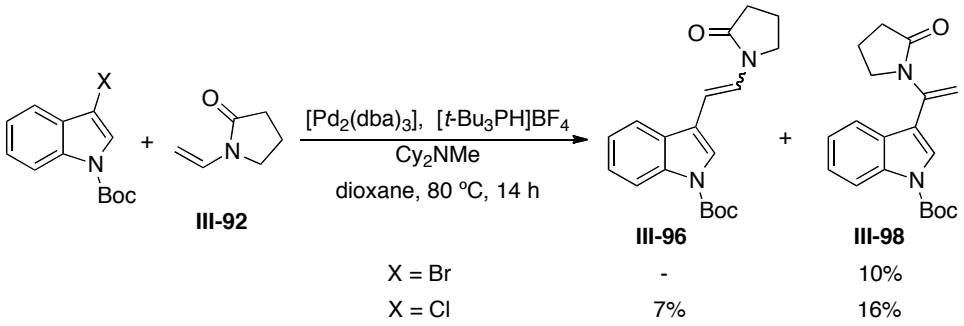


Figure 12. *N-heterocyclic carbene IPr*

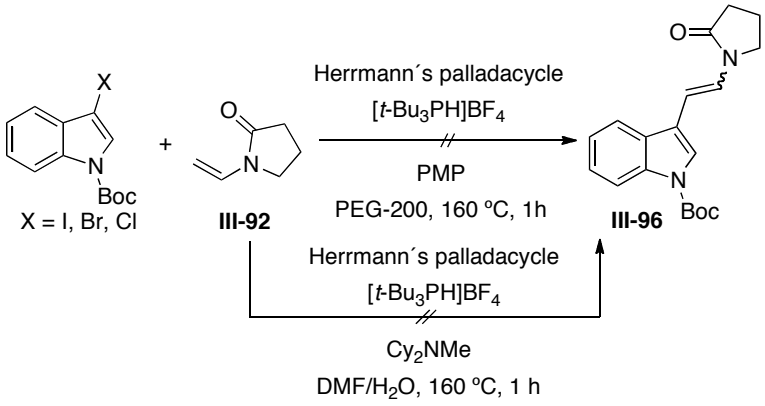
Using the Fu conditions, no reaction was observed at room temperature, neither with bromo indole **III-94** nor chloro indole **III-95**.[272] However, in the case of bromo indole **III-94**, the reaction was done at 80 ºC and the α-enamide **III-98** was formed in a 10% yield.

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 74).



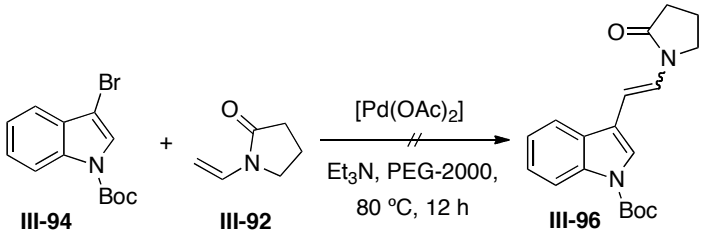
Scheme 74. *Fu conditions for the indol-functionalization of vinyl pyrrolidine* ***III-92***

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 75).[279] 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 75. *Larhed conditions for the indol-functionalization of enamide* ***III-92***

Finally, using the Chandrasekhar conditions[276] for the Heck reaction of *N*-vinyl pyrrolidone **III-92** and bromo indole **III-94** (Scheme 76), only a complex mixture was isolated.



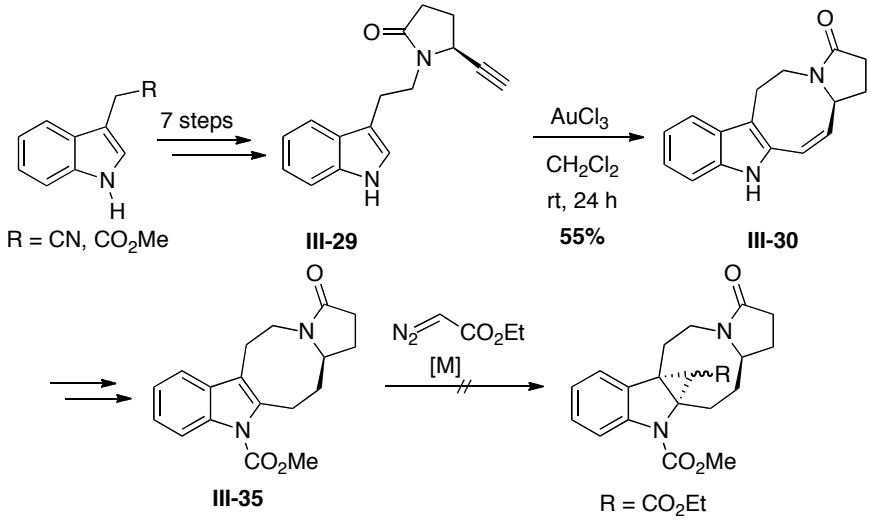
Scheme 76. *Chandrasekhar conditions for the indol-functionalization of enamide* ***III-92***

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.

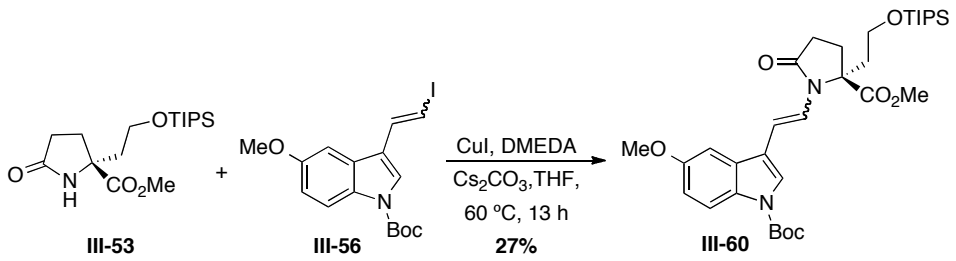
3.4 Conclusions

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 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**.[63b] 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.



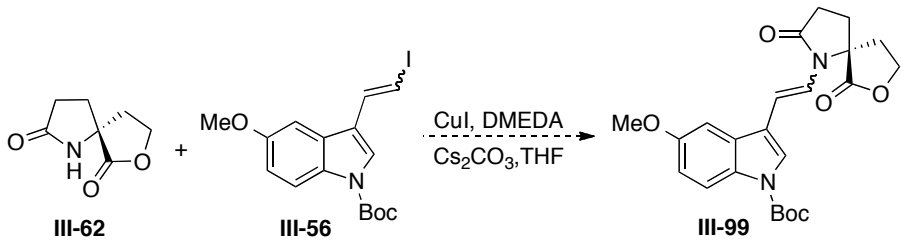
Scheme 77. *Intermolecular approach toward the total synthesis of lundurines*

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.[217c] 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 78). We believe that this is mainly due to the high steric hindrance around the quaternary center of the lactam **III-53**.



Scheme 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 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 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**) (Figure 13) will be also accessible using the gold(I)-catalyzed intramolecular reaction of indoles with alkynes.

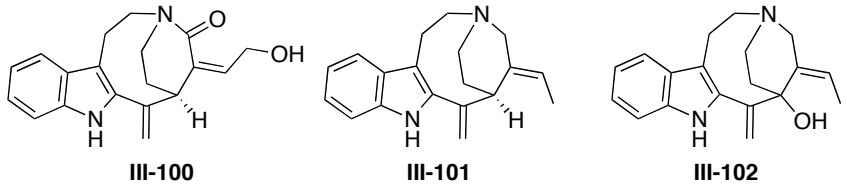


Figure 13. *Structure of pericidine, pericine and subincanidine D*

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 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.

3.5.2 Preparation of Substrates

Catalyst phosphine gold(I) **6**, IMes gold(I) **15**,[25] phosphite gold(I) **20**,[24e] open carbene gold(I) **21**,[28] gold(III) **22**,[31] platinacycle **24**,[19c] NHC copper(I) **25-29**,[193] and copper(I) **30**[194] were synthesized according to reported procedure

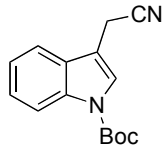
Compound *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (**III-23a**),[180] *tert*-butyl 3-formyl-5-methoxy-1*H*-indole-1-carboxylate,[288] (3*R*,7a*S*)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**III-43**),[198] (3*R*,7a*R*)-7a-allyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (**III-45**),[201] (3*R*,7a*S*)-3-(*tert*-butyl)dihydropyrrolo[1,2-*c*]oxazole-1,5(3*H*,6*H*)-dione (**III-46a**),[203b] (3*R*,7a*S*)-3-(trichloromethyl)dihydropyrrolo[1,2-*c*]oxazole-1,5(3*H*,6*H*)-dione (**III-46b**),[202a] (*R*)-methyl 2-allylpyrrolidine-2-carboxylate (**III-47**),[201] (*S*)-methyl 5-oxopyrrolidine-2-carboxylate

288 Oliveira, D. d. J.; Coelho, F. *Synth. Commun.* **2000**, *30*, 2143–2159.

(**III-54**),[225] 3-(2-bromoethyl)-1-methyl-1*H*-indole,[236] potassium salt of the pyrrolidin-2-one **III-69**,[237] (4-iodobut-1-yn-1-yl)trimethylsilane,[289] 4-iodobut-1-yne,[245] tert-butyl 3-iodo-1H-indole-1-carboxylate **III-79Boc**,[254] 1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole (**III-80Tos**),[253c] *tert*-butyl 3-((bromotriphenylphosphoranyl)methyl)-1*H*-indole-1-carboxylate (**III-87**),[265a] N-formyl imide **III-89**,[263] tert-butyl 3-bromo-1*H*-indole-1-carboxylate (**III-94**),[286] were synthesized according to reported procedures.

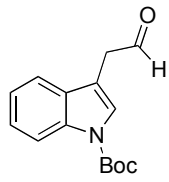
The 5 M $Zn(BH_4)_2$ solution in Et_2O[209] was synthesized according to reported procedure.

***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 ºC. ^{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)**



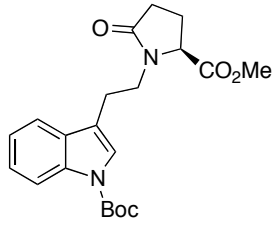
289 Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 6317–6319.

Procedure A:[290] 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 3M 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

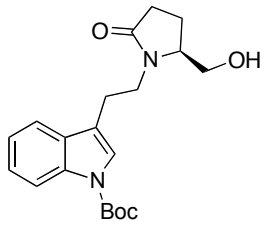
(S)-*tert*-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-25)



290 Procedure reported in the Catalina Ferrer Llabrés Doctoral Thesis (Prof. Antonio Echavarren, January 2008).

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)



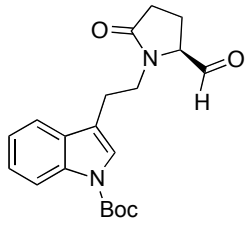
Procedure A: Lithium borohydride (198 mg, 8.19 mmol, 4 equiv) was added to a solution of ester **III-25** (1710 mg, 2.05 mmol, 1 equiv) in a mixture of THF (27 mL) and Et_2O (21 mL) at 0 °C. The reaction was allowed to warm up to room temperature and was left to stir for 16 h. Then, an appropriate amount 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:[290] 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, $CHCl_3$).

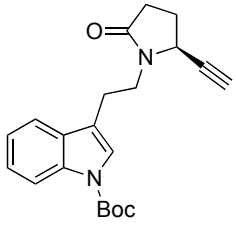
(*S*)-*tert*-Butyl 3-(2-(2-Formyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (III-27)



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

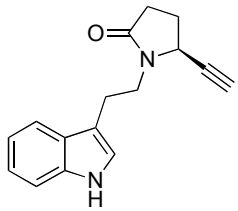
MHz, $CDCl_3$, DEPT) δ 198.6 (CH), 175.3 (C), 149.6 (C), 136.1 (C), 135.5 (C), 124.6 (CH), 123.2 (CH), 122.6 (CH), 118.8 (CH), 117.2 (C), 115.3 (CH), 83.7 (C), 66.1 (CH), 42.6 (CH_2), 29.3 (CH_2), 28.2 (CH_3, 3C), 23.3 (CH_2), 19.4 (CH_2).

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



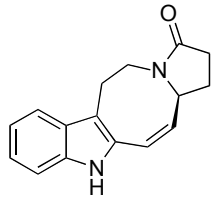
Potassium carbonate (614 mg, 4.44 mmol, 2.1 equiv) was added to a stirring solution of aldehyde **III-27** (765 mg, 2.15 mmol, 1 equiv) and dimethyldiazo-2-oxopropylphosphonate (495 mg, 2.58 mmol, 1.2 equiv) in MeOH (12 mL). The resulting solution was stirred for 12 h and was then quenched with water (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)



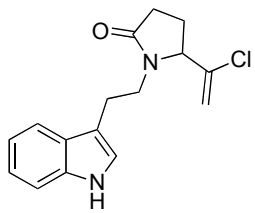
A solution of **III-28** (626 mg, 1.78 mmol, 1 equiv) in TFA/CH_2Cl_2 (18/5 mL) was stirred at room temperature for 10 min. Then, the solvent was evaporated and the residue was diluted in EtOAc and washed with $NaHCO_3$. The aqueous phase was extracted with EtOAc several times, and then the solvent was 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



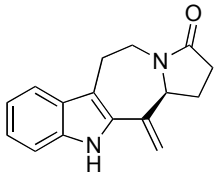
$AuCl_3$ (3 mg, 0.008 mmol, 5 mol%) was added to a solution of **III-29** (45 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 16 h. The residue was purified by chromatography (1:2 hexane-EtOAc) to give 25 mg of tetracyclic compound **III-30** (55%). ^{1}H NMR (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)



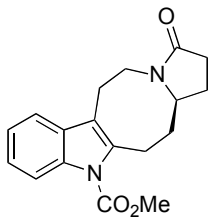
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.22 (td, J = 7.9, 0.8 Hz, 1H), 7.14 (td, J = 7.7, 0.7 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 5.33 (d, J = 1.5Hz, 1H), 5.18 (d, J = 1.5 Hz, 1H), 4.07-3.96 (m, 2H), 3.18-2.95 (m, 3H), 2.55 (ddd, J = 17.3, 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[231]



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, λ = 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).

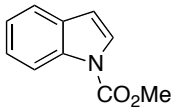
NaHMDS (1 M solution in THF, 170 μL, 0.17 mmol, 1.2 equiv) was added to a solution of compound **III-33** (35 mg, 0.14 mmol, 1 equiv) in dry THF (2 mL) at -78 °C. After 30 min, methyl chloroformate (14 μL, 0.18 mmol, 1.3 equiv) was added dropwise. The reaction was quenched by addition of MeOH (0.3 mL) 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 minutes, and the reaction mixture was allowed to warm to room temperature. After 1h, 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.).

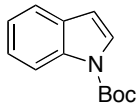
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br dd, *J* = 7.2, 2.2 Hz, 1H), 7.45 (br dd, *J* = 6.8, 1.8 Hz, 1H), 7.31-7.23 (overlapping of signal, ~2H), 4.52-4.47 (m, 1H), 4.67 (s, 1H), 3.41 (dt, *J* = 14.5, 4.1 Hz, 1H), 3.34-3.28 (m, 1H), 3.07-2.98 (m, 2H), 2.88-2.78 (m, 2H), 2.59 (ddd, *J* = 16.5, 11.3, 8.1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

Methyl 1*H*-indole-1-carboxylate[291]



A solution of NaHMDS (1M 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 ºC. 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**[291]



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,

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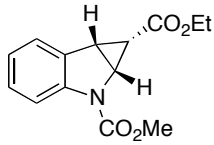
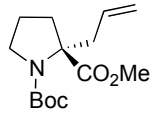
0.45 mmol, 5 mol%) in CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred overnight. Then, it was diluted with CH_2Cl_2 and washed with a sat. NH_4Cl solution. The aqueous phase was extracted 2 times with CH_2Cl_2, and finally the organic phases were washed with brine, dried over $MgSO_4$ 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)[173c]



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.

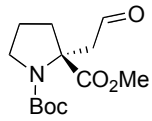
(*R*)-1-*tert*-Butyl 2-methyl 2-allylpyrrolidine-1,2-dicarboxylate (III-48)



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 1M 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).

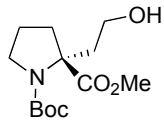
(*R*)-1-*tert*-Butyl 2-methyl 2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (III-49)



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 ºC. 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 9.81-980 (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

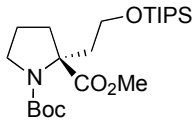
m/z calcd for $C_{13}H_{21}NO_5Na$ $[M+Na]^+$ 294.1317, found 294.1305. $[\alpha]_D$ = 44.5 (c = 0.08, CH_2Cl_2).

(*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 ºC. 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 ºC 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).

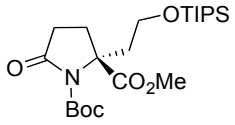
(*R*)-1-*tert*-Butyl 2-methyl 2-(2-((Triisopropylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate (III-51)



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).

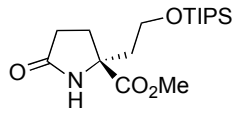
(*R*)-1-*tert*-Butyl 2-methyl 5-oxo-2-(2-((Triisopropylsilyl)oxy)ethyl)pyrrolidine-1,2-dicarboxylate (III-52)



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 ºC. The mixture was stirred at 0 ºC for 1h 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),

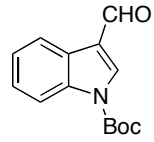
18.1 (CH_3, 3C), 12.0 (CH_3, 3C). HRMS-ESI *m/z* calcd for $C_{22}H_{41}NO_6SiNa$ $[M+Na]^+$ 466.2601, found 466.2602. $[\alpha]_D = 41.1$ (c = 0.12, CH_2Cl_2).

(*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**[288]



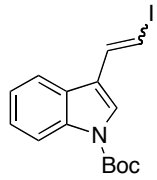
Di-*t*-butyl dicarbonate (15.92 g, 69.30 mmol, 1.2 equiv) was slowly added to a solution of 1*H*-indole-3-carbaldehyde (5.03 g, 36.40 mmol, 1 equiv) [292] and DMAP (0.43 g, 3.46 mmol, 10 mol%) in CH_2Cl_2 (69 mL).[293] The reaction mixture was stirred for 2 h. Then, the reaction mixture was diluted with 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,

292 Coowar, D.; Bouissac, J.; Hanbali, M.; Paschaki, M.; Mohier, E.; Luu, B. *J. Med. Chem.* **2004**, *47*, 6270-6282.

293 Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E.-M. *Synthesis* **1998**, 1501-1505.

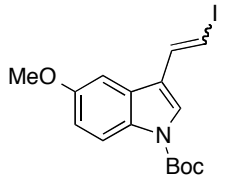
dried over $MgSO_4$ and concentrated. 6.39 g of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate was isolated (75%), which was used in the next step without further purification.

***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 ºC. 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).

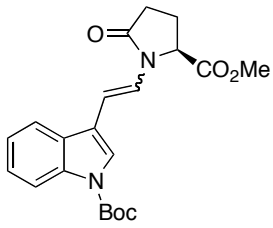
***tert*-Butyl 3-(2-iodovinyl)-5-methoxy-1*H*-indole-1-carboxylate (III-56)**



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 ºC. 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).

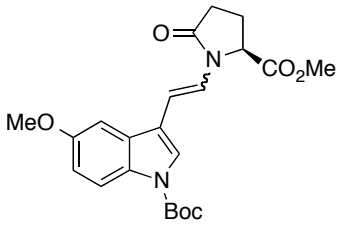
(*S*)-*tert*-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)vinyl)-1*H*-indole-1-carboxylate (III-57)



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 ºC 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

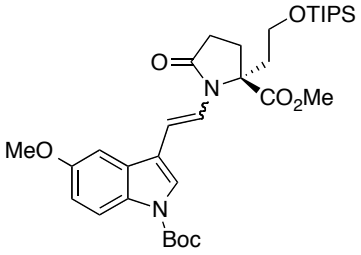
(overlapping signals, 2H), 6.92 (d, *J* = 9.8 Hz, 1H), 5.95 (dd, *J* = 9.8, 1.4 Hz, 1H), 4.37 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.36 (s, 3H), 2.49-2.43 (overlapping signals, 2H), 1.98-1.91 (m, 1H), 2.23 (apparent br t, 1H), 1.69 (s, 9H).

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



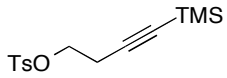
N,*N*´-Dimethylethane-1,2-diamine (3.1 μL, 0.03 mmol, 20 mol%) and a solution of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (24,9 mg, 0.17 mmol, 1.2 equiv) in THF (0.7 mL) were added to a solution of *tert*-butyl 3-(2-iodovinyl)-5-methoxy-1*H*-indole-1-carboxylate (**III-56**) (*E*/*Z* = 4.3.1.0; 57.9 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 ºC 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 ºC 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[294]



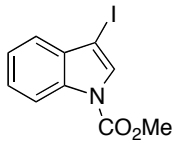
Et_3N (5.16 mL, 37.23 mmol, 1.5 equiv), DMAP (0.09 g, 0.74 mmol, 3 mol%) and tosyl chloride (5.76 g, 29.60 mmol, 1.2 equiv) were added to a solution of 4-(trimethylsilyl)but-3-yn-1-ol (5.51 g, 24.67 mmol, 1 equiv)[295] in CH_2Cl_2 (241 mL) at 0 ºC. The resulting mixture

294 Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5383–5396.

295 Dieter, R. K.; Chen, N. *J. Org. Chem.* **2006**, *71*, 5674–5678.

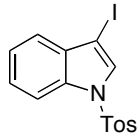
was stirred for 6 h before the reaction was quenched with sat. aq. NH_4Cl. A standard extractive work up followed by flash chromatography (15:1 *c*-hexane/EtOAc) afforded 2.54 g of 4-(trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate as a pale yellow oil (35%).[296]

Methyl 3-iodo-1*H*-indole-1-carboxylate (III-79CO_2Me)[253b]



A solution of NaHMDS (1M solution in THF; 4.90 mL, 4.90 mmol, 1.2 equiv) was added dropwise to a solution of 3-iodo-1*H*-indole[254] (0.99 g, 4.09 mmol, 1 equiv) in THF (15mL) at -78 ºC. 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. [297] 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)[254]



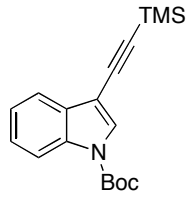
Tetrabutylammonium hydrogensulfate (0.10 g, 0.29 mmol, 7 mol%), potassium hydroxide (50% aq. solution; 5 mL), and a solution of *p*-toluenesulfonyl chloride (0.97 g, 4.99 mmol, 1.2 equiv) in toluene (7 mL) were added to a solution of 3-iodo-1*H*-indole[254] (1.11 g, 4.16 mmol, 1 equiv) in toluene (4 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%),

296 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.* **2009**, *15*, 3983–4010.

297 Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, 2676–2686.

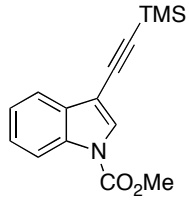
which weas used in the next step without further purification.[298]

***tert*-Butyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate (III-80Boc)**[253a]



$[PdCl_2(PPh_3)_2]$ (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%).[299]

Methyl 3-((trimethylsilyl)ethynyl)-1*H*-indole-1-carboxylate (III-80CO_2Me)[253b]

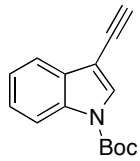


$[PdCl_2(PPh_3)_2]$ (53.76 mg, 0.07 mmol, 2 mol%), trimethylsilylacetylene (0.63 mL, 4.42 mmol, 1.2 equiv) and CuI (35.68 mg, 0.18 mmol, 5 mol%) were added to a solution of compound **III-79CO_2Me** (1.02 g, 3.68 mmol, 1 equiv) in Et_3N (12 mL). The mixture was stirred at room temperature overnight. 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.[299]

298 Wang, K.; Liu, Z. *Synth. Commun.* **2009**, *40*, 144–150.

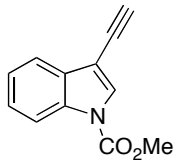
299 Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413–5418.

***tert*-Butyl 3-ethynyl-1*H*-indole-1-carboxylate (III-81Boc)**[300]



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)[301]

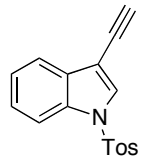


KF (0.27 g, 4.64 mmol, 1.5 equiv) was added to a stirred solution of **III-80CO_2Me** (0.84 g, 3.09 mmol, 1 equiv) in DMSO (12 mL) with a few drops of water at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with water and dried over $MgSO_4$. After column chromatography (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.

300 Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809-7811.

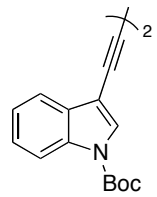
301 Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132–1134.

3-Ethynyl-1-tosyl-1*H*-indole (III-81Tos)[302]



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

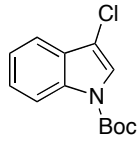


In a Slenck tube, $CuCl_2$ (115 mg, 0.86 mmol, 0.2 equiv), lactam **III-54** (307 mg, 2.15 mmol, 5 equiv), and Cs_2CO_3 (280 mg, 0.86 mmol, 2 equiv) were combined. Then reaction flask was purged with oxygen gas. After 15 minutes, dry DMSO (2.1 mL) was added to the reaction. A balloon filled with oxygen gas was connected to the Slenck tube via a needle, then it was placed in an oil bath and heated to 70 ºC. 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

302 Wada, A.; Babu, G.; Shimomoto, S.; Ito, M. *Synlett* **2011**, 1759–1762.

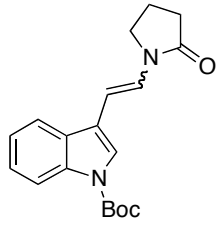
(CH, 2C), 123.7 (CH, 2C), 120.5 (CH, 2C), 115.6 (CH, 2C), 102.4 (C, 2C), 84.8 (C, 2C), 74.3 (C, 2C), 28.3 (CH_3, 2C). LRMS-ESI *m/z* calcd for $C_{30}H_{28}N_2O_4Na$ $[M+Na]^+$ 503.947, found 503.1

***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 ºC 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%). [303] ^{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)**

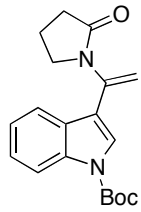


Cy_2MeN (74 µL, 0.34 mmol, 1.1 equiv) and *N*-vinyl pyrrolidine (51.4 µL, 0.46 mmol, 1.1 equiv) were added to a mixture of **III-95** (105.8 mg, 0.42 mmol, 1 equiv) $[Pd_2(dba)_3]$ (5.77 mg, 0.06 mmol, 15 mol%) and P(*t*-Bu)$_3$ (16.3 µL, 0.01 mmol, 3 mol%) in dioxane (1 mL). The reaction mixture, it was heated to 80 ºC 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-**

303 Liégault, B. t.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem*. **2010**, *75*, 1047–1060.

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 ºC 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).