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Catalina Ferrer Llabrés
ISBN:978-84-691-1870-2 / D.L.: T.304-2008

Cyclization of Indoles and Enol Ethers with Alkynes Catalyzed by Platinum and Gold

MEMORIA que para optar al grado de

DOCTORA EN QUÍMICA

Presenta

CATALINA FERRER LLABRÉS

Madrid/Tarragona

Enero 2008

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A mon pare i ma mare

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"Tampoco acierto al decir que me equivoco,
la certidumbre es la lógica del loco.
Prefiero el vértigo del error
al signo de un faro cegador
que me anuncie el peligro bajo su foco.

Y es muy probable
que si el error cierra una puerta
es para que otra quede abierta
de par en par."

Luis Eduardo Aute

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Este trabajo de investigación ha sido realizado en el Departamento de Química Orgánica de la Universidad Autónoma de Madrid (octubre 2002-febrero 2004) y en el Institut Català d'Investigació Química (ICIQ) en Tarragona (marzo 2004-diciembre 2007) bajo la dirección del Profesor Antonio M. Echavarren, a quien quiero agradecer sus enseñanzas, su dedicación y su afán por contagiarnos el espíritu de superación en todo lo que hacemos.

El trabajo recogido en esta memoria se ha llevado a cabo gracias a una Beca Predoctoral de Formación de Personal Investigador de la Generalitat de Cataluña (AGAUR) desde abril de 2004, a la financiación del Ministerio de Educación y Ciencia (Proyecto CTQ2004-02869), del Institut Català d'Investigació Química (ICIQ) y se ha desarrollado en el marco del proyecto Diseño de Catalizadores para una Química Sostenible: Una Aproximación Integrada (INTECAT) (CDS2006-0003) perteneciente al Programa Consolider-Ingenio 2010.

Durante este período he realizado una estancia de tres meses, gracias a una beca BE de la Generalitat de Catalunya, en el laboratorio del Prof. Dalibor Sames (Columbia University of New York, octubre-diciembre 2005) a quien quiero agradecer el haberme brindado la posibilidad de trabajar en un ambiente nuevo y diferente para mí.

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Dra. Cristina García-Yebra y Guillermo Rodríguez; y a los de Tarragona: Almudena Díaz, Cristina Nieto-Oberhuber, Eloísa Jiménez-Núñez, Dra. Salomé López, Dr. Domingo García-Cuadrado, Dra. Christelle Claverie, Patricia Pérez-Galán, Paula de Mendoza, Dr. Sergio Pascual, Dr. Antonio Rosellón, Dra. Cristina Rodríguez, Dra. Noemí Cabello, Dr. Thorsten Lauterbach, Verónica López-Carrillo, Dr. Christophe Bour, Ana Escribano, Dr. Dominic Janssen, Nicolas Delpont y César Rogelio Solorio, por su ayuda y colaboración en tantos momentos compartidos, de todos he aprendido algo.

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Però sobretot, a qui els hi vull donar les gràcies és a mon pare i a ma mare, que sempre han confiat en jo i m'han recolzat en les decisions que he pres, i que han estat prou generosos per encoratjar-me a partir encara que jo sé que s'haurien estimat més que m'hagués quedat amb ells, o al manco no hagués anat tan enfora. Sense ells no hauria estat possible. Moltes gràcies de veres.

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

"New Annulations via Platinum-Catalyzed Enyne Cyclization and Cyclopropane Cleavage"
Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6,* 3191-3194.

"Gold-Catalyzed Intramolecular Reaction of Indoles with Alkynes: Facile Formation of Eight Membered Ring and Unexpected Allenylation"
Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109.

"Gold(I)-Catalyzed Arylation of 1,6-Enynes: Different Site Reactivity of Cyclopropyl Gold Carbenes"
Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Comm.* **2007**, 698-700.

"Intra- and Intermolecular Reactions of Indoles with Alkynes Catalyzed by Gold"
Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358-1373.

"Missing Cyclizations Pathways and New Rearrangements Unveiled in the Gold(I) and Platinum(II)-Catalyzed Cyclization of 1,6-Enynes"
Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* (50th Anniversary) **2007**, *63*, 6306-6316.

Universitat Rovira i Virgili
La universitat pública de Tarragona
Ministerio de Educación y Ciencia
AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca
UAM Universidad Autonoma de Madrid
ICIQ Institut Català d'Investigació Química
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Esta memoria del trabajo de la Tesis Doctoral se ha divido en cuatro capítulos, que constan cada uno de una introducción, unos objetivos, un apartado de resultados y discusión, conclusiones y finalmente la parte experimental.

La introducción del primer capítulo contiene una revisión de la reacción de hidroarilación de alquinos y también se recogen los ejemplos publicados en la bibliografía de las reacciones de indoles con alquinos y con alquenos no activados catalizadas por metales de transición. A continuación, se exponen los resultados obtenidos en la reacción de indoles con alquinos catalizada por oro, tanto intra- como intermolecular, junto con una discusión sobre el mecanismo de esta reacción.

En el segundo capítulo se presentan los resultados obtenidos en el estudio de la aplicación de la metodología sintética descrita en el primer capítulo a la síntesis de una familia de productos naturales.

La introducción del tercer capítulo trata de la reacción de cicloisomerización de 1,6-eninos catalizada por platino y por oro, centrándose el las reacciones de hidroxi- y alcoxiciclación, y en la obtención de biciclo[4.1.0]heptenos. No se incluyen en esta introducción las reacciones de tipo Alder-énicas y tampoco las de reordenamiento de esqueleto, por no estar relacionadas con los resultados descritos en este capítulo. En el apartado de resultados y discusión, se recogen los resultados obtenidos en la reacción de éteres de enol con alquinos catalizada por platino y por oro.

En el último capítulo se discute la reacción de ciclación de alquinil iminas para dar pirroles catalizada por cobre.

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Resumen

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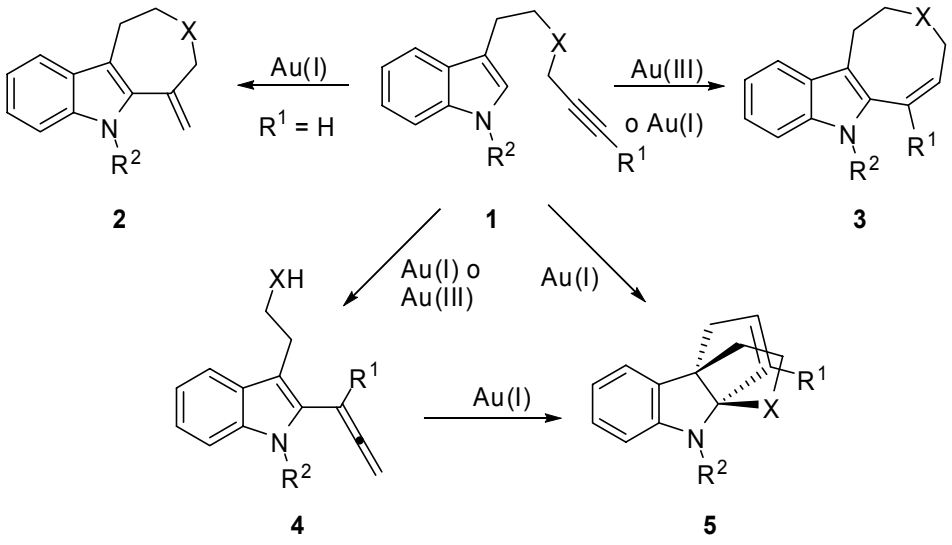
El indol es uno de los heterociclos aromáticos presente en mayor número de productos naturales y compuestos con propiedades farmacológicas. Aunque se han desarrollado diferentes métodos para sintetizar derivados de indoles y para modificar su sustitución, la búsqueda de nuevas metodologías para obtener nuevos compuestos es todavía un tema de gran interés en química orgánica. Un método interesante para sintetizar derivados de indol es la reacción de hidroarilación de alquinos, también conocida como alquenilación de arenos.

En el primer capítulo de esta Tesis están recogidos los resultados del estudio de la reacción intramolecular de indoles con alquinos catalizada por oro en compuestos de tipo **1** (Esquema 1). Cuando la reacción de sustratos de tipo **1** se lleva a cabo en presencia de complejos catiónicos de oro(I) se obtienen azepino[4,5,*b*]indoles **2** en una reacción de tipo 7-*exo-dig*. En cambio, cuando el catalizador utilizado en este proceso es $AuCl_3$, los productos obtenidos son indoloazocinas **3** en una reacción de tipo 8-*endo-dig*. En algunos casos, cuando las reacciones se llevan a cabo a temperatura más alta o durante tiempos de reacción más prolongados, también se ha observado la formación de alenos **4** o de tetraciclos **5**.

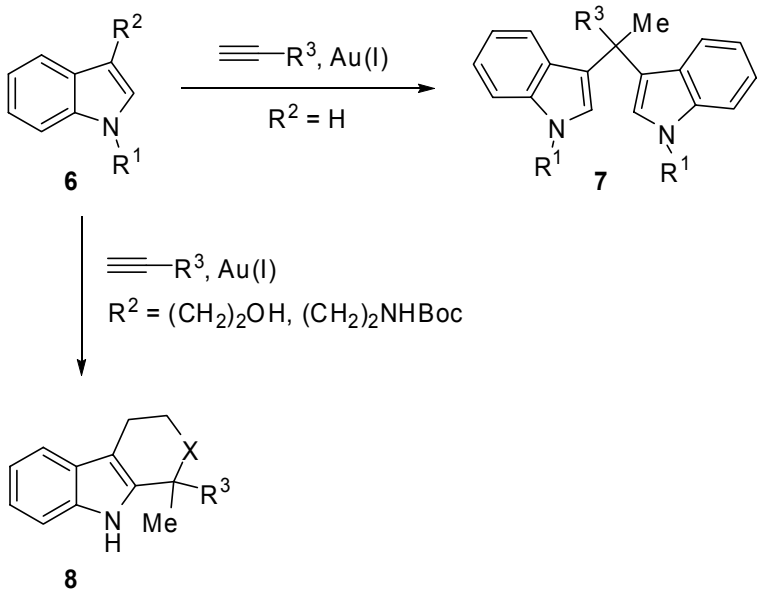


Esquema 1

Hemos observado que los sustratos que contienen tres átomos en lugar de cuatro entre el indol y el alquino reaccionan en un proceso de tipo 6-*exo-dig*, mientras que los que tienen dos átomos reaccionan de forma 6-*endo-dig*. El mecanismo que proponemos para esta transformación, basado en los resultados experimentales, consiste en la

activación del alquino por parte del metal, seguido por el ataque nucleófilo del indol en la posición tres, en un proceso de tipo Friedel-Crafts. El espiro derivado que se forma sufre una migración 1,2 y tras la rearomatización y protodemetalación de este intermedio se obtienen los productos con anillos de siete y ocho miembros observados. Los alenos y también los tetraciclos se forman a partir de un intermedio común.

También hemos desarrollado la reacción intermolecular catalizada por oro entre indoles y alquinos. Indoles sencillos **6** reaccionan con alquinos terminales en presencia de catalizadores de oro(I) para formar aductos 2:1 de tipo **7** (Esquema 2). En el caso de la reacción de derivados de triptofol y triptamina con alquinos terminales se forman compuestos de tipo **8**, en un proceso similar a la reacción de Pictet-Spengler.



Esquema 2

En el segundo capítulo de la Tesis se recoge un estudio preliminar de la síntesis de un producto natural de la familia de las lundurinas (Figura 1), cuya estructura posee una indoloazocina. Para eso, hemos aplicado la metodología sintética desarrollada para la reacción intramolecular de indoles con alquinos. Mediante la ciclación catalizada por $AuCl_3$ del sustrato adecuado hemos conseguido sintetizar la estructura tetracíclica característica de esta familia de compuestos.

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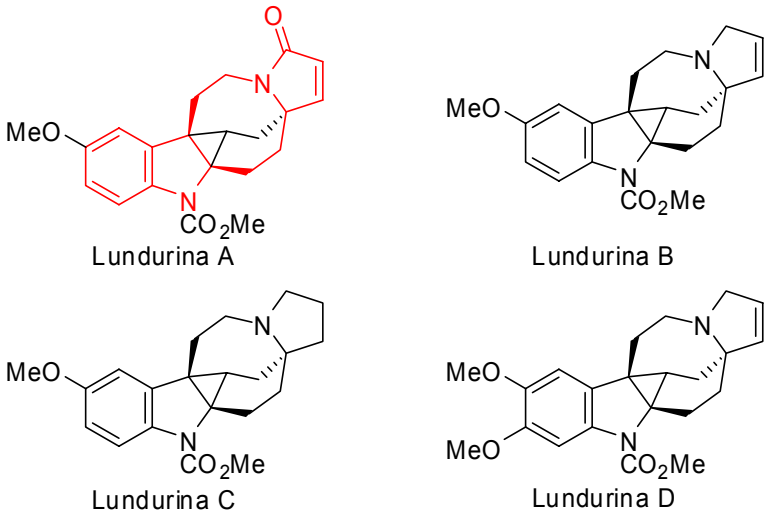
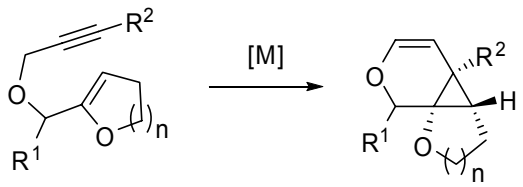


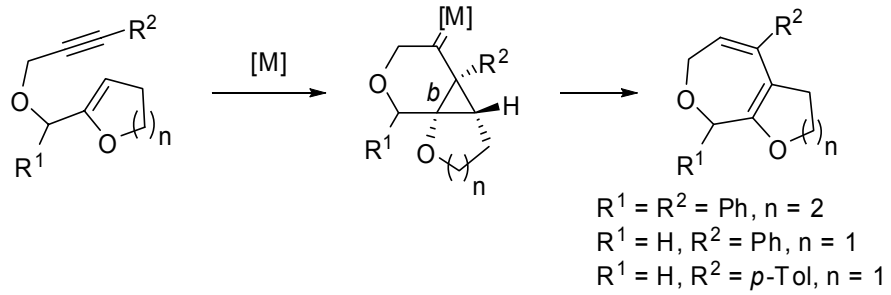
Figura 1

En el tercer capítulo de esta Tesis se recogen los resultados obtenidos en una nueva reacción de ciclación de éteres de enol ω-acetilénicos catalizada por platino y también por oro. Cuando uno de los átomos del puente entre el alquino y el éter de enol es un oxígeno se obtienen 3-oxa-biciclo[4.1.0]hept-4-enos mediante la ciclopropanación intramolecular de éteres de enol por alquinos catalizada por Pt(II) u Au(I) (Esquema 3).



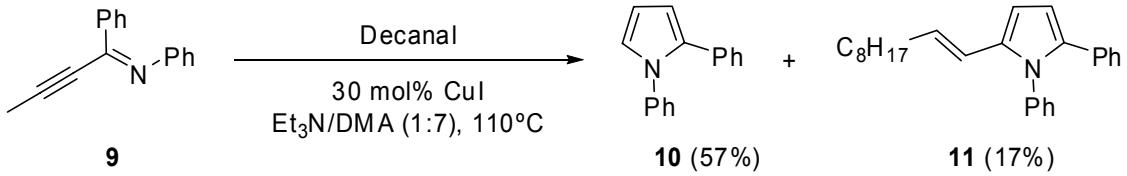
Esquema 3

De acuerdo con el mecanismo propuesto para la adición de nucleófilos a 1,6-eninos catalizada por Pt(II), el ciclopropil carbeno metálico que se forma después de una ciclación de tipo 6-*endo*-*dig* puede evolucionar mediante la ruptura del enlace *b* hacia compuestos que contienen un anillo de siete miembros en su estructura (Esquema 4). Esta transformación ha sido realizada por primera vez utilizando complejos de Au(I) y Pt(II) electrófilos.



Esquema 4

En el capítulo cuatro de esta Tesis se recoge el estudio de la reacción de ciclación catalizada por cobre de alquinil iminas para formar pirroles desarrollada por el grupo de Gevorgyan. En la reacción de la alquinil imina **9** en presencia de decanal aislaron, aparte del pirrol **10**, otro compuesto que asignaron como **11** (Esquema 5). Basándose en este dato, y también en experimentos de deuteración, propusieron un mecanismo para la ciclación de alquinil iminas catalizada por Cu(I).



9 **10** (57%) **11** (17%)

Esquema 5

El compuesto **11** ha sido sintetizado de forma independiente y hemos podido demostrar que éste no es el que se forma, si no el compuesto **12** (Figura 2). Por tanto el mecanismo propuesto por Gevorgyan es incorrecto y hemos propuesto un nuevo mecanismo que explica satisfactoriamente los resultados experimentales. También hemos intentado desarrollar una metodología para la síntesis de pirroles substituidos en C-3 atrapando diferentes tipos de electrófilos.

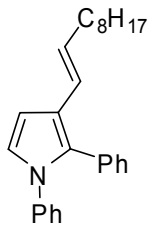


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Figura 2

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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" *J. Org. Chem.* **2007**, *70*, 13A-27A. Additionally, I have also used the following ones:

Cy:	cyclohexyl
dba:	dibenzylideneacetone
DNBS:	2,4-dinitrobenzenesulfonyl
IBX:	iodoxybenzoic acid
IPr:	*N*,*N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
KDA:	potassium diisopropylamide
Napht:	naphtyl
Nf:	nonaflate
SEM:	(2-methoxyethyl)trimethylsilane
TBAF:	tetrabutylammonium fluoride
TPPTS:	*m*-sulfonated triphenylphosphine

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Chapter 1. Introduction

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The activation of alkynes by transition metals to increase their reactivity towards nucleophiles has emerged as a very powerful tool to obtain molecular complexity and diversity. Although several metals, like Pd, Pt, Ru, Ni, Rh or Cu,[1] activate alkynes effectively, in the last few years Au has come out as the best transition metal catalysts for this purpose.[2]

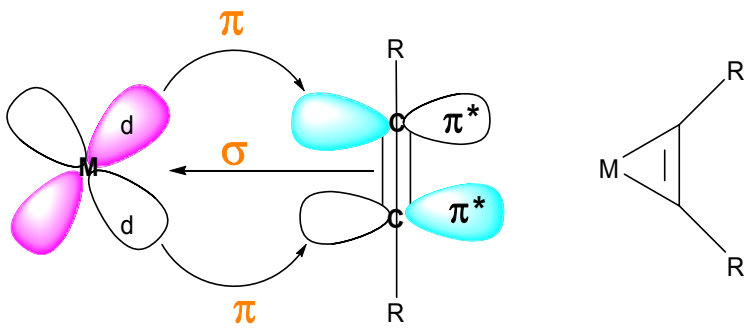
The interaction between a metal and an alkyne can be explained in terms of the accepted Dewar-Chatt-Duncansson[3] model. Accordingly, the metal-acetylenic bonding

1 Reviews: (a) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Pergamon: Oxford, **1991**; Vol 5, pp 1163-1184. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539-546. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635-662. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127-2198. (f) Schore, N. E. *Chem. Rev.* **1998**, *88*, 1081-1119. (g) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523-596.

2 Recent reviews on gold catalyzed reactions: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403. (c) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. (e) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.

3 (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, 51-79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939-2947.

is described as the combination of a σ-interaction (donation of the unsaturated moiety to empty dsp orbitals of the metal), and a back-bonding π-interaction (donation of the metal to the π* orbitals of the alkyne). The formation of this complex alters the structures of the metal fragment and the alkyne. The model predicts an elongation and a bending of the triple bond as a consequence of the resultant rehybridization. In its extreme form, two M-C bonds are formed and rehybridization of the carbon atoms occurs to form a metalacyclopropane (Scheme 1). The thus formed complex is susceptible of nucleophilic attack on the unsaturated atoms and its reactivity depends on the substituents on the alkyne, the ligands on the metal, and the nucleophile.



Scheme 1

In the case of gold-alkyne complexes, the contributions of the individual σ and π terms have been analyzed by high level computational methods in a quantitative fashion.[4] For the parent Au^+-acetylene complex $[Au^+(C_2H_2)]$ the σ interaction accounts for 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%). Thus, alkynes are strong two electron σ donors but quite weak π acceptors toward Au(I), although some back-bonding does occur and cannot be ignored.

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

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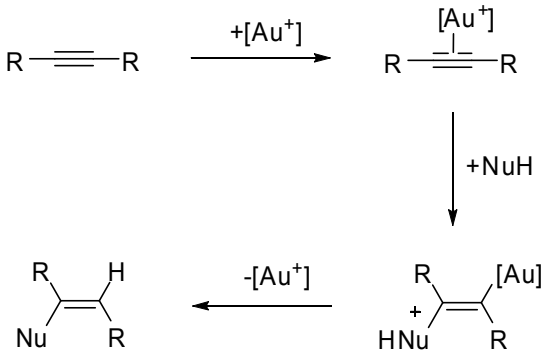
1. Gold-Catalyzed Nucleophilic Additions to Alkynes

The gold-catalyzed reaction of nucleophiles with alkynes can be envisaged as an *anti* attack[5] of the nucleophile onto the Au-alkyne intermediate formed by the coordination of the gold complex to the alkyne. The thus formed vinyl-gold species then gives rise to the product by protodemetalation and regenerates the catalyst (Scheme 2).



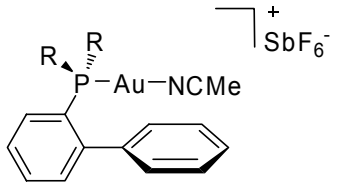
Scheme 2

Even though simple AuCl or $AuCl_3$ can catalyze the reaction of alkynes with nucleophiles, higher turnovers are usually obtained by using $[AuCl(PPh_3)]$[6] or related phosphine complexes with one equivalent of a silver salt to abstract the chloride and generate *in situ* the active cationic gold species. The use of preformed cationic complexes **1** or **2** allows reactions to be performed in the absence of silver salts (Figure 1).[7] Nucleophilic additions using gold catalysts also have many advantages: they are operationally safe, simple and practical to perform, and also do not generally require rigorously inert reaction conditions.

5 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2408. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527. (c) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391-4394.

6 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

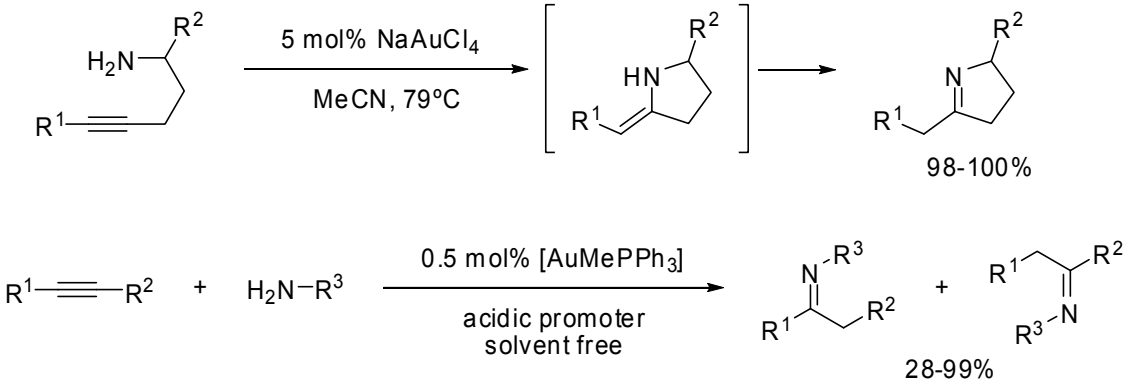
7 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694-1702. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.



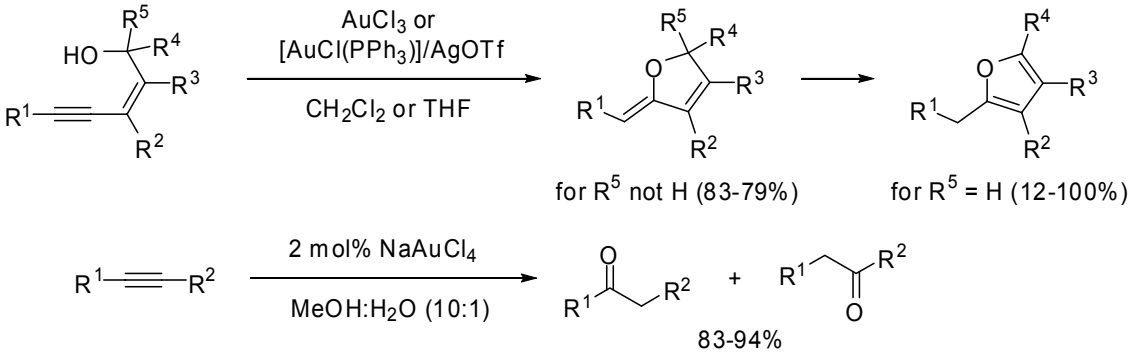
1 R = *t*-Bu
2 R =Cy

Figure 1

The addition of a wide variety of carbon- and hetero-nucleophiles to alkynes has been shown to lead to a wide variety of products. Representative examples featuring heteroatom-carbon bond formation include hydroamination (Scheme 3)[8] and hydration and hydroalkoxylation reactions (Scheme 4).[9]



Scheme 3



Scheme 4

8 (a) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975-978. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352.

9 (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem*. **1991**, *56*, 3729-3731. (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288. (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409-5412.

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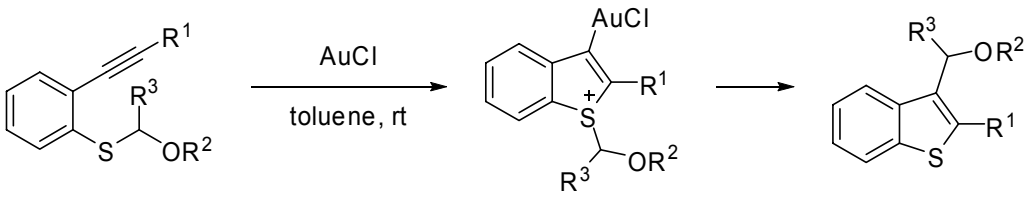
More recently, Yamamoto[10] described the reaction of sulfur-nucleophiles with alkynes to afford benzotiophenes (Scheme 5).



Scheme 5

The addition of carbon-nucleophiles to alkynes allows the formation of C-C bonds in an atom economic way.[11] Although a large number of reactions of alkenes with alkynes catalyzed by gold and other metals have been described, this introduction will be mainly focused on the reaction of arenes and heteroarenes with alkynes.[12] This reaction is also known as hydroarylation of alkynes or alkenylation of arenes.

2. Metal-Catalyzed Hydroarylation of Alkynes

Reactions of alkynes with aromatic rings catalyzed by transition metals allow the direct synthesis of styrene derivatives **3**. This procedure is, in principle, simpler than those based on Heck reactions[13] or cross-coupling methods,[14] which require the use of haloarenes or other arene electrophiles. The intramolecular reaction of substrates of type **4** is of particular interest, since valuable carbon- and heterocycles **5** can be readily formed under relatively mild conditions (Scheme 6).

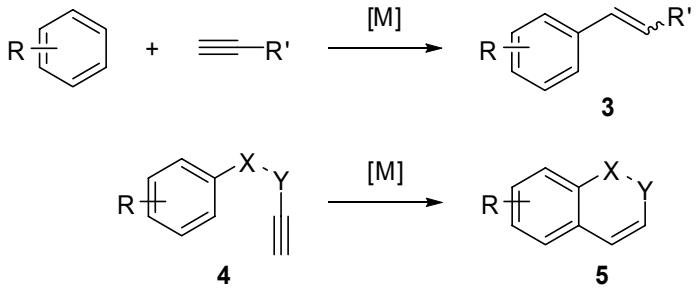
10 (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475. (b) Nakamura, I.; Sato, T.; Tereda, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081-4083.

11 Trost, B. M. *Science* **1991**, *254*, 1471-1477.

12 Reviews on hydroarylation of alkynes: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167-182. (b) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527-3544.

13 For general references: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1994**, *33*, 2379-2411. (b) Belteskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066. (c) Crisp, G. T. *Chem. Soc. Rev*. **1998**, *27*, 427-436. (d) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F.; de Meijere, A.; Eds.; Wiley VCH: Weinheim, **2004**, Chapt. 5.

14 Farina, V.; Krishnamurthy, V.; Scott, W. K. *Organic Reactions*, Vol. 50; Wiley: New York, **1997**.

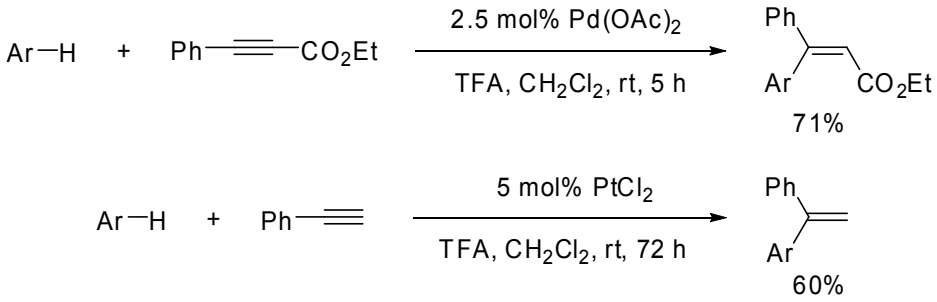


Scheme 6

Although these processes could be categorized as metal-catalyzed C-H functionalization, a direct interaction of the arene with the metal has not been demonstrated in any of these reactions. Indeed, mechanistically these transformations, at least formally, are closer to electrophilic aromatic substitutions in which the electrophile is an alkyne-metal complex.

2.1. Intermolecular hydroarylation of alkynes

In 2000, Fujiwara and coworkers reported the catalytic hydroarylation of alkynes using electrophilic Pd(II) and Pt(II) cationic complexes generated *in situ* in trifluoroacetic acid (Scheme 7).[15] The reaction proceeded regio- and stereoselectively, affording thermodynamically unfavorable *Z*-aryl-alkenes from alkynes.



Scheme 7

A mechanism involving C-H activation of the arene followed by *trans*-addition of a palladium-arene bond across an alkyne was initially proposed. Later studies by

15 (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992-1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc*. **2000**, *122*, 7252-7263.

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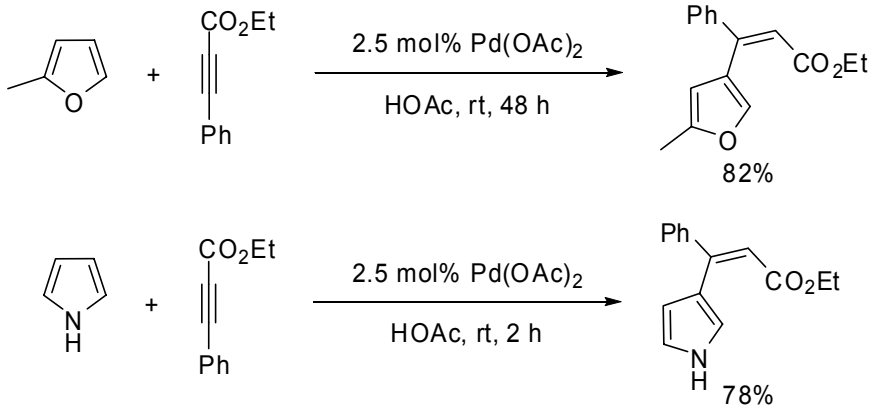
Tunge[16] based on kinetic isotope effects of intramolecular hydroarylation with deuterated arene substrates, showed that this reaction exhibits an inverse kinetic isotope effect that is not consistent with known kinetic isotope effects for C-H activation by electrophilic palladium. These observations, together with the stereochemical data, suggest that the reaction proceeds by electrophilic aromatic substitution.

The Pd(II)/acid system is also efficient in the reaction of electron-rich heteroaromatic compounds, such as furans and pyrroles with alkynes at room temperature to give, in most cases, *Z*-alkenes (Scheme 8).[17]



Scheme 8

The use of $PtCl_2$/AgOTf in the hydroarylation of propiolic acids with electron-rich arenes to give exclusively (2*Z*)-cinnamic acids has been described more recently by Kitamura.[18]

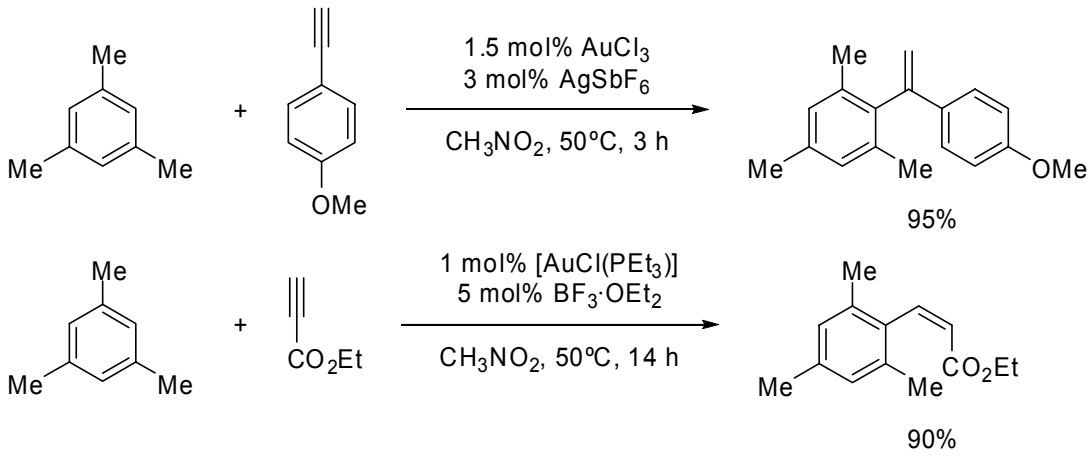
The first example of gold catalyzed intermolecular hydroarylation of alkynes was described by Reetz and coworkers.[19] They observed that aryl-substituted terminal alkynes react with electron-rich arenes in the presence of $AuCl_3$ and $AgSbF_6$ to give 1,1-diarylethenes in good to excellent yields under mild conditions with complete regioselectivity (Scheme 9). Interestingly, with electron-poor alkynes, such as ethyl propiolate, gold(I) complexes such as [AuCl(PEt_3)], activated by silver salts or $BF_3{\cdot}OEt_2$, are the best catalysts, resulting in opposite regioselectivity and high degrees of *Z*-selectivity.

16 Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440-6444.

17 Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett*. **2000**, *2*, 2927-2930.

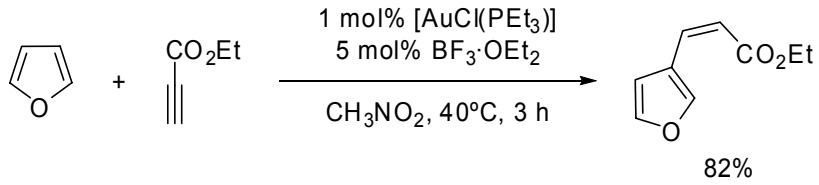
18 Oyamada, J.; Kitamura, T. *Tetrahedron Lett.* **2005**, *46*, 3823-3827.

19 Reetz, M.; Sommer, K. *Eur. J. Org. Chem*. **2003**, 3485-3496.



Scheme 9

Furan reacts under mild conditions to give selectively ethyl (*Z*)-3-(furan-2-yl)acrylate (Scheme 10).



Scheme 10

Similar results were obtained by He and coworkers in the reaction of arenes with ethyl propiolate and related electron-poor alkynes using $AuCl_3$/3AgOTf as the catalytic system in CH_2Cl_2.[20]

Auration of the arene as a key step seems unlikely. He and coworkers, however, have proposed auration as a the key step in the gold(III)-catalyzed nitrene insertion into simple aromatic rings.[21] Presumably, in the case of phenylacetylene with $AuCl_3$ (Scheme 9), the π complex undergoes a type of electrophilic aromatic substitution with the electron-rich arene to form intermediate **6** (Scheme 11). The simultaneously released H^+ protonates this intermediate, releasing the product and regenerating the catalyst. The exact nature of the catalytic active species is not clear, although it is supposed to be cationic. In the case of Au(I), after coordination to the alkyne, the nucleophilic attack of the arene occurs from the opposite side leading to intermediate **7**, which is stereo-

20 Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669-3671.

21 Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058-12059.

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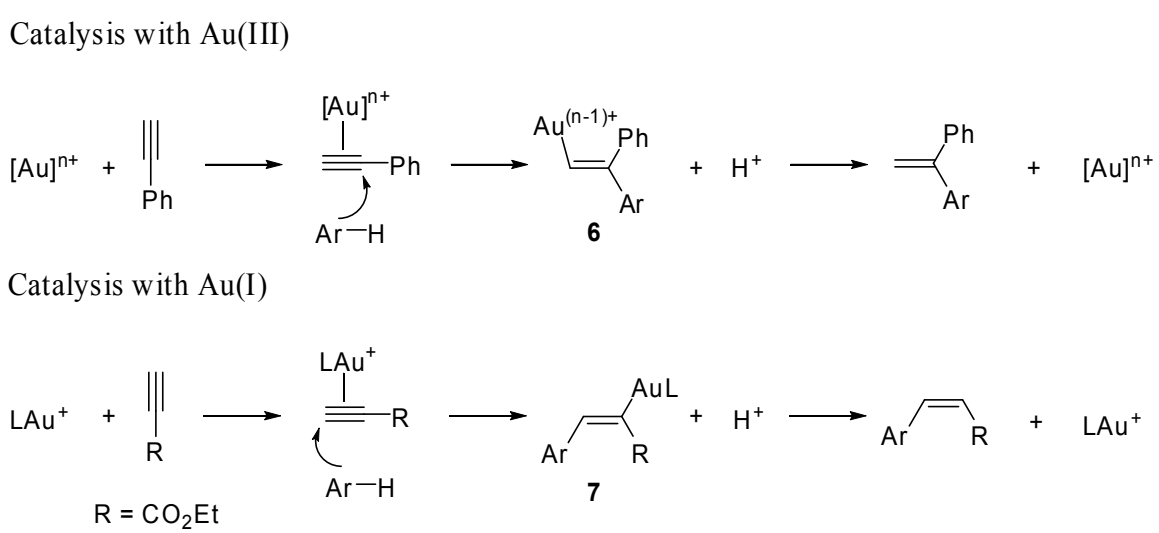
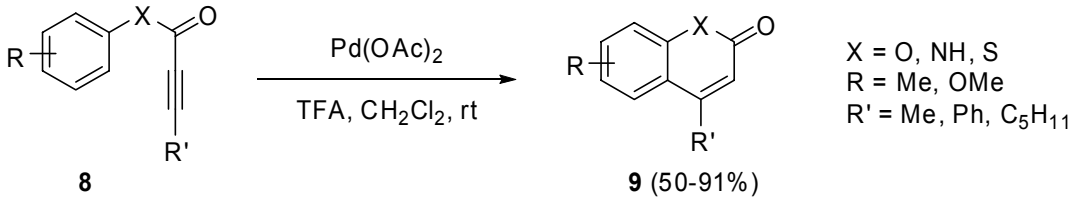
specifically protonated with final formation of the *Z*-olefin. Regioselectivity is determined by electronic rather than steric factors.



Scheme 11

2.2. Intramolecular hydroarylation of alkynes

The catalytic system based on $Pd(OAc)_2$ and TFA[15] developed by Fujiwara has been successfully applied in the intramolecular hydroarylation of alkynes. Accordingly, aryl alkynoates and alkynanilides **8** cyclize in the presence of catalytic amounts of $Pd(OAc)_2$ in TFA, yielding coumarins and quinolin-2(1*H*)-ones **9**, respectively, in good to excellent yields (Scheme 12).[22] Similar reactions have been carried out using $AuCl_3$/AgOTf as the catalytic system.[20]

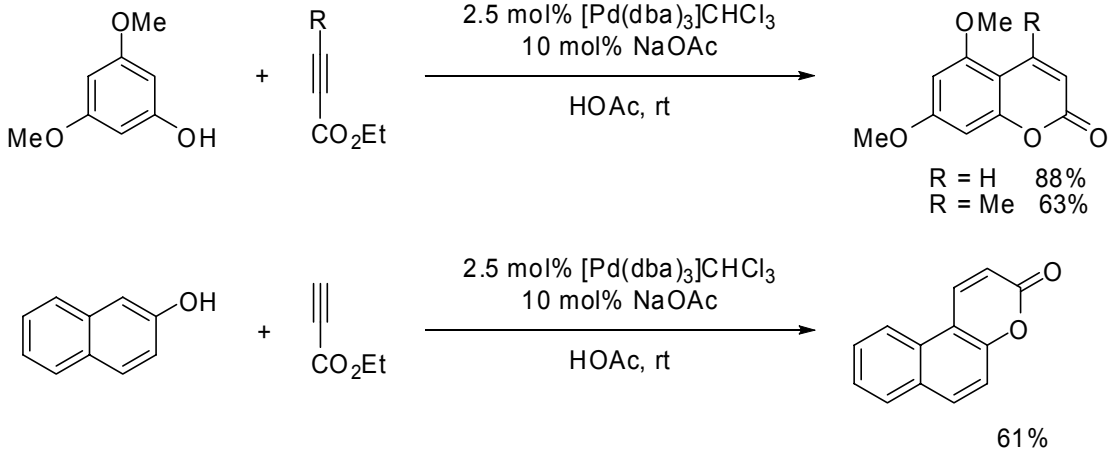


Scheme 12

15 (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992-1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc*. **2000**, *122*, 7252-7263.

22 Jia, C.; Lu, W.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem*. **2000**, *65*, 7516-7522.

Trost developed a Pd(0)-catalyzed synthesis of coumarins by addition of phenols to alkynoates via an overall C-H insertion (Scheme 13).[23] The same kind of reactivity has been described by Kitamura using $Pt(OAc)_2$/TFA.[24] The coumarin synthesis developed by Trost could also be carried out with Ag(I), albeit a stoichiometric amount of Ag(I) salt was required.



Scheme 13

Murai and coworkers reported the cycloisomerization of ω-aryl-1-alkynes in which aromatic rings act as nucleophiles towards π-alkyne-transition metal complexes without invoking metalation of the arene moiety. Treatment of aryl-1-alkynes with catalytic amounts of $PtCl_2$ or $[RuCl_2(CO)_3]_2$ at 80ºC in toluene results in the formation of dihydronaphthalenes or dihydrobenzocycloheptenes (Scheme 14). Different cyclization modes are observed depending on the length of the tether: *exo-dig* cyclization is preferred when the alkyne and the arene are separated by three or four carbon atoms, while *endo-dig* cyclization is observed in substrates with two carbon atoms in the tether.[25]

23 (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305-6306. (b) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518-4526.

24 Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918-6925.

25 Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913-4918.

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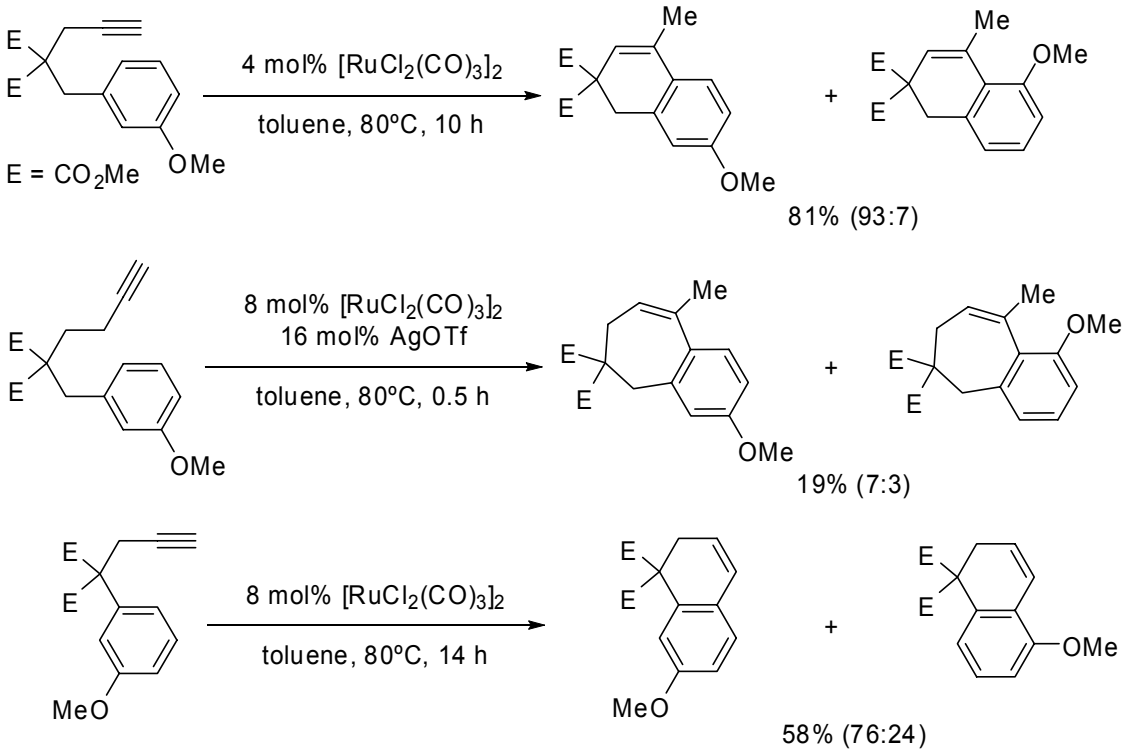
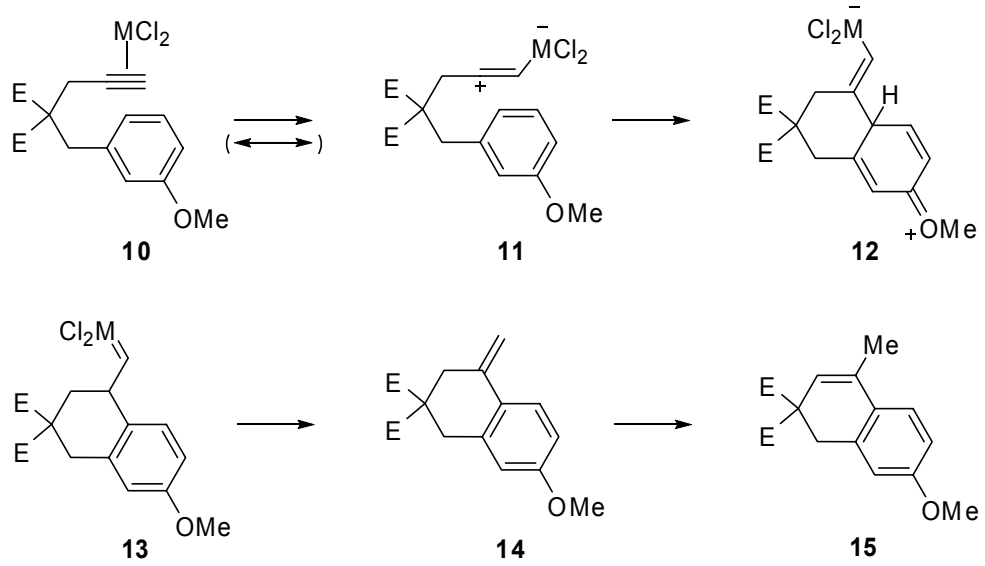


Scheme 14

The first step in the proposed reaction mechanism is the formation of a complex depicted as **10** or vinyl cation **11** (Scheme 15), which are just two different resonance forms of an alkyne-metal complex.[26] Subsequently, **12** is formed from **10** or **11** by electrophilic aromatic substitution. 1,2-Hydrogen shift and aromatization of **12** leads to the formation of carbene **13**. β-Hydrogen elimination then generates a metal hydride complex which affords **14** after reductive elimination. Although the *exo*-methylene product is initially formed, it isomerizes to the more stable *endo*-alkene **15** under the reactions conditions.

26 (a) Pilette, D.; Moreau, S.; Le Bozec, H.; Dixneuf, P. H.; Corrigan, J. F.; Carty, A. J. *Chem. Commun.* **1994**, 409-410. (b) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *67*, 1071-1087.



Scheme 15

This transformation, catalyzed by Pt(II) or Ru(II), is limited to substrates having an electron-rich aromatic ring. The scope of the reaction was extended to substrates where the arene moiety does not posses strong electron-donating groups by using $GaCl_3$ as catalyst.[27]

Fürstner has described a similar reaction in which biphenyl derivatives containing an alkyne unit at one of their *ortho*-positions are converted into substituted phenantrenes. The best results in this cyclization are obtained using $PtCl_2$ as catalyst, although AuCl, $AuCl_3$, $GaCl_3$ or $InCl_3$ in toluene are also active in this transformation. In most of the reported examples the 6-*endo*-cyclization is preferred; only in the case of an alkyne bearing a strongly withdrawing group the 5-*exo*-cyclization was observed (Scheme 16).[28]

27 Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414-1417.

28 (a) Fürstner, A.; Mamane, V. *J. Org. Chem*. **2002**, *67*, 6264-6267. (b) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.

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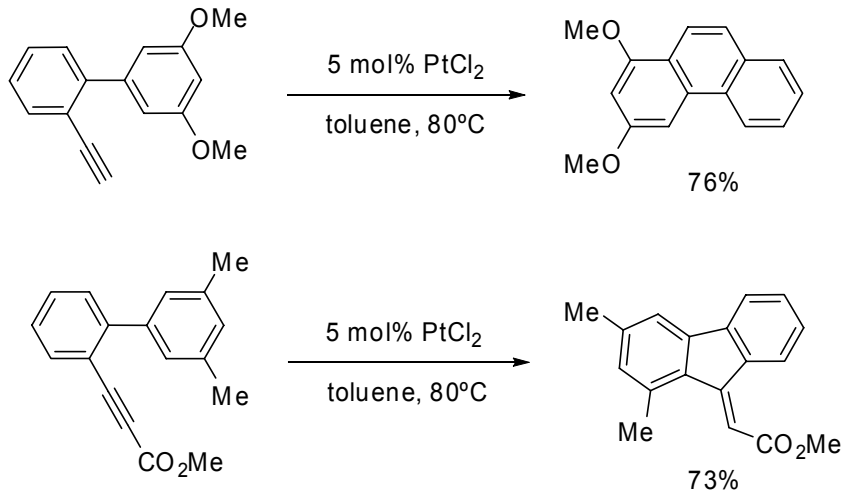
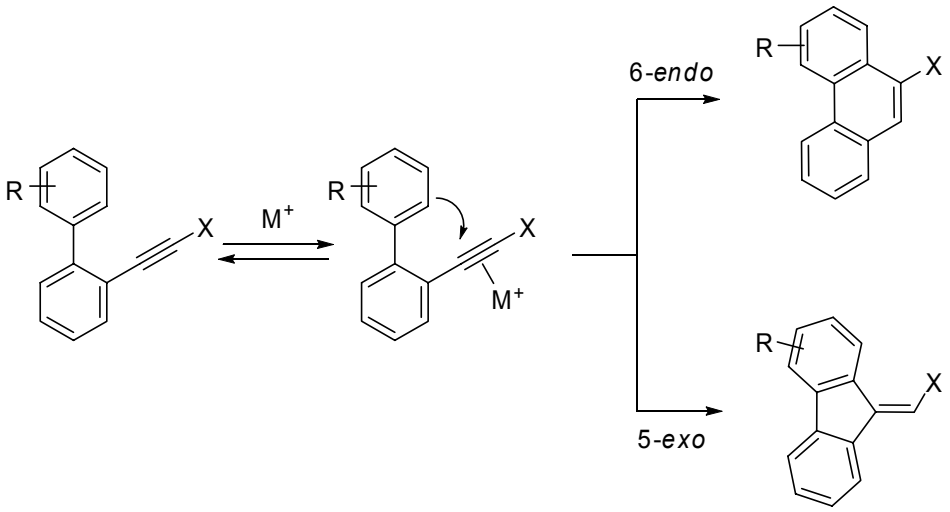


Scheme 16

The Pt(II)-catalyzed phenantrene synthesis works equally well or even better with non-terminal alkynes. Activation of the alkyne by coordination to Pt(II) explains the observed ring closure (Scheme 17).

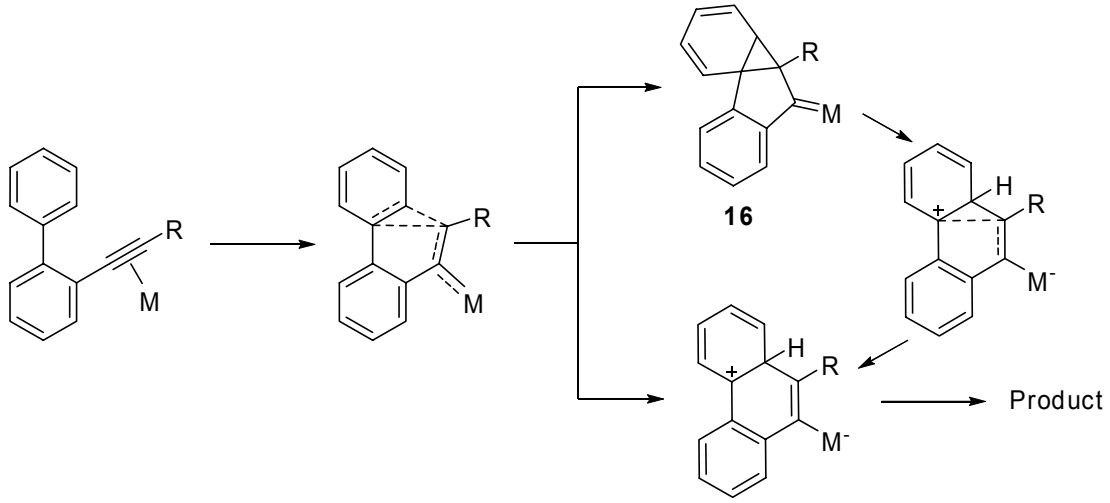


Scheme 17

The high *endo* selectivity observed in many of the cyclizations suggests that the mechanism might actually be more complex than a simple Friedel-Crafts reaction. It has been proposed that the involvement of electrophilic carbenes would explain the outcome of the reaction.[29] Recent computational studies highlight the tendency of platinum compounds to form carbene intermediates. These calculations indicate that

29 Méndez, M.; Mamane, V.; Fürstner V. *Chemtracts* **2003**, *16*, 397-425.

although a Friedel-Crafts mechanism and the cyclopropanation pathway via a metalcyclopropyl carbene show very similar activation energies, platinum cyclopropyl carbenes of type **16** are the stationary points with the lowest energy (Scheme 18).[30,31]



Scheme 18

This methodology has been extended to the preparation of a variety of heterocycles like benzoindoles, naphthothiophenes as well as bridgehead nitrogen heterocycles such as pyrrolo[1,2-*a*]quinolines by the reaction of pyrroles or thiophenes with activated alkynes as shown is Scheme 19.[28] There is no need for protecting groups since no attack of the nitrogen atom as nucleophile was observed in the case of the pyrroles. In these examples, however, $PtCl_2$ is not necessarily the best catalyst; only in the case of terminal alkynes was it found to be effective, whereas some of the substrates bearing an internal alkyne required the use of either $GaCl_3$ or $InCl_3$ for productive cyclization.

30 Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.

31 Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542-4553.

28 (a) Fürstner, A.; Mamane, V. *J. Org. Chem*. **2002**, *67*, 6264-6267. (b) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.

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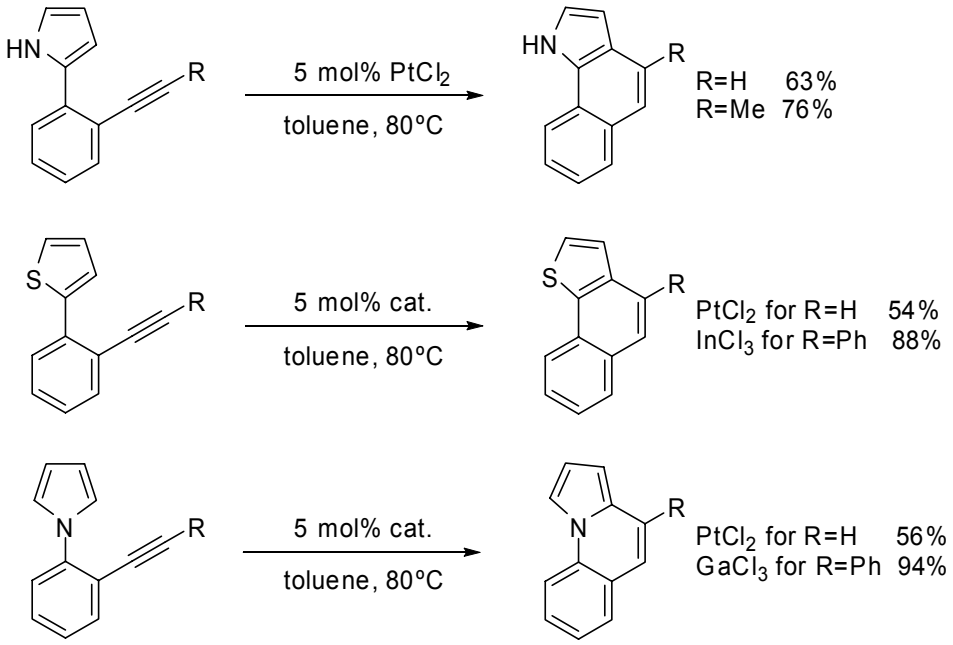
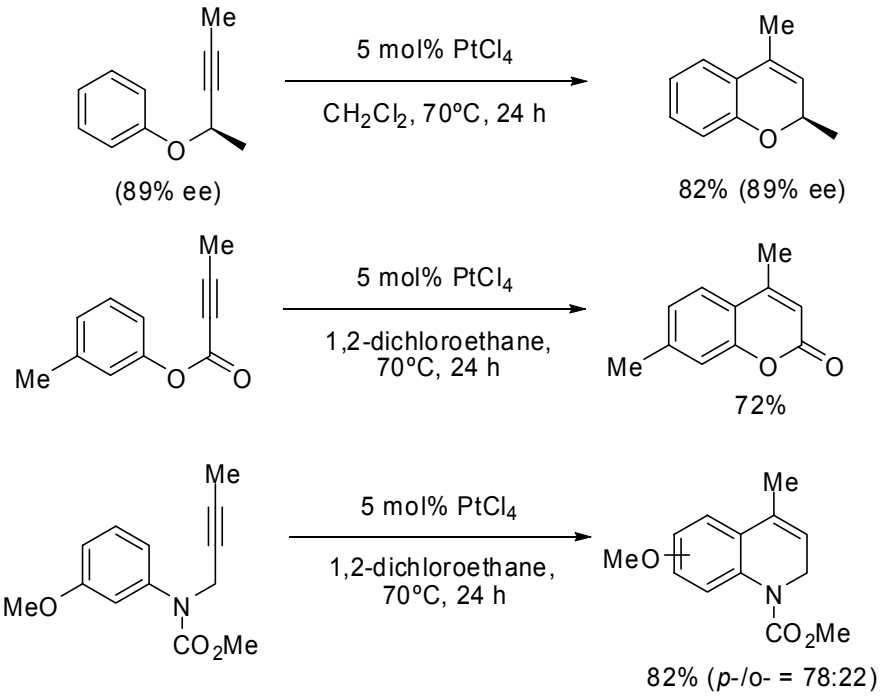


Scheme 19

Sames has developed a $PtCl_4$-catalyzed hydroarylation that proceeds under mild conditions for the synthesis of 2*H*-chromenes, coumarins and 1,2-dihydroquinolines (Scheme 20).[32] In all cases, 6-*endo-dig* cyclization was observed regardless of the electronic nature of the alkyne. Stereogenic centers are retained under the reaction conditions, excluding a Claisen rearrangement followed by electrocyclic ring closure as the reaction course.[33] Although a Heck type mechanism was also considered as a possibility, activation of the alkyne via coordination of $PtCl_4$ (as shown in Scheme 17), seems to be the most likely reaction pathway.

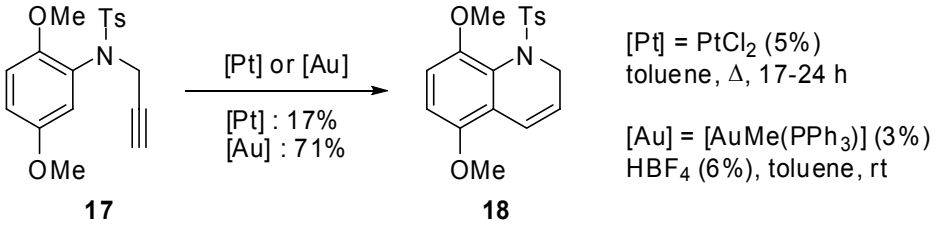
32 (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett*. **2003**, *5*, 1055-1058. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859-8868.

33 Synthesis of 2*H*-chromenes by thermal cyclization of aryl propargyl ethers: (a) Anderson, W.; K.; La Voie, E. J.; Whitkop, P. G. *J. Org. Chem.* **1974**, *39*, 881-884. (b) Rao, U.; Balasubramanian, K. K. *Tetrahedron Lett.* **1983**, *24*, 5023-5024. (c) Rhoads, S. J.; Raulins, N. C. *Organic Reactions*, Vol. 22; Wiley: New York, **1975**, 1-252. For a Rh(I) catalyzed synthesis of indoles by amino-Claisen rearrangement: Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem. Int. Ed.* **2007,** *46*, 3931-3933.



Scheme 20

Our group has also shown that 4-aryl-1-alkynes **17** react with $PtCl_2$ in toluene under reflux to form 1,2-dihydroquinolines **18** in low to moderate yields (Scheme 21).[34] Using a cationic Au(I) catalyst formed *in situ* from [AuMe(PPh_3)] and HBF_4 1,2-dihydroquinolines were obtained at 23-50ºC in good yields.[5a] These reactions were best performed in toluene, using an excess of protic acid to efficiently generate the cationic Au(I) species.



Scheme 21

34 Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2003**, *125*, 5757-5766.

5 (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2408.

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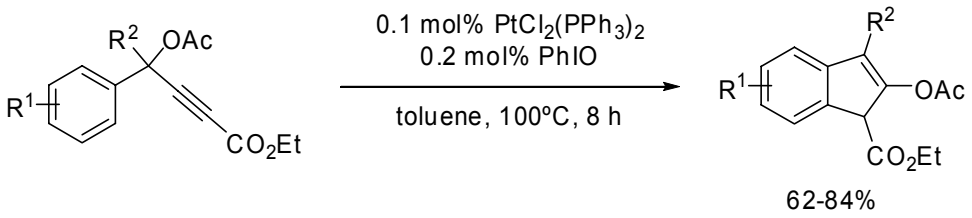
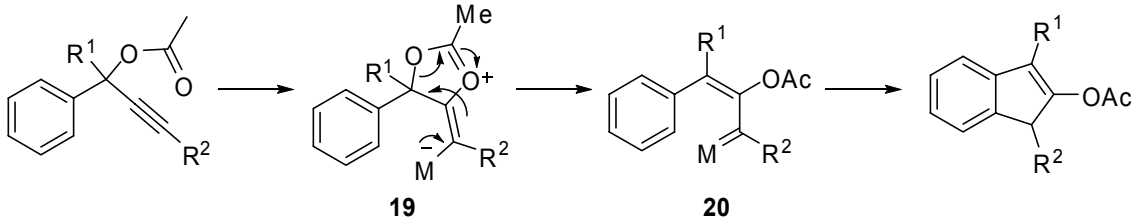
Sarpong and coworkers described an efficient synthesis of indenes from the platinum-catalyzed reaction of arenes with propargylic esters. The reaction only proceeds when the substitution on the alkyne is an electron withdrawing group, in the presence of an oxidant and using toluene at 100ºC (Scheme 22).[35]



Scheme 22

In this case, an alternative mechanism which does not involve direct attack of an arene on an alkyne-metal complex has been put forward. Whether the catalytic active species is Pt(II) or Pt(IV) is not clear. Regardless of the oxidation state of the metal, the reaction has been proposed to occur via a 1,2-migration of the acetate[36] to give intermediate **19**, which after C-O bond cleavage forms metal-carbene **20**. Finally, C-H insertion into the aryl moiety gives rise to the indene products (Scheme 23).



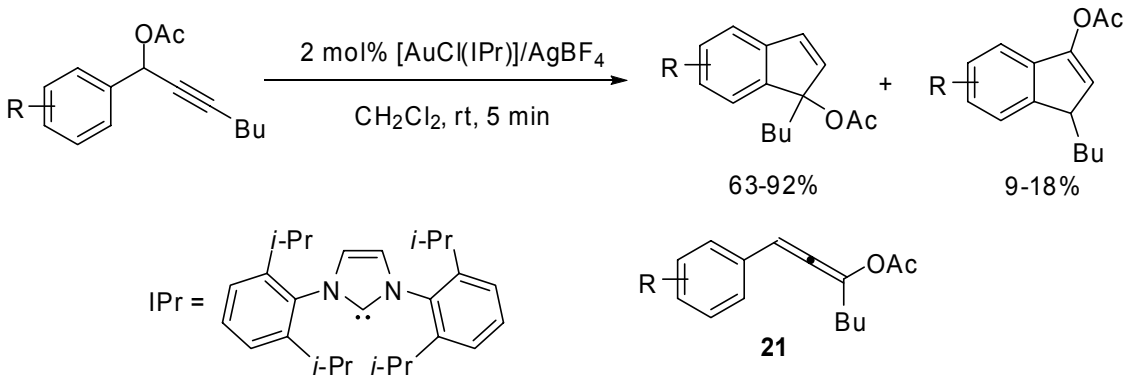
Scheme 23

More recently, Nolan has developed a similar transformation catalyzed by Au(I) under milder conditions. Two isomers were obtained in this reaction: the major product

35 Prasad, B. B. A.; Yoshimoto, F. Y.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468-12469. For a single example of indene synthesis using Ru: Miki, M.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505-8513.

36 (a) Frey, L. F.; Tillyer, R. D.; Ouellet, S. G.; Reamer, R. A.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1215-1216. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655. (c) Harrak, Y.; Biaszykowski, C.; Benard, M.; Carlou, K.; Manetti, E.; Mouriés, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656-8657.

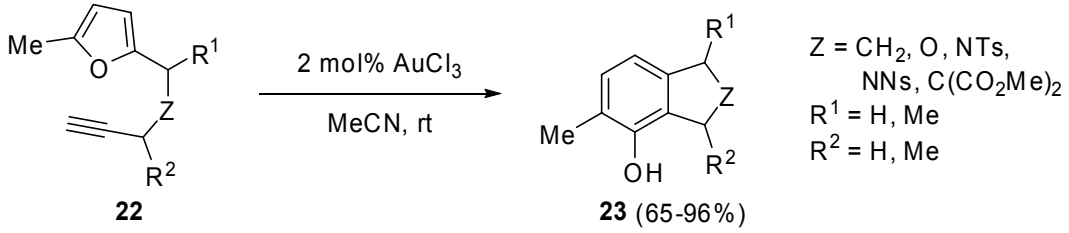
was the one having the acetate in the 1-position and the minor product had the acetate in the 3-position (Scheme 24). The observed regioselectivity is different than that observed in indene synthesis catalyzed by Pt, in which the main product is the isomer substituted in the 2-position (Scheme 22).[37] Allene **21**, formed after 1,3-migration, has been proposed as an intermediate for this reaction.



Scheme 24

3. Synthesis of Phenols by Metal-Catalyzed Reaction of Furans with Alkynes

Contrary to the usual Friedel-Crafts-like cyclizations of arenes with alkynes, Hashmi found that reaction of alkynyl furans **22** affords phenols **23** in good to excellent yields by using $AuCl_3$ as catalyst.[38,39] Reaction of substrate **24**, unsubstituted at C-5 of the furan, led to mixtures of phenols **25** and **26** (Scheme 25).



37 Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3647-3650.

38 Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554.

39 For reactions of furans with alkynes catalyzed by Ru involving vinylidene intermediates see: Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319-11320.

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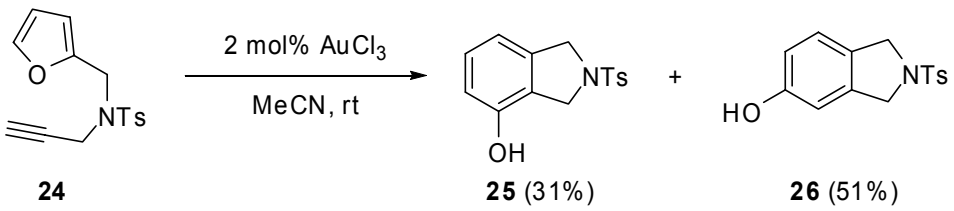
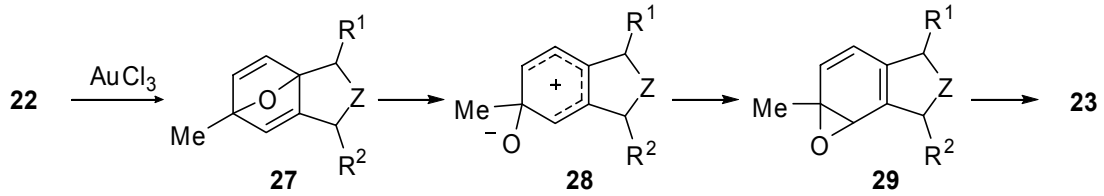


Scheme 25

This reaction was proposed to proceed via an intramolecular [4+2] cycloaddition promoted by the coordination of $AuCl_3$ to the alkyne to form oxabicyclic adduct **27**, followed by C-O cleavage to give intermediate **28** (Scheme 26). Arene oxide **29** is formed by intramolecular nucleophilic attack of the oxygen. Although attack of water to form a 1,2-diol was also originally considered, experiments in the presence of $H_2{}^{18}O$ revealed that the oxygen transfer is intramolecular.[40] In a more recent mechanistic study, Hashmi has provided experimental evidence of the formation of **29**.[41] Finally, isomerization of **29** gives rise to phenols **23**.



Scheme 26

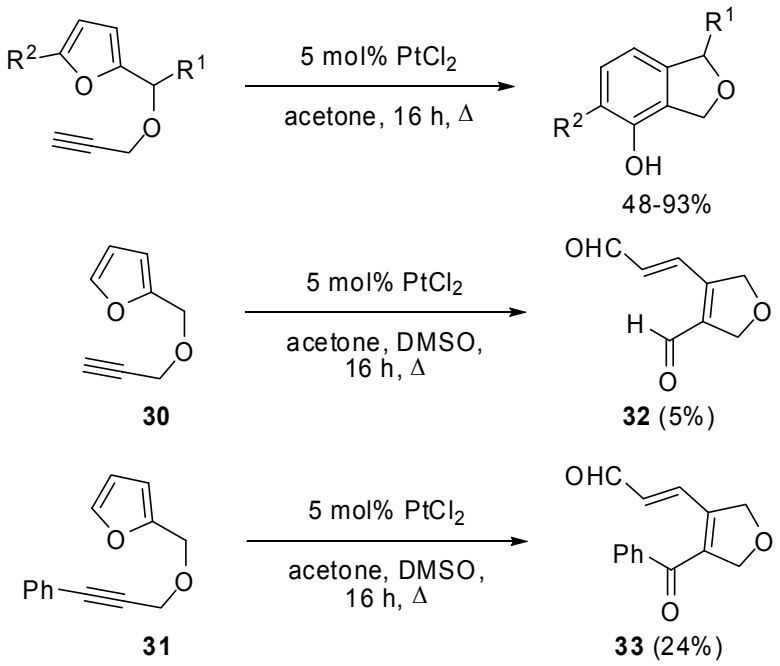
In our group, the intramolecular reaction of furans with alkynes was also found to proceed with Pt(II) catalysts.[34,42] Interestingly, when the reactions of furans **30** and **31** were carried out in aqueous acetone or in DMSO-acetone mixtures, the products obtained were **32** and **33** respectively, albeit in low yield because of their labile nature (Scheme 27).

40 Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769-3771.

41 Hashmi, A. S. K.; Rudolph, M.; Weyrauch, J. P.; Wölfle, M.; Frey, W.; Bats, J. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 2798-2801.

34 Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2003**, *125*, 5757-5766.

42 Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4754-4756.



Scheme 27

The isolation of compounds **32** and **33** indicates that formation of the C-C bond between C-2 of the furan and C-2 of the alkyne precedes formation of the second C-C bond, which is not compatible with the mechanism shown in Scheme 26. Based on these experimental results and on theoretical mechanistic studies, an alternative mechanism involving cyclopropyl Pt(II) carbenes was proposed for this cyclization (Scheme 28).[34] Accordingly, nucleophilic attack of the furan to the alkyne-metal complex affords platinum cyclopropyl carbene **34**, very similar to the intermediates formed in reactions of enynes with Pt(II) or other metal complexes.[43] Cleavage of a C-C and a C-O bond from tricyclic intermediate **34** leads to carbonyl compound **35**, which cyclizes to give oxepine **36**, upon elimination of the metal. In the presence of water, carbene intermediate **35** can evolve into aldehyde **32**. Oxepine **36** is in equilibrium with the arene oxide **29**, which upon opening gives the final phenols.

34 Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2003**, *125*, 5757-5766.

43 Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431-436.

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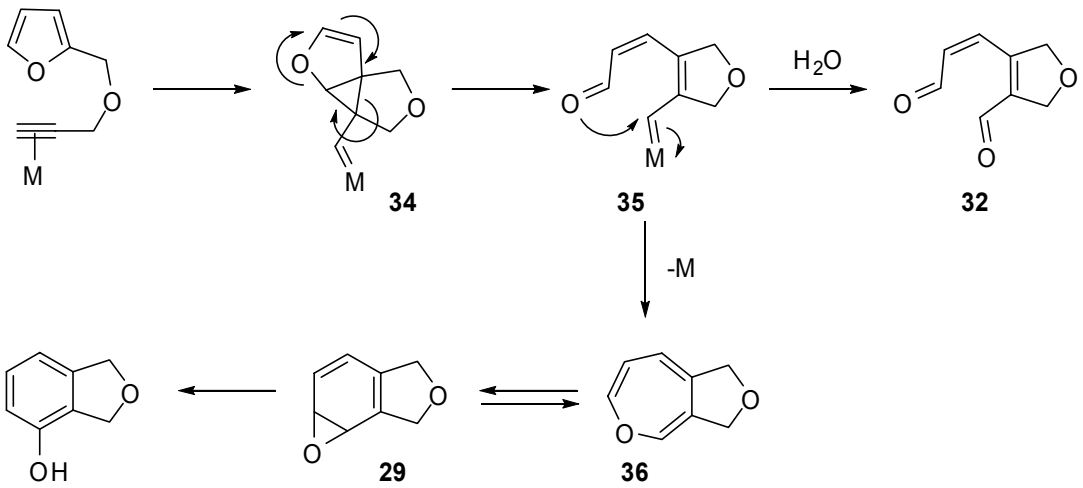


Scheme 28

4. Metal-Catalyzed Reaction of Indoles with Alkynes

4.1. Metal-catalyzed intermolecular reaction of indoles with alkynes

Although indoles have attracted the attention of many organic chemists and a vast range of indole based products have been synthesized using different methodologies,[44] only a few examples of indole derivatives prepared by hydroarylation of alkynes have been described.

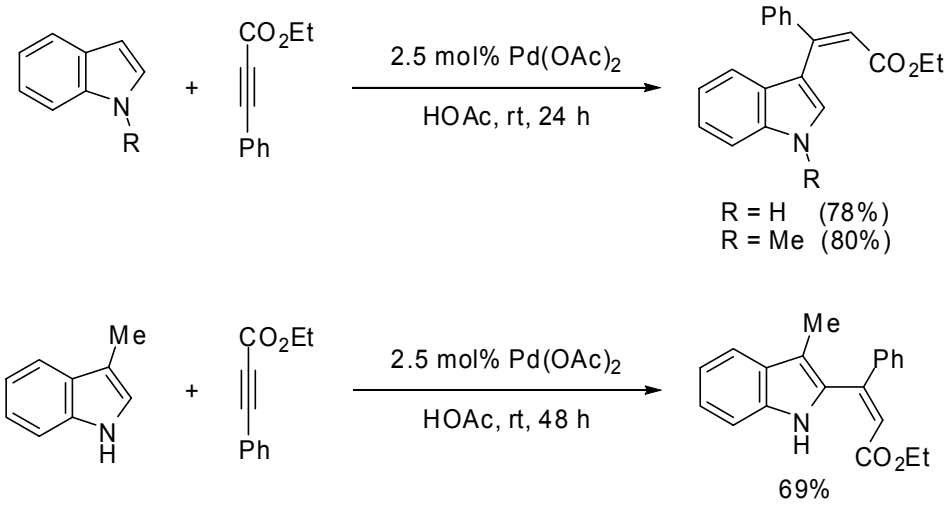
Fujiwara applied his methodology for the synthesis of *Z*-aryl-alkenes from alkynes catalyzed by $Pd(OAc)_2$/TFA (see introduction section 2.1) to the intermolecular reaction of indoles with alkynes to give also *Z*-indole-alkenes.[17] For indole and 1-methylindole, the reaction occurred predominantly at the 3-position while only trace amounts (< 3%) of 2-substituted adducts could be detected in the reaction mixture by NMR. When the 3-position of the indole was substituted by a methyl group, the reaction proceeded smoothly at the 2-position, even tough it is not a favorable position for the electrophilic substitution[45] (Scheme 29).

---

44 (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, Blackwell, Oxford, **2000**, pp 589. (b) Sundberg, R. J. *Indoles*, Academic Press, San Diego, **1996**, pp 175.

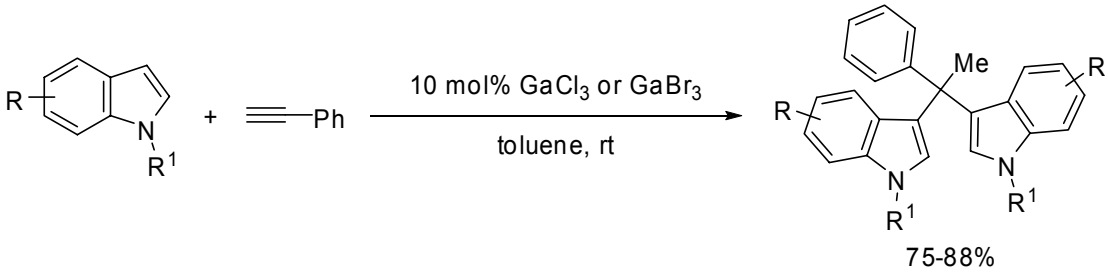
17 Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett*. **2000**, *2*, 2927-2930.

45 (a) Jackson, A. H. In *Comprehensive Organic Chemistry*, Vol. 4; Sammes, P. G., Ed.; Pergamon: Oxford, **1979**; pp 282-290. (b) Brown, R. T.; Joule, J. A. In *Comprehensive Organic Chemistry*, Vol. 4; Sammes, P. G., Ed.; Pergamon: Oxford, **1979**; pp 418-434. (c) Baxier, R. L.; Scott, A. I. In *Comprehensive Heterocyclic Chemistry*, Vol. 1; Katritzky, A. R., Ress, C. W.,



Scheme 29

Yadav and coworkers developed the synthesis of bis(indolyl)phenyl ethanes from a variety of substituted indoles and phenylacetylene using 10 mol% of $GaCl_3$ or $GaBr_3$ as catalyst in toluene at room temperature. On the other hand, diphenylacetylene and alkyl-substituted alkynes, such as *n*-octyne, failed to produce the desired compounds, even on heating under reflux (Scheme 30).[46]



Scheme 30

A single example of a reaction of *N*-methylindole with ethyl propiolate catalyzed by $AuCl_3$ to give a bis-indole product similar to the one showed in Scheme 30 was described by He. In this case, with an electron-deficient alkyne, the regioselectivity of

Eds.; Pergamon: Oxford, **1984**; pp 85-172. (d) Gibble, G. W. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R., Ress, C. W., Servien, E. F. V., Eds.; Pergamon: Oxford, **1996**; pp 207- 258.

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

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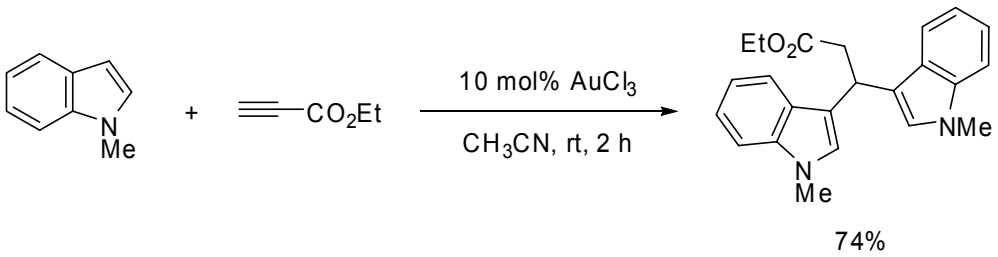
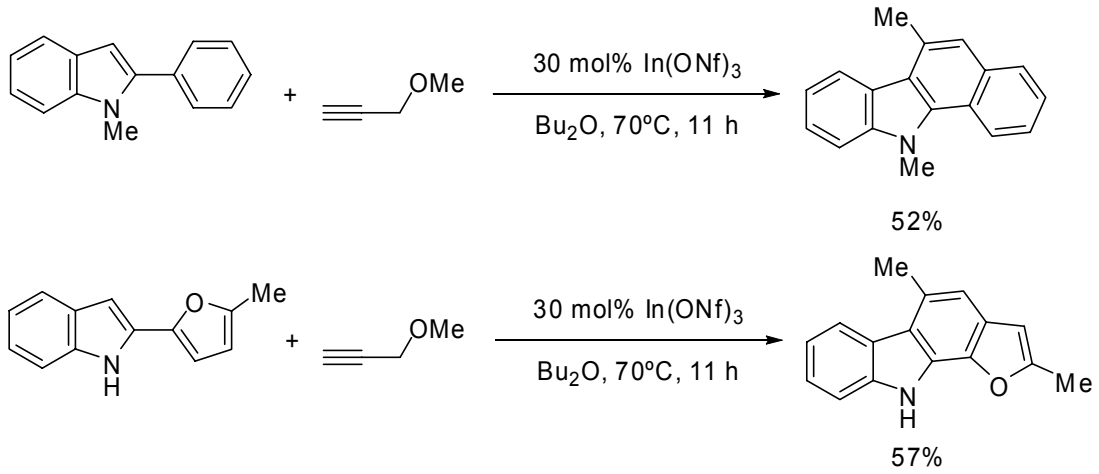
the reaction was the opposite to that of the reaction with phenylacetylene (Scheme 31).[47] This is in agreement with the regioselectivity observed in the intermolecular reaction of arenes with electron-rich and electron-deficient alkynes (see introduction section 2.1). For this reaction it was proposed that the first addition of the arene to ethyl propiolate gives an activated alkene, which reacts with the second equivalent of indole to afford the final product.



Scheme 31

Tsuchimoto *et al.* reported a new method for the synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles that uses an indium-catalyzed addition-substitution sequence of various 2-arylindoles with propargyl ethers. The reaction is best performed using $In(ONf)_3$ (Nf = nonaflate, $C_4F_9CO_3$) as catalyst in Bu_2O at 70ºC (Scheme 32).[48]

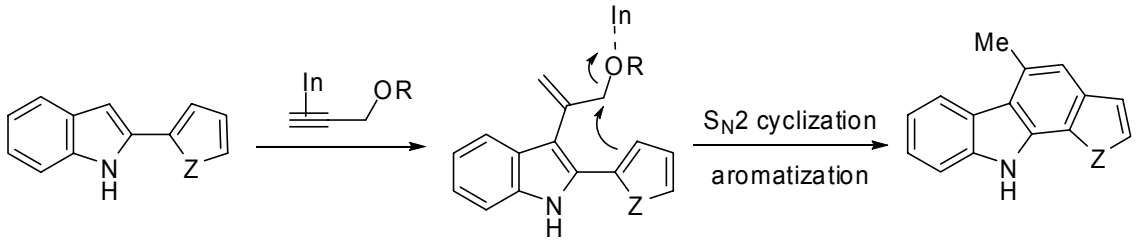


Scheme 32

47 Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049-5054.

48 Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 1336-1340.

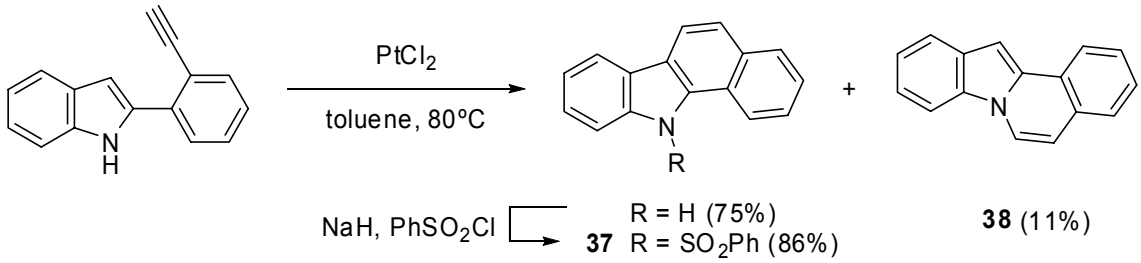
This annulation reaction is proposed to involve three distinct steps that comprise addition of the indole to a carbon-carbon triple bond activated by the indium, substitution of an alkoxy group with the arene and aromatization (Scheme 33).



Scheme 33

4.2. Metal-catalyzed intramolecular reaction of indoles with alkynes

Fürstner and coworkers extended their Pt(II)-catalyzed synthesis of phenantrenes (see introduction section 2.2) to the preparation of benzocarbazoles via the intramolecular reaction of indoles with alkynes.[28b] They applied this methodology to the synthesis of the antitumor agent **37**.[49] In this cyclization, small amounts of the isomeric product **38,** formed by attack of the unprotected indole nitrogen onto the alkyne, were also obtained. *N*-sulfonylation of the cyclized carbazole gave the antitumor agent **37** in very good overall yield (Scheme 34).



Scheme 34

One single example of a Pt(II)-catalyzed reaction of an indole bearing a propargylic ester has also been described by Sarpong in the synthesis of indenes discussed in this introduction, section 2.2 (Scheme 35).[35]

28 (b) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.

49 Pindur, U.; Lemster, T. *Recent Res. Dev. Org. Bioorg. Chem.* **1997**, 35-54.

35 Prasad, B. B. A.; Yoshimoto, F. Y.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127***,** 12468-12469.

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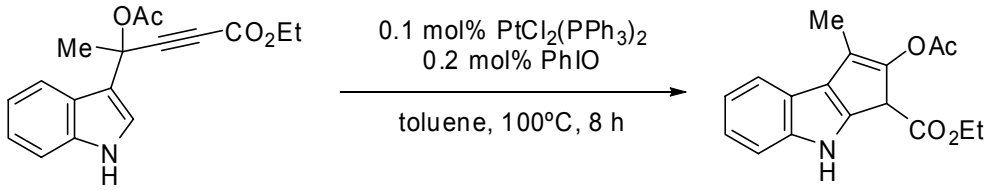
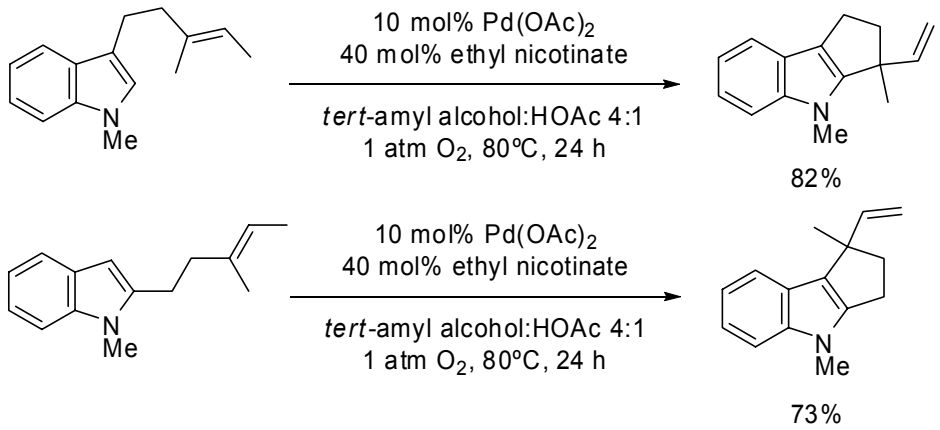


Scheme 35

5. Metal-Catalyzed Reaction of Indoles with Unactivated Alkenes

Analogously to the cyclizations of aryl alkynes, compounds containing carbon-carbon double bonds have also been shown to be valuable reagents for aromatic electrophilic substitution. Their use in catalytic alkylation processes has been developed to a lesser extent than the hydroarylation of alkynes. Several examples of reactions of indoles with unactivated alkenes, however, have been described in literature.

Stoltz and coworkers reported the aerobic oxidative annulation of indoles catalyzed by Pd(II)-pyridine complexes. The use of atmospheric oxygen as stoichiometric reoxidant for the Pd(0) allowed for the reaction to occur under mild conditions for both 2- and 3-subtituted indoles (Scheme 36).[50]

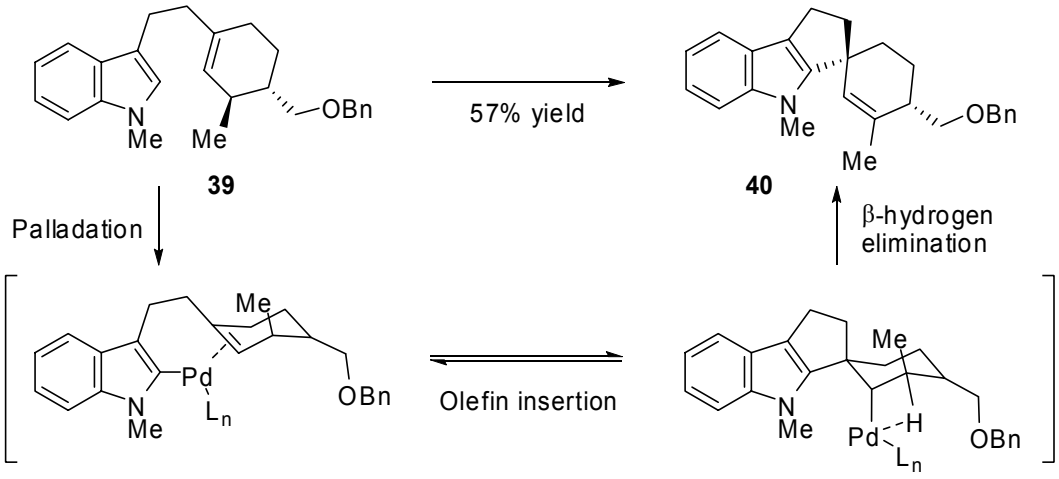


Scheme 36

Two possible mechanisms were proposed for this transformation: palladation at C-2 of the indole, followed by olefin insertion and β-hydrogen elimination (Heck type mechanism) and a mechanism involving Pd-mediated olefin activation and subsequent attack by the indole. To distinguish between these two possibilities, substrate **39** was

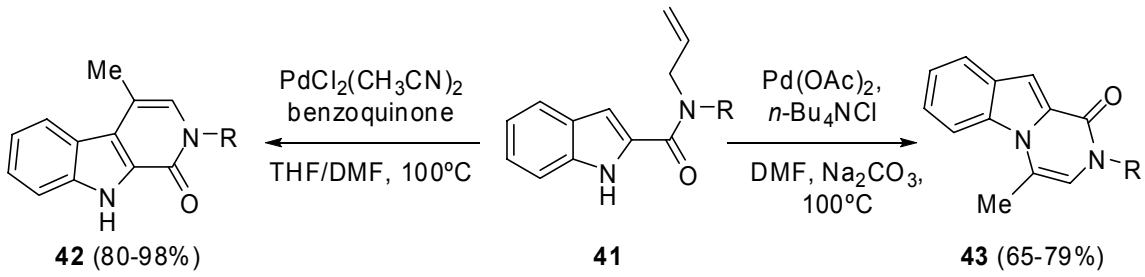
50 Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579.

subjected to the reaction conditions affording tetracycle **40** as a single diastereomer. The observed configuration of **40** supports a mechanism involving initial palladation, since the requirements for *syn* migratory insertion and *syn*-β-hydrogen elimination are operative (Scheme 37).



Scheme 37

An interesting change in the regioselectivity of this type of reactions depending on the catalyst used was observed by Beccalli and coworkers. When the reaction of indole-2-carboxamide **41** was carried out in the presence of $[PdCl_2(CH_3CN)_2]$ and benzoquinone as reoxidant, β-carbolinone **42** was obtained as the only product in excellent yield. When, on the other hand, $Pd(OAc)_2$ was used as catalyst, pyrazino[1,2-*a*]indole **43** was the only product formed (Scheme 38).[51]



Scheme 38

51 (a) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919-1921. (b) Abbiati, G.; Beccali, E. M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625-76-28.

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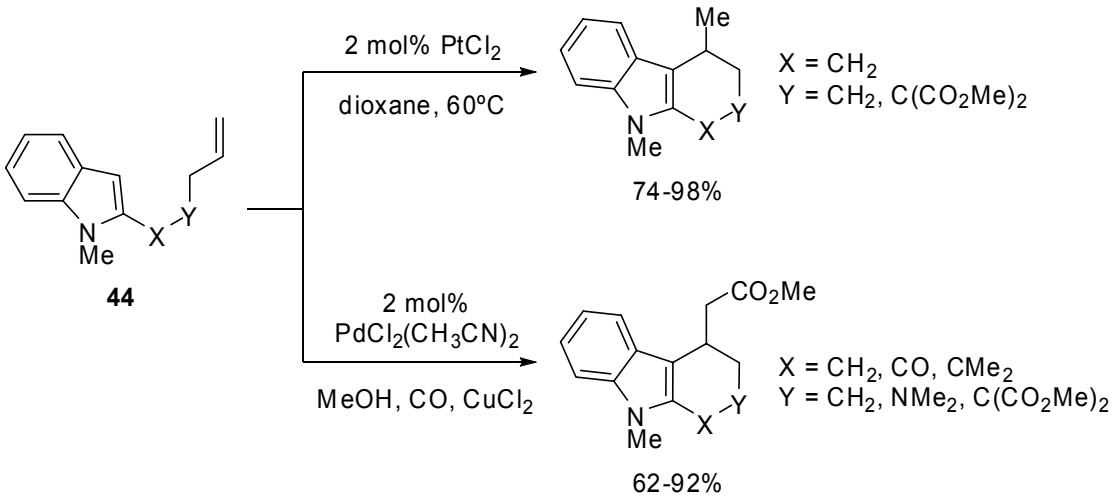
Widenhoefer and coworkers described the synthesis of biologically relevant tetrahydrocarbazoles and tetrahydro-β-carbolinones in good yields by cyclization and cyclization/carboalkoxylation of 2-(4-pentyl)indole derivatives **44** in the presence of platinum[52] and palladium[53] catalysts, respectively. The protocol proceeds by a chemo-selective 6-*exo-trig* cyclization and, in the case of the reactions catalyzed by Pd, stoichiometric amounts of Cu(II) salts are used as re-oxidants of the Pd(0) (Scheme 39).

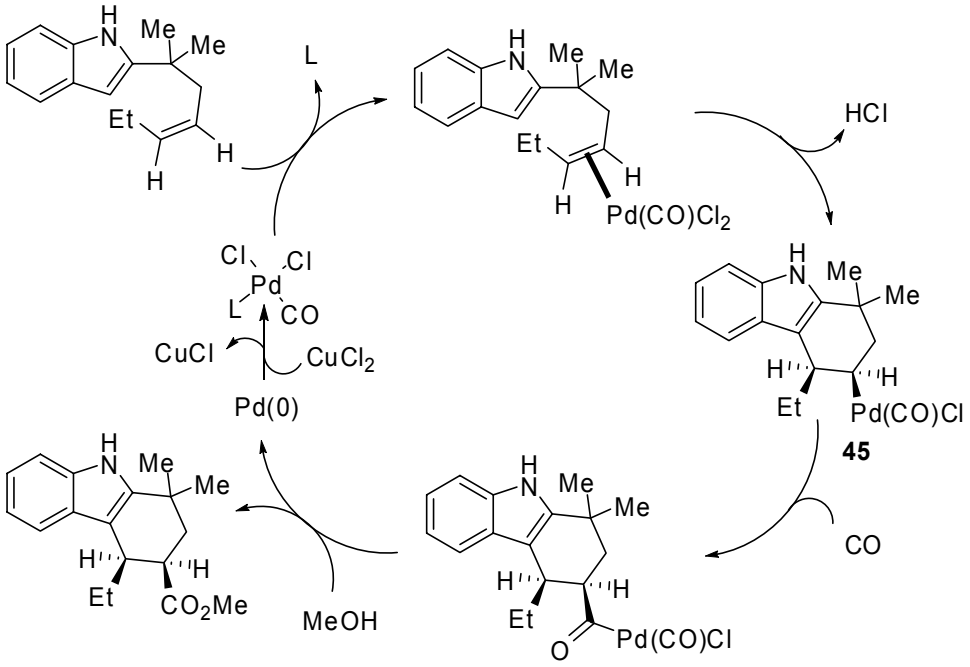


Scheme 39

In the reaction catalyzed by Pd, the cyclization and carboalkoxylation proceeded in a highly stereospecific way. Thus, *cis*-products were obtained from *Z*-alkenes and *trans*-products were formed from *E*-alkenes. Because the insertion of CO into a metal-carbon bond occurs with retention of stereochemistry at the metal-bound carbon atom, the stereospecific outcome of this reaction establishes *anti* addition of the indole and palladium across the carbon-carbon bond of the olefin. In contrast to the mechanistic proposal by Stoltz, this implies a mechanism involving attack of the indole on the palladium-olefin complex (Scheme 40). Subsequent loss of HCl forms the palladium alkyl intermediate **45**, followed by α-migratory insertion of CO into the Pd-C bond and methanolysis to release tetrahydrocarbazole and form a Pd(0) complex. $CuCl_2$ regenerates the catalyst by oxidation of the Pd(0) to Pd(II).

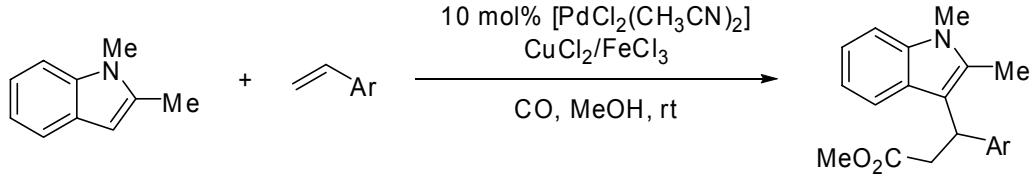
52 Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. *J. Am. Chem. Soc.* **2004**, *126*, 3700-3701.

53 Liu, C.; Widenhoefer, R. *J. Am. Chem. Soc.* **2004**, *126*, 10250-10251.



Scheme 40

More recently, Widenhoefer has developed an intermolecular arylation/ carboalkoxylation of vinyl arenes with indoles catalyzed by Pd in the presence of an excess of $CuCl_2$ and $FeCl_3$, in methanol at room temperature (Scheme 41).[54]



Scheme 41

A palladium-mediated intramolecular coupling between indole and tethered unactivated olefins has also been employed by Corey as the key step for the preparation of synthetically challenging indoloazocine tricyclic systems such as (+)-austamide (**46**) (Scheme 42). This reaction proceeds in the presence of a stoichiometric amount of Pd(II), using a mixture of THF and water and an oxygen atmosphere.[55,56]

54 (a) Liu, C.; Widenhoefer, R. A. *Chem. Eur. J.* **2006**, *12*, 2371-2382. (b) Zhang, Z.; Wang, X.; Widenhoefer, R. *Chem. Commun.* **2006**, 3717-3719.

55 (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.

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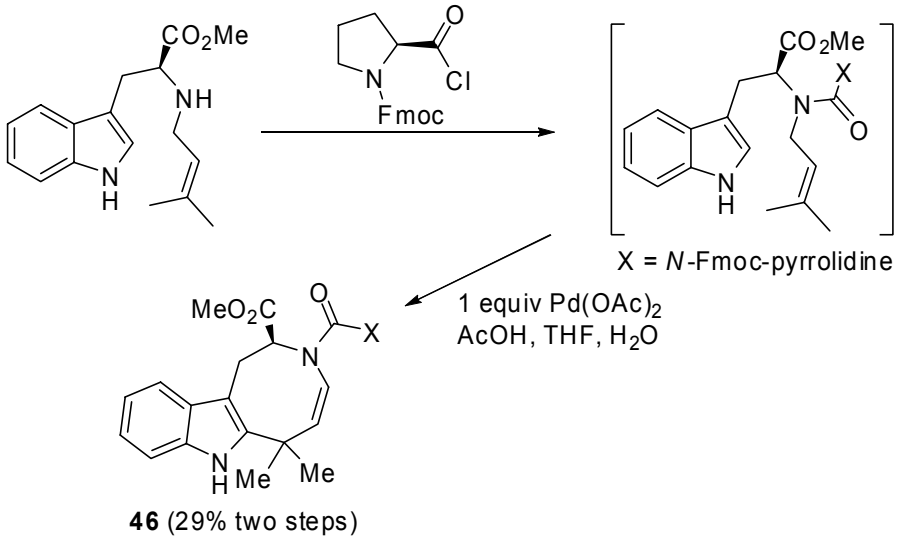


46 (29% two steps)

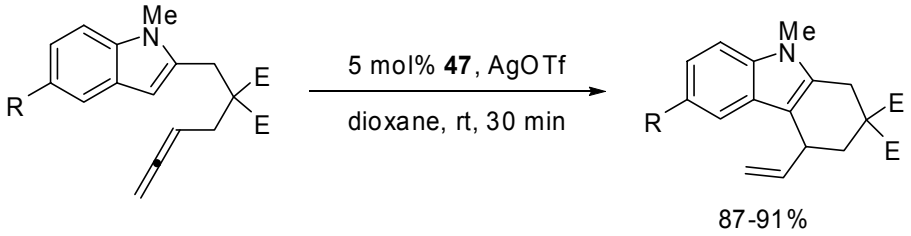
Scheme 42

6. Metal-Catalyzed Reaction of Indoles with Allenes

Widenhoefer and coworkers have also described the intramolecular reaction of indoles with allenes catalyzed by gold. Thus, mixtures of [AuCl(P(*t*-Bu)$_2$(*o*-byphenyl))] (**47**) and AgOTf in dioxane catalyze the room temperature 6-*exo*-*trig* hydroarylation of 2-allenyl indoles to form functionalized tetrahydrocarbazoles (Scheme 43).[57] Other metals, such as palladium or platinum, proved to be ineffective for this transformation. This reaction works well for allenyl indoles that posses either an electron-donating or an electron-withdrawing group on the indole moiety, and the protocol tolerates substitution at either the internal or terminal allenyl carbon atom. Also one example of a 7-*exo*-*trig* cyclization has been described. The reaction has been proposed to proceed via activation of the allene by gold followed by attack of the indole.

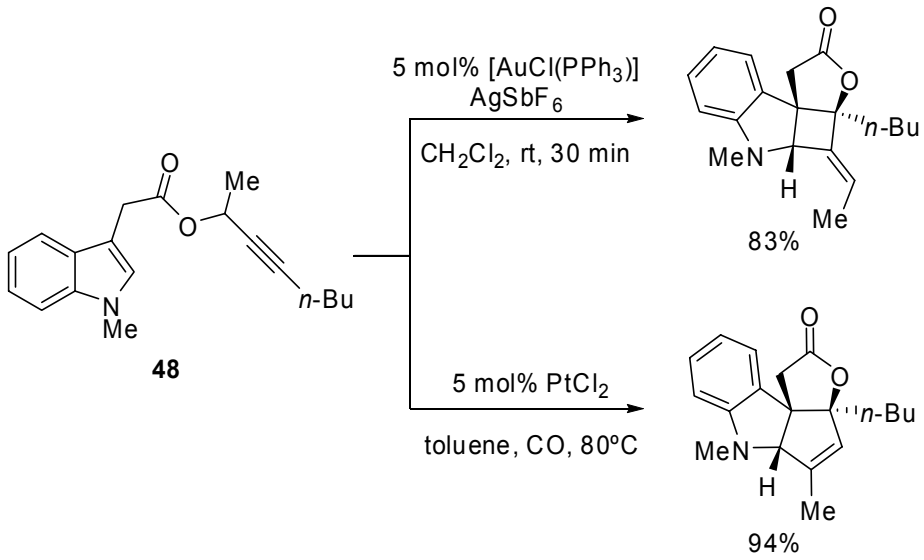
56 For other total synthesis involving reaction of indoles with unactivated alkenes with stoichiometric amounts of Pd see: (a) Trost, B. M.; Godleski, S. A.; Genêt, J.-P. *J. Am. Chem. Soc.* **1978**, *100*, 3930-3931. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323-9324.

57 Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073. For an enantioselective version of this reaction: Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935-1938.



Scheme 43

Another interesting change in reactivity depending on the catalyst was observed by Zhang and coworkers in the reaction of propargylic indole acetates of type **48** (Scheme 44). When the reaction was carried out with a gold catalyst tetracyclic 2,3-indoline-fused cyclobutanes were the main product obtained.[58] When the catalyst used was $PtCl_2$, however, the products formed were tetracyclic 2,3-indoline-fused cyclopentenes.[59]



Scheme 44

The first step in the mechanism proposed for this transformation is a metal-catalyzed 3,3-rearrangement to form carboxyallene **49** (Scheme 45), which can be further activated by the same catalyst. Nucleophilic attack of the indole 3-position forms the metal-containing lactone which diverges into different products: in the case of Au

58 Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805.

59 Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358-11359.

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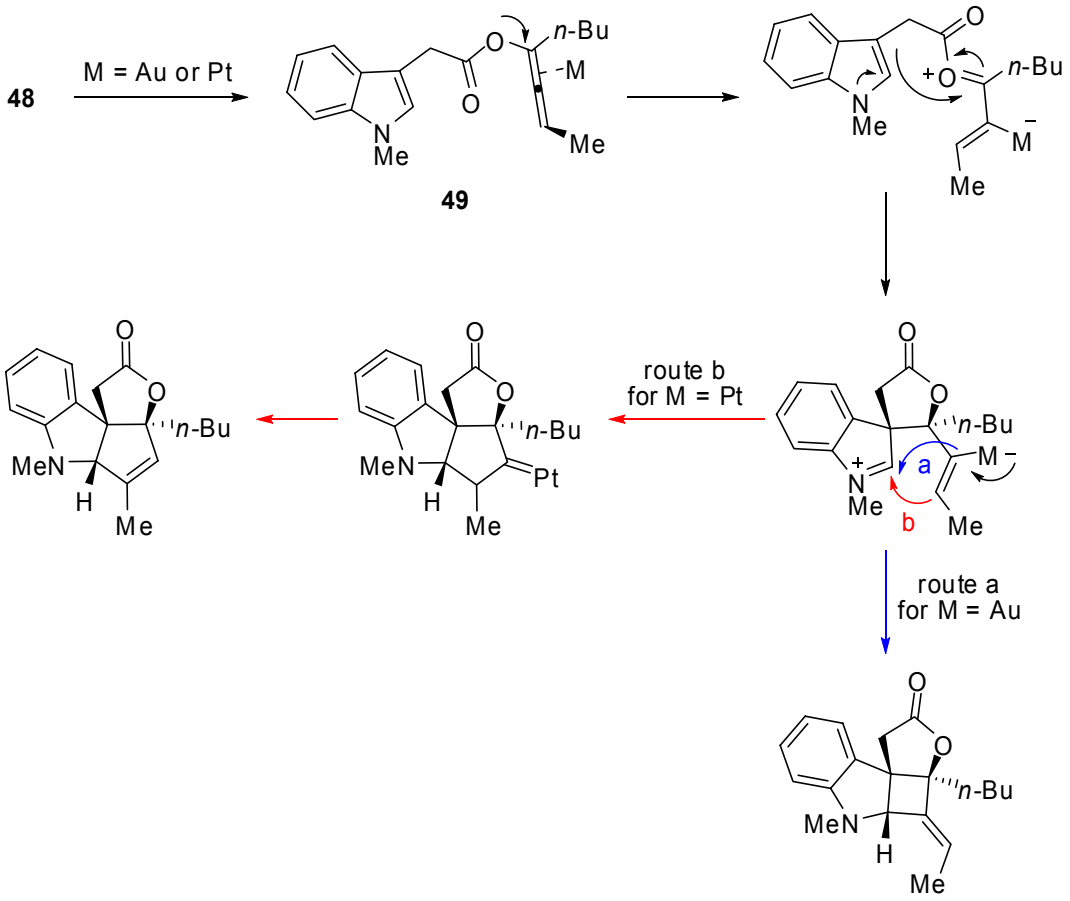
(route a) a cyclobutene is formed in a formal [2+2] cycloaddition, and in the case of Pt (route b) a 5-*exo* cyclization occurs to give the observed cyclopentenes.



Scheme 45

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Chapter 1. Objectives

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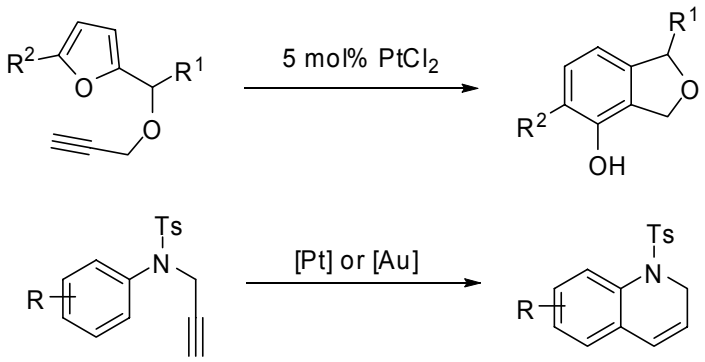
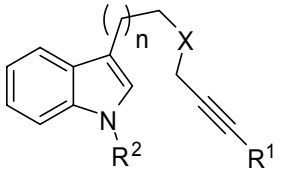
Based on the work carried out in our group on the reactions of furans with alkynes, and the reactions of arenes with alkynes described in the introduction and summarized in Scheme 46, we decided to study in detail the reactivity of indoles with alkynes.



Scheme 46

Given the very few literature precedents of intramolecular reactions of indoles with alkynes, we wanted to investigate the reactivity of compounds of type **50** (Figure 2). In particular, we were interested in the regiochemistry of the ring-closure step (*exo vs*. *endo* cyclizations) and the scope and limitations with regard to protecting- and other functional groups present in the starting substrates. Because of the high catalytic activity demonstrated for new gold complexes developed in our group, gold was chosen as the catalyst for these reactions.



50

Figure 2

We were also interested in expanding the scope of the intermolecular reaction of indoles with alkynes and in gaining a better understanding of the mechanism of the hydroarylation of alkynes with indoles.

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Chapter 1. Results and discussion

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1. Cyclization of Indoles with Alkynes[60,61]

We tested new Au(I) complexes bearing bulky phosphines in the reaction of indoles with alkynes. In general, for most of the reactions, the best catalyst is cationic gold(I) complex **1**,[7] which allows the reactions to be carried out in the absence of silver salts. This complex is an air-stable white solid, which is readily prepared from the corresponding gold-chloride complex. In addition to catalyst **1**, we routinely screened in most cases the performance of Au(I) catalysts **51**, **52**,[62] Au(III) catalyst **53**,[63] (Figure 3) as well as AuCl and $AuCl_3$.

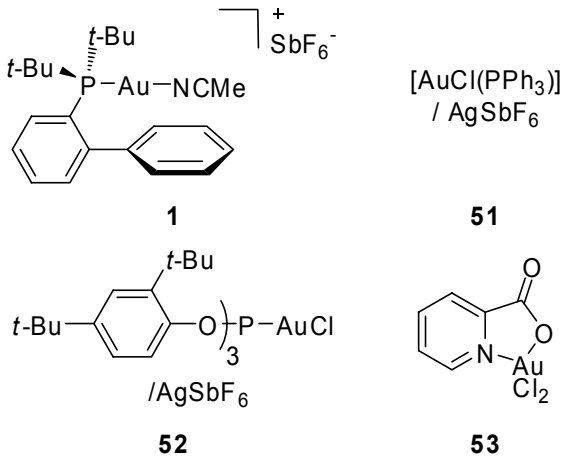


Figure 3

Among the solvents screened ($MeNO_2$, acetone, DMF, CH_2Cl_2, toluene), the best results were usually obtained in CH_2Cl_2, although toluene could also be used. Thus,

60 Taken from: Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105-1109 and Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358-1373.

61 Part of this work has been done in collaboration with Dr. Catelijne H. M. Amijs.

7 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694-1702. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

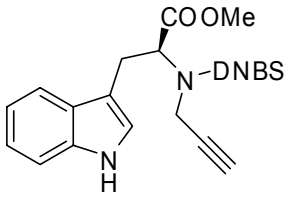
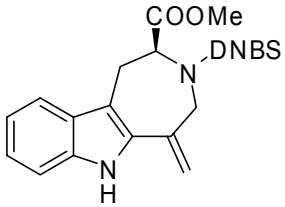
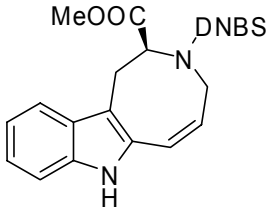
62 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032.

63 (a) Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc., Dalton Trans.* **1992**, 1907-1913. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

tryptophane derivative **54** reacted with complex **1** as catalyst at room temperature for 30 min to give cleanly azepino[4,5-*b*]indole **55** in a 7-*exo-dig* cyclization (Table 1, entry 1).[64] In contrast, reaction of **54** with $AuCl_3$ gave cleanly indoloazocine **56**, formed in a rare 8-*endo-dig* process (Table 1, entry 2). Reaction with AuCl also provided **56**, although in this case significant amounts of depropargylated starting material were also obtained (Table 1, entry 3). Reaction of **54** with catalyst **51** was less selective and a 1.3:1 mixture of **55** and **56** was obtained (Table 1, entry 4). Similar results were obtained from indole derivatives **57** and **61** (Table 1, entries 5-9), although in these cases reaction with $AuCl_3$ gave indoloazocines **59** and **63** along with seven-membered ring derivatives **60** and **64**, respectively (Table 1, entries 6 and 9). Reactions with AuCl only led to low conversions. *N*-Allylindole **65** provided seven-membered ring derivative **66** with catalyst **1** (Table 1, entry 10).

Surprisingly, when indole **65** was treated with $AuCl_3$ in CH_2Cl_2 at room temperature for 16 h, allene **67** was obtained as a result of an overall intramolecular allenylation at C-2 of the indole by the *N*-propargyl chain (Table 1, entry 11).

Table 1. Cyclization of tryptophane and tryptamine derivatives with terminal alkynes.[a]

	Indole	Cat.	t (h)	Products (ratio, yield)
1	 **54**	**1**	0.5	 **55** (82%)
2	**54**	$AuCl_3$	0. 5	 **56** (75%)
3	**54**	AuCl	1	**56** (70%)
4	**54**	**51**	0.5	**55** + **56** (1.3:1, 80%)

64 See the experimental section for the synthesis and characterization data of starting indoles.

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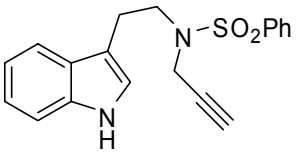
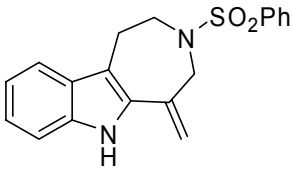
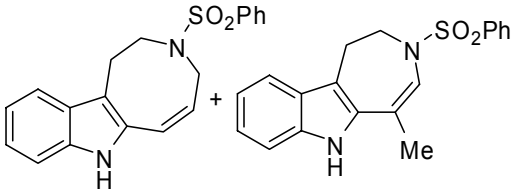
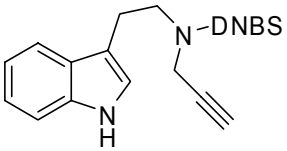
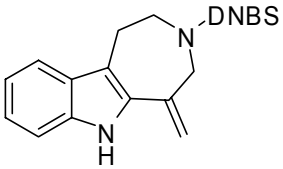
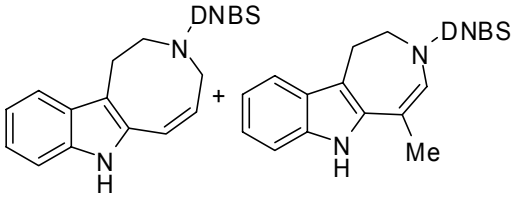
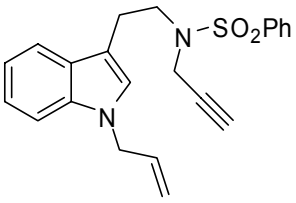
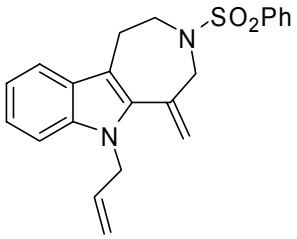
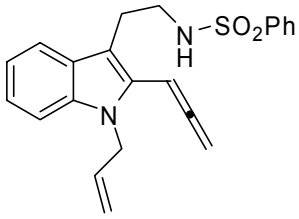
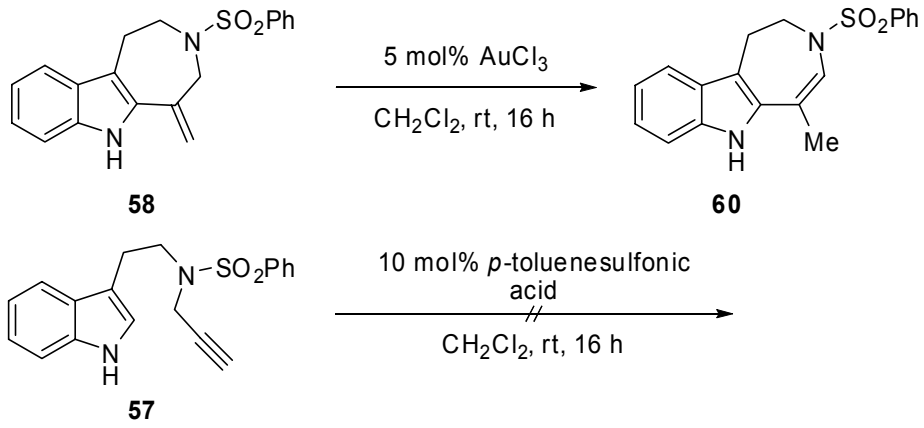
	Indole	Cat.	t (h)	Products (ratio, yield)
5	 **57**	**1**	16	 **58** (65%)
6	**57**	$AuCl_3$	24	 **59** (58%) **60** (13%)
7	**57**	**51**	16	**58** + **59** (4:1, 65%)
8	 **61**	**1**	16	 **62** (77%)
9	**61**	$AuCl_3$	16	 **63** (64%) **64** (23%)
10	 **65**	**1**	0.5	 **66** (68%)
11	**65**	$AuCl_3$	16	 **67** (62%)

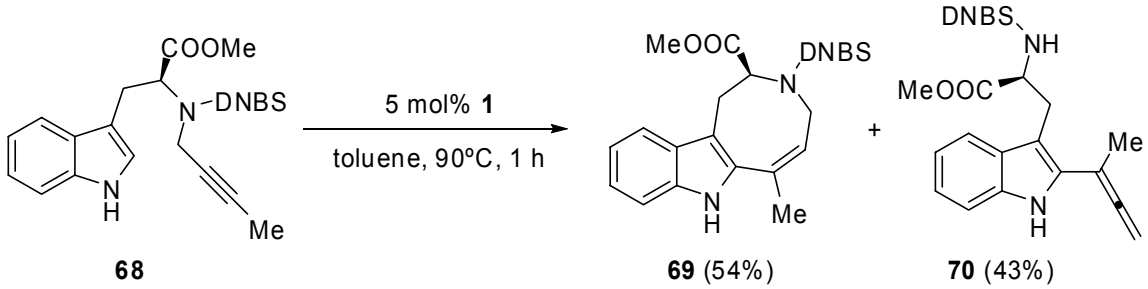
(a) Reactions in CH_2Cl_2 at room temperature with 5 mol% of catalyst.

As expected, treatment of **58** with 5 mol% $AuCl_3$ led quantitatively to **60** (Scheme 47). Protic acids do not promote the cyclization of these substrates. Thus, treatment of **57** with *p*-toluenesulfonic acid for 16 h led only to unchanged starting material (Scheme 47).



Scheme 47

The reaction of tryptophane derivative **68** with a non terminal alkyne provided indoloazocine **69** and allene **70**, after being heated in toluene at 90°C with catalyst **1** (Scheme 48). This reaction did not proceed at room temperature. Allene **72** was obtained in 62% yield in the reaction of **71**. On the other hand, **73** gave tetracyclic derivative **74** which structure was confirmed by X-ray crystallography (Figure 4). Only unreacted starting material was recovered when these reactions were carried out with **51** or $AuCl_3$ as catalyst.



68 **69** (54%) **70** (43%)

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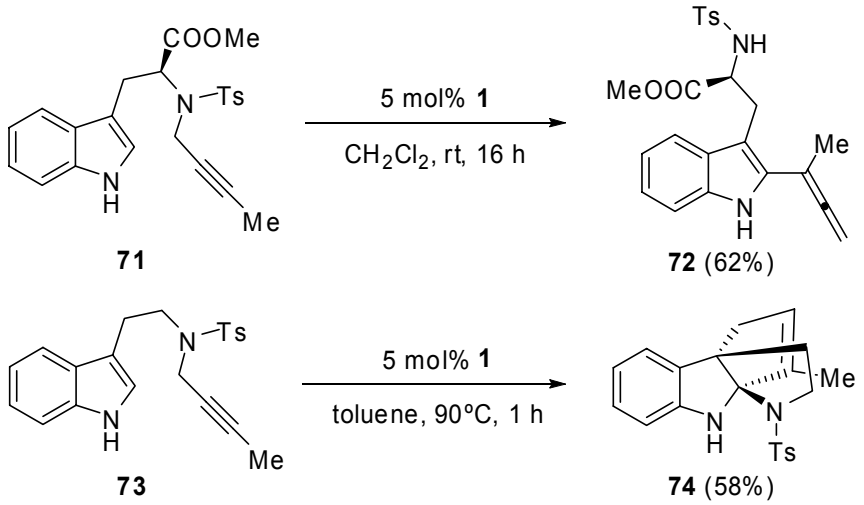


Scheme 48

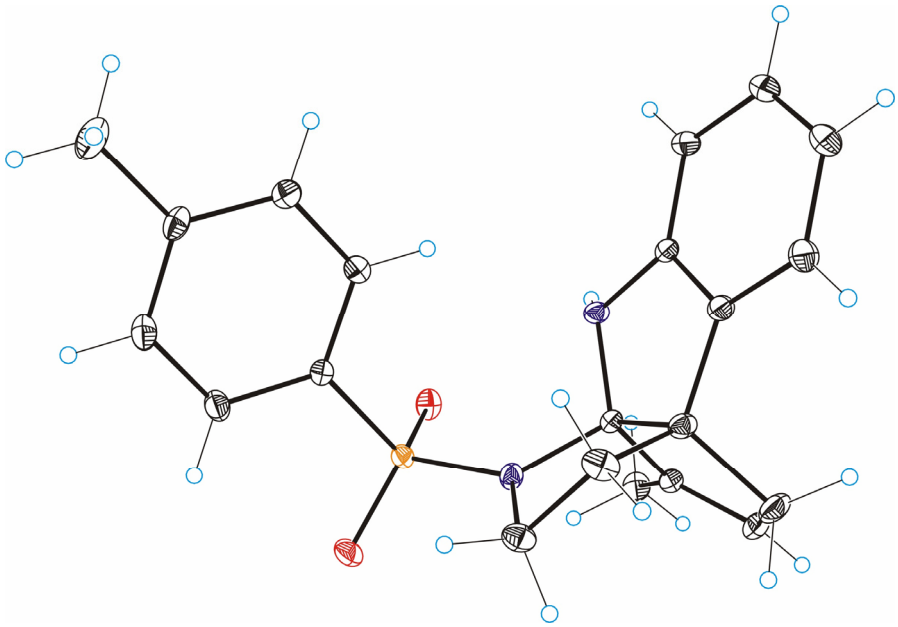
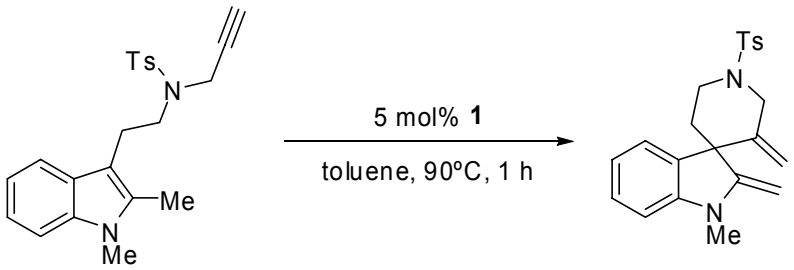


Figure 4. X–Ray structure of **74**

Importantly from a mechanistic point of view (see below), tryptamine derivative **75**, with a methyl group at the 2-position, underwent cyclization with catalyst **1** to form cleanly spiro 2-methyleneindolenenine **76** (Scheme 49).[65]

65 For other spiro derivatives obtained by attack of the 3-postion of the indole: (a) Pawda, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256-4268. (b) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907-2910.

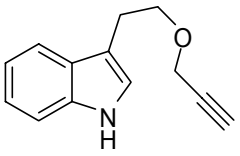
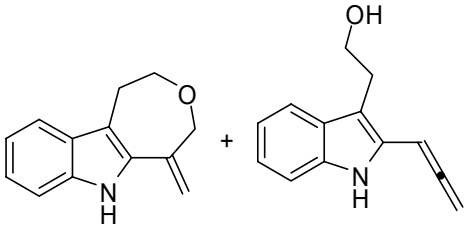
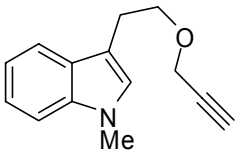
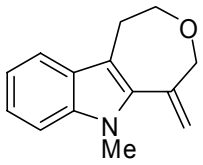


75 **76**

Scheme 49

Propargylic tryptophol derivatives also led to cyclized compounds with gold(I) catalysts (Table 2). Thus **77** reacted with catalyst **1** at room temperature to give a mixture of oxepino[4,5-*b*]indole **78** and allene **79** (Table 2, entry 1). Oxepino[4,5-*b*]indole **81** was the exclusive product in the cyclization of **80** with catalyst **1**, whereas AuCl or catalyst **53** led to mixtures of **81** and allene **82** (Table 2, entries 2-4). Similar results were obtained in the reactions of **83** and **86** with catalyst **1** (Table 2, entries 5 and 6). Only traces of eight-membered ring compounds were detected in the crude reaction mixtures when $AuCl_3$ or AuCl were used as catalysts in transformations of tryptophol derivatives.

Table 2. Cyclization of tryptophol derivatives with terminal alkynes.[a]

	Indole	Cat.	t (h)	Products (ratio, yield)
1	 **77**	**1**	16	 **78** (64%) + **79** (25%)
2	 **80**	**1**	1	 **81** (86%)

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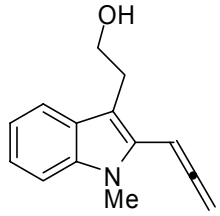
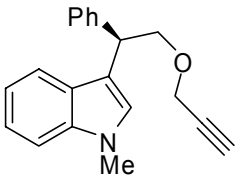
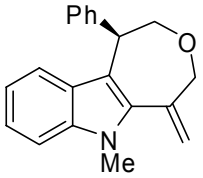
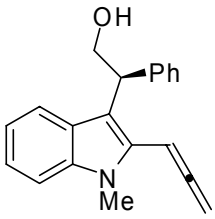
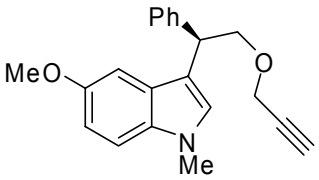
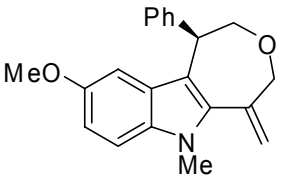
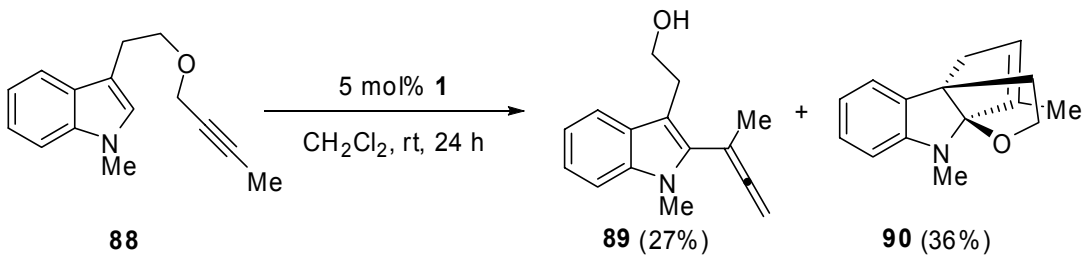
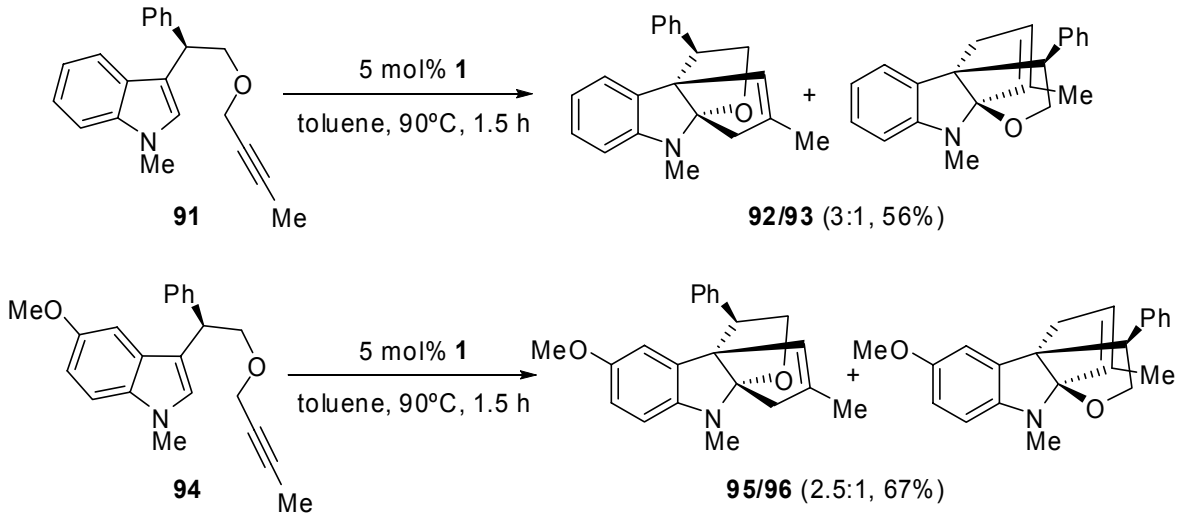
	Indole	Cat.	t (h)	Products (ratio, yield)
3	**80**	AuCl	36	**81** (14%) +  **82** (27%)
4	**80**	**53**	16	**81** (22%) + **82** (38%)
5	 **83**	**1**	0.5	 +  **84** (69%) **85** (17%)
6	 **86**	**1**	1	 **87** (89%)

(a) Reactions in CH_2Cl_2 at room temperature with 5 mol% of catalyst.

Reaction of substrate **88** with a disubstituted alkyne proceeded more sluggishly to furnish allene **89** and tetracycle **90** (Scheme 50). Tetracyclic derivative **90** was the only isolated product after 1.5 hours with 67% yield when the reaction was carried out in toluene at 90°C. Cyclization of **91** and **94** with catalyst **1** proceeded similarly to give mixtures of diastereomers **92**/**93** and **95**/**96**, respectively.



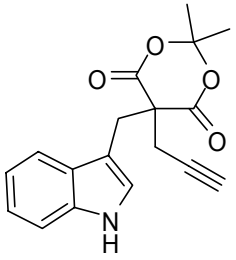
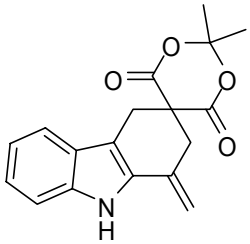
88 **89** (27%) **90** (36%)



Scheme 50

Substrate **97**, with a tether of only three atoms, reacted satisfactorily with catalyst **1** by a 6-*exo-dig* pathway to give **98** (Table 3, entry 1), whereas catalyst **51** gave **98** in lower yield (Table 3, entry 2) along with dimer **99** (Figure 5). The configuration of **99** at the exocyclic double bond was determined by a NOESY experiment. Decomposition of **97** was observed with $AuCl_3$. Derivative **100**, a substrate with a tether of only two atoms, reacted by a 6-*endo-dig* pathway with Au(I) catalyst **1** or **51** to give **101** (Table 3, entries 3 and 4). In this case, no cyclization was observed with $AuCl_3$. Reaction of **102,** with an unprotected propargyl alcohol moiety, proceeded uneventfully with Au(I) catalyst **1** and **51** to give **103**, although with catalyst **51** the yield was lower (Table 3, entries 5 and 6). In contrast, reaction of **102** with $AuCl_3$ furnished ketone **104**, as a result of isomerization of the exocyclic double bond (Table 3, entry 7).

Table 3. Cyclization of indoles with alkynes tethered by 2-3 carbons chains.[a]

	Indole	Cat.	t (h)	Products (ratio, yield)
1	 **97**	**1**	0.2	 **98** (68%)
2	**97**	**51**	0.5	**98** (54%) + **99** (25%)

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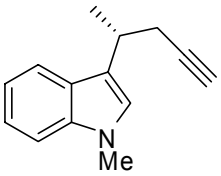
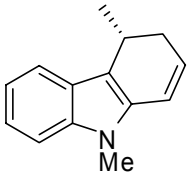
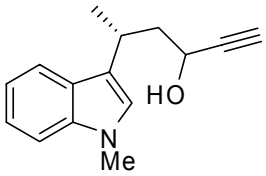
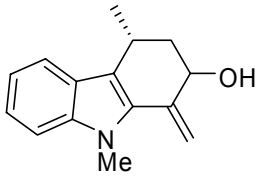
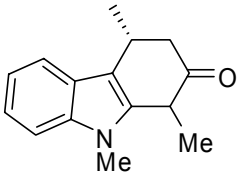
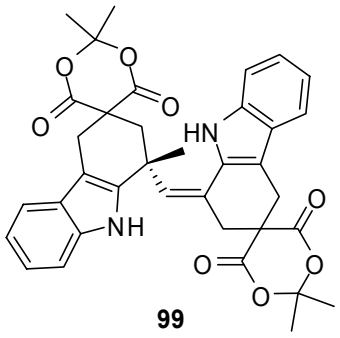
	Indole	Cat.	t (h)	Products (ratio, yield)
3	 **100**	**1**	1	 **101** (92%)
4	**100**	**51**	16	**101** (63%)
5	 **102**	**1**	0.2	 **103** (72%)
6	**102**	**51**	0.2	**103** (60%)
7	**102**	$AuCl_3$	0.2	 **104** (100%)

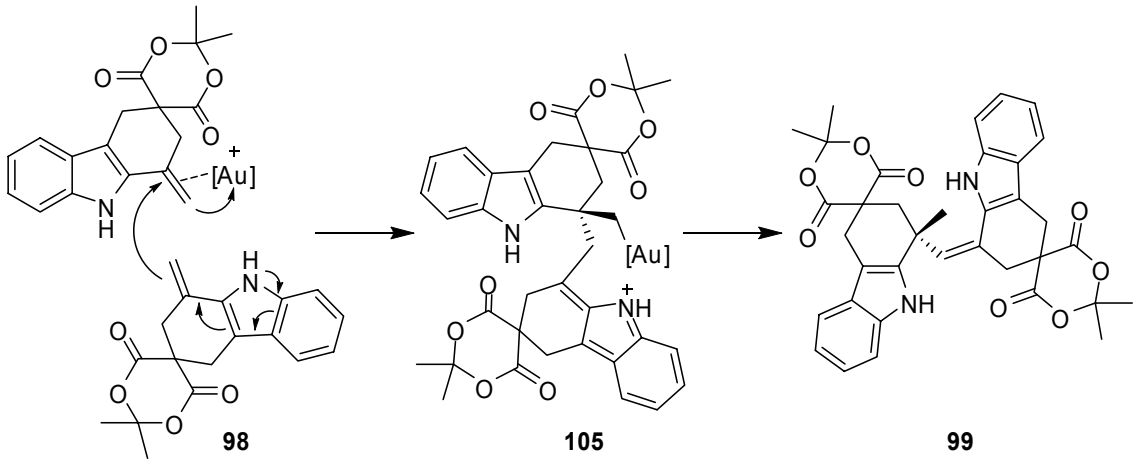
(a) Reactions in CH_2Cl_2 at room temperature with 5 mol% of catalyst.



99

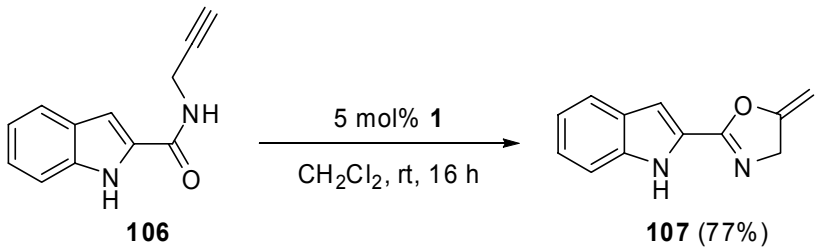
Figure 5

We propose that the formation of dimer **99** proceeds through the activation of the alkene in compound **98** by gold. The activated alkene-gold complex suffers nucleophilic attack of another indole unit **98**, leading to intermediate **105**, which evolves by protonation of the carbon-gold bond and rearomatization of the indole to give the observed product (Scheme 51). A similar proton-catalyzed reaction, however, cannot be excluded.



Scheme 51

Amide **106** afforded 5-methylene-4,5-dihydrooxazole **107** in 77% yield with catalyst **1** (Scheme 52). Catalyst **51** and $AuCl_3$ led also to **107**, albeit in lower yield (56-57%, 16 h, room temperature). This type of reactivity has been described by Hashmi[66] using $AuCl_3$ as catalyst, although it was reported that the 5-methylene-4,5-dihydrooxazoles suffered isomerization to the oxazoles under the reaction conditions. In our case, **107** proved to be remarkably stable and did not isomerize to the corresponding oxazole with Au(I) or Au(III) catalysts.



Scheme 52

2. Intermolecular Reaction of Indoles with Alkynes

The reaction of simple indoles with terminal alkynes proceeded satisfactorily in the presence of Au(I) catalysts to give bisindoles **109** in a general way (Table 4). The best results were again obtained with catalyst **1**, although the more electrophilic catalyst **52** could also be used. For this intermolecular process, toluene proved to be the solvent of choice in most cases. The reaction of indoles **108a-b** with aryl alkynes gave

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

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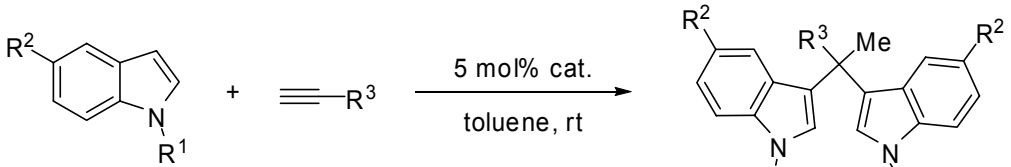
bisindoles **109a-g** (Table 4, entries 1-7). A single regioisomer was obtained in all cases, regardless on the nature of the substituents on the aryl. This regiochemistry is in contrast to that found by He and coworkers in the reaction of **108b** with ethyl propiolate using $AuCl_3$ as catalyst (Scheme 31).[47] The reaction shows that substituents on the indole or the aryl are well tolerated. Unlike $GaCl_3$, which was only active with phenylacetylene (Scheme 30),[46] cationic gold(I) complexes also catalyze the reaction of indoles with alkyl-substituted alkynes (Table 4, entries 8-14).

Table 4. Intermolecular reaction of indoles with alkynes.



108a $R_1 = R_2 = H$
108b $R_1 = Me$, $R_2 = H$
108c $R_1 = H$, $R_2 = CN$
108d $R_1 = H$, $R_2 = Br$

109a-n

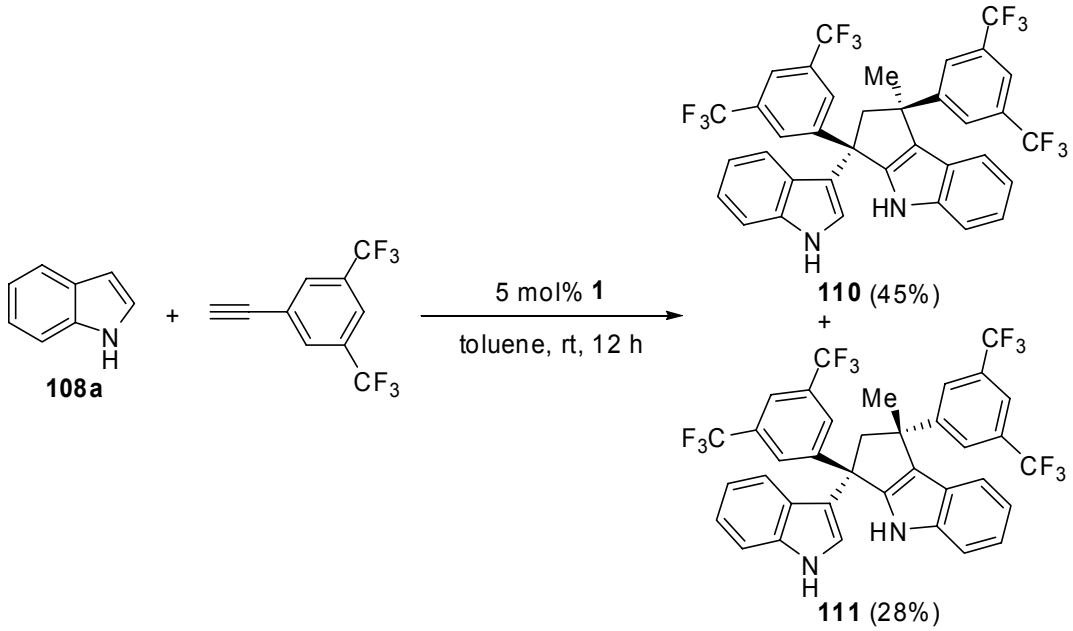
	Indole	R^3	Cat.	t (h)	Product	Yield (%)
1	**108a**	Ph	**1**	6	**109a**	99
2	**108b**	Ph	**1**	20	**109b**	89
3	**108a**	*p*-$MeOC_6H_4$	**1**	24	**109c**	71
4	**108a**	*p*-$O_2NC_6H_4$	**1**	6	**109d**	82
5[a]	**108a**	3,5-$(F_3C)_2C_6H_3$	**1**	6	**109e**	98
6	**108a**	3,5-$F_2C_6H_3$	**1**	6	**109f**	99
7	**108a**	1-pyrenyl	**52**	72	**109g**	53
8	**108a**	*n*-C_7H_{15}	**1**	6	**109h**	82
9	**108b**	*n*-C_7H_{15}	**1**	8	**109i**	84
10	**108a**	$ClCH_2(CH_2)_3$-	**1**	6	**109j**	73
11	**108a**	$NCCH_2(CH_2)_3$-	**1**	8	**109k**	83
12[a]	**108c**	*n*-C_7H_{15}	**1**	72	**109l**	67
13	**108d**	$NCCH_2(CH_2)_3$-	**1**	8	**109m**	76
14[a]	**108a**	cyclopropyl	**52**	15	**109n**	89

(a) Reaction in CH_2Cl_2 at room temperature with 5 mol% of catalyst.

47 Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049-5054.

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

In contrast to the clean formation of **109e** in the reaction between indole (**108a**) and 3,5-bis(trifluoromethyl)phenylacetylene carried out in CH_2Cl_2 (Table 4, entry 5), when the reaction was performed in toluene a mixture of [2+2] adducts **110/111** was obtained (Scheme 53). Related dimers have been obtained in the acid-catalyzed reaction of indoles with ketones.[67]



Scheme 53

Interestingly, reaction of indole (**108a**) with prop-1-ynylbenzene led to **112** by reaction at the carbon β to the phenyl (Scheme 54), which is in contrast to that observed with aryl substituted terminal alkynes (Table 4). The reaction can also be extended to pyrroles. Thus, 2-ethylpyrrole (**113**) reacted with phenylacetylene to give 2+1 adduct **114** in very good yield.

67 Black, D. S. C.; Craig, D. C.; Kumar, N. *Tetrahedron Lett.* **1991**, *32*, 1587-1590.

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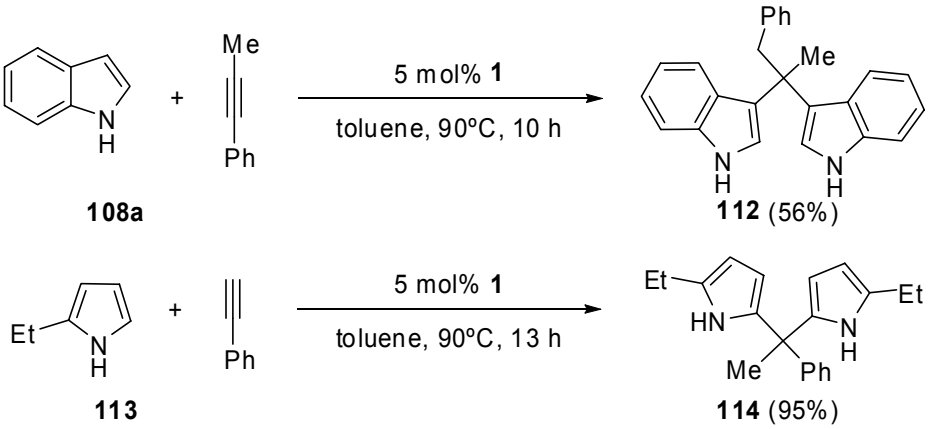
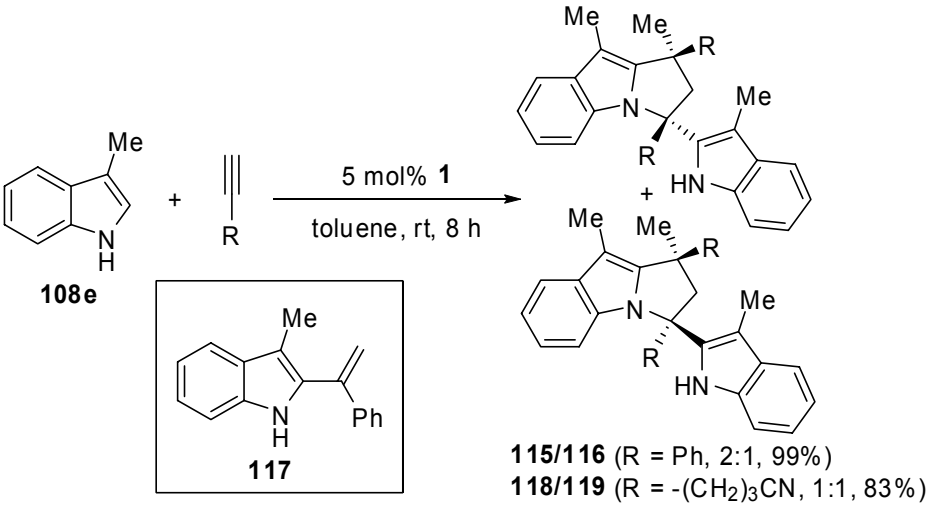


Scheme 54

When the C-3 position was substituted, the alkenylation occurred at C-2. Thus, skatole (**108e**) reacted with phenylacetylene to give a mixture of **115/116** as a result of the dimerization of the initially formed **117**,[68] which could not be isolated under these reaction conditions. Similarly, **118/119** were obtained in the reaction of **108e** with hex-5-ynenitrile (Scheme 55).

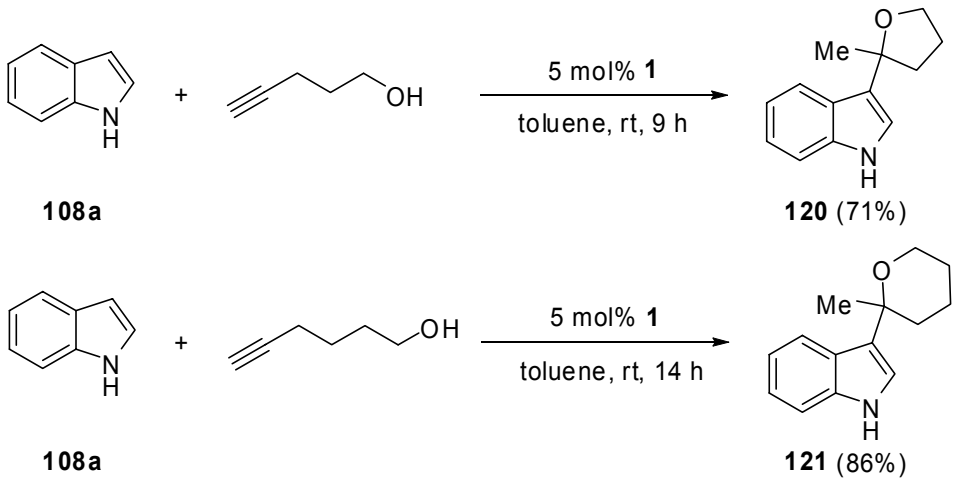


Scheme 55

When the reaction of **108a** was carried out with pent-4-yn-1-ol and catalyst **1**, tetrahydrofurane **120** was obtained as the only product (Scheme 56). Similarly, hex-5-yn-1-ol furnished **121**.[69]

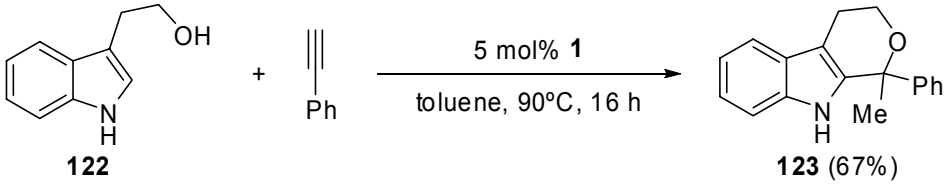
68 Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *4*6, 2979-2981.

69 The same kind of reactions catalyzed by $PtCl_2$ has been described recently: Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2007**, *13***,** 8285-8293.



Scheme 56

Reaction of tryptophol (**122**) with phenylacetylene occurred at the free C-2 position, followed by trapping of the resulting alkene by the alcohol to give tetrahydropyrano[3,4-*b*]indole **123** (Scheme 57). Compounds with this type of ring system have attracted attention as pharmaceuticals.[70]



Scheme 57

The alkenyl derivative **125** could be obtained in 69% yield in the reaction of protected tryptamine **124** with phenylacetylene (Scheme 58). In this case, the cyclization to give **126** did not occur under the reaction conditions, but could be carried out by treatment of **125** with trifluoroacetic acid. The reaction of **127** proceeded intramolecularly to give **128** and **129**.

70 Zhang, H.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett.* **2005**, *7*, 2043-2046, and references therein.

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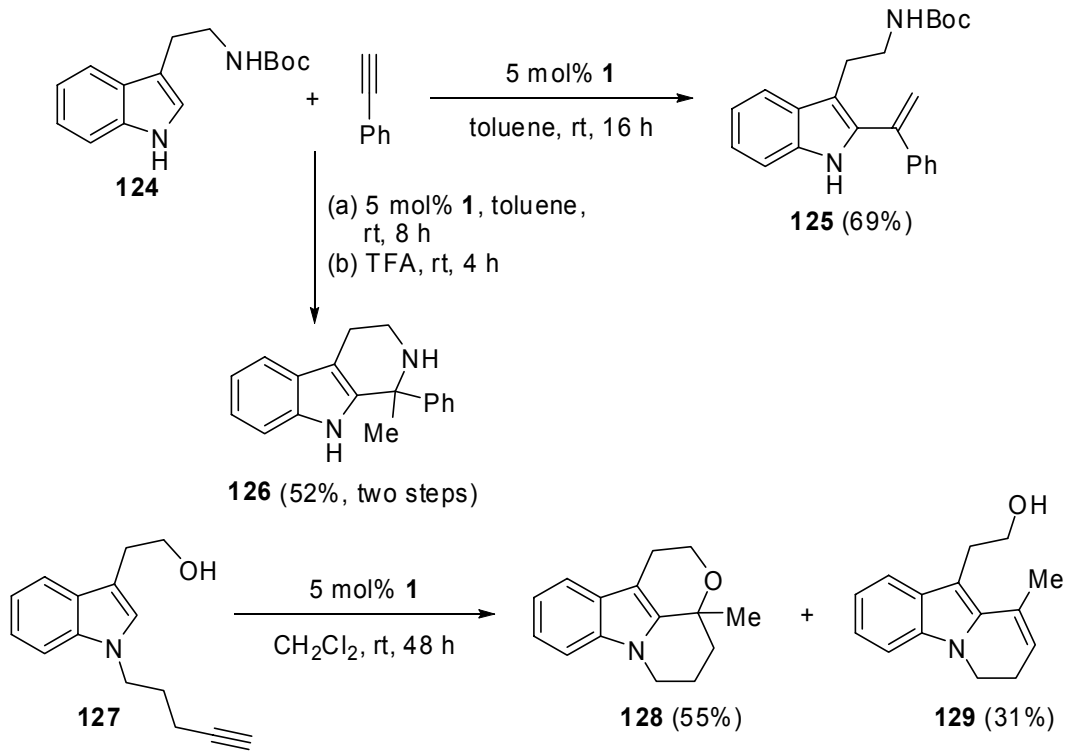


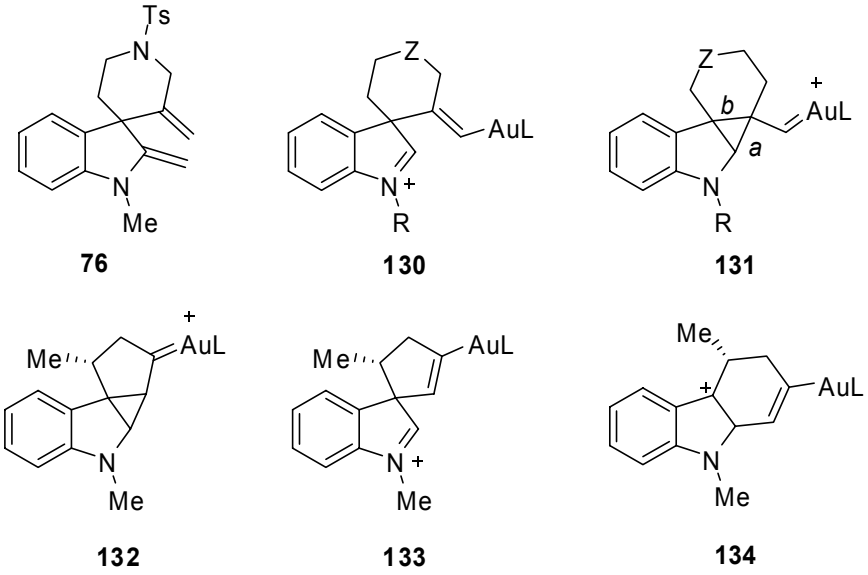
Scheme 58

3. Mechanistic Discussion

The isolation of spiro derivative **76** (Scheme 49) suggests that gold(I) catalyzed cyclizations of C-3 substituted indoles can take place by first forming a C-C bond at C-3, followed by a 1,2-migration to give the final indoles.[71] Thus, the 7-*exo*-*dig* cyclizations shown in Tables 1 and 2 presumably proceed via spiro derivatives of type **130** (Scheme 59). Intermediates **130** could be formed directly by a Friedel-Crafts-type reaction or indirectly, by opening of cyclopropyl carbenes **131** at C-C bond *a*.[30] Opening of **131** at C-C bond *b* however, cannot be excluded. Similar intermediates are probably involved in the 6-*exo*-*dig* cyclizations shown in Table 3. On the other hand, the 6-*endo*-*dig* cyclization of indole **100** (Table 3, entry 3 and 4) probably proceeds through intermediate **132**,[30] which can then open to form **133** or **134**.

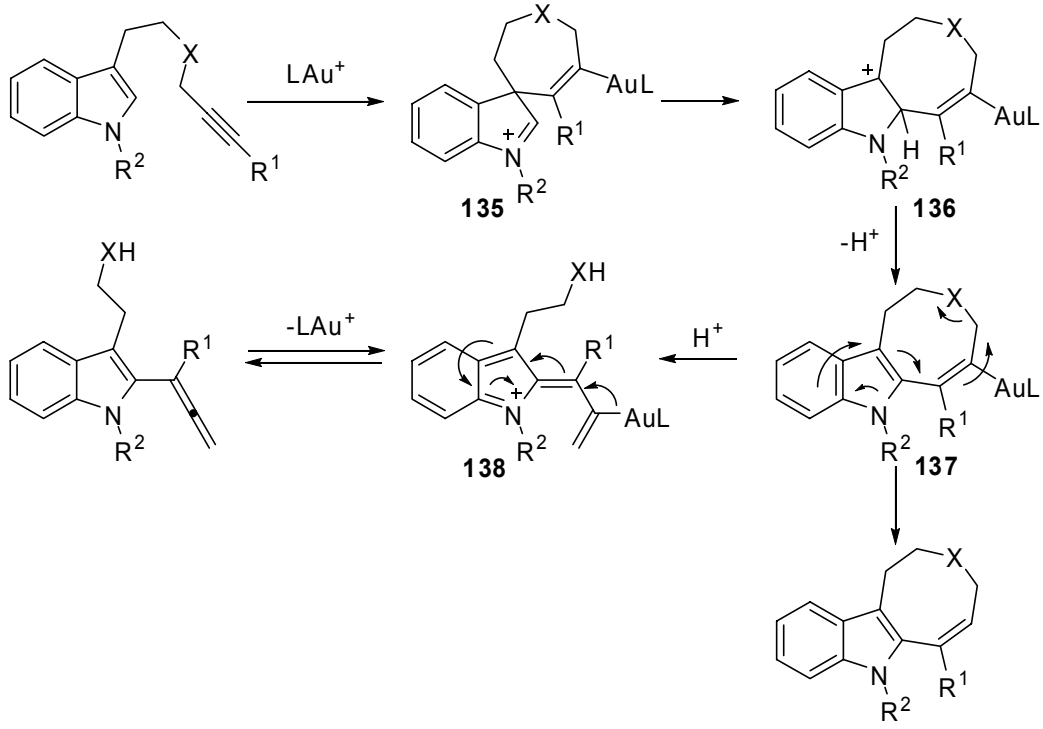
71 Involvement of 3,3-disubstituted indolenines in 1,2-migrations to form indoles: (a) Jackson, A. H.; Smith, P. *J. Chem. Soc., Chem. Commun.* **1967**, 264-266. (b) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 403-413. (c) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227-2239. (d) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439-440.

30 Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.



Scheme 59

Eight-membered ring compounds may also arise by a 1,2-shift of the initially formed seven-membered ring iminium cation **135** to form **136** (Scheme 60). Proton loss from **136** gives **137**, from which eight-membered ring compounds are formed by protodemetalation. An alternative elimination from **137** yields allenes via cationic intermediate **138**, upon protodemetalation and rearomatization.



Scheme 60

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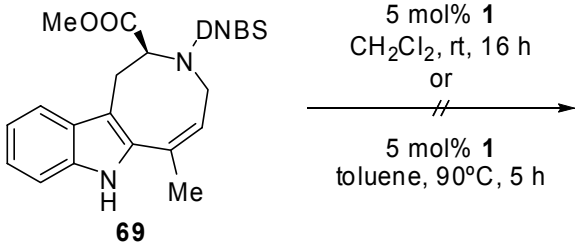
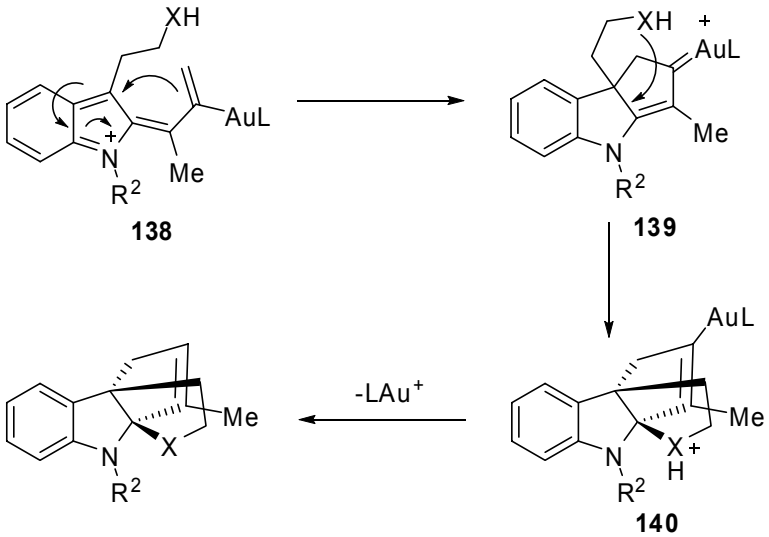
Fragmentation does not occur once the final indoloazocines have been formed. Thus, treatment of **69** with complex **1** in CH_2Cl_2 at room temperature for 16 h or in toluene at 90°C for 5 h led only to unchanged starting material (Scheme 61). Importantly, the fact that substrate **68**, with a methyl at C-2 of the alkyne, gives an indoloazocine of type **69** excludes the involvement of gold vinylidenes in these cyclizations.[30]



Scheme 61

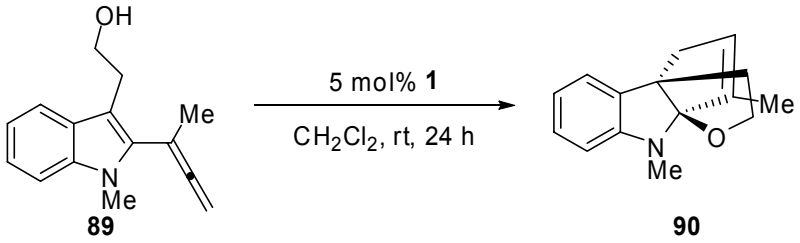
Formation of tetracyclic compounds such as **74** (Scheme 48) and **90-96** (Scheme 50) can be explained by a cyclization of intermediates **138** to give conjugated gold carbene **139**, whose Michael-type cyclization forms **140**. A protodemetalation then leads to the observed tetracyclic compounds (Scheme 62).



Scheme 62

30 Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.

Indeed, tetracycles can be formed from allenes. This was confirmed by a separate reaction in which isolated allene **89** was converted to tetracycle **90** with 5 mol% of catalyst **1** (Scheme 63).



Scheme 63

The reaction of **88** (Scheme 50) was monitored by ^{1}H-NMR in CD_2Cl_2 (3 mol%, catalyst **1**) from -40 to 0 ºC. At -23 ºC a low conversion to the allene **89** was observed, which increased to *ca*. 50% upon raising the temperature to 0 ºC. The NMR tube was then left overnight at room temperature and the spectra showed that a complete conversion from the allene **89** to the tetracycle **90** had occurred. No other compounds were observed in this experiment.

The different regiochemical outcome observed in reactions catalyzed by Au(I) complex **1** and $AuCl_3$ (Table 1, entries 1/2, 5/6, and 8/9) is intriguing and suggests that different mechanisms are involved in these reactions. It is noteworthy that in these cases the most electrophilic Au(III) catalyst leads to indoloazocines, which according to PM3 and *ab intio* (B3LYP/6-31G(d)) calculations, are *ca.* 2-5 kcal mol^{-1} less stable than their seven-membered ring isomers. The different regioselectivity observed in the intramolecular reactions appears to depend more on the presence or absence of phosphine ligands than on the valence of the gold since similar results are often obtained using AuCl and $AuCl_3$ as catalyst.

In the intermolecular processes, upon reaction of the indole with the activated alkyne, intermediates **141** or **142** may be obtained and they can lead to alkene **143** via protodemetalation (Scheme 64). The formed 3-alkenylindoles **143** (or the 2-alkenyl regioisomer) can further react with a nucleophile to form the observed bisindoles (Table 4 and Scheme 54) or the cyclic derivatives shown in Schemes 56, 57 and 58. Although these secondary processes may be promoted by gold, it is also possible that these

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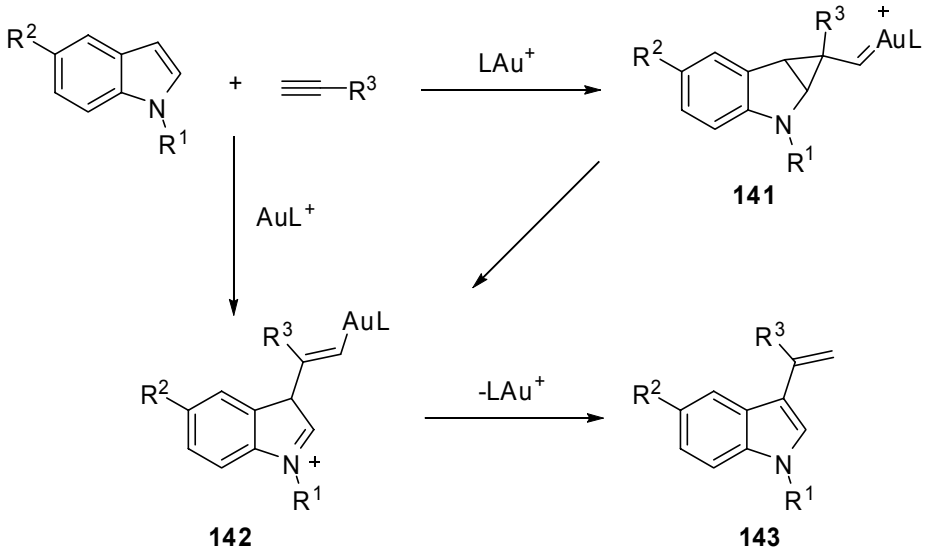
reactions are simple Brönsted acid-catalyzed reactions since protons are formed in the catalytic cycles.[72]



Scheme 64

With terminal alkynes, the regioselectivity in the first C-C bond formation can be explained by the exclusive formation of the more substituted η^1-alkenyl-gold(I) cation. In the formation of **112** (Scheme 54) by reaction of indole (**108a**) with prop-1-ynylbenzene, both cations **144** and **145** may be in equilibrium, in which **144** might be the more electrophilic species (Scheme 65). Alternatively, the attack of indole (**108a**) might take place preferentially at the carbon bearing the methyl substitiuent in a η^2-alkyne-gold(I) complex.

Scheme 65

72 For pertinent discussions on the role of Brönsted acids in additions of nucleophiles to alkenes: (a) Li, Z.; Zhang, J.; Brouer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175-4178. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Itsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179-4182.

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Chapter 1. Conclusions

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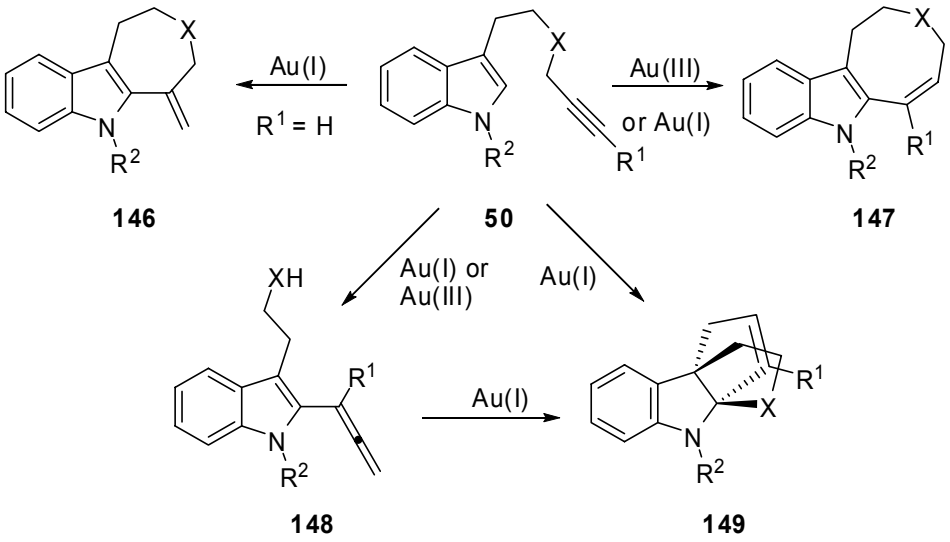
We found that substrates **50** cyclize readily with cationic gold(I) complex **1** to give azepino[4,5-*b*]indole derivatives **146** in a 7-*exo-dig* process, whereas the use of $AuCl_3$ leads to indoloazocines **147** by a 8-*endo-dig* process, a cyclization that has not been observed in other hydroarylations of alkynes (Scheme 66). In certain cases, by performing the reactions with Au(I) catalysts for longer reaction times, allenes **148** could also be formed. These allenes **148** can react further with Au(I) to form tetracyclic compounds **149**. The remarkable domino transformation of **50** into **149** could be done in one step by using Au(I) as catalyst.

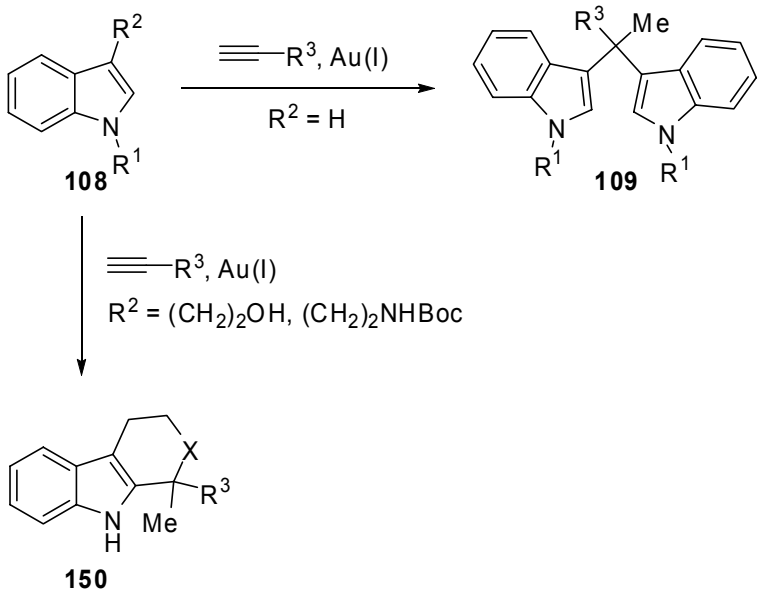


Scheme 66

We have also observed that substrates bearing a tether of three atoms between the indole and the alkyne cyclize in a 6-*exo-dig* mode, while substrates with a tether of only two atoms cyclizes in a 6-*endo-dig* mode.

The mechanism that we propose for these transformations, based on the experimental results, involves reaction of the indole at the 3-position with the gold-alkyne complex, followed by a 1,2-migration, in a Friedel-Crafts type of reaction.

We have also found that simple indoles **108** react with terminal alkynes to form 2:1 adducts **109** in the presence of Au(I) catalysts (Scheme 67). Furthermore, in the case of tryptophol and tryptamine derivatives, this reaction leads to compounds **150**, in a reaction that is reminiscent of the Pictet-Spengler process.



Scheme 67

In these intermolecular reactions, we propose that the alkene form ed after the attack of the indole into the gold-alkyne complex is further activated and suffers the attack of another nucleophile, leading to bisindoles **109** or cyclic compounds of type **150**.

Importantly, in these gold catalyzed reactions between indoles and alkynes, both inter- and intramolecular, no attack of the indole nitrogen on the alkynes was observed. Therefore, these reactions can be carried out without the use of protecting groups.

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Chapter 1. Experimental section

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1. General Methods

All reactions were carried out under N_2 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 and Bruker Avance 500 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. Catalysts

The following complexes and salts were used as received: AuCl (Aldrich), $AuCl_3$ (Johnson Mattey PLC), $AgSbF_6$ (Aldrich) and [$AuCl(PPh_3)$] (Stream). Complexes **1**,[7] **52**,[62] and **53**[63] were prepared according to the described procedures.

---

7 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694-1702. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

62 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032.

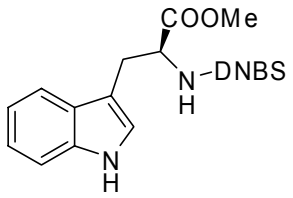
63 (a) Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc., Dalton Trans.* **1992**, 1907-1913. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

3. Intramolecular Reaction of Indoles with Alkynes

3.1. General procedure for the synthesis of *N*-protected indole derivatives

To a solution containing 1 equiv of the corresponding indole in CH_2Cl_2 (volume necessary to make the concentration of indole 0.5 M) was added 1 equiv of triethylamine. The mixture was stirred at 0ºC and the protecting agent (1 equiv) dissolved in CH_2Cl_2 (volume necessary to make the concentration 1.5 M) was added over a period of 5 min. The reaction was stirred at room temperature for 16 h. The *N*-protected indole derivatives were obtained after extractive workup (CH_2Cl_2) and chromatography (4:1 hexane-EtOAc).

(*S*)-Methyl 2-(2,4-Dinitrobenzensulfonylamino)-3-(1*H*-indol-3-yl)propanoate



(*S*)-Methyl 2-(2,4-dinitrobenzensulfonylamino)-3-(1*H*-indol-3-yl)propanoate was obtained as an orange solid (5.34 g, 87%): mp 232-234ºC. $[\alpha]_D$ = 54.4 (c = 1.0, $(CH_3)_2SO$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.70 (br s, 1H), 9.11 (d, J = 8.1 Hz, 1H), 8.37 (d, J = 2.3 Hz, 1H), 7.92 (dd, J = 8.6, 2.2 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.34-7.31 (m, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.99-6.97 (m, 1H), 6.88-6.86 (m, 2H), 4.25-4.19 (br m, 1H), 3.68 (s, 3H), 3.15 (dd, J = 14.4, 4.2 Hz, 1H), 2.96 (dd, J = 14.6, 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 171.41 (C), 148.32 (C), 145.79 (C), 137.03 (C), 135.74 (C), 130.18 (CH), 126.15 (C), 125.86 (CH), 124.97 (CH), 120.71 (CH), 118.95 (CH), 118.37 (CH), 117.84 (CH), 110.98 (CH), 108.16 (C), 56.54 (CH), 52.32 (CH_3), 27.20 (CH_2). Anal calcd for $C_{18}H_{16}N_4O_8S$: C, 48.21; H, 3.60; N, 12.49; S, 7.15; found: C, 48.45; H, 3.85; N, 12.13; S, 7.08. HRMS-ESI *m/z* calcd for $C_{18}H_{16}N_4O_8SNa$: 471.0578; found: 471.0564 [M^++Na].

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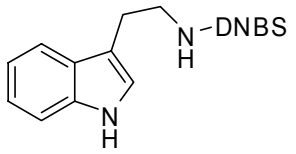
***N*-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dintrobenzensulfonyl)amine**



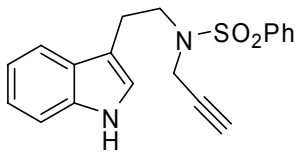
N-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dintrobenzensulfonyl)amine was obtained as an orange solid (6.65 g, 91%): mp 208-210ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.72 (br s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.43 (br s, 1H), 8.26 (dd, J = 8.7, 2.3 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 6.96 (td, J = 8.2, 1.2 Hz, 1H), 6.90 (td, J = 7.8, 1.1 Hz, 1H), 3.32 (t, J = 7.1 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 148.81 (C), 146.71 (C), 137.76 (C), 136.00 (C), 130.58 (CH), 126.68 (CH), 126.59 (C), 123.48 (CH), 120.77 (CH), 119.51 (CH), 118.24 (CH), 118.03 (CH), 111.14 (CH), 110.37 (C), 43.67 (CH_2), 25.14 (CH_2). Anal calcd for $C_{16}H_{14}N_4O_6S$: C, 49.23; H, 3.61; N, 14.35; S, 8.21; found: C, 48.90; H, 3.78; N, 13.80; S, 8.04. HRMS-CI *m/z* calcd for $C_{16}H_{15}N_4O_6S$: 391.0712; found: 391.0695 [M^++H].

3.2. General Procedure for the Synthesis of the Alkylated Indole Derivatives

A solution containing 1.2 equiv of NaH (60% in mineral oil) in DMF (volume of DMF necessary to make the concentration of NaH 1.0 M) was cooled at 0°C. A 1.0 equiv solution of the corresponding indole derivative in DMF (volume of DMF necessary to make the concentration of the indole 1.0 M) was added dropwise. The mixture was warmed up to room temperature and stirred for 20 min and 1.0 equiv of the alkylating agent was added. The reaction was stirred at room temperature for 16 h and after extractive workup (EtOAc) it was purified by chromatography.

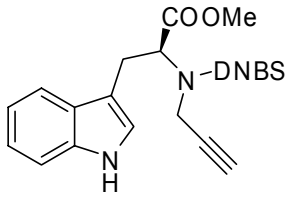
The following product has been described previously in the literature:

***N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide**[73] **(57)**



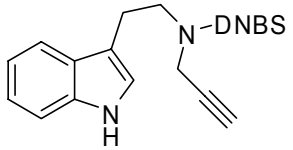
73 Cassachi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 607-615.

(*S*)-Methyl 2-(*N*-(Prop-2-ynyl)-*N*-(2,4-dinitrobezensulfonylamino))-3-(1*H*-indol-3-yl)propanoate (54)



(*S*)-Methyl 2-(2,4-dinitrobenzenesulfonylamino)-3-(1*H*-indol-3-yl)propanoate (1.70 g, 3.79 mmol) was alkylated following the general procedure using propargyl bromide (0.33 mL, 3.79 mmol). The crude product was purified by chromatography (4:1 hexane-EtOAc) to give **54** as an orange solid (840 mg, 45%): mp 178-180ºC. $[\alpha]_D$ = 6.4 (c = 1.0, $(CH_3)_2SO$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.82 (br s, 1H), 8.54 (d, *J* = 2.3 Hz, 1H), 7.98 (dd, *J* = 9.3, 2.0 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.45-7.43 (m, 1H), 7.18 (d, *J* = 1.9 Hz, 1H), 7.12-7.10 (m, 1H), 6.96-6.90 (m, 2H), 4.82 (dd, *J* = 10.2, 5.1 Hz, 1H), 4.50-4.39 (m, 2H), 3.63 (s, 3H), 3.38 (t, *J* = 3.0 Hz, 1H), 3.37-3.31 (m, 1H), 3.27 (dd, *J* = 14.9, 10.3 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 169.87 (C), 148.93 (C), 146.64 (C), 135.85 (C), 135.81 (C), 131.08 (CH), 126.34 (C), 125.57 (CH), 124.77 (CH), 120.98 (CH), 119.03 (CH), 118.51 (CH), 117.98 (CH), 111.16 (CH), 108.06 (C), 78.96 (CH), 75.94 (C), 59.67 (CH), 52.23 (CH_3), 34.43 (CH_2), 27.20 (CH_2). Anal calcd for $C_{21}H_{18}N_4O_8S$: C, 51.85; H, 3.73; N, 11.52; S, 6.59; found: C, 51.85; H, 3.80; N, 11.42; S, 6.61. HRMS-ESI *m/z* calcd for $C_{21}H_{18}N_4O_8SNa$: 509.0743; found: 509.0751 [M^++Na].

***N*-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dinitrobenzensulfonyl)prop-2-yn-1-amine (61)**



N-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dintrobenzensulfonyl)amine (2.00 g, 5.12 mmol) was alkylated following the general procedure using propargyl bromide (0.44 mL, 5.12 mmol). The crude product was purified by chromatography (4:1 hexane-EtOAc) to give **61** as an orange solid (658 mg, 30%): mp 138-140ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.78 (br s, 1H), 8.73 (d, *J* = 2.5 Hz, 1H), 8.25 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 6.99 (td, *J* = 7.1, 1.2 Hz, 1H), 6.94 (td, *J* = 7.6, 1.2 Hz, 1H), 4.38 (d, *J* = 2.3 Hz, 2H), 3.64 (t, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 2.3 Hz, 1H), 3.00 (t, *J* = 7.4 Hz, 2H);

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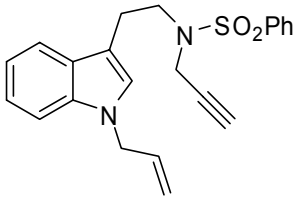
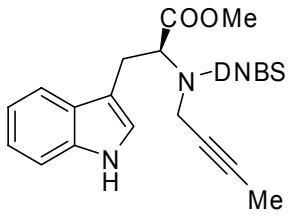
^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 149.42 (C), 146.88 (C), 136.06 (C), 135.91 (C), 131.65 (CH), 126.67 (C), 126.32 (CH), 123.63 (CH), 120.94 (CH), 119.65 (CH), 118.35 (CH), 118.05 (CH), 111.28 (CH), 109.84 (C), 77.45 (CH), 76.60 (C), 47.34 (CH_2), 36.13 (CH_2), 23.10 (CH_2). Anal calcd for $C_{19}H_{16}N_4O_6S$: C, 53.27; H, 3.76; N, 13.08; S, 7.48; found: C, 53.24; H, 3.93; N, 12.98; S, 7.02. HRMS-CI *m/z* calcd for $C_{19}H_{17}N_4O_6S$: 429.0869; found: 429.0863 [M^++H].

_N_-(2-(1-Allyl-1_H_-indol-3-yl)ethyl)-_N_-(prop-2-ynyl)benzenesulfonamide (65)



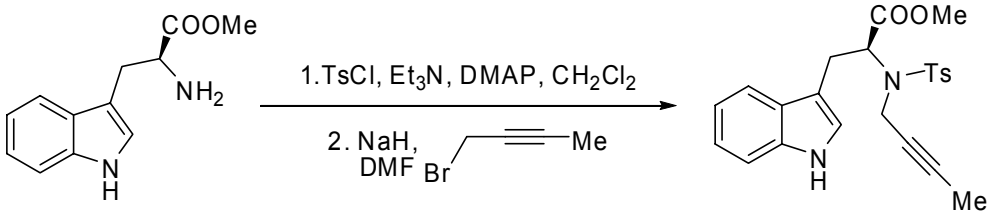
N-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (**57**) (300 mg, 0.88 mmol) was alkylated following the general procedure using allyl bromide (0.08 mL, 0.88 mmol). The crude product was purified by chromatography (10:1 hexane-EtOAc) to give **65** as a white solid (150 mg, 45%): mp 93-95ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.56-7.53 (m, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 5.97 (ddt, J = 17.0, 10.6, 5.5 Hz, 1H), 5.19 (dd, J = 10.2, 1.6 Hz, 1H), 5.09 (dd, J = 17.1, 1.2 Hz, 1H), 4.67 (d, J = 5.4 Hz, 2H), 4.19 (d, J = 2.3 Hz, 2H), 3.53 (t, J = 7.6 Hz, 2H), 3.08 (t, J = 8.0 Hz, 2H), 2.04 (t, J = 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 139.01 (C), 136.41 (C), 133.48 (CH), 132.64 (CH), 128.85 (CH, 2C), 127.90 (C), 127.62 (CH, 2C), 125.91 (CH), 121.74 (CH), 119.14 (CH), 118.85 (CH), 117.31 (CH_2), 111.13 (C), 109.67 (CH), 76.75 (C), 73.74 (CH), 48.71 (CH_2), 47.19 (CH_2), 36.78 (CH_2), 24.37 (CH_2). Anal calcd for $C_{22}H_{22}N_2O_2S$: C, 69.81; H, 5.86; N, 7.40; S, 8.4; found: C, 69.99; H, 6.15; N, 7.95; S, 8.04. HRMS-ESI *m/z* calcd for $C_{22}H_{22}N_2O_2SNa$: 401.1300; found: 401.1306 [M^++Na].

(*S*)-Methyl 2-(*N*-(But-2-ynyl)-2,4-dinitrophenylsulfonamido)-3-(1*H*-indol-3-yl) propanoate (68)



(*S*)-Methyl 2-(2,4-dinitrobenzenesulfonylamino)-3-(1*H*-indol-3-yl)propanoate (2.00 g, 3.99 mmol) was alkylated following the general procedure using 1-bromobut-2-yne (0.34 mL, 3.99 mmol). The crude product was purified by chromatography (4:1 hexane-EtOAc) to give **68** as an orange solid (1.24 g, 62%): mp 166-168ºC. $[\alpha]_D$ = 5.4 (c = 0.6, acetone). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.81 (br s, 1H), 8.54 (d, *J* = 2.2 Hz, 1H), 8.01 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 7.0 Hz, 1H), 7.17 (d, *J* = 2.6 Hz, 1H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.96 (t, *J* = 7.0 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 4.83 (dd, *J* = 10.4, 5.4 Hz, 1H), 4.38 (br s, 2H), 3.64 (s, 3H), 3.38 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.27 (dd, *J* = 15.6, 10.4 Hz, 1H), 1.76 (br s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 170.03 (C), 148.89 (C), 146.74 (C), 136.17 (C), 135.87 (C), 130.95 (CH), 126.40 (C), 125.52 (CH), 124.70 (CH), 120.96 (CH), 118.97 (CH), 118.50 (CH), 117.98 (CH), 111.17 (CH), 108.21 (C), 81.72 (CH), 74.22 (C), 59.72 (CH), 52.34 (CH_3), 35.01 (CH_2), 24.63 (CH_2), 2.99 (CH_3). Anal calcd for $C_{22}H_{20}N_4O_8S$: C, 52.80; H, 4.03; N, 11.19; S, 6.41; found: C, 52.67; H, 4.01; N, 11.24; S, 6.41. HRMS-ESI *m/z* calcd for $C_{22}H_{20}N_4O_8SK$: 539.0639; found: 539.0646 [M^++K].

(*S*)-Methyl 2-(*N*-(But-2-ynyl)-*N*-tosylamino)-3-(1*H*-indol-3-yl)propanoate (71)



To a solution of L-tryptophane methyl ester hydrochloride (3.00 g, 13.72 mmol) in CH_2Cl_2 (40 mL) was added *N,N*-dimethylaminopyridine (84 mg, 0.68 mmol) and triethylamine (5.7 mL, 41.23 mmol). The mixture was stirred at 0ºC and a solution of 4-methylbenzenesulfonyl chloride (2.62 g, 13.72 mmol) was added. The reaction was stirred at room temperature for 16 h and after extractive workup (CH_2Cl_2) the crude product was dissolved in DMF and alkylated following the general procedure using 1-

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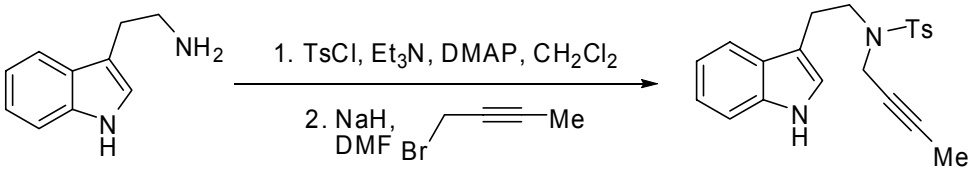
bromobut-2-yne (1.2 mL, 13.72 mmol). The crude product was purified by chromatography (3:1 hexane-EtOAc) to give **71** as a white solid (2.42 g, 43%): mp 102-103ºC. $[\alpha]_D$ = -26.4 (c = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.87 (t, *J* = 7.6 Hz, 1H), 4.23 (t, *J* = 2.2 Hz, 2H), 3.52 (dd, *J* = 14.8, 8 Hz, 1H), 3.49 (s, 3H), 3.22 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.38 (s, 3H), 1.63 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 171.12 (C), 143.18 (C), 137.13 (C), 136.09 (C), 129.04 (CH, 2C), 127.68 (C), 127.17 (CH, 2C), 123.36 (CH), 122.04 (CH), 119.54 (CH),118.51 (CH), 111.19 (CH), 110.54 (C), 80.80 (C), 74.25 (C), 59.43 (CH), 51.97 (CH_3), 34.68 (CH_2), 26.29 (CH_2), 21.53 (CH_3), 3.47 (CH_3). Anal calcd for $C_{23}H_{24}N_2O_4S$: C, 65.07; H, 5.70; N, 6.60; S, 7.55; found: C, 64.74; H, 5.67; N, 6.57; S, 7.39. HRMS-CI *m/z* calcd for $C_{23}H_{24}N_2O_4S$: 424.1457; found: 424.1441 [M^+].

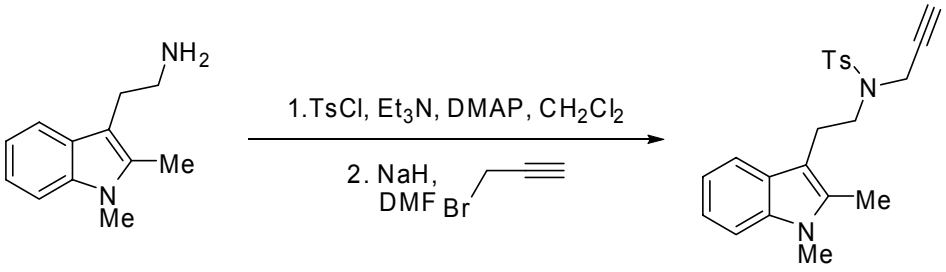
_N_-(2-(1_H_-Indol-3-yl)ethyl)-_N_-tosylbut-2-yn-1-amine (73)



To a solution of tryptamine (3.00 g, 18.72 mmol) in CH_2Cl_2 (40 mL) was added *N,N*-dimethylaminopyridine (84 mg, 0.68 mmol) and triethylamine (5.70 mL, 41.23 mmol). The mixture was stirred at 0ºC and a solution of 4-methylbenzenesulfonyl chloride (2.62 g, 13.74 mmol) was added. The reaction was stirred at room temperature for 16 h and after extractive workup (CH_2Cl_2) the crude product was dissolved in DMF and alkylated following the general procedure using 1-bromobut-2-yne (1.64 mL, 18.72 mmol). The crude product was purified by chromatography (3:1 hexane-EtOAc) to give **73** as a white solid (4.32 g, 63%): mp 112-115ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.11 (overlapping td, *J* = 7.8, .08 Hz, 1H), 7.09 (overlapping d, *J* = 2.4 Hz, 1H), 4.11 (q, *J* = 2.4 Hz, 2H), 3.48 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.57 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 143.13 (C), 136.64 (C), 136.26 (C), 129.25 (CH, 2C), 127.79 (C), 127.34 (CH, 2C), 122.17 (CH), 122.09 (CH), 119.44 (CH), 118.70 (CH), 112.57 (C), 111.17 (CH), 81.58 (C), 72.09 (C), 46.93 (CH_2), 37.24 (CH_2), 24.32 (CH_2),

21.48 (CH_3), 3.27 (CH_3). Anal calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64; S, 8.75; found: C, 68.53; H, 6.06; N, 7.64; S, 8.74. HRMS-CI *m/z* calcd for $C_{21}H_{22}N_2O_2S$: 366.1402; found: 366.1419 [M^+].

_N_-(2-(1,2-Dimethyl-1_H_-indol-3-yl)ethyl)-4-methyl-_N_-(prop-2-ynyl) benzenesulfonamide (75)



To a solution of 2-(1,2-dimethyl-1*H*-indol-3-yl)ethanamine[74] (550 mg, 2.92 mmol) in CH_2Cl_2 (10 mL) was added *N,N*-dimethylaminopyridine (18 mg, 0.14 mmol) and triethylamine (0.80 mL, 5.84 mmol). The mixture was stirred at 0ºC and a solution of 4-methylbenzenesulfonyl chloride (557 mg, 2.92 mmol) was added. The reaction was stirred at room temperature for 16 h and after extractive workup (CH_2Cl_2) the crude product was dissolved in DMF and alkylated following the general procedure using propargyl bromide (0.26 mL, 2.92 mmol). The crude product was purified by chromatography (20:1 hexane-EtOAc) to give **75** as a white solid (520 mg, 56%): mp 151-153ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.52-7.22 (m, 3H), 7.15 (dt, J = 7.0, 1.1 Hz, 1H), 7.07 (td, J = 7.0, 1.0 Hz, 1H), 4.18 (d, J = 2.6 Hz, 2H), 3.03 (s, 3H), 3.37-3.33 (m, 2H), 3.06-3.02 (m, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 2.08 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 143.36 (C), 136.56 (C), 136.02 (C), 133.79 (C), 129.44 (CH, 2C), 127.62 (CH, 2C), 127.44 (C), 120.72 (CH), 119.00 (CH), 117.73 (CH), 108.62 (CH), 107.05 (C), 77.22 (C), 73.65 (CH), 47.21 (CH_2), 37.06 (CH_2), 29.53 (CH_3), 23.97 (CH_2), 21.51 (CH_3), 10.20 (CH_3). Anal calcd for $C_{22}H_{24}N_2O_2S$: C, 69.44; H, 6.36; N, 7.36; S, 8.43; found: C, 69.16; H, 6.22; N, 7.57; S, 8.35. HRMS-CI *m/z* calcd for $C_{22}H_{25}N_2O_2S$: 381.1637; found: 381.1638 [M^++H].

74 Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M.; *Tetrahedron Lett*. **2004**, *45*, 3123-3126.

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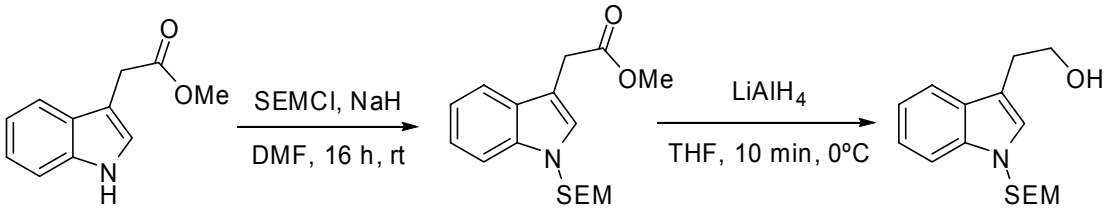
2-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)ethanol



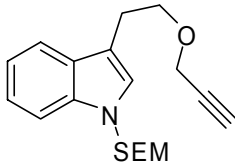
(i). To a stirred solution of methyl 2-(1*H*-indol-3-yl)acetate (1.20 g, 6.34 mmol) in DMF (15 mL) was added sodium hydride (228 mg, 9.51 mmol) at 0ºC. The mixture was allowed to stir at room temperature for 15 minutes and then (2-(chloromethoxy)ethyl)trimethylsilane (1.12 mL, 6.34 mmol) was added at 0ºC. The reaction was stirred at room temperature for 16 h and after extractive workup (EtOAc/10%HCl water solution) the residue was purified by chromatography (20:1 hexane-EtOAc) to give methyl 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acetate[75] as a yellow oil (320 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 7.18 (overlapping t, J = 7.7 Hz, 1H), 7.18 (overlapping s, 1H), 5.47 (s, 2H), 3.79 (s, 2H), 3.72 (s, 2H), 3.50 (t, J = 8.1 Hz, 2H), 0.90 (t, J = 8.1 Hz, 2H), -0.03 (s, 9H).

(ii). To a suspension of lithium aluminum tetrahydride (292 mg, 7.70 mmol) in THF (15 mL) at 0ºC was added a solution of methyl 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)acetate (1.23 g, 3.85 mmol) in THF (15 mL). The reaction was allowed to stir at room temperature for 10 minutes. The mixture was quenched with the equivalents of water needed to neutralize the lithium aluminum tetrahydride and it was stirred with $MgSO_4$ heptahydrate for an hour. Then it was filtered trough celite and the solvent evaporated under reduced pressure to give 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)ethanol (1.10 g, 98%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.28 (dt, J = 7.5, 1.1 Hz, 1H), 7.18 (dt, J = 7.0, 0.9 Hz, 1H), 7.09 (s, 1H), 5.47 (s, 2H), 3.93 (q, J = 6.1 Hz, 2H), 3.50 (dd, J = 16.2, 8.1 Hz, 2H), 3.05 (t, J = 6.3 Hz, 2H), 1.55 (t, J = 6.1 Hz, 1H), 0.91 (dd, J = 16.3, 8.2 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.95 (C), 128.59 (C), 126.37 (CH), 122.36 (CH), 119.85 (CH), 119.03 (CH), 112.20 (C), 110.04 (CH), 75.43 (CH_2), 65.86 (CH_2), 62.62 (CH_2), 28.65 (CH_2), 17.73 (CH_2), -1.42 (CH_3, 3C). Anal calcd for $C_{16}H_{25}NO_2Si$: C, 65.93; H, 8.65; N, 4.81; found: C,

75 Eils, S.; Winterfeldt, E. *Synthesis* **1999**, 275-281.

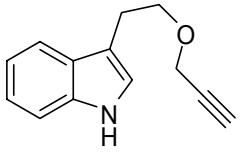
66.30; H, 8.46; N, 4.81. HRMS-EI *m/z* calcd for $C_{16}H_{25}NO_2Si$: 291.1655; found: 291.1652 [M^+].

3-(2-(Prop-2-ynyloxy)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole



2-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)ethanol (1.06 g, 3.65 mmol) was alkylated following the general procedure using propargyl bromide (0.39 mL, 4.38 mmol) as the alkylating agent. The crude mixture was purified by chromatography (10:1 hexane-EtOAc) to give 3-(2-(prop-2-ynyloxy)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole as a colorless oil (700 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.25 (dt, J = 7.7, 1.2 Hz, 1H), 7.16 (dt, J = 7.5, 0.9 Hz, 1H), 7.07 (s, 1H), 5.46 (s, 2H), 4.21 (d, J = 2.3 Hz, 2H), 3.84 (t, J = 7.2 Hz, 2H), 3.84 (dd, J = 16.3, 8.1 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 2.3 Hz, 1H), 0.90 (dd, J = 16.3, 8.2 Hz, 2H), -0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.68 (C), 128.70 (C), 125.94 (CH), 122.11 (CH), 119.66 (CH), 118.94 (CH), 112.60 (C), 109.92 (CH), 79.89 (C), 75.42 (CH_2), 74.30 (CH), 70.17 (CH_2), 65.74 (CH_2), 58.11 (CH_2), 25.46 (CH_2), 17.72 (CH_2), -1.42 (CH_3, 3C). Anal calcd for $C_{19}H_{27}NO_2Si$: C, 69.26; H, 8.26; N, 4.25; found: C, 68.82; H, 7.98; N, 4.25. HRMS-EI *m/z* calcd for $C_{19}H_{27}NO_2Si$: 329.1811; found: 329.1815 [M^+].

3-(2-(Prop-2-ynyloxy)ethyl)-1*H*-indole (77)



To a solution of 3-(2-(prop-2-ynyloxy)ethyl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-indole (580 mg, 1.76 mmol) in DMF (5 mL), was added tetrabutyl-ammonium fluoride trihydrate (1.66 g, 5.28 mmol) and ethylenediamine (0.53 mL, 7.92 mmol). The reaction was heated at 80ºC overnight and then was diluted with water and the product extracted with EtOAc. The residue was purified by chromatography (20:1 hexane-EtOAc) to give **77** as a colorless oil (230 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.19 (dt, J =

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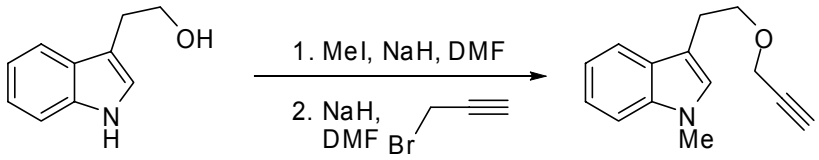
7.2, 1.1 Hz, 1H), 7.12 (dt, J = 7.4, 1.1 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 4.19 (d, J = 2.3 Hz, 2H), 3.84 (t, J = 7.1 Hz, 2H), 3.08 (td, J = 7.2, 0.8 Hz, 2H), 2.43 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.19 (C), 127.54 (C), 122.00 (CH, 2C), 119.32 (CH), 118.81 (CH), 112.80 (C), 111.10 (CH), 79.94 (C), 74.28 (CH), 70.27 (CH_2), 58.11 (CH_2), 25.60 (CH_2). Anal calcd for $C_{13}H_{13}NO \cdot 1/6H_2O$: C, 77.20; H, 6.64; N, 6.93; found: C, 77.54; H, 6.67; N, 7.10. HRMS-EI *m/z* calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.0997 [M^+].

1-Methyl-3-(2-(prop-2-ynyloxy)ethyl)-1*H*-indole (80)



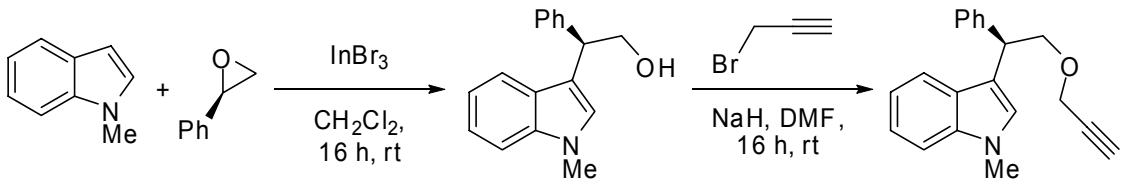
Tryptophol (500 mg, 3.10 mmol) was alkylated following the general procedure using MeI (0.19 mL, 3.10 mmol). The solution was allowed to react for 3 hours and after extractive workup (Et_2O) the crude product was dissolved in DMF and alkylated following the general procedure using propargyl bromide (0.33 mL, 2.93 mmol). The residue was purified by chromatography (100:3 hexane-EtOAc) to give **80** as light yellow crystals (319 mg, 51%): mp 52°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.22 (dt, J = 7.2, 1.1 Hz, 1H), 7.11 (dt, J = 7.3, 1.1 Hz, 1H), 6.93 (s, 1H), 4.20 (d, J = 2.3 Hz, 2H), 3.82 (t, J = 7.2 Hz, 2H), 3.75, (s, 3H) 3.07 (dt, J = 7.2, 0.8 Hz, 2H), 2.43 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.1 (C), 128.1 (C), 127.0 (CH), 121.7 (CH), 119.1 (CH), 118.9 (CH), 111.3 (C), 109.4 (CH), 74.4 (C), 70.6 (CH_2), 58.3 (CH_2), 32.8 (CH_3), 25.7 (CH_2). Anal calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; found: C, 78.48; H, 7.15; N, 6.54. HRMS-ESI *m/z* calcd for $C_{14}H_{15}NONa$: 236.1051; found: 236.1045 [M^++Na].

3.3. General procedure for the synthesis of (*R*)-2-indolyl-2-phenylethanol derivatives

A two-necked flask was charged with CH_2Cl_2 (volume of CH_2Cl_2 necessary to make the concentration of indole 0.75 M), 0.01 equiv of $InBr_3$ and 1 equiv of the indole. The mixture was stirred for a few minutes and then 0.65 equiv of (*R*)-styrene epoxide was added. The clear solution was stirred for 16 hours and then the reaction was

quenched with a saturated solution of $NaHCO_3$ and extracted with Et_2O. The crude product mixture was purified by flash chromatography.

(*R*)-1-Methyl-3-(1-phenyl-2-(prop-2-ynyloxy)ethyl)-1*H*-indole (83)



(i). *N*-Methyl indole (1.63 g, 12.48 mmol) was reacted with styrene oxide (0.95 mL, 8.32 mmol) following the general procedure. The crude mixture was purified by chromatography (10:1 hexane-EtOAc) to give (*R*)-2-(1-methyl-1*H*-indol-3-yl)-2-phenylethanol[76] as a yellow oil (1.13 g, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 1H), 7.40-7.32 (m, 5H), 7.28-7.22 (m, 2H), 7.08 (t, J = 7.7 Hz, 1H), 6.99 (s, 1H), 4.51 (t, J = 6.6 Hz, 1H), 4.26 (dd, J = 10.5, 6.8 Hz, 1H), 4.19 (dd, J = 10.8, 7.1 Hz, 1H), 3.79 (s, 3H), 1.64 (br s, 1H).

(ii). (*R*)-2-(1-Methyl-1*H*-indol-3-yl)-2-phenylethanol (2.63 g, 10.46 mmol) was alkylated following the general procedure using propargyl bromide (1.12 mL, 12.55 mmol). The crude mixture was purified by chromatography (30:1 hexane-EtOAc) to give **83** as a yellow oil (2.51 g, 83%): $[\alpha]_D$ = -7.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.0 Hz, 1H), 7.37-7.35 (m, 2H), 7.32-7.27 (m, 3H), 7.23-7.18 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.95 (s, 1H), 4.60 (t, J = 6.9 Hz, 1H), 4.25-4.06 (m, 4H), 3.76 (s, 3H), 2.46-2.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 142.32 (C), 137.12 (C), 128.37 (CH, 2C), 128.27 (CH, 2C), 127.45 (C), 126.80 (CH), 126.45 (CH), 121.60 (CH), 119.48 (CH), 118.84 (CH), 115.20 (C), 109.17 (CH), 79.85 (C), 74.53 (CH), 73.51 (CH_2), 58.21 (CH_2), 42.88 (CH), 32.74 (CH_3). Anal calcd for $C_{20}H_{19}NO \cdot 1/5H_2O$: C, 81.99; H, 6.67; N, 4.78; found: C, 82.27; H, 6.59; N, 4.94. HRMS-EI *m/z* calcd for $C_{20}H_{19}NO$: 289.1467; found: 289.1469 [M^+].

76 Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386-5389.

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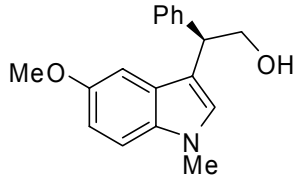
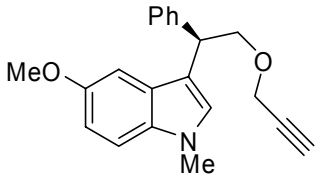
(*R*)-2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-phenylethanol



(*R*)-2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-phenylethanol was synthesized following the general procedure using 5-methoxy-1-methyl-1*H*-indole (1.12 g, 6.95 mmol) and (*R*)-styrene oxide (0.53 mL, 4.64 mmol). The crude mixture was purified by chromatography (20:1 hexane-EtOAc) to give (*R*)-2-(5-methoxy-1-methyl-1*H*-indol-3-yl)-2-phenylethanol (906 mg, 69%) as a yellow oil: $[\alpha]_D$ = 41.3 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.23 (tt, *J* = 7.1, 1.5 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.92 (s, 1H), 6.88-6.86 (m, 2H), 4.43 (t, *J* = 7.0 Hz, 1H), 4.25-4.13 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 1.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 153.9 (C), 141.9 (C), 132.8 (C), 128.8 (CH), 128.4 (CH), 127.9 (C), 127.4 (CH), 126.8 (CH), 114.0 (C), 112.1 (CH), 110.2 (CH), 101.5 (CH), 66.6 (CH_2), 56.0 (CH), 45.7 (CH_3), 33.1 (CH_3). Anal calcd for $C_{18}H_{19}NO_2 \cdot 1/3H_2O$: C, 75.24; H, 6.90; N, 4.87; found: C, 75.23; H, 6.70; N, 4.95. HRMS-ESI *m/z* calcd for $C_{18}H_{19}NO_2Na$: 304.1313; found: 304.1305 [M^++Na].

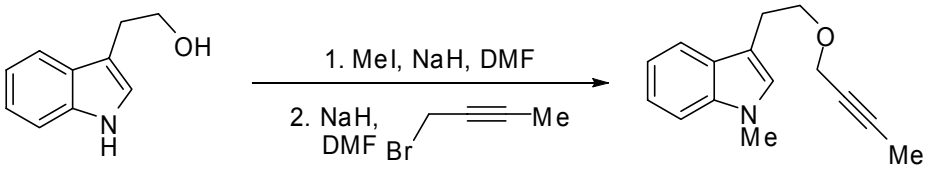
(*R*)-5-Methoxy-1-methyl-3-(1-phenyl-2-(prop-2-ynyloxy)ethyl)-1*H*-indole (86)



(*R*)-2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-phenylethanol (141 mg, 0.50 mmol) was alkylated following the general procedure using propargyl bromide (0.06 mL, 0.55 mmol). The crude mixture was purified by chromatography (20:1 hexane-EtOAc) to give **86** (110 mg, 86%) as a yellow solid: mp 81°C. $[\alpha]_D$ = 25.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 7.31-7.28 (m, 2H), 7.21 (tt, *J* = 7.1, 1.5 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.89 (s, 1H), 6.85-6.83 (m, 2H), 4.53 (t, *J* = 7.0 Hz, 1H), 4.22 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.17 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.16 (dd, *J* = 9.5, 7.4 Hz, 1H), 4.05 (dd, *J* = 9.5, 7.4 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.44 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 153.8 (C), 142.4 (C), 132.7 (C), 128.6 (CH), 128.4 (CH), 127.9 (C), 127.6 (CH), 126.6 (CH), 114.8 (C), 111.8 (CH),

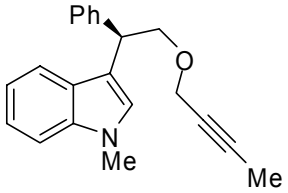
110.1 (CH), 101.7 (CH), 74.7 (C), 73.6 (CH_2), 58.4 (CH), 56.1 (CH_3), 43.1 (CH), 33.1 (CH_3). Anal calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39, found: C, 78.47; H, 6.58; N, 4.39. HRMS-ESI *m/z* calcd for $C_{21}H_{21}NO_2Na$: 342.1470; found: 342.1485 [M^++Na].

3-(2-(But-2-ynyloxy)ethyl)-1-methyl-1*H*-indole (88)



Tryptophol (500 mg, 3.10 mmol) was alkylated following the general procedure using MeI (0.19 mL, 3.10 mmol). The solution was allowed to react for 3 hours and after extractive workup (Et_2O) the crude product was dissolved in DMF and alkylated following the general procedure using 1-bromo-2-butyne (0.28 mL, 3.10 mmol). The residue was purified by chromatography (100:3 hexane-EtOAc) to give **88** as a yellow oil (472 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.22 (dt, J = 7.9, 1.0 Hz, 1H), 7.11 (dt, J = 7.9, 1.0 Hz, 1H), 6.93 (s, 1H), 4.16 (q, J = 2.3 Hz, 2H), 3.79 (t, J = 7.2 Hz, 2H), 3.75, (s, 3H) 3.07 (t, J = 7.2 Hz, 2H), 1.86 (t, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.1 (C), 128.1 (C), 127.0 (CH), 121.7 (CH), 119.1 (CH), 118.9 (CH), 109.3 (CH), 82.5 (C), 75.5 (C), 70.4 (CH_2), 58.8 (CH_2), 32.8 (CH_3), 25.7 (CH_2) 3.8 (CH_3). Anal calcd for $C_{15}H_{17}NO\cdot 1/3H_2O$: C, 77.22; H, 7.63, N, 6.00; found: C, 77.31; H, 7.29; N, 6.16. HRMS-ESI *m/z* calcd for $C_{15}H_{17}NONa$: 250.1208; found: 250.1209 [M^++Na].

(*R*)-3-(2-(But-2-ynyloxy)-1-phenylethyl)-1-methyl-1*H*-indole (91)



(*R*)-2-(1-Methyl-1*H*-indol-3-yl)-2-phenylethanol (500 mg, 1.98 mmol) was alkylated following the general procedure using 1-bromo-2-butyne (0.21 mL, 2.38 mmol). The crude mixture was purified by chromatography (20:1 hexane-EtOAc) to give **91** as a yellow oil (410 mg, 68%): $[\alpha]_D$ = -13.2 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.9 Hz, 1H), 7.36-7.34 (m, 2H), 7.30-7.26 (m, 3H), 7.22-7.16 (m, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.93 (s, 1H), 4.58 (t, J = 7.1 Hz, 1H), 4.19-4.10

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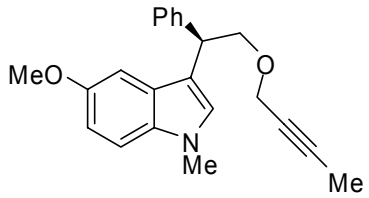
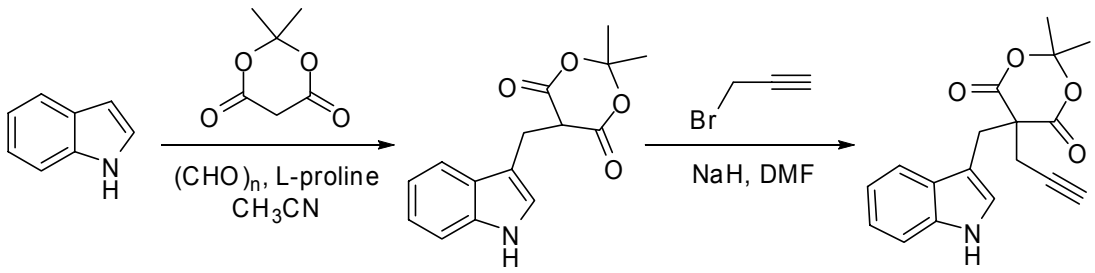
(m, 3H), 4.03 (dd, J = 9.5, 7.3 Hz, 1H), 3.75 (s, 3H), 1.86 (t, J = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 142.49 (C), 137.12 (C), 128.33 (CH, 2C), 128.27 (CH, 2C), 127.48 (C), 126.80 (CH), 126.37 (CH), 121.54 (CH), 119.51 (CH), 118.77 (CH), 115.39 (C), 109.13 (CH), 82.47 (C), 75.27 (C), 73.32 (CH_2), 58.71 (CH_2), 42.89 (CH), 32.74 (CH_3), 3.64 (CH_3). Anal calcd for $C_{21}H_{21}NO \cdot 1/2H_2O$: C, 80.74; H, 7.10; N, 4.48; found: C, 80.70; H, 6.71; N, 4.66. HRMS-EI *m/z* calcd for $C_{21}H_{21}NO$: 303.1623; found: 303.1629 [M^+].

(*R*)-3-(2-(But-2-ynyloxy)-1-phenylethyl)-5-methoxy-1-methyl-1*H*-indole (94)



(*R*)-2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-phenylethanol (184 mg, 0.65 mmol) was alkylated following the general procedure using 1-bromo-2-butyne (0.07 mL, 0.79 mmol). The crude mixture was purified by chromatography (20:1 hexane-EtOAc) to give **94** (128 mg, 59%) as a colorless oil: $[\alpha]_D$ = 18.9 (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.33-7.29 (m, 2H), 7.22 (tt, J = 7.2, 1.2 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 6.89-6.85 (m, 2H), 4.54 (t, J = 7.1 Hz, 1H), 4.22-4.11 (m, 3H), 4.04 (dd, J = 9.4, 7.5 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 1.87 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 153.7 (C), 142.6 (C), 132.7 (C), 128.5 (CH), 128.4 (CH), 127.9 (C), 127.6 (CH), 126.5 (CH), 115.0 (C), 111.7 (CH), 110.0 (CH), 101.8 (CH), 82.6 (C), 75.4 (C), 73.5 (CH_2), 58.9 (CH_2), 56.0 (CH_3), 43.1 (CH), 33.0 (CH_3), 3.8 (CH_3). Anal calcd for $C_{22}H_{23}NO_2 \cdot H_2O$: C, 75.19; H, 7.17; N, 3.99; found: C, 75.33; H, 6.50; N, 4.14. HRMS-ESI *m/z* calcd for $C_{22}H_{23}NO_2Na$: 356.1626; found: 356.1616 [M^++Na].

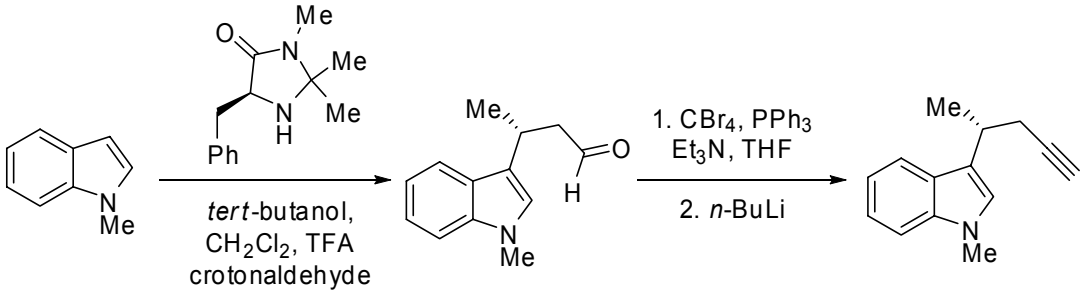
5-((1*H*-Indol-3-yl)methyl)-2,2-dimethyl-5-(prop-2-ynyl)-1,3-dioxane-4,6-dione (97)



(i). To a solution of indole (2.00 g, 17.07 mmol) in CH_3CN (20 mL) was added Meldrum's acid (2.46 g, 17.07 mmol), paraformaldehyde (512 mg, 17.07 mmol) and L-proline (98 mg, 0.85 mmol). The reaction mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was dissolved in warm methanol and recrystallized. 5-((1*H*-Indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[77] was obtained as a white solid (1.75 mg, 53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.21-7.12 (m, 3H), 3.77 (t, J = 4.8 Hz, 1H), 3.66 (d, J = 4.8 Hz, 2H), 1.69 (s, 3H), 1.45 (s, 3H).

(ii). 5-((1*H*-Indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.00 g, 3.65 mmol) was alkylated following the general procedure using propargyl bromide (0.58 mL, 3.65 mmol) as the alkylating agent. The crude product was purified by chromatography (4:1 hexane-EtOAc) to give **97** as a white solid (382 mg, 37%): mp 173-175ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.18-7.14 (m, 1H), 7.14-7.10 (m, 1H), 7.04 (d, J = 2.68 Hz, 1H), 3.49 (s, 2H), 3.06 (d, J = 2.6 Hz, 2H), 2.14 (t, J = 2.6 Hz, 1H), 1.60 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 168.56 (C), 135.77 (C), 126.68 (C), 124.55 (CH), 122.58 (CH), 120.39 (CH), 119.45 (CH), 111.02 (CH), 108.94 (C), 106.37 (C), 78.61 (CH), 72.70 (C), 56.60 (C), 35.31 (CH_2), 30.17 (CH_3), 28.30 (CH_3), 24.17 (CH_2). Anal calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50; found: C, 69.45; H, 5.61; N, 4.56. HRMS-EI *m/z* calcd for $C_{18}H_{17}NO_4$: 311.1158; found: 311.1154 [M^+].

(*R*) 1-Methyl-3-(-pent-4-yn-2-yl)-1*H*-indole (100)



(i). A flask protected from the light was charged with (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (332 mg, 1.52 mmol), *tert*-butanol (2.50 mL), trifluoroacetic acid (0.11 mL, 1.52 mmol) and CH_2Cl_2, and placed at -40ºC. The solution was stirred for 5 min before addition of crotonaldehyde (1.90 mL, 22.87

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mmol). After stirring for an additional 10 min 1-methyl-1*H*-indole (0.97 mL, 7.62 mmol) was added in one portion. The resulting suspension was stirred at constant temperature for 48 h. The reaction mixture was then passed cold through a silica gel plug with Et_2O and then concentrated. The resulting residue was purified by chromatography (toluene) to give (*R*)-3-(1-methyl-1*H*-indol-3-yl)butanal[78] as a colorless oil (766 mg, 66% yield, 67% ee): $[\alpha]_D$ = -3.4 (c = 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.3 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 3.76 (s, 3H), 3.71-3.67 (m, 1H), 2.88 (ddd, *J* = 16.2, 6.8, 2.3 Hz, 1H), 2.72 (ddd, *J* = 16.3, 7.4, 2.2 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a *Chiralpak AD* column (1:99 ethanol/hexanes), flow = 1 ml/min, λ = 254 nm. Retention times: 17.77 min, minor isomer; 19.23 min, major isomer.

(ii). Tetrabromomethane (2.37 g, 7.15 mmol) was dissolved in 45 mL of THF and cooled at -20ºC, then a solution of triphenylphosphine (1.87 g, 7.15 mmol) in 85 mL of THF was added and left to react for 30 min. After cooling to -60ºC, a mixture of (*R*)-3-(1-methyl-1*H*-indol-3-yl)butanal (720 mg, 3.57 mmol) and triethylamine (0.5 mL, 3.57 mmol) in 20 mL of THF, was slowly added and stirred for 30 min at -60ºC. The reaction mixture was then heated at room temperature and left for 16 h. Then *n*-BuLi (42 mmol) was added at -78ºC and it was left to react with stirring for 1 h and then warmed to room temperature. The reaction mixture was left to react for 16 h, cooled again at -78ºC, hydrolyzed with 0.01M NaOH and extracted with ether. The organic phase was washed with brine twice and the solvent evaporated. The mixture was purified by chromatography (10:1 hexane-EtOAc) to give **100** as a yellow oil (479 mg, 68%): $[\alpha]_D$ = 10.1 (c = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.23-7.19 (m, 1H), 7.11-7.07 (m, 1H), 6.88 (s, 1H), 3.72 (s, 3H), 3.35-3.26 (m, 1H), 2.67 (ddd, *J* = 16.8, 5.2, 2.4 Hz, 1H), 2.44 (ddd, *J* = 16.4, 8.0, 2.4 Hz, 1H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.06 (C), 126.90 (C), 124.96 (CH), 121.52 (CH), 119.24 (C), 119.07 (CH), 118.63 (CH), 109.25 (CH), 83.60 (C), 69.38 (CH), 32.60 (CH), 30.14 (CH_3), 27.03 (CH_2), 20.22 (CH_3). Anal calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10; found:

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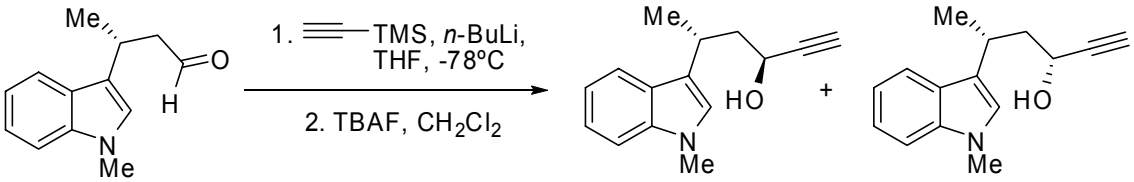
C, 85.10; H, 8.09; N, 6.66. HRMS-CI *m/z* calcd for $C_{14}H_{16}N$: 198.1283; found: 198.1292 [M^++H].

(3*R*,5*R*)-5-Methyl-1*H*-indol-3-yl)hex-1-yn-3-ol + (3*S*,5*R*)-5-Methyl-1*H*-indol-3-yl)hex-1-yn-3-ol (102)



To a stirred solution of trimethylsilylacetylene (0.77 mL, 5.46 mmol) in 20 mL of THF at -78ºC was added *n*-BuLi (5.46 mmol) and it was left to react for 15 min. Then (*R*)-3-(1-methyl-1*H*-indol-3-yl)butanal was added (1.00 g, 4.96 mmol) dissolved in 40 mL of THF and it was left to react for 2 hours at -78ºC. The reaction was quenched with NH_4Cl 10%, and after extractive workup (EtOAc) the mixture was dissolved in CH_2Cl_2 (25 mL) and tetrabutylammonium fluoride trihydrate (2.34 g, 7.44 mmol) was added and it was left to react for 10 minutes. After another extractive workup (EtOAc), the mixture was purified by chromatography (10:1 hexane-EtOAc), to give a 2:1 isomer mixture of **102** as a yellow oil (541 mg, 48%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dt, J = 8.0, 0.8 Hz, 1H, major), 7.69 (dt, J = 7.9, 0.8 Hz, 1H, minor),7.29 (dd, J = 8.2, 0.9 Hz, 1H), 7.22 (td, J = 7.1, 1.2 Hz, 1H), 7.10 (td, J = 7.9, 1.2 Hz, 1H), 6.86 (s, 1H), 4.32 (dd, J = 7.5, 1.9 Hz, 1H, minor), 4.31 (dd, J = 6.9, 1.8 Hz, 1H, major), 3.75 (s, 3H, minor), 3.74 (s, 3H, major), 3.42-3.36 (m, 1H, minor), 3.34-3.27 (m, 1H, major), 2.50 (d, J = 2.1, 1H, major), 2.46 (d, J = 2.2, 1H, minor), 2.26 (ddd, J = 13.2, 8.6, 6.7 Hz, 1H, major), 2.17 (ddd, J = 13.7, 8.8, 5.1 Hz, 1H, minor), 2.09 (ddd, J = 13.7, 8.4, 6.0 Hz, 1H, minor), 2.01 (ddd, J = 13.4, 7.3, 5.6 Hz, 1H, major), 1.79 (br s, 1H), 1.42 (d, J = 6.9, 3H, major), 1.41 (d, J = 6.5, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$, DEPTQ) δ 137.23 (C), 126.88 (C), 125.30 (CH, minor), 125.12 (CH, major), 121.60 (CH, minor), 121.56 (CH, major), 119.51 (CH), 118.70 (CH, minor), 118.63 (CH, major), 109.29 (CH, minor), 109.26 (CH, major), 108.51 (C, minor), 108.43 (C, major), 85.29 (CH), 73.08 (C, major), 72.72 (C, minor), 61.46 (CH, major), 60.86 (CH, minor), 45.84 (CH_2, major), 45.77 (CH_2, minor), 32.61 (CH_3), 27.75 (CH, major), 27.32 (CH, minor), 22.04 (CH_3). Anal calcd for $C_{15}H_{17}NO\cdot 1/2H_2O$: C, 76.24; H, 7.68; N, 5.93; found: C, 76.54; H, 7.29; N, 6.02. HRMS-CI *m/z* calcd for $C_{15}H_{18}NO$: 228.1388; found: 228.1388 [M^++H].

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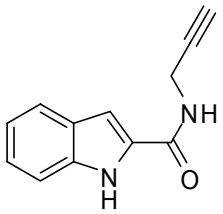
***N*-(Prop-2-ynyl)-1*H*-indole-2-carboxamide (106)**

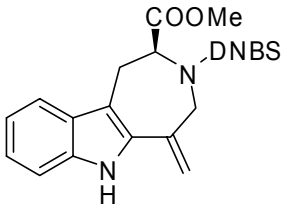


To a solution of indole-2-carboxylic acid (1.00 g, 6.21 mmol) in CH_2Cl_2 (30 mL), oxalyl chloride (1.57 mL, 18.61 mmol) and DMF (0.30 mL) were added. The reaction was heated to reflux for 1 h and then the solvent was evaporated to dryness in vacuum. The residue was taken up with CH_2Cl_2 (30 mL) and propargylamine (1.28 mL, 18.61 mmol) added at 0ºC. After 1 h at room temperature and extractive workup (CH_2Cl_2), the residue was purified by chromatography (4:1 hexane-EtOAc), to give **106** as a white solid (464 mg, 38%): mp 198-200ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.91 (t, J = 5.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 4.09 (dd, J = 5.6, 2.4 Hz, 2H), 3.14 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 160.80 (C), 136.47 (C), 131.06 (C), 126.98 (C), 123.43 (CH), 121.55 (CH), 119.75 (CH), 112.29 (CH), 102.86 (CH), 86.02 (CH), 79.92 (C), 28.02 (CH_2). HRMS-ESI *m/z* calcd for $C_{12}H_9N_2O$: 197.0715; found: 197.0711 [M^+-H].

3.4. General procedure for the cyclization of indole derivatives

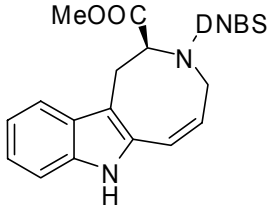
A mixture 1 equiv of indole derivative and 0.05 equiv of catalyst **1** in CH_2Cl_2 (volume necessary to make the concentration of the indole derivative 0.5 M) were stirred at room temperature for the time indicated in Tables 1, 2 and 3 and Schemes 48, 49, 50 and 52. The mixture was filtered trough silica gel and the solvent evaporated. The residue was purified by chromatography to give the product. The same procedure was followed when complex $[Au(PPh_3)Cl]/AgSbF_6$, **52**, **53**, AuCl or $AuCl_3$ were used as catalysts.

(*S*)-Methyl 1,2,3,4,5,6-Hexahydro-5-methylene-3-(2,4-dinitrobenzensulfonyl) azepino[4,5-*b*]indole-2-carboxylate (55)



(*S*)-Methyl 2-(*N*-(prop-2-ynyl)-*N*-(2,4-dinitrobezenesulfonylamino))-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.10 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **55** as an orange solid (41 mg, 82%): mp 204-206ºC. $[\alpha]_D$ = -110.9 (c = 1.0, $(CH_3)_2SO$). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 10.75 (br s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 7.95-7.89 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 8.0, 1.2 Hz, 1H), 6.99 (td, *J* = 8.0, 1.2 Hz, 1H), 5.38 (s, 1H), 5.19 (s, 1H), 4.96 (dd, *J* = 11.6, 6.4 Hz, 1H), 4.68 (d, *J* = 17.2 Hz, 1H), 4.54 (d, *J* = 17.2 Hz, 1H), 3.70 (s, 3H), 3.55 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.33 (dd, *J* = 15.2, 11.2 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 170.78 (C), 149.09 (C), 146.73 (C), 136.01 (C), 135.90 (C), 135.74 (C), 132.69 (C), 131.15 (CH), 127.12 (C), 125.37 (CH), 122.36 (CH), 118.89 (CH), 118.68 (CH), 118.17 (CH), 110.95 (CH_2), 110.55 (CH), 108.97 (C), 60.42 (CH), 52.38 (CH_3), 48.45 (CH_2), 24.17 (CH_2). Anal calcd for $C_{21}H_{18}N_4O_8S \cdot 1/2\ H_2O$: C, 50.91; H, 3.87; N, 11.31; S, 6.47; found: C, 51.33; H, 3.88; N, 11.30; S, 6.39. HRMS-ESI *m/z* calcd for $C_{21}H_{18}N_4O_8SNa$: 509.0743; found: 509.0738 [M^++Na].

(*S*,*Z*)-Methyl 2,3,4,7-Tetrahydro-3-(2,4-dinitrobenzensulfonyl)-1*H*-azocino[5,4,*b*] indole-2-carboxylate (56)



(*S*)-Methyl 2-(*N*-(prop-2-ynyl)-*N*-(2,4-dinitrobezenesulfonylamino))-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.10 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **56** as a dark red solid (38 mg, 75%): mp 261-263ºC. $[\alpha]_D$ = 30.5 (c = 0.5, $(CH_3)_2SO$). ^1H NMR (500 MHz, 420K, $(CD_3)_2SO$) δ 10.35 (br s, 1H), 8.31 (d, *J* = 2.2 Hz, 1H), 8.12 (dd, *J* = 8.7,

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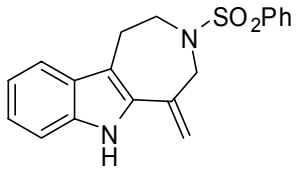
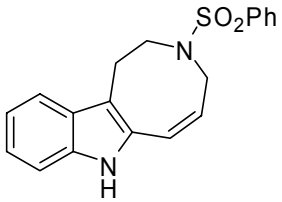
2.2 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.1 Hz, 1H), 7.05-6.99 (m, 2H), 6.45 (dd, *J* = 11.9, 1.3 Hz, 1H), 5.76 (ddd, *J* = 11.9, 5.6, 3.8 Hz, 1H), 4.82 (t, *J* = 7.5 Hz, 1H), 4.65 (dd, *J* = 19.4, 5.7 Hz, 1H), 4.25 (ddd, *J* = 19.4, 3.5, 2.7 Hz, 1H), 3.70 (s, 3H), 3.29 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, 420K, $(CD_3)_2SO$, DEPTQ) δ 170.5 (C)*, 149.5 (C)*, 148.0 (C)*, 137.0 (C)*, 133.5 (C)*, 132.0 (C)*, 131.86 (CH), 127.5 (C)*, 127.04 (CH), 126.35 (CH), 122.21 (CH), 121.16 (CH), 119.50 (CH), 119.29 (CH), 118.17 (CH), 111.31 (CH), 108.0 (C)*, 59.47 (CH), 52.55 (CH_3), 45.41 (CH_2), 26.26 (CH_2). *Determined in the HMBC experiment. Anal calcd for $C_{21}H_{18}N_4O_8S$: C, 51.85; H, 3.73; N, 11.52; S, 6.59; found: C, 51.71; H, 3.92; N, 11.24; S, 6.26. HRMS-ESI *m/z* calcd for $C_{21}H_{18}N_4O_8S$: 486.0845; found: 486.0826 [M^+].

1,2,3,4,5,6-Hexahydro-5-methylene-3-benzenesulfonylazepino[4,5-*b*]indole (58)



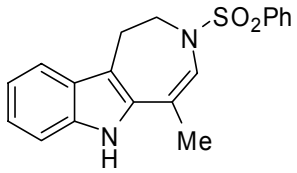
N-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.14 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **58** as a white solid (33 mg, 65%): mp 140-142ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.39 (br s, 1H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.59-7.44 (m, 3H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 5.49 (s, 1H), 5.20 (s, 1H), 4.31 (s, 2H), 3.56 (t, *J* = 5.9 Hz, 2H), 3.04 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 139.23 (C), 137.41 (C), 136.03 (C), 133.16 (C), 132.54 (CH), 129.10 (CH, 2C), 127.81 (C), 126.71 (CH, 2C), 122.33 (CH), 118.60 (CH), 118.31 (CH), 111.93 (C), 111.39 (CH_2), 110.76 (CH), 51.54 (CH_2), 48.61 (CH_2), 22.99 (CH_2). Anal calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47; found: C, 67.00; H, 5.38; N, 8.34; S, 9.52. HRMS-EI *m/z* calcd for $C_{19}H_{18}N_2O_2S$: 338.1089; found: 338.1085 [M^+].

(*Z*)-3-(Phenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azocino[5,4-b]indole (59)



N-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.14 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **59** as a white solid (29 mg, 58%): mp 178-180ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 2H), 7.61 (br s, 1H), 7.46-7.42 (m, 2H), 7.35-7.31 (m, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.16 (t, J = 7.1 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.49 (d, J = 11.2 Hz, 1H), 5.84 (dt, J = 11.1, 6.6 Hz, 1H), 3.99 (d, J = 6.6 Hz, 2H), 3.58 (t, J = 5.3 Hz, 2H), 2.9 8 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 140.04 (C), 136.04 (C), 132.06 (CH), 131.44 (C), 128.75 (CH, 2C), 127.95 (C), 127.31 (CH), 126.86 (CH, 2C), 123.02 (CH), 122.70 (CH), 119.72 (CH), 118.16 (CH), 112.26 (C), 110.70 (CH), 46.21 (CH_2), 45.93 (CH_2), 24.29 (CH_2). Anal calcd for $C_{19}H_{18}N_2O_2S{\cdot}H_2O$: C, 64.02; H, 5.66; N, 7.86; S, 9.00; found: C, 63.72; H, 5.38; N, 7.58; S, 9.61. HRMS-ESI *m/z* calcd for $C_{19}H_{19}N_2O_2S$: 339.1176; found: 339.1152 [M^++H].

(Z)-5-Methyl-3-(phenylsulfonyl)-1,2,3,6-tetrahydroazepino[4,5-b]indole (60)



N-(2-(1*H*-Indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.14 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **60** as a white solid (7 mg, 13%): mp 101-103ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.84 (d, J = 7.2 Hz, 2H), 7.56-7.46 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.76 (s, 1H), 3.78 (t, J = 4.8 Hz, 2H), 2.97 (t, J = 4.9 Hz, 2H), 2.20 (d, J = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 139.58 (C), 134.88 (C), 132.92 (CH), 131.83 (C), 129.28 (CH, 2C), 128.53 (C), 126.28 (CH, 2C), 124.06 (CH), 122.42 (CH), 119.76 (CH), 118.13 (CH), 113.35 (C), 111.19 (C), 110.61 (CH), 45.89 (CH_2), 26.62 (CH_2), 18.89 (CH_3). Anal calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47; found: C, 67.30; H, 5.67; N, 8.08; S, 9.11. HRMS-ESI *m/z* calcd for $C_{19}H_{19}N_2O_2S$: 339.1176; found: 339.1175 [M^++H].

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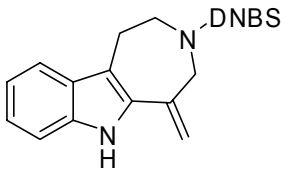
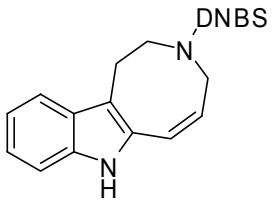
3-(2,4-Dinitrophenylsulfonyl)-5-methylene-1,2,3,4,5,6-hexahydroazepino[4,5-b] indole (62)



N-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dinitrobenzensulfonyl)prop-2-yn-1-amine (50 mg, 0.12 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2:hexane, 3:1) to give **62** as an orange solid (39 mg, 77%): mp 190-192ºC. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.10 (br s, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 8.7, 2.2 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 5.51 (s, 1H), 5.30 (s, 1H), 4.58 (s, 2H), 3.94 (t, J = 6.3 Hz, 2H), 3.26 (t, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6, DEPT) δ 150.58 (C), 142.66 (C), 138.51 (C), 138.41 (C), 137.48 (C), 133.89 (C), 132.59 (CH), 129.13 (C), 126.90 (CH), 123.71 (CH), 120.09 (CH), 120.06 (CH), 119.35 (CH), 113.07 (C), 111.99 (CH), 111.60 (CH_2), 52.69 (CH_2), 50.02 (CH_2), 23.90 (CH_2). Anal calcd for $C_{19}H_{16}N_4O_6S$: C, 53.27; H, 3.76; N, 13.08; S, 7.48; found: C, 53.01; H, 3.98; N, 12.64; S, 7.26. HRMS-ESI *m/z* calcd for $C_{19}H_{17}N_4O_6S$: 429.0869; found: 429.0877 [M^++H].

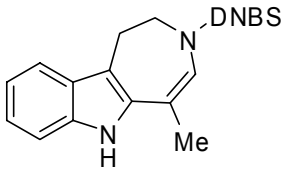
(*Z*)-3-(2,4-Dinitrophenylsulfonyl)-2,3,4,7-tetrahydro-1*H*-azocino[5,4-b]indole (63)



N-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dinitrobenzensulfonyl)prop-2-yn-1-amine (50 mg, 0.12 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2:hexane, 3:1) to give **63** as an orange solid (29 mg, 58%): mp 213-215ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.71 (br s, 1H), 8.57 (d, J = 2.2 Hz, 1H), 8.15 (dd, J = 8.7, 2.3 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 6.8 Hz, 1H), 6.94 (t, J = 6.9 Hz, 1H), 6.43 (d, J = 12.0 Hz, 1H), 5.73 (dt, J = 12.0, 4.8 Hz, 1H), 4.27 (d, J = 4.8 Hz, 2H), 3.66 (t, J = 5.4 Hz, 2H), 3.01 (t, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, DEPT) δ 149.01 (C), 146.82 (C), 136.04 (C), 135.70 (C), 132.24 (C), 130.67 (CH), 127.10 (C), 126.40 (CH),

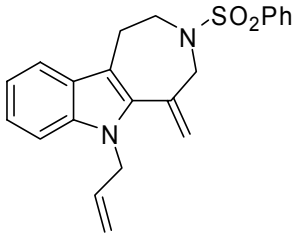
126.13 (CH), 121.44 (CH), 121.02 (CH), 118.95 (CH), 118.59 (CH), 117.90 (CH), 110.61 (CH), 109.20 (C), 47.95 (CH_2), 46.85 (CH_2), 22.80 (CH_2). Anal calcd for $C_{19}H_{16}N_4O_6S \cdot 3/2H_2O$: C, 50.11; H, 4.20; N, 12.30; S, 7.04; found: C, 50.43; H, 3.79; N, 12.01; S, 6.74. HRMS-CI *m/z* calcd for $C_{19}H_{17}N_4O_6S$: 429.0869; found: 429.0854 [M^++H].

(*Z*)-3-(2,4-Dinitrophenylsulfonyl)-5-methyl-1,2,3,6-tetrahydroazepino[4,5-b]indole (64)



N-(2(1*H*-Indol-3-yl)ethyl)-*N*-(2,4-dinitrobenzensulfonyl)prop-2-yn-1-amine (50 mg, 0.12 mmol) was cyclized following the general procedure. The residue was purified by chromatography (CH_2Cl_2:hexane, 3:1) to give **64** as an orange solid (12 mg, 24%): ^{1}H NMR (400 MHz, acetone-d_6) δ 10.06 (br s, 1H), 8.81 (d, J = 1.8 Hz, 1H), 8.64 (dd, J = 8.7, 1.6 Hz, 1H), 8.44 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 7.1 Hz, 1H), 7.02 (t, J = 7.1 Hz, 1H), 6.70 (s, 1H), 3.96 (t, J = 4.9 Hz, 2H), 3.17 (t, J = 5.0 Hz, 2H), 2.30 (d, J = 1.1 Hz, 3H). HRMS-ESI *m/z* calcd for $C_{19}H_{17}N_4O_6S$: 429.0869; found: 429.0895 [M^++H].

6-Allyl-5-methylene-3-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (66)



N-(2-(1-Allyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.13 mmol) was cyclized following the general procedure. The residue was purified by chromatography (5:1 hexane-EtOAc) to give **66** as a white solid (34 mg, 68%): mp 168-170ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.4 Hz, 2H), 7.50-7.39 (m, 4H), 7.22-7.09 (m, 3H), 5.94 (ddt, J = 17.1, 10.4, 4.2 Hz, 1H), 5.56 (s, 1H), 5.29 (s, 1H), 5.16 (d, J = 10.5 Hz, 1H), 4.89 (d, J = 17.0 Hz, 1H), 4.66-4.65, (m, 2H), 4.19 (s, 2H), 3.70 (t, J =

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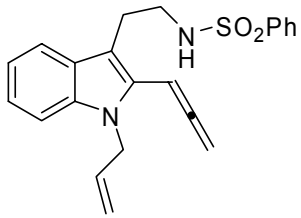
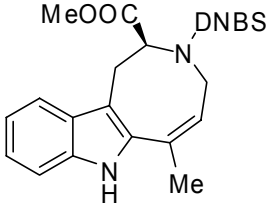
5.4 Hz, 2H), 3.03 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 139.98 (C), 137.69 (C), 135.91 (C), 135.70 (C), 133.89 (CH), 132.31 (CH), 128.92 (CH, 2C), 127.32 (C), 127.03 (CH, 2C), 122.60 (CH), 119.77 (CH), 119.16 (CH_2), 118.46 (CH), 116.38 (CH_2), 112.68 (C), 110.27 (CH), 55.00 (CH_2), 47.55 (CH_2), 46.42 (CH_2), 25.38 (CH_2). Anal calcd for $C_{22}H_{22}N_2O_2S\cdot 3/2H_2O$: C, 65.16; H, 6.21; N, 6.91; S, 7.91; found: C, 62.25; H, 5.68; N, 6.57; S, 7.62. HRMS-ESI *m/z* calcd for $C_{22}H_{23}N_2O_2S$: 379.1480; found: 379.11464 [M^++H].

_N_-(2-(1-Allyl-2-(propa-1,2-dienyl)-1_H_-indol-3-yl)ethyl)benzenesulfonamide (67)



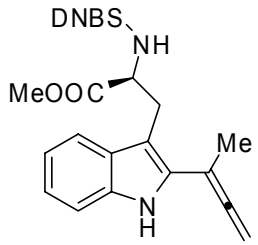
N-(2-(1-Allyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.13 mmol) was reacted following the general procedure. The residue was purified by chromatography (2:1 hexane-EtOAc) to give **67** as a yellow oil (23 mg, 46%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.44-7.37 (m, 3H), 7.26-7.15 (m, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.26 (t, J = 7.1 Hz, 1H), 5.91 (ddt, J = 16.0, 9.7, 4.8 Hz, 1H), 5.16 (d, J = 7.1 Hz, 2H), 5.12 (d, J = 10.4 Hz, 1H), 4.87 (d, J = 17.2 Hz, 1H), 4.79 (d, J = 3.1 Hz, 2H), 4.43 (t, J = 5.5 Hz, 1H), 3.25 (q, J = 6.5 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 211.01 (C), 139.95 (C), 137.11 (C), 133.33 (CH), 132.43 (CH), 128.95 (CH, 2C), 128.37 (C), 127.55 (C), 126.94 (CH, 2C), 122.25 (CH), 119.76 (CH), 118.10 (CH), 116.37 (CH_2), 109.78 (C), 109.35 (CH), 83.09 (CH), 78.54 (CH_2), 45.82 (CH_2), 43.41 (CH_2), 24.86 (CH_2). HRMS-ESI *m/z* calcd for $C_{22}H_{22}N_2O_2S$: 379.1480; found: 379.1479 [M^+].

(_S_,_Z_)-Methyl 3-(2,4-Dinitrophenylsulfonyl)-6-methyl-2,3,4,7-tetrahydro-1_H_-azocino[5,4-b]indole-2-carboxylate (69)



To a solution of (*S*)-methyl 2-(*N*-(but-2-ynyl)-2,4-dinitrophenylsulfonamido)-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.10 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (CH_2Cl_2) to give **69** as a red solid (27 mg, 54%): mp 128-130ºC. $[\alpha]_D$ = -116.4 (c = 0.7, acetone). ^{1}H NMR (500 MHz, 420K, $(CD_3)_2SO$) δ 10.50 (br s, 1H), 8.48 (d, *J* = 1.8 Hz, 1H), 8.33 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.06 (td, *J* = 7.9, 0.9 Hz, 1H), 7.01 (td, *J* = 7.9, 0.6 Hz, 1H), 5.77 (t, *J* = 6.2 Hz, 1H), 4.83 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.43 (dd, *J* = 17.3, 6.0 Hz, 1H), 3.78 (dd, *J* = 17.0, 6.2 Hz, 1H), 3.59 (dd, *J* = 14.8, 8.3 Hz, 1H), 3.56 (s, 3H), 2.96 (dd, *J* = 14.8, 2.6 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, 420K, $(CD_3)_2SO$, DEPT) δ 170.33 (C), 149.0 (C)*, 137.68 (C), 137.10 (C), 136.76 (C), 136.5 (C)*, 132.34 (CH), 131.0 (C)*, 127.83 (C), 126.74 (CH), 123.95 (CH), 122.20 (CH), 119.77 (CH), 119.45 (CH), 118.66 (CH), 111.56 (CH), 108.00 (C), 56.65 (CH), 52.26 (CH_3), 45.01 (CH_2), 27.43 (CH_2), 22.53 (CH_3). *Determined in the HMBC experiment. HRMS-ESI *m/z* calcd for $C_{22}H_{20}N_4O_8SNa$: 523.0900; found: 523.0892 [M^++Na].

(*S*)-Methyl 3-(2-(Buta-2,3-dien-2-yl)-1*H*-indol-3-yl)-2-(2,4-dinitrophenylsulfonamido)propanoate (70)



To a solution of (*S*)-methyl 2-(*N*-(but-2-ynyl)-2,4-dinitrophenylsulfonamido)-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.10 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (CH_2Cl_2) to give **70** as a brown solid (22 mg, 43%): mp 177-179ºC. $[\alpha]_D$ = 102.6 (c = 0.8, acetone). ^{1}H NMR (500 MHz, acetone-d_6) δ 10.50 (br s, 1H), 8.48 (d, *J* = 1.8 Hz, 1H), 8.33 (dd, *J* = 8.7, 1.9 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.06 (td, *J* = 7.9, 0.9 Hz, 1H), 7.01 (td, *J* = 7.9, 0.6 Hz, 1H), 5.77 (t, *J* = 6.2 Hz, 1H), 4.83 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.43 (dd, *J* = 17.3, 6.0 Hz, 1H), 3.78 (dd, *J* = 17.0, 6.2 Hz, 1H), 3.59 (dd, *J* = 14.8, 8.3 Hz, 1H), 3.56 (s, 3H), 2.96 (dd, *J* = 14.8, 2.6 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 210.34, 172.02, 139.45,

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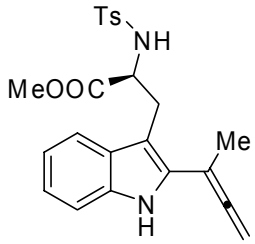
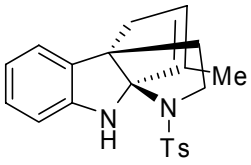
136.23, 134.44, 130.47, 129.88, 128.50, 127.35, 125.94, 122.26, 120.24, 119.98, 119.44, 111.38, 111.24, 105.65, 78.00, 52.82, 27.92, 18.48 (one carbon is missing). HRMS-ESI *m/z* calcd for $C_{22}H_{20}N_4O_8SNa$: 523.0900; found: 523.0895 [M^++Na].

(*S*)-Methyl 3-(2-(Buta-2,3-dien-2-yl)-1*H*-indol-3-yl)-2-(4-methylphenylsulfonamido)propanoate (72)



(*S*)-Methyl 2-(*N*-(but-2-ynyl)-*N*-tosylamino)-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.12 mmol) was reacted following the general procedure. The residue was purified by chromatography (CH_2Cl_2) to give **72** as a white solid (31 mg, 62%): mp 144-146ºC. $[\alpha]_D$ = 0.6 (c = 0.6, acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (br s, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 8.03-8.02 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.76-6.68 (m, 3H), 5.11 (dq, *J* = 12.0, 3.1 Hz, 1H), 5.06 (dq, *J* = 12.5, 3.2 Hz, 1H), 4.55 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.63 (s, 3H), 3.30 (dd, *J* = 14.8, 3.9 Hz, 1H), 3.17 (dd, *J* = 14.8, 11.3 Hz, 1H), 2.08 (t, *J* = 3.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 209.28 (C), 172.21 (C), 143.11 (C), 136.43 (C), 135.12 (C), 130.63 (C), 129.17 (CH, 2C), 129.05 (C), 126.92 (CH, 2C), 122.27 (CH), 119.87 (CH), 118.06 (CH),110.40 (CH), 106.90 (C), 93.30 (C), 77.89 (CH_2), 56.13 (CH), 52.34 (CH_3), 28.53 (CH_2), 21.48 (CH_3), 17.83 (CH_3). HRMS-ESI *m/z* calcd for $C_{23}H_{24}N_2O_4SNa$: 447.1354; found: 447.1342 [M^++Na].

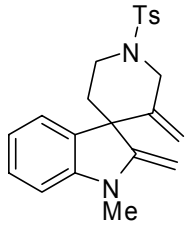
Tetracycle 74



To a solution of *N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-tosylbut-2-yn-1-amine (50 mg, 0.14 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (4:1 hexane-EtOAc) to give **74** as a white solid (29 mg, 58%): mp 199-201ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz , 1H),

7.18 (d, *J* = 8.1 Hz, 1H), 7.06 (td, *J* = 7.7, 1.2 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.71 (td, *J* = 7.4, 0.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.44-5.42 (m, 2H), 3.35 (ddd, *J* = 10.5, 8.6, 5.8 Hz, 1H), 3.22 (ddd, *J* = 10.5, 6.9, 4.5 Hz, 1H), 2.64-2.54 (m, 2H), 2.34 (s, 3H), 2.08 (ddd, *J* = 12.4, 5.8, 4.5 Hz, 1H), 2.00-1.99 (m, 3H), 1.86 (ddd, *J* = 12.4, 8.6, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 148.30 (C), 142.94 (C), 139.74 (C), 137.15 (C), 133.57 (C), 129.35 (CH, 2C), 128.49 (CH), 128.20 (CH), 127.70 (CH, 2C), 123.13 (CH), 119.09 (CH), 109.38 (CH), 103.19 (C), 66.12 (C), 48.61 (CH_2), 43.83 (CH_2), 37.91 (CH_2), 21.41 (CH_3), 13.38 (CH_3). Anal calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64; S, 8.75; found: C, 68.67; H, 6.10; N, 7.91; S, 8.68. HRMS-CI *m/z* calcd for $C_{21}H_{23}N_2O_2S$: 367.1480; found: 367.1489 [M^++H].

1-Methyl-2,3'-dimethylene-1'-tosylspiro[indoline-3,4'-piperidine] (76)



To a solution of *N*-(2-(1,2-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide (50 mg, 0.13 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was filtered through silica to give **76** as a white solid (40 mg, 80%): mp 133-135ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.12 (td, *J* = 7.6, 1.1 Hz, 2H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 5.04 (s, 1H), 4.73 (s, 1H), 4.08 (d, *J* = 13.9 Hz, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.93 (d, *J* = 2.3 Hz, 1H), 3.68 (d, *J* = 2.3 Hz, 1H), 3.60-3.54 (m, 1H), 3.43 (ddd, *J* = 12.8, 7.8, 5.1 Hz, 1H), 2.99 (s, 3H), 2.48 (s, 3H), 1.91-1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 158.06 (C), 146.30 (C), 143.69 (C), 143.02 (C), 133.81 (C), 133.45 (C), 129.77 (CH, 2C), 128.22 (CH), 127.88 (CH, 2C), 123.65 (CH), 118.07 (CH), 115.38 (CH_2), 105.60 (CH), 78.03 (CH_2), 51.47 (C), 49.85 (CH_2), 41.96 (CH_2), 37.78 (CH_2), 28.76 (CH_3), 21.59 (CH_3). Anal calcd for $C_{22}H_{24}N_2O_2S \cdot 1/3H_2O$: C, 68.36; H, 6.43; N, 7.25; S, 8.30; found: C, 68.84; H, 6.30; N, 7.41; S, 8.17. HRMS-EI *m/z* calcd for $C_{22}H_{24}N_2O_2S$: 380.1559; found: 380.1567 [M^+].

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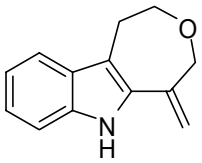
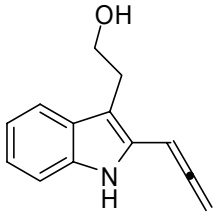
5-Methylene-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-b]indole (78)



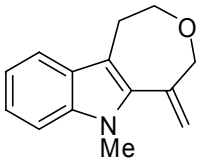
3-(2-(Prop-2-ynyloxy)ethyl)-1*H*-indole (50 mg, 0.25 mmol) was cyclized following the general procedure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **78** as a white solid (29 mg, 58%): mp 69-71ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.20 (td, J = 6.9, 1.1 Hz, 1H), 7.10 (td, J = 6.8, 1.0 Hz, 1H), 5.28 (s, 1H), 5.18 (s, 1H), 4.48 (s, 2H), 4.12 (t, J = 5.4 Hz, 2H), 3.10 (t, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 141.08 (C), 135.93 (C), 133.30 (C), 128.94 (C), 123.13 (CH), 119.63 (CH), 118.85 (CH), 114.07 (C), 110.90 (CH), 110.62 (CH_2), 75.95 (CH_2), 72.49 (CH_2), 27.50 (CH_2). HRMS-ESI *m/z* calcd for $C_{13}H_{14}NO$: 200.1075; found: 200.1077 [M^++H].

2-(2-(Propa-1,2-dienyl)-1*H*-indol-3-yl)ethanol (79)



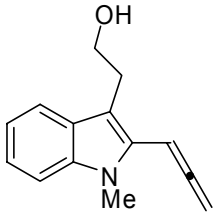
3-(2-(Prop-2-ynyloxy)ethyl)-1*H*-indole (50 mg, 0.25 mmol) was reacted following the general procedure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **79** as a yellow oil (10 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.46 (t, J = 6.7 Hz, 1H), 5.34 (d, J = 6.9 Hz, 2H), 3.89-3.86 (m, 2H), 3.05 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 209.59 (C), 136.25 (C), 129.07 (C), 128.05 (C), 122.68 (CH), 119.60 (CH), 118.46 (CH), 110.52 (C), 110.42 (CH), 84.66 (CH), 80.62 (CH_2), 62.89 (CH_2), 27.53 (CH_2). HRMS-ESI *m/z* calcd for $C_{13}H_{13}NONa$: 222.0895; found: 222.0897 [M^++Na].

6-Methyl-5-methylene-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-b]indole (81)



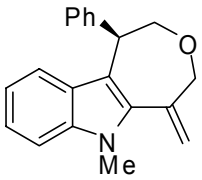
1-Methyl-3-(2-(prop-2-ynyloxy)ethyl)-1*H*-indole (50 mg, 0.23 mmol) was reacted following the general procedure. The residue was purified by chromatography (50:1 hexane-EtOAc) to give **81** as a yellow solid (43 mg, 85%): mp 67°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.25 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.13 (dt, *J* = 7.9, 1.1 Hz, 1H), 5.62 (d, *J* = 0.7 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 4.36 (s, 2H), 4.06-4.04 (m, 2H), 3.75 (s, 3H), 3.08-3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 139.6 (C), 138.5 (C), 127.4 (C), 122.5 (CH), 119.7 (CH), 119.1 (CH_2), 118.7 (CH), 113.6 (C), 109.9 (CH), 76.9 (CH_2), 71.5 (CH_2), 31.7 (CH_3), 27.8 (CH_2). Anal calcd for $(C_{14}H_{15}NO)_5 \cdot H_2O$: C, 77.53; H, 7.16; N, 6.46; found: C, 78.01; H, 7.14; N, 6.60. HRMS-ESI *m/z* calcd for $C_{14}H_{16}NO$: 214.1232; found: 214.1227 [M^++H].

2-(2-(Buta-2,3-dien-2-yl)-1-methyl-1*H*-indol-3-yl)ethanol (82)



1-Methyl-3-(2-(prop-2-ynyloxy)ethyl)-1*H*-indole (50 mg, 0.23 mmol) was reacted following the general procedure. The residue was purified by chromatography (50:1 hexane-EtOAc) to give **82** as a colorless oil (14 mg, 27%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.11 (dt, *J* = 7.0, 1.0 Hz, 1H), 4.85 (q, *J* = 3.3 Hz, 2H), 3.87 (t, *J* = 6.5 Hz, 2H), 3.70 (s, 3H), 3.05 (t, *J* = 6.6 Hz, 2H), 2.06 (t, *J* = 3.2 Hz, 3H) 1.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 209.6 (C), 137.4 (C), 135.5 (C), 128.0 (C), 121.9 (CH), 119.4 (CH), 118.9 (CH), 109.4 (CH), 108.2 (C), 91.3 (C), 74.4 (CH_2), 63.3 (CH_2), 30.6 (CH_3), 28.6 (CH_2), 20.5 (CH_3). HRMS-EI *m/z* calcd for $C_{15}H_{17}NO$: 227.1310; found: 227.1310 [M^+].

(*R*)-6-Methyl-5-methylene-1-phenyl-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-b]indole (84)



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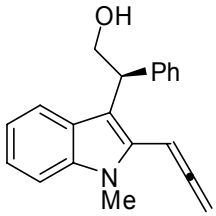
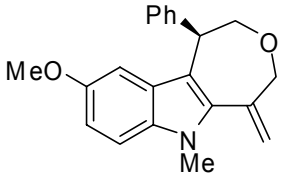
(*R*)-1-Methyl-3-(1-phenyl-2-(prop-2-ynyloxy)ethyl)-1*H*-indole (100 mg, 0.34 mmol) was cyclized following the general procedure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **84** as a yellow oil (69 mg, 69%): $[\alpha]_D$ = 43.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz , 1H), 7.24-7.14 (m, 7H), 6.98 (t, *J* = 7.3 Hz, 1H), 5.69 (s, 1H), 5.36 (s, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.51-4.48 (m, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.22 (dd, *J* = 12.0, 5.9 Hz, 1H), 4.15 (dd, *J* = 12.1, 3.7 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 142.55 (C), 138.79 (C), 138.47 (C), 136.12 (C), 128.38 (CH, 2C), 128.28 (CH, 2C), 127.19 (C), 126.35 (CH), 122.41 (CH), 119.53 (CH), 119.52 (CH_2), 119.33 (CH), 115.24 (C), 109.61 (CH), 76.92 (CH_2), 74.95 (CH_2), 45.62 (CH), 31.41 (CH_3). HRMS-EI *m/z* calcd for $C_{20}H_{19}NO$: 289.1467; found: 289.1475 [M^+].

(*S*)-2-(1-Methyl-2-(propa-1,2-dienyl)-1*H*-indol-3-yl)-2-phenylethanol (85)



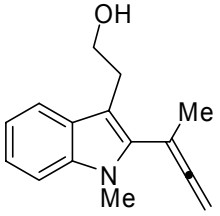
(*R*)-1-Methyl-3-(1-phenyl-2-(prop-2-ynyloxy)ethyl)-1*H*-indole (100 mg, 0.34 mmol) was reacted following the general procedure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **85** as a yellow oil (17 mg, 17%): $[\alpha]_D$ = 7.3 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 1H), 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 7.21-7.17 (m, 2H), 7.01 (td, *J* = 7.0, 1.0 Hz, 1H), 6.44 (t, *J* = 7.0 Hz, 1H), 5.16 (d, *J* = 7.1 Hz, 2H), 4.68 (t, *J* = 7.6 Hz, 1H), 4.37-4.35 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 211.20 (C), 141.54 (C), 138.08 (C), 130.16 (C), 128.42 (CH, 2C), 127.99 (CH, 2C), 126.60 (C), 126.31 (CH), 121.91 (CH), 119.90 (CH), 119.51 (CH), 112.32 (C), 109.23 (CH), 83.54 (CH), 78.42 (CH_2), 65.23 (CH_2), 45.10 (CH), 30.94 (CH_3). HRMS-EI *m/z* calcd for $C_{20}H_{19}NO$: 298.1467; found: 298.1467 [M^+].

(*R*)-9-Methoxy-6-methyl-5-methylene-1-phenyl-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-b]indole (87)



(*R*)-5-Methoxy-1-methyl-3-(1-phenyl-2-(prop-2-ynyloxy)ethyl)-1*H*-indole (50 mg, 0.15 mmol) was cyclized following the general procedure. The residue was purified by chromatography (20:1 hexane-EtOAc) to give **87** as a yellow solid (45 mg, 89%): $[\alpha]_D$ = 125.9 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.23 (m, 4H), 7.19 (d, *J* = 9.0 Hz, 1H), 7.19-7.13 (m, 1H), 6.85 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 5.67 (s, 1H), 5.34 (s, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.43 (dd, *J* = 5.7, 3.8 Hz, 1H), 4.23 (dd, *J* = 12.1, 5.8 Hz, 1H), 4.16 (dd, *J* = 12.1, 3.8 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 154.2 (C), 142.6 (C), 139.0 (C), 134.1 (C), 128.6 (CH), 128.5 (CH), 127.7 (C), 126.5 (CH), 119.6 (CH_2), 115.0 (C), 112.6 (CH), 110.5 (CH), 101.5 (CH), 100.5 (C), 77.1 (CH_2), 75.2 (CH_2), 56.0 (CH_3), 45.8 (CH), 31.7 (CH_3). Anal calcd for $(C_{21}H_{21}NO_2)_4 \cdot 3H_2O$: C, 75.76; H, 6.81; N, 4.21; found: C, 75.71; H, 6.53; N, 5.12. HRMS-ESI *m/z* calcd for $C_{21}H_{21}NO_2Na$: 342.1470; found: 342.1469 [M^++Na].

2-(2-(Buta-2,3-dien-2-yl)-1-methyl-1*H*-indol-3-yl)ethanol (89)



3-(2-(But-2-ynyloxy)ethyl)-1-methyl-1*H*-indole (50 mg, 0.22 mmol) was cyclized following the general procedure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **89** as a colorless oil (14 mg, 27%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.11 (dt, *J* = 7.0, 1.0 Hz, 1H), 4.85 (q, *J* = 3.3 Hz, 2H), 3.87 (t, *J* = 6.5 Hz, 2H), 3.70 (s, 3H), 3.05 (t, *J* = 6.6 Hz, 2H), 2.06 (t, *J* = 3.2 Hz, 3H) 1.47, (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 209.6 (C), 137.4 (C), 135.5 (C), 128.0 (C), 121.9 (CH), 119.4 (CH), 118.9 (CH), 109.4 (CH), 108.2 (C), 91.3 (C), 74.4 (CH_2), 63.3 (CH_2), 30.6

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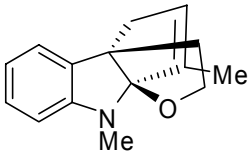
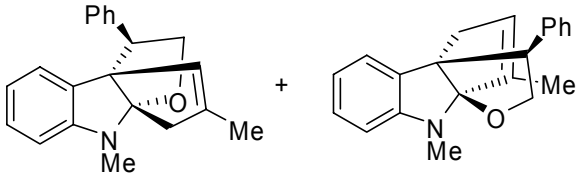
(CH_3). 28.6 (CH_2), 20.5 (CH_3). HRMS-EI *m/z* calcd for $C_{15}H_{17}NO$: 227.1310; found: 227.1310 [M^+].

Tetracycle 90



To a solution of 3-(2-(but-2-ynyloxy)ethyl)-1-methyl-1*H*-indole (50 mg, 0.22 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **90** as a yellow solid (34 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dt, J = 7.7, 1.3 Hz, 1H), 7.06 (dd, J = 7.3, 1.1 Hz, 1H), 6.66 (dt, J = 7.4, 0.9 Hz, 1H), 6.34 (d, J = 7.9 Hz, 1H), 5.38 (q, J = 1.6 Hz, 1H), 4.02 (ddd, J = 8.8, 6.8, 2.0 Hz, 1H), 3.57 (ddd, J = 10.7, 8.8, 5.0 Hz, 1H), 2.97 (s, 3H), 2.65 (dquint, J = 17.0, 2.3 Hz, 1H), 2.60 (dquint, J = 17.0, 2.3 Hz, 1H), 2.34 (ddd, J = 11.9, 5.0, 2.2 Hz, 1H), 2.11 (ddd, J = 11.9, 10.8, 6.8 Hz, 1H), 1.93 (q, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 152.1 (C), 139.0 (C), 133.7 (C), 128.4 (CH), 127.8 (CH), 123.5 (CH), 118.2 (C), 117.6 (CH), 105.5 (CH), 68.7 (CH_2), 62.4 (C), 44.3 (CH_2), 43.6 (CH_2), 30.1 (CH_3), 13.5 (CH_3). Anal calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; found: C, 79.31; H, 7.54; N, 6.52. HRMS-ESI *m/z* calcd for $C_{15}H_{17}NONa$: 250.1208; found: 250.1216 [M^++Na].

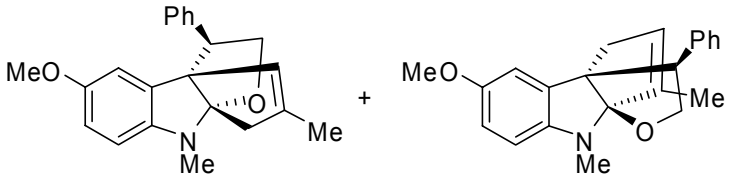
Tetracycle 92/93



To a solution of (*R*)-3-(2-(but-2-ynyloxy)-1-phenylethyl)-1-methyl-1*H*-indole (50 mg, 0.16 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (20:1 hexane-EtOAc) to give a 3:1 isomer mixture of **92/93** as a colorless oil (28 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H, minor), 7.28-7.25 (m, 3H, major), 7.15 (td, J = 7.6, 1.3 Hz, 1H, minor), 7.11 (dd, J = 7.3, 1.1 Hz, 1H, minor), 7.04 (td, J = 7.6, 1.2 Hz, 1H, major), 6.99-6.97 (m, 2H, major), 6.71 (td, J = 7.4, 0.9 Hz, 1H, minor), 6.42 (d, J = 7.8 Hz, 1H, minor), 6.36 (d, J = 7.9 Hz, 1H, major), 6.32 (td, J = 7.4, 0.9 Hz, 1H, major), 5.83 (dd, J = 7.4,

0.9 Hz, 1H, major), 5.48-5.46 (m, 1H, major), 5.27-5.25 (m, 1H, minor), 4.20 (dd, *J* = 8.6, 6.2 Hz, 1H, major), 4.12 (dd, *J* = 9.1, 4.6 Hz, 1H, minor), 4.05 (dd, *J* = 9.0, 5.8 Hz, 1H, minor), 3.90 (dd, *J* = 11.6, 8.6 Hz, 1H, major), 3.54 (dd, *J* = 11.8, 6.1 Hz, 1H), 3.07 (s, 3H, minor), 3.04 (s, 3H, major), 2.92 (dq, *J* = 16.9, 2.2 Hz, 1H, major), 2.50 (dq, *J* = 16.9, 2.2Hz, 1H, major), 2.27 (dq, *J* = 17.6, 2.1 Hz, 1H, minor), 2.18 (dq, *J* = 17.6, 2.4 Hz, 1H, minor), 1.99 (dt, *J* = 3.8, 2.1 Hz, 3H, major), 1.97 (dt, *J* = 7.4, 0.9 Hz, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 152.34 (C, major), 151.14 (C, minor), 140.75 (C, minor), 139.42 (C, major), 138.05 (C, minor), 136.35 (C, major), 135.14 (C, minor), 129.22 (CH, minor), 128.93 (CH, 2C, major), 128.90 (C), 128.53 (CH, 2C, minor), 128.33 (CH, 2C, minor), 128.29 (CH, minor), 128.19 (CH, major), 127.89 (CH, 2C, major), 127.62 (CH, major), 127.17 (CH, major), 126.85 (CH, minor), 126.31 (CH, major), 123.40 (CH, minor), 118.50 (C), 117.44 (CH, minor), 116.40 (CH, major), 105.54 (CH, minor), 104.62 (CH, major), 73.00 (CH_2, minor), 71.57 (CH_2, major), 66.14 (C, minor), 65.77 (C, major), 58.55 (CH, major), 57.72 (CH, minor), 44.75 (CH_2, major), 39.20 (CH_2, minor), 29.95 (CH_3, minor), 29.72 (CH_3, major), 13.31 (CH_3, minor), 13.22 (CH_3, major). HRMS-ESI *m/z* calcd for $C_{21}H_{21}NONa$: 326.1521; found: 326.1521 [M^++Na].

Tetracycle 95/96



To a solution of (*R*)-3-(2-(but-2-ynyloxy)-1-phenylethyl)-5-methoxy-1-methyl-1*H*-indole (100 mg, 0.30 mmol) in toluene was added catalyst **1** and the mixture was stirred at 90ºC. The residue was purified by chromatography (50:1 hexane-EtOAc) to give a 2.5:1 isomer mixture of **95/96** as a colorless oil (67 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H), 7.25-7.23 (m, 3H), 7.19-7.16 (m, 1H), 7.00-6.98 (m, 2H), 6.75 (d, *J* = 2.6 Hz, 1H, minor), 6.71 (dd, *J* = 8.4, 2.6 Hz, 1H, minor), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1H, major), 6.33 (d, *J* = 8.4 Hz, 1H, minor), 6.27 (d, *J* = 8.5 Hz, 1H, major), 5.44 (s, 1H), 5.43 (s, 1H), 5.23 (q, *J* = 1.6 Hz, 1H, minor), 4.19 (dd, *J* = 8.6, 6.2 Hz, 1H, major), 4.09 (dd, *J* = 9.1, 4.7 Hz, 1H, minor), 4.03 (dd, *J* = 9.1, 5.8 Hz, 1H, minor), 3.90 (dd, *J* = 11.7, 8.7 Hz, 1H, major), 3.77 (s, 3H, minor), 3.52 (dd, *J* = 11.7, 6.2 Hz, 1H, major), 3.50-3.48 (m, 1H), 3.39 (s, 3H, major), 3.01 (s, 3H, minor), 2.98 (s, 3H, major),

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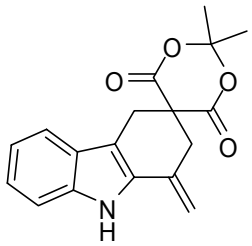
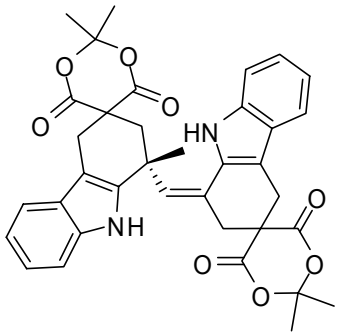
2.89 (dquint, J = 16.9, 2.1 Hz, 1H, major), 2.48 (dquint, J = 16.9, 2.4 Hz, 1H, major), 2.23 (dquint, J = 17.4, 2.3 Hz, 1H, minor), 2.17 (dquint, J = 17.4, 2.3 Hz, 1H, minor), 1.96 (q, J = 1.8 Hz, 3H, major), 1.94 (q, J = 1.7 Hz, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 153.0 (C, minor), 151.9 (C, major), 147.2 (C, major), 140.8 (C, minor), 139.9 (C, major), 138.5 (C, minor), 136.6 (C, minor), 136.5 (C. major), 130.0 (C, major), 129.1 (CH, major), 129.0 (CH, minor), 128.8 (CH, minor), 128.5 (CH, minor), 128.2 (CH, major), 127.4 (CH, major), 127.3 (CH, major), 127.1 (CH, minor), 119.1 (C, minor), 114.6 (CH, major), 113.1 (CH, major), 112.8 (CH, minor), 111.4 (CH, minor), 106.2 (CH, minor), 105.6 (CH, major), 73.3 (CH_2, minor), 71.8 (CH_2, major), 66.5 (C, minor), 66.2 (C, major), 58.3 (CH, major), 57.8 (CH, minor), 56.4 (CH_3, minor), 56.2 (CH_3, major), 44.5 (CH_2, major), 39.1 (CH_2, minor), 30.9 (CH_3, minor), 30.6 (CH_3, major), 13.3 (CH_3, minor), 13.2 (CH_3, major). Anal calcd for $(C_{22}H_{23}NO_2)_2 \cdot H_2O$: C, 77.16; H, 7.06; N, 4.09; found: C, 77.25; H, 6.74; N, 4.46. HRMS-ESI *m/z* calcd for $C_{22}H_{23}NO_2Na$: 356.1626; found: 356.1624 [M^++Na].

1,2,3,4-Tetrahydro-1-methylenecarbazol-3-spiro-5'-(1,3-dioxane-4,6-dione) (98)



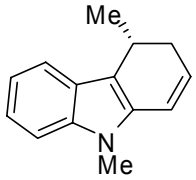
5-((1*H*-Indol-3-yl)methyl)-2,2-dimethyl-5-(prop-2-ynyl)-1,3-dioxane-4,6-dione (50 mg, 0.16 mmol) was cyclized following the general procedure. The residue was purified by chromatography (4:1 hexane-EtOAc) to give **98** as a white solid (34 mg, 68%): mp 152-154ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.19 (td, J = 7.1, 1.1 Hz, 1H), 7.08 (td, J = 7.6, 0.9 Hz, 1H), 5.29 (s, 1H), 5.01 (s, 1H), 3.49 (s, 2H), 3.15 (s, 2H), 1.82 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 168.66 (C), 136.88 (C), 131.64 (C), 131.46 (C), 126.86 (C), 123.52 (CH), 119.90 (CH), 118.52 (CH), 111.10 (CH), 108.82 (C), 107.03 (CH_2), 105.09 (C), 49.85 (C), 39.06 (CH_2), 29.99 (CH_2), 29.28 (CH_3), 28.09 (CH_3). HRMS-CI *m/z* calcd for $C_{18}H_{18}NO_4$: 312.1236; found: 312.1227 [M^++H].

Dimer 99



5-((1*H*-Indol-3-yl)methyl)-2,2-dimethyl-5-(prop-2-ynyl)-1,3-dioxane-4,6-dione (50 mg, 0.16 mmol) was reacted following the general procedure. The residue was purified by chromatography (4:1 hexane-EtOAc) to give **99** as a brown solid (12 mg, 25%): mp 285-287ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.12 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.93 (td, J = 6.5, 1.4 Hz, 1H), 6.88 (t, J = 7.0 Hz, 1H), 6.81-6.76 (m, 2H), 6.74 (d, J = 7.4 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.56 (s, 1H), 3.73 (d, J = 16.2 Hz, 1H), 3.65 (d, J = 16.0 Hz, 1H), 3.61 (d, J = 16.3 Hz, 1H), 3.49 (d, J = 15.7 Hz, 1H), 3.13 (d, J = 13.0 Hz, 1H), 2.64 (d, J = 14.1 Hz, 1H), 2.51 (d, J = 14.4 Hz, 1H), 2.32 (d, J = 13.2 Hz, 1H), 1.99 (s, 3H), 1.94 (s, 3H), 1.86 (s, 3H), 1.85 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPTQ) δ 171.00 (C), 170.41 (C), 169.88 (C), 136.85 (C), 136.68 (C), 134.20 (C), 133.90 (C), 132.25 (C), 125.37 (C), 124.82 (C), 122.10 (CH), 121.78 (CH), 119.41 (CH), 118.89 (CH), 118.62 (CH), 117.35 (CH), 117.20 (CH), 111.35 (CH), 110.95 (CH), 106.16 (C), 105.87 (C), 102.40 (C), 52.97 (C), 49.44 (C), 46.67 (CH_2), 41.89 (CH_2), 35.51 (C), 32.44 (CH_2), 29.98 (CH_3), 29.96 (CH_3), 29.52 (CH_3), 28.63 (CH_3), 28.56 (CH_3), 28.19 (CH_2). HRMS-CI *m/z* calcd for $C_{36}H_{35}N_2O_8$: 623.2393; found: 623.2393 [M^++H]. The configuration at the exocyclic double bond was determined by NOESY experiments.

(*R*)-4,9-Dihydro-4,9-dimethyl-3H-carbazole (101)



(*R*)-1-Methyl-3-(pent-4-yn-2-yl)-1*H*-indole (50 mg, 0.25 mmol) was cyclized following the general procedure. The residue was purified by chromatography (50:1 hexane-EtOAc) to give **101** as a white solid (46 mg, 92%): mp 75-77ºC. $[\alpha]_D$ = -9.6 (c =

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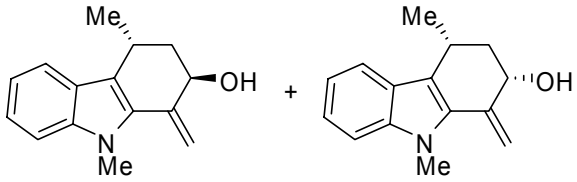
0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, J = 8.0, 0.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.13 (td, J = 6.8 1.2 Hz, 1H), 7.06 (td, J = 8.0, 0.8 Hz, 1H), 6.52 (ddd, J = 10.0, 2.4, 1.6 Hz, 1H), 5.95 (ddd, J = 10.0, 5.2, 4.0 Hz, 1H), 3.67 (s, 3H), 3.30-3.21 (m, 1H), 2.63 (ddd, J = 17.2, 4.0, 2.8 Hz, 1H), 2.25 (ddd, J = 17.2, 5.2, 1.6 Hz, 1H), 1.27 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.24 (C), 133.81 (C), 126.94 (CH), 125.87 (C), 120.81 (CH), 119.18 (CH), 118.54 (CH), 116.39 (CH), 113.78 (C), 109.03 (CH), 32.91 (CH_2), 29.04 (CH_3), 26.48 (CH), 20.17 (CH_3). HRMS-CI *m/z* calcd for $C_{13}H_{13}N$: 198.1283; found: 198.1287 [M^++H].

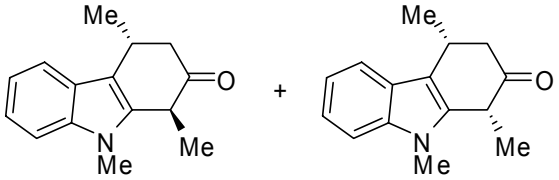
(2*S*,4*R*)-2,3,4,9-Tetrahydro-4,9-dimethyl-1-methylene-1*H*-carbazol-2-ol + (2*R*,4*R*)-2,3,4,9-Tetrahydro-4,9-dimethyl-1-methylene-1*H*-carbazol-2-ol (103)



(3*R*,5*R*)-(5-Methyl-1*H*-indol-3-yl)hex-1-yn-3-ol + (3*S*,5*R*)-(5-methyl-1*H*-indol-3-yl)hex-1-yn-3-ol (50 mg, 0.22 mmol) were cyclized following the general procedure. The mixture was purified by chromatography (4:1 hexane-EtOAc) to give a 2:1 isomer mixture of **103** as a white solid (36 mg, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 1H, minor), 7.61 (d, J = 8.0 Hz, 1H, major),7.30 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.6 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H, major), 7.07 (t, J = 7.6 Hz, 1H, minor), 5.47 (s, 1H, minor), 5.42 (s, 1H, major), 5.36 (s, 1H, major), 5.34 (s, 1H, minor), 4.60 (br d, J = 7.4 Hz, 1H, major), 4.44 (br d, J = 10.0 Hz, 1H, minor), 3.82 (s, 3H, major), 3.81 (s, 3H, minor), 3.43-3.35 (m, 1H, major), 3.35-3.31 (m, 1H, minor), 2.35 (ddd, J = 12.6, 6.2, 3.9 Hz, 1H, minor), 2.18 (ddd, J = 12.8, 8.8, 6.6, 1H, major), 1.90 (ddd, J = 13.1, 5.3, 3.6, 1H, major), 1.77 (br s, 1H), 1.65 (ddd, J = 12.0, 10.7, 5.4, 1H, minor), 1.49 (d, J = 6.8 Hz, 3H, minor), 1.44 (d, J = 6.5 Hz, 3H, major). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 141.35 (C, minor), 140.89 (C, major), 139.88 (C, minor), 139.81, (C, major), 132.52 (C, minor), 131.79 (C, major), 125.73 (C, minor), 125.67 (C, major), 122.64 (CH, major), 122.51 (CH, minor), 120.25 (CH, minor), 119.87 (CH, major), 119.26 (CH, major), 119.21 (CH, minor), 118.08 (C, major), 117.78 (C, minor), 109.46 (CH, minor), 109.39 (CH, major), 107.09 (CH_2, major), 105.80 (CH_2, minor), 71.43 (CH, minor), 70.39 (CH, major), 42.95 (CH_2, minor), 41.34 (CH_2, major), 31.92 (CH, major),

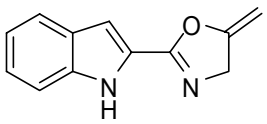
31.74 (CH, minor), 27.52 (CH_3, minor), 25.33 (CH_3, major), 22.16 (CH_3, minor), 21.66 (CH_3, major). HRMS-ESI *m/z* calcd for $C_{15}H_{18}NO$: 228.1388; found: 228.1384 [M^++H].

(4*R*,1*S*)-3,4-Dihydro-1,4,9-trimethyl-1*H*-carbazol-2(9*H*)-one + (4*R*,1*R*)-3,4-Dihydro-1,4,9-trimethyl-1*H*-carbazol-2(9*H*)-one (104)



(3*R*,5*R*)-(5-Methyl-1*H*-indol-3-yl)hex-1-yn-3-ol + (3*S*,5*R*)-(5-methyl-1*H*-indol-3-yl)hex-1-yn-3-ol (50 mg, 0.22 mmol) were cyclized following the general procedure. The mixture was purified by chromatography (4:1 hexane-EtOAc) to give a 2:1 isomer mixture of **104** as a white solid (50 mg, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 1H, major), 7.56 (d, J = 9.0 Hz, 1H, minor),7.29 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 8.04 Hz, 1H), 7.12 (td, J = 7.9, 1.0 Hz, 1H), 3.66 (s, 3H, major), 3.63 (s, 3H, minor), 3.62-3.56 (m, 2H, major), 3.50-3.45 (m, 2H, minor), 3.10 (dd, J = 13.3, 6.8 Hz, 1H, minor), 2.80 (dd, J = 14.0, 6.3 Hz, 1H, major), 2.64 (dd, J = 14.0, 4.6 Hz, 1H, major), 2.37 (dd, J = 13.3, 3.1 Hz, 1H, minor), 1.52 (d, J = 7.2 Hz, 3H, major), 1.50 (d, J = 7.0, 3H, minor), 1.38 (d, J = 6.9, 3H, major), 1.31 (d, J = 6.9, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$, DEPTQ) δ 211.51 (C, minor), 211.24 (C, major), 138.28 (C, minor), 138.10 (C, major), 136.29 (C, major), 135.56 (C, minor), 125.54 (C, major), 125.46 (C, minor), 121.52 (CH), 119.37 (CH), 118.61 (CH), 113.82 (C, major), 113.61 (C, minor), 109.11 (CH, minor), 109.09 (CH, major), 46.64 (CH_2, major), 44.16 (CH_2, minor), 42.65 (CH_3, minor), 41.61 (CH_3, major), 29.81 (CH, major), 29.63 (CH, minor), 28.07 (CH, minor), 27.54 (CH, major), 23.18 (CH_3, major), 22.66 (CH_3, minor), 19.80 (CH_3, major), 18.52 (CH_3, major). HRMS-ESI *m/z* calcd for $C_{15}H_{18}NO$: 228.1388; found: 228.1381 [M^++H].

2-(4,5-Dihydro-5-methyleneoxazol-2-yl)1*H*-indole (107)



N-(Prop-2-ynyl)-1*H*-indole-2-carboxamide (50 mg, 0.25 mmol) was cyclized following the general procedure. The residue was purified by chromatography (5:1

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hexane-EtOAc) to give **107** as a white solid (39 mg, 77%): mp 175-177ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (br s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.15 (s, 1H), 4.88 (q, J = 2.9 Hz, 1H), 4.69 (t, J = 2.6 Hz, 2H), 4.43 (q, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 159.02 (C), 158.26 (C), 137.35 (C), 127.63 (C), 124.90 (CH), 124.20 (C), 122.16 (CH), 120.68 (CH), 111.59 (CH), 107.26 (CH), 84.40 (CH_2), 57.11 (CH_2). HRMS-CI *m/z* calcd for $C_{12}H_{11}N_2O$: 199.0871; found: 199.0872 [M^++H].

4. Intermolecular Reaction of Indoles with Alkynes

The following known compounds, showed spectroscopic data consistent with those described: **109a**,[79] **109b**,[79] **109c**,[80] **109d**,[81] **109n**,[82] and **126**.[83]

4.1. General procedure for the gold-catalyzed intermolecular reactions of indoles with alkynes (Table 4 and Schemes 53-58).

The alkyne (0.6 equiv) was added to a mixture of indole derivative (1 equiv) and 0.05 mol equiv of gold catalyst in toluene (volume necessary to make the concentration of the indole derivative 0.5 M). The reaction mixtures were stirred at room temperature (unless stated otherwise) for the stated time. The mixtures were filtered through silica gel with CH_2Cl_2 and the solvent evaporated. The residues were purified by chromatography to give the desired products.

79 Noland, W.; Venkiteswaran, M. R. *J. Org. Chem.* **1961**, *26*, 4263-4269.

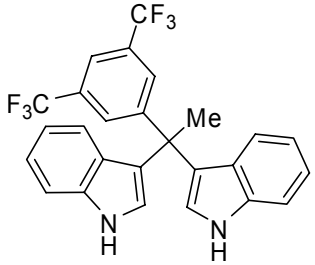
80 Zolfigol, M.; Salehi, P.; Shiri, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 4043-4045.

81 Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Synthesis* **2005**, 1949-1954.

82 Gibbs, T. J. K.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2005**, *3*, 4043-4045.

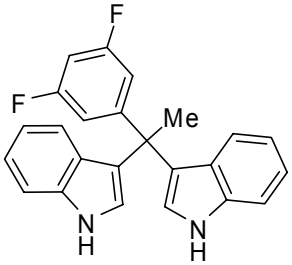
83 Horiguchi, Y.; Nakamura, M.; Kida, A.; Kodama, H.; Saitoh, T.; Sano, T. *Heterocycles* **2003**, *59*, 691-705.

3,3'-(1-(3,5-Bis(trifluoromethyl)phenyl)ethane-1,1-diyl)bis(1*H*-indole) (109e)



Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 2H), 7.88 (br s, 2H), 7.73 (br s, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.17 (dt, J = 7.0, 1.0 Hz, 2H), 6.96 (dt, J = 1.1, 7.2 Hz, 2H), 6.65 (d, J = 2.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 151.0 (C), 137.4 (C), 131.1 (q, J_{CF} = 33.1 Hz, C), 128.5 (d, J_{CF} = 3.1 Hz, CH), 126.0 (C), 123.6 (CH), 123.1 (C), 122.6 (C), 122.2 (CH), 121.6 (CH), 120.2 (CH), 119.6 (CH), 111.6 (CH), 44.1 (C), 28.9 (CH_3). HRMS-ESI *m/z* calcd for $C_{26}H_{18}N_2F_6Na$: 495.1272; found: 495.1268 [M^++Na].

3,3'-(1-(3,5-Difluorophenyl)ethane-1,1-diyl)bis(1*H*-indole) (109f)



Yellow solid; mp 171°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.17 (dt, J = 7.1, 1.1 Hz, 2H), 6.99 (dt, J = 7.1, 1.0 Hz, 2H), 6.94 (dd, J_{HF} = 9.4 Hz, J_{HH} = 2.2 Hz, 2H), 6.66 (tt, J_{HF} = 8.7, J_{HH} = 2.3 Hz, 1H), 6.63 (d, J = 2.6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 162.9 (dd, J_{CF} = 246.8, 13.0 Hz, C), 152.8 (t, J_{CF} = 7.8 Hz, C), 137.3 (C), 126.2 (C), 123.6 (C), 123.5 (CH), 122.0 (CH), 121.9 (CH), 119.4 (CH), 111.5 (CH), 111.3 (q, J_{CF} = 6.6 Hz, CH), 101.5 (t, J_{CF} = 25.6 Hz, CH), 44.1 (C), 28.7 (CH_3). Anal calcd for $(C_{24}H_{18}F_2N_2)_3 \cdot H_2O$: C, 76.17; H, 4.97; N, 7.40; found: C, 76.00; H, 4.97; N, 7.63. HRMS-ESI *m/z* calcd for $C_{24}H_{18}N_2F_2Na$: 395.1336; found: 395.1353 [M^++Na].

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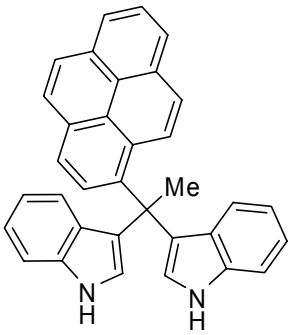
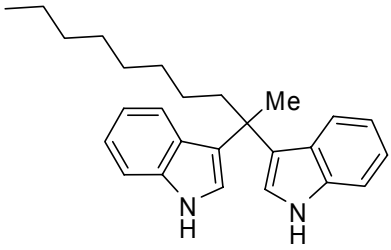
3,3'-(1-(Pyren-1-yl)ethane-1,1-diyl)bis(1*H*-indole) (109g)



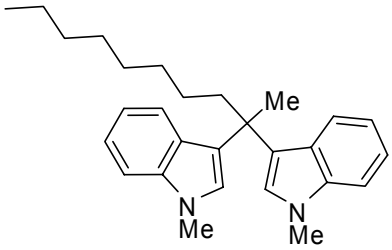
Beige solid; mp 210°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 9.5 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 8.11 (dd, J = 7.5, 1.1 Hz, 1H), 8.03 (q, J = 8.9 Hz, 2H), 8.00 (d, J = 7.5 Hz, 1H), 7.93-7.89 (m, 3H), 7.66 (d, J = 9.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 9.1 Hz, 2H), 7.11 (dt, J = 7.1, 1.0 Hz, 2H), 6.88 (dt, J = 7.2, 1.0 Hz, 2H), 6.76 (d, J = 2.4 Hz, 2H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 142.0 (C), 137.3 (C), 131.6 (C), 130.6 (C), 130.5(C), 129.9 (C), 127.7 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 126.7 (C), 126.2 (C), 125.8 (CH), 125.3 (CH), 125.2 (C), 125.1 (C), 124.9 (CH), 124.8 (CH), 124.7 (CH), 124.0 (CH), 122.2 (CH), 121.8 (CH), 119.3 (CH), 111.4 (CH). 45.4 (C), 30.6 (CH_3). Anal calcd for $(C_{34}H_{24}N_2)_3 \cdot 4H_2O$: C, 84.27; H, 5.55; N, 5.78; found: C, 84.23; H, 5.69; N, 5.54. HRMS-ESI *m/z* calcd for $C_{34}H_{24}N_2Na$: 483.1837; found: 483.1839 [M^++Na].

3,3'-(Decane-2,2-diyl)bis(1*H*-indole) (109h)



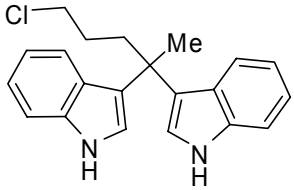
Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 2.4 Hz, 2H), 7.05 (dt, J = 7.2, 1.1 Hz, 2H), 6.84 (dt, J = 7.0, 0.9 Hz, 2H), 2.38-2.33 (m, 2H), 1.84 (s, 3H), 1.24-1.13 (m, 8H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (C), 126.7 (C), 124.7 (C), 121.5 (CH), 121.4 (CH), 121.3 (CH), 118.7 (CH), 111.1 (CH), 40.7 (CH_2), 38.6 (C), 32.1 (CH_2), 30.2 (CH_2), 27.1 (CH_3), 24.7 (CH_2), 22.9 (CH_2), 14.3 (CH_3). Anal calcd for $(C_{24}H_{28}N_2)_2 \cdot H_2O$: C, 81.54; H, 8.27; N, 7.92; found: C, 81.32; H, 8.15; N, 7.55. HRMS-ESI *m/z* calcd for $C_{24}H_{28}N_2Na$: 367.2150; found: 367.2162 [M^++Na].

3,3'-(Decane-2,2-diyl)bis(1-methyl-1*H*-indole) (109i)



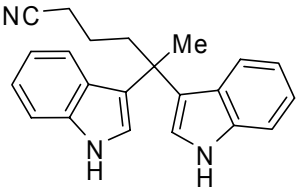
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.15 (dt, J = 7.1, 0.8 Hz, 2H), 6.93 (s, 2H), 6.90 (dt, J = 7.1, 0.8 Hz, 2H), 3.78 (s, 6H), 2.42-2.38 (m, 2H), 1.88 (s, 3H), 1.33-1.17 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.8 (C), 127.1 (C), 126.3 (CH), 123.3 (C), 121.7 (CH), 120.9 (CH), 118.1 (CH), 109.1 (CH), 41.1 (CH_2), 38.6 (C), 32.8 (CH_3), 32.0 (CH_2), 30.3 (CH_2), 27.5 (CH_3), 24.8 (CH_2), 22.9 (CH_2), 14.3 (CH_3). Anal calcd for $(C_{26}H_{32}N_2)_3 \cdot H_2O$: C, 82.49; H, 8.70; N, 7.40; found: C, 82.42; H, 8.27; N, 7.55. HRMS-ESI *m/z* calcd for $C_{26}H_{32}N_2Na$: 395.2463; found: 395.2458.0 [M^++Na].

3,3'-(5-Chloropentane-2,2-diyl)bis(1*H*-indole) (109j)



White solid; mp 146°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 2.4 Hz, 2H), 7.07 (dt, J = 7.1, 1.2 Hz, 2H), 6.85 (dt, J = 7.1, 1.1 Hz, 2H), 3.45 (t, J = 6.7 Hz, 2H), 2.52-2.48 (m, 2H), 1.86 (s, 3H), 1.70-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.2 (C), 126.4 (C), 123.9 (C), 121.7 (CH), 121.4 (CH), 121.3 (CH), 118.9 (CH), 111.2 (CH), 46.2 (CH_2), 38.3 (C), 38.1 (CH_2), 28.5 (CH_2), 27.3 (CH_3). Anal calcd for $C_{21}H_{21}ClN_2$: C, 74.88; H, 6.28; N, 8.32; found: C, 74.17; H, 6.28; N, 8.31. HRMS-ESI *m/z* calcd for $C_{21}H_{21}ClN_2Na$: 359.1291; found: 359.1300 [M^++Na].

5,5-Di(1*H*-indol-3-yl)hexanenitrile (109k).



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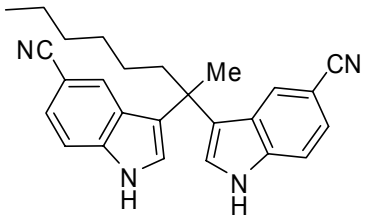
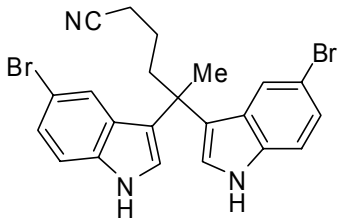
White solid; mp 185-187°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br s, 2H), 7.34-7.31 (m, 4H), 7.08 (dt, J = 7.0, 1.1, 2H), 7.07 (d, J = 2.5, 2H), 6.86 (dt, J = 7.1, 1.1 Hz, 2H), 2.52-2.48 (m, 2H), 2.20 (t, J = 7.2 Hz, 2H), 1.86 (s, 3H), 1.57-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.2 (C), 126.3 (C), 123.5 (C), 121.8 (CH), 121.4 (CH), 121.2 (CH), 120.2 (C), 119.1 (C), 111.3 (CH), 39.8 (CH_2), 38.4 (C), 27.3 (CH_3), 21.3 (CH_2), 17.8 (CH_2). Anal calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.46; N, 12.83; found: C, 80.23; H, 6.53; N, 12.66. HRMS-ESI *m/z* calcd for $C_{22}H_{21}N_3Na$: 350.1633; found: 350.1630 [M^++Na].

3,3'-(Octane-2,2-diyl)bis(1*H*-indole-5-carbonitrile) (109l)



White solid; mp 206°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 2H) 7.43 (s, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 2.4 Hz, 2H), 7.27 (dd, J = 8.6, 1.4 Hz, 2H), 2.28-2.24 (m, 2H), 1.77 (s, 3H), 1.26-1.08 (m, 8H), 0.81 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 138.9 (C), 126.4 (CH), 126.1 (C), 125.0 (C), 124.8 (CH), 122.9 (CH), 121.2 (C), 112.4 (CH), 102.0 (C), 40.6 (CH_2), 38.0 (C), 32.0 (CH_2), 30.0 (CH_2), 27.2 (CH_3), 24.4 (CH_2), 22.8 (CH_2), 14.2 (CH_3). Anal calcd for $C_{26}H_{26}N_4$: C, 79.16; H, 6.64; N, 14.20; found: C, 78.70; H, 6.70; N, 13.75. HRMS-ESI *m/z* calcd for $C_{26}H_{26}N_4Na$: 417.2055; found: 417.2075 [M^++Na].

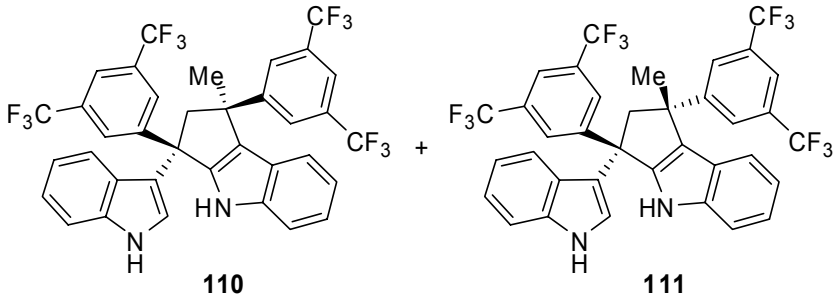
5,5-Bis(5-bromo-1*H*-indol-3-yl)hexanenitrile (109m)



White solid; mp 203°C. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.32 (br s, 2H), 7.48 (d, J = 2.6 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 1.9 Hz, 2H), 7.05 (dd, J = 8.6, 2.0 Hz, 2H), 2.51-2.47 (m, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.55-1.48 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6, DEPT) δ 137.1 (C), 128.9 (C), 124.5 (CH), 124.0 (CH), 123.4 (CH), 123.2 (C), 120.7 (C), 114.0 (CH), 111.9 (C), 40.3 (CH_2), 38.3 (C),

27.4 (CH_3), 22.0 (CH_2), 17.5 (CH_2). Anal calcd for $C_{22}H_{19}Br_2N_3$: C, 54.46; H, 3.95; N, 8.66; found: C, 54.14; H, 3.92; N, 8.79. HRMS-ESI *m/z* calcd for $C_{22}H_{19}Br_2N_3Na$: 505.9843; found: 505.9859 [M^++Na].

1,3-Bis(3,5-bis(trifluoromethyl)phenyl)-3-(1*H*-indol-3-yl)-1-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole (110/111)



110 **111**

110: yellow solid; mp 106-108°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.96 (br s, 1H), 7.82 (br s, 3H), 7.75 (br s, 2H), 7.64 (br s, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.32 (d J = 8.2 Hz, 1H), 7.27-7.23 (m, 1H), 7.16 (t, J = 7.7 Hz, 2H), 7.01-6.95 (m, 2H), 6.57 (d, J = 2.7 Hz, 1H), 3.72 (AB, J = 13.4 Hz, 1H), 3.33 (AB, J = 13.4 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 151.8 (C), 149.6 (C), 145.3 (C), 141.6 (C), 137.3 (C), 132.3 (d, J_{CF} = 33.1 Hz, C), 131.9 (d, J_{CF} = 16.1 Hz, C), 131.8 (d, J_{CF} = 33.1 Hz, C), 131.6 (d, J_{CF} = 16.1 Hz, C), 127.8 (d, J_{CF} = 2.8 Hz, CH), 126.7 (d, J_{CF} = 2.2 Hz, CH), 125.3 (C), 124.9 (d, J_{CF} = 9.9 Hz, C), 124.4 (C), 123.5 (C), 123.1 (CH), 122.9 (CH), 122.6 (CH), 122.1 (d, J_{CF} = 9.9 Hz, C), 121.1 (m, CH), 121.0 (CH), 120.5 (CH), 120.1 (m, CH), 119.6 (CH), 119.3 (C), 119.1 (CH), 112.8 (CH), 112.0 (CH), 64.7 (CH_2), 52.0 (C), 47.7 (C), 29.3 (CH_3). Anal calcd for $(C_{36}H_{22}F_{12}N_2)_2 \cdot H_2O$: C, 60.00; H, 3.22; N, 3.89; found: C, 60.14; H, 3.39; N, 3.83. HRMS-ESI *m/z* calcd for $C_{36}H_{23}N_2F_{12}$: 711.1670; found: 711.1698 [M^++H].

111: yellow solid; mp 107-108°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 8.07 (s, 1H), 7.65 (s, 2H), 7.58-7.55 (m, 3H), 7.50 (s, 2H), 7.42 (t, J = 8.3 Hz, 2H), 7.29-7.20 (m, 3H), 7.03-6.96 (m, 2H), 6.54 (d, J = 2.7 Hz, 1H), 3.76 (AB, J = 13.4 Hz, 1H), 3.49 (AB, J = 13.4 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 151.6 (C), 147.9 (C), 145.5 (C), 141.4 (C), 137.4 (C), 132.5-131.1 (m, C, 2C), 127.4 (br s, CH), 126.5 (br s, CH), 125.5 (C), 124.8 (d, J_{CF} = 11.6 Hz, C), 124.1 (C), 123.7 (C), 123.1 (CH), 123.0 (CH), 122.6 (CH), 122.2 (d, J_{CF} = 11.6 Hz, C), 121.2 (CH), 120.7 (m, CH), 120.6 (CH), 120.2 (m, CH), 119.8 (C), 119.7 (CH), 119.0 (CH), 112.9 (CH), 112.0 (CH), 63.7 (CH_2), 51.8 (C), 47.8 (C), 30.2 (CH_3). Anal calcd for $C_{36}H_{22}F_{12}N_2$: C, 60.85;

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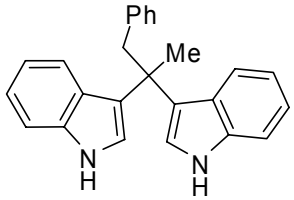
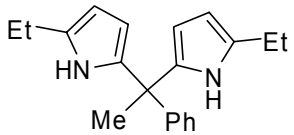
H, 3.12; N, 3.94; found: C, 60.74; H, 3.52; N, 4.13. HRMS-ESI *m/z* calcd for $C_{36}H_{23}N_2F_{12}$: 711.1670; found: 711.1694 [M^++H].

3,3'-(1-Phenylpropane-2,2-diyl)bis(1*H*-indole) (112)



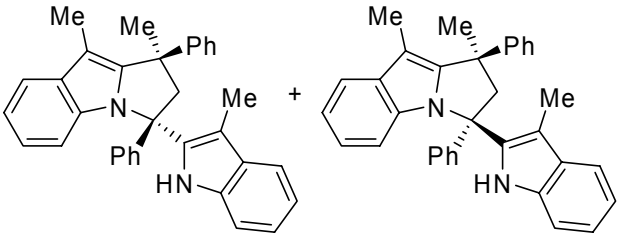
White solid; mp 197°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 2H), 7.36 (d, J = 8.2 Hz), 7.34 (d, J = 8.2 Hz, 2H), 7.11-7.01 (m, 5H), 7.00 (d, J = 2.6 Hz, 2H), 6.85 (dt, J = 7.1, 0.9 Hz, 2H), 6.60 (d, J = 7.1 Hz, 2H), 3.69 (s, 2H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 138.8 (C), 137.2 (C), 130.9 (CH), 127.2 (CH), 126.7 (C), 125.9 (CH), 123.8 (C), 121.6 (CH), 121.5 (CH), 121.3 (CH), 119.0 (CH), 111.2 (CH), 45.9 (CH_2), 39.4 (C), 26.7 (CH_3). Anal calcd for $C_{25}H_{22}N_2 \cdot 1/2H_2O$: C, 83.53; H, 6.45; N, 7.79; found: C, 82.90; H, 6.18; N, 7.75. HRMS-ESI *m/z* calcd for $C_{25}H_{22}N_2Na$: 373.1681; found: 373.1691 [M^++Na].

5,5'-(1-Phenylethane-1,1-diyl)bis(2-ethyl-1*H*-pyrrole) (114)



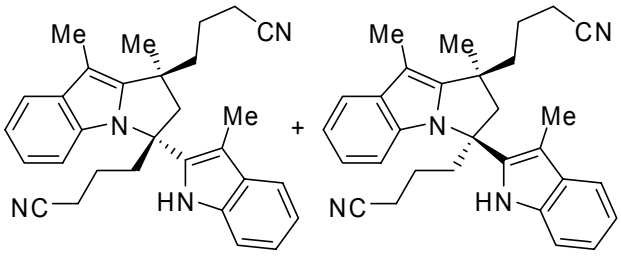
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 2H), 7.30-7.19 (m, 3H), 7.16-7.14 (m, 2H), 5.83 (t, J = 3.1 Hz, 2H), 5.80 (t, J = 3.0 Hz, 2H), 2.54 (q, J = 7.7 Hz, 4H), 2.00 (s, 3H), 1.19 (t, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 147.8 (C), 136.2 (C), 133.7 (C), 128.2 (CH), 127.6 (CH), 126.7 (CH), 106.4 (CH), 104.0 (CH), 44.9 (C), 28.9 (CH_3), 21.0 (CH_2), 13.6 (CH_3). Anal calcd for $(C_{20}H_{24}N_2)_7 \cdot H_2O$: C, 81.43; H, 8.30; N, 9.50; found: C, 81.68; H, 7.97; N, 9.20. HRMS-ESI *m/z* calcd for $C_{20}H_{24}N_2Na$: 315.1837; found: 315.1851 [M^++Na].

1,9-Dimethyl-3-(3-methyl-1H-indol-2-yl)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (115/116)



2:1 Isomer mixture as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 1H, major), 7.61 (d, J = 8.2 Hz, 1H, minor), 7.54 (br s, 1H, minor), 7.43 (br s, 1H, major), 7.41-7.34 (m, 7H), 7.29-7.00 (m, 10H), 6.96 (t, J = 7.8 Hz, 2H), 6.90 (dt, J = 7.1, 1.2 Hz, 2H), 6.44 (d, J = 9.1 Hz, 1H, minor), 6.42 (d, J = 8.6 Hz, 1H, major), 3.85 (AB, J = 13.1 Hz, 1H, major) 3.67 (AB, J = 12.7 Hz, 1H, minor), 3.58 (AB, J = 12.7 Hz, 1H, minor), 3.39 (AB, J = 13.1 Hz, 1H, major), 2.25 (s, 3H, major), 2.15 (s, 3H, minor), 2.10 (s, 3H, minor), 1.96 (s, 3H, major), 1.75 (s, 3H, major), 1.60 (s, 3H, minor); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 146.8 (C), 146.4 (C), 145.9 (C), 145.7 (C), 141.9 (C), 141.1 (C), 134.9 (C), 134.3 (C) 134.2 (C), 134.0 (C), 133.7 (C), 133.3 (C), 132.1 (C), 131.8 (C), 130.2 (C), 130.0 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 126.6 (CH), 126.5 (CH), 126.2 (CH), 125.9 (CH), 122.0 (CH), 121.8 (CH), 121.5 (CH), 119.6 (CH), 119.5 (CH), 119.3 (CH), 119.2 (CH), 119.1 (CH), 119.0 (CH), 118.6 (CH), 118.3 (CH), 111.2 (CH), 110.8 (CH), 110.6 (CH), 110.4 (CH), 108.6 (C), 108.2 (C), 102.8 (C), 102.2 (C), 68.0 (C), 65.4 (CH_2), 64.6 (CH_2), 53.6 (C), 45.4 (C), 46.2 (C), 27.5 (CH_3), 26.1 (CH_3), 10.4 (CH_3), 10.1 (CH_3), 8.8 (CH_3), 8.5 (CH_3). Anal calcd for $(C_{34}H_{30}N_2)_3 \cdot H_2O$: C, 86.40; H, 6.54; N, 5.93; found: C, 86.61; H, 6.67; N, 6.03. HRMS-ESI *m/z* calcd for $C_{34}H_{30}N_2Na$: 489.2307; found: 489.2328 [M^++Na].

4,4'-(1,9-Dimethyl-3-(3-methyl-1*H*-indol-2-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-1,3-diyl)dibutanenitrile (118/119)



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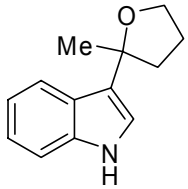
1:1 Isomer mixture. **118**: yellow solid; mp 96°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.56-7.54 (m, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.21-7.14 (m, 2H), 7.12-7.11 (m, 3H), 2.97 (AB, J = 13.5 Hz, 1H) 2.81 (AB, J = 13.5 Hz, 1H), 2.72 (ddd, J = 14.3, 12.5, 4.2 Hz, 1H), 2.49 (ddd, J = 14.5, 12.3, 4.2 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.26-2.20 (m, 2H), 2.02 (t, J = 7.0 Hz, 2H), 1.66-1.61 (m, 3H), 1.60 (s, 3H), 1.50-.139 (m, 2H), 1.08-1.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 146.3 (C), 138.2 (C), 134.5 (C), 133.8 (C), 131.5 (C), 130.5 (C), 122.1 (CH), 122.0 (CH), 120.0 (CH), 119.7 (CH), 119.4 (CH), 119.4 (C), 119.2 (C), 118.4 (CH), 111.1 (CH), 110.2 (CH), 105.1 (C), 102.2 (C), 64.5 (C), 55.5 (CH_2), 41.2 (CH_2), 41.1 (C), 38.2 (CH_2), 26.2 (CH_3), 21.7 (CH_2), 20.0 (CH_2), 17.6 (CH_2), 17.2 (CH_2), 10.2 (CH_3), 8.6 (CH_3). Anal calcd for $C_{30}H_{32}N_4 \cdot 3/4H_2O$: C, 76.24; H, 7.39; N, 11.85; found: C, 76.33; H, 7.01; N, 11.67. HRMS-ESI *m/z* calcd for $C_{30}H_{32}N_4Na$: 471.2525; found: 471.2513 [M^++Na].

119: yellow solid; mp 105-106°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 1H), 7.54-7.51 (m, 1H), 7.37 (br s, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.21-7.13 (m, 2H), 7.10-7.06 (m, 3H), 2.92 (AB, J = 12.9 Hz, 1H), 2.81-2.74 (m, 1H), 2.75 (AB, J = 12.9, 1H), 2.65-2.57 (m, 1H), 2.45 (t, J = 6.9 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.34-2.32 (m, 2H), 2.07-2.03 (m, 2H), 1.83-1.58 (m, 2H), 1.37-1.31 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 146.3 (C), 138.2 (C), 134.3 (C), 133.8 (C), 131.4 (C), 130.4 (C), 122.0 (CH), 121.9 (CH), 120.0 (CH), 119.6 (CH), 119.5 (C), 119.3 (CH), 119.2 (C), 118.3 (CH), 111.1 (CH), 109.9 (CH), 105.1 (C), 101.3 (C), 64.6 (C), 52.7 (CH_2), 41.1 (C), 39.1 (CH_2), 37.7 (CH_2), 27.4 (CH_3), 21.6 (CH_2), 20.1 (CH_2), 17.9 (CH_2), 17.3 (CH_2), 10.1 (CH_3), 8.3 (CH_3). Anal calcd for $C_{30}H_{32}N_4 \cdot H_2O$: C, 77.22; H, 7.34; N, 12.01; found: C, 77.24; H, 7.21; N, 11.44. HRMS-ESI *m/z* calcd for $C_{30}H_{32}N_4Na$: 471.2525; found: 471.2513 [M^++Na].

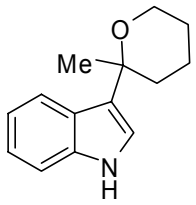
3-(2-Methyltetrahydrofuran-2-yl)-1*H*-indole (120)



White solid; mp 88°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 4.06-3.95 (m, 2H), 2.44-2.38 (m, 1H), 2.09-2.02 (m, 2H),

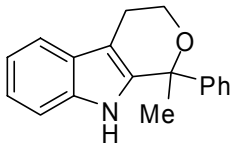
1.99-1.91 (m, 1H), 1.70 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.2 (C), 125.3 (C), 123.3 (C), 122.0 (CH), 120.6 (CH), 120.5 (CH), 119.5 (CH), 111.4 (CH), 82.0 (C), 67.5 (CH_2), 38.6 (CH_2), 28.7 (CH_3), 26.3 (CH_2). Anal calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; found: C, 77.55; H, 7.35; N, 7.13. HRMS-EI *m/z* calcd for $C_{13}H_{15}NO$: 201.1154; found: 201.1163 [M^+].

3-(2-Methyltetrahydro-2H-pyran-2-yl)-1*H*-indole (121)



White solid; mp 153-155°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.20 (dt, J = 7.1, 1.2 Hz, 1H), 7.11 (dt, J = 7.0, 1.1 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 3.76-3.71 (m, 1H), 3.46 (dt, J = 11.3, 2.8 Hz, 1H), 2.27-2.21 (m, 1H), 1.81-1.60 (m, 4H), 1.57 (s, 3H), 1.44-1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.0 (C), 1.26.1 (C), 122.1 (CH), 121.8 (CH), 121.7 (CH), 120.3 (C), 119.7 (CH), 111.2 (CH), 74.4 (C), 63.0 (CH_2), 35.7 (CH_2), 31.3 (CH_3), 26.0 (CH_2), 20.4 (CH_2). Anal calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51; found: C, 77.60; H, 7.72; N, 6.69. HRMS-ESI *m/z* calcd for $C_{14}H_{17}NO$: 215.1310; found: 215.1311 [M^+].

1-Methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole (123)



Yellow solid; mp 152°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.38-7.35 (m, 3H), 7.34-7.28 (m, 3H), 7.21 (dt, J = 7.1, 1.2 Hz, 1H), 7.15 (dt, J = 6.9, 1.0 Hz, 1H), 4.03 (ddd, J = 11.7, 5.7, 3.0 Hz, 1H), 3.73 (ddd, J = 11.6, 9.5, 4.3 Hz, 1H), 3.01 (ddd, J = 15.3, 9.6, 5.7 Hz, 1H), 2.74 (ddd, J = 15.4, 4.2, 3.1 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 144.6 (C), 136.8 (C), 136.1 (C), 128.4 (CH), 128.0 (CH), 127.2 (C), 126.9 (CH), 122.2 (CH), 119.9 (CH), 118.7 (CH), 111.1 (CH), 108.5 (C), 76.2 (C), 60.9 (CH_2), 28.2 (CH_3), 22.5 (CH_2). Anal calcd

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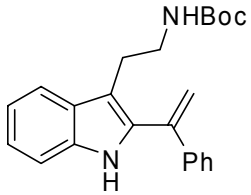
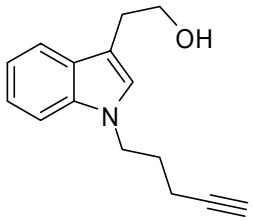
for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32; found: C, 81.71; H, 6.42; N, 5.41. HRMS-ESI *m/z* calcd for $C_{18}H_{17}NO$: 263.1310; found: 263.1310 [M^+].

tert-Butyl-2-(2-(1-phenylvinyl)-1*H*-indol-3-yl)ethylcarbamate (125)



White solid; mp 151°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.35 (s, 5H), 7.30 (d, J = 8.1 Hz, 1H), 7.20 (dt, J = 7.0, 1.2 Hz, 1H), 7.13 (dt, J = 7.0, 1.1 Hz, 1H), 5.71 (d, J = 1.0 Hz, 1H), 5.53 (d, J = 1.0 Hz, 1H), 4.52 (br s, 1H), 3.36 (q, J = 6.7 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 156.0 (C), 141.2 (C), 140.2 (C), 135.6 (C), 135.0 (C), 128.8 (C), 128.7 (CH), 128.6 (CH), 127.9 (CH), 122.8 (CH), 119.9 (CH), 119.4 (CH), 117.1 (CH_2), 112.3 (C), 111.0 (CH), 79.1 (C), 41.2 (CH_2), 28.6 (CH_3), 25.4 (CH_2). HRMS-ESI *m/z* calcd for $C_{23}H_{26}N_2O_2Na$: 385.1892; found: 385.1898 [M^++Na].

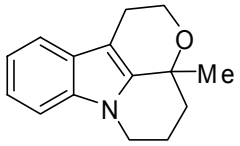
2-(1-(Pent-4-ynyl)-1H-indol-3-yl)ethanol (127)



A solution of tryptophol (0.70 g, 4.34 mmol) in DMF (15 mL) was added to a suspension of NaH (0.174 g, 4.34 mmol, 60 wt%) in DMF (5 mL) at 0 ºC. The reaction mixture was stirred for 20 min, after which 5-chloro-1-pentyne (0.44 mL, 4.13 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. After extractive workup (Et_2O), the residue was purified by chromatography (10:1 hexane-EtOAc) to give **127** as a yellow oil (0.82 g, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.23 (dt, J = 7.0, 1.2 Hz, 1H), 7.12 (dt, J = 7.0, 1.1 Hz, 1H), 7.02 (s, 1H), 4.25 (t, J = 6.8 Hz, 2H), 3.90 (t, J = 6.2 Hz, 2H), 3.03, (dt, J = 6.4, 0.6 Hz, 2H), 2.17 (td, J = 6.8, 2.6 Hz, 2H), 2.07 (t, J = 2.6 Hz, 1H), 2.05-2.00 (m, 2H), 1.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.6 (C), 128.2 (C), 126.6 (CH), 121.9 (CH), 119.23 (CH), 119.17 (CH), 111.1 (C),

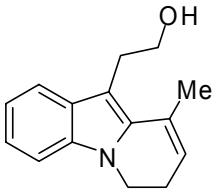
109.6 (CH), 83.1 (CH), 69.8 (C), 62.9 (CH_2), 44.7 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 16.0 (CH_2). HRMS-ESI *m/z* calcd for $C_{15}H_{17}NO$ 250.1208; found 250.1213 [M^++Na].

Tetracycle 128



White solid; mp 96-98°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 7.1, 1.3 Hz, 1H), 7.14 (t, J = 7.4, 1.2 Hz, 1H), 4.35 (ddd, J = 11.9, 10.7, 5.2 Hz, 1H), 4.25 (ddd, J = 11.4, 6.6, 1.8 Hz, 1H), 4.15 (ddd, J = 12.0, 7.1, 1.4 Hz, 1H), 3.54 (td, J = 11.6, 6.1 Hz, 1H), 3.02 (ddd, J = 15.5, 10.6, 7.2 Hz, 1H), 2.74 (ddd, J = 15.5, 5.1, 1.3 Hz, 1H), 2.39-2.26 (m, 1H), 2.20-2.12 (m, 1H), 2.07 (dt, J = 12.2, 3.7 Hz, 1H), 1.68 (td, J = 13.1, 4.1 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 140.5 (C), 139.3 (C), 128.9 (C), 121.4 (CH), 120.1 (CH), 118.5 (CH), 110.4 (CH), 104.2 (C), 70.9 (C), 59.9 (CH_2), 43.1 (CH_2), 34.9(CH_2), 24.2 (CH_3), 22.4 (CH_2), 21.0 (CH_2). Anal calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; found: C, 78.57; H, 7.41; N, 6.59. HRMS-ESI *m/z* calcd for $C_{15}H_{17}NONa$: 250.1208; found: 250.1217 [M^++Na].

2-(9-Methyl-6,7-dihydropyrido[1,2-*a*]indol-10-yl)ethanol (129)



White solid; mp 117°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.9 Hz, 1H), 7.24-7.23 (m, 1H), 7.22 (dt, J = 8.2, 1.0 Hz, 1H), 7.08 (dt, J = 6.5, 1.5 Hz, 1H), 5.77-5.74 (m, 1H), 4.04 (t, J = 6.9 Hz, 2H), 3.88 (t, J = 6.6 Hz, 2H), 3.26 (t, J = 6.6 Hz, 2H), 2.57-2.52 (m, 2H), 2.29 (q, J = 1.7 Hz, 3H), 1.46 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.3 (C), 133.4 (C), 129.1 (C), 128.8 (C), 122.6 (CH), 122.5 (CH), 119.3 (CH), 118.9 (CH), 108.7 (CH), 108.1 (C), 63.9 (CH_2), 39.9 (CH_2), 28.5 (CH_2), 24.4 (CH_2), 21.2 (CH_3). HRMS-ESI *m/z* calcd for $C_{15}H_{17}NONa$: 250.1208; found: 250.1217 [M^++Na].

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5. X-Ray Structure of Tetracycle 74

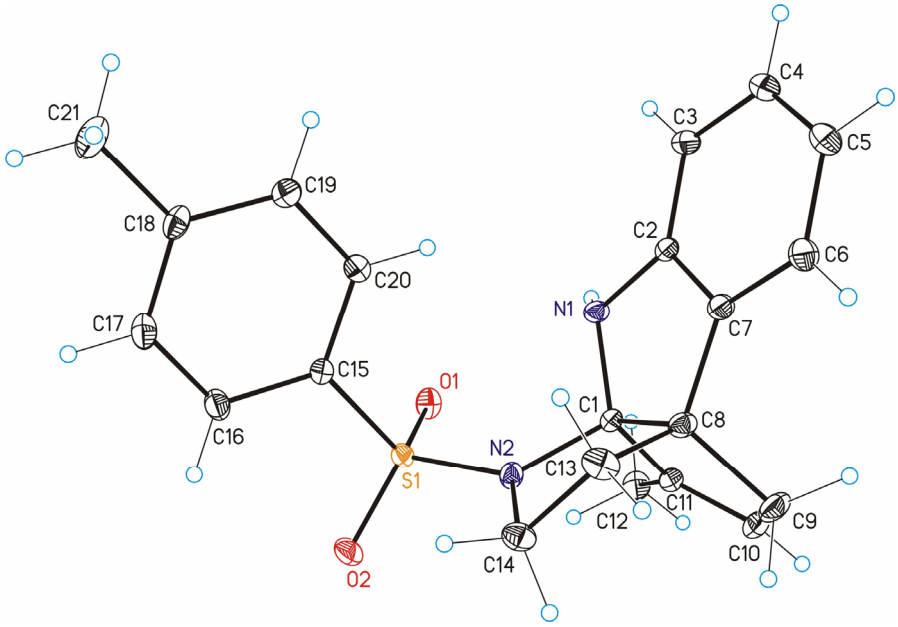

Table 1. Crystal data and structure refinement for **74**

Empirical formula	C21 H22 N2 O2 S	
Formula weight	366.47	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4990(10) Å	α= 110.109(4)°.
	b = 10.7814(13) Å	β= 101.219(4)°.
	c = 11.423(2) Å	γ= 103.200(3)°.
Volume	913.3(2) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.195 mm^{-1}	
F(000)	388	
Crystal size	0.10 x 0.10 x 0.10 mm^3	
Theta range for data collection	3.45 to 39.52°.	
Index ranges	-15<=h<=5, -19<=k<=9, -13<=l<=20	

Reflections collected	9455
Independent reflections	6244 [R(int) = 0.0197]
Completeness to theta = 39.52°	56.8 %
Absorption correction	SADABS (Bruker-Nonius)
Max. and min. transmission	0.9807 and 0.9807
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6244 / 0 / 241
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1404
R indices (all data)	R1 = 0.0448, wR2 = 0.1433
Largest diff. peak and hole	0.618 and -0.810 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for **74**.

S(1)-O(2)	1.4372(7)	C(5)-C(4)	1.3839(18)
S(1)-O(1)	1.4421(8)	C(5)-C(6)	1.4035(13)
S(1)-N(2)	1.6068(10)	C(9)-C(10)	1.5024(16)
S(1)-C(15)	1.7665(11)	C(14)-C(13)	1.5261(14)
C(1)-N(1)	1.4560(12)	C(20)-C(19)	1.3854(16)
C(1)-N(2)	1.4927(11)	C(20)-C(15)	1.3984(12)
C(1)-C(11)	1.5145(14)	C(15)-C(16)	1.3959(13)
C(1)-C(8)	1.5664(15)	C(16)-C(17)	1.3883(16)
N(1)-C(2)	1.3968(12)	C(19)-C(18)	1.4016(14)
N(2)-C(14)	1.4670(13)	C(17)-C(18)	1.3969(14)
C(2)-C(7)	1.3884(15)	C(21)-C(18)	1.5014(17)
C(2)-C(3)	1.3959(11)	O(2)-S(1)-O(1)	118.79(5)
C(7)-C(6)	1.3858(14)	O(2)-S(1)-N(2)	108.56(5)
C(7)-C(8)	1.5115(11)	O(1)-S(1)-N(2)	106.14(5)
C(8)-C(9)	1.5419(17)	O(2)-S(1)-C(15)	106.33(4)
C(8)-C(13)	1.5450(13)	O(1)-S(1)-C(15)	108.35(5)
C(3)-C(4)	1.3962(15)	N(2)-S(1)-C(15)	108.33(5)
C(11)-C(10)	1.3345(17)	N(1)-C(1)-N(2)	113.52(9)
C(11)-C(12)	1.4896(15)	N(1)-C(1)-C(11)	115.58(7)

N(2)-C(1)-C(11)	111.24(7)	C(20)-C(15)-S(1)	119.97(7)
N(1)-C(1)-C(8)	106.36(7)	C(17)-C(16)-C(15)	119.13(8)
N(2)-C(1)-C(8)	103.90(7)	C(20)-C(19)-C(18)	121.31(8)
C(11)-C(1)-C(8)	105.03(9)	C(16)-C(17)-C(18)	121.47(9)
C(2)-N(1)-C(1)	108.53(8)	C(17)-C(18)-C(19)	118.26(10)
C(14)-N(2)-C(1)	110.98(8)	C(17)-C(18)-C(21)	120.30(9)
C(14)-N(2)-S(1)	121.28(7)	C(19)-C(18)-C(21)	121.43(9)
C(1)-N(2)-S(1)	126.08(6)		
C(7)-C(2)-C(3)	121.64(9)		
C(7)-C(2)-N(1)	111.86(7)		
C(3)-C(2)-N(1)	126.48(10)		
C(6)-C(7)-C(2)	120.35(8)		
C(6)-C(7)-C(8)	129.98(10)		
C(2)-C(7)-C(8)	109.65(8)		
C(7)-C(8)-C(9)	114.40(8)		
C(7)-C(8)-C(13)	114.75(8)		
C(9)-C(8)-C(13)	114.16(8)		
C(7)-C(8)-C(1)	101.82(7)		
C(9)-C(8)-C(1)	105.36(8)		
C(13)-C(8)-C(1)	104.44(8)		
C(2)-C(3)-C(4)	117.49(10)		
C(10)-C(11)-C(12)	127.29(10)		
C(10)-C(11)-C(1)	110.53(9)		
C(12)-C(11)-C(1)	122.16(10)		
C(4)-C(5)-C(6)	120.37(10)		
C(10)-C(9)-C(8)	104.44(10)		
C(11)-C(10)-C(9)	113.78(10)		
C(7)-C(6)-C(5)	118.73(11)		
C(5)-C(4)-C(3)	121.39(8)		
N(2)-C(14)-C(13)	102.35(7)		
C(14)-C(13)-C(8)	103.90(8)		
C(19)-C(20)-C(15)	119.24(8)		
C(16)-C(15)-C(20)	120.59(9)		
C(16)-C(15)-S(1)	119.34(7)		

Symmetry transformations used to generate equivalent atoms.

Table 3. Torsion angles [°] for **74**.

N(2)-C(1)-N(1)-C(2)	127.19(8)
C(11)-C(1)-N(1)-C(2)	-102.55(9)
C(8)-C(1)-N(1)-C(2)	13.56(10)
N(1)-C(1)-N(2)-C(14)	-127.20(9)
C(11)-C(1)-N(2)-C(14)	100.40(10)
C(8)-C(1)-N(2)-C(14)	-12.10(10)
N(1)-C(1)-N(2)-S(1)	38.12(11)
C(11)-C(1)-N(2)-S(1)	-94.27(10)
C(8)-C(1)-N(2)-S(1)	153.22(7)
O(2)-S(1)-N(2)-C(14)	-50.26(9)
O(1)-S(1)-N(2)-C(14)	-179.01(7)
C(15)-S(1)-N(2)-C(14)	64.81(8)
O(2)-S(1)-N(2)-C(1)	145.81(8)
O(1)-S(1)-N(2)-C(1)	17.05(9)
C(15)-S(1)-N(2)-C(1)	-99.12(8)
C(1)-N(1)-C(2)-C(7)	-9.84(11)
C(1)-N(1)-C(2)-C(3)	171.72(9)
C(3)-C(2)-C(7)-C(6)	-1.41(16)
N(1)-C(2)-C(7)-C(6)	-179.94(9)
C(3)-C(2)-C(7)-C(8)	-179.88(9)
N(1)-C(2)-C(7)-C(8)	1.59(12)
C(6)-C(7)-C(8)-C(9)	-58.68(14)
C(2)-C(7)-C(8)-C(9)	119.60(10)
C(6)-C(7)-C(8)-C(13)	76.08(15)
C(2)-C(7)-C(8)-C(13)	-105.64(11)
C(6)-C(7)-C(8)-C(1)	-171.77(11)
C(2)-C(7)-C(8)-C(1)	6.51(11)
N(1)-C(1)-C(8)-C(7)	-11.94(10)
N(2)-C(1)-C(8)-C(7)	-132.01(8)

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C(11)-C(1)-C(8)-C(7)	111.07(8)
N(1)-C(1)-C(8)-C(9)	-131.62(7)
N(2)-C(1)-C(8)-C(9)	108.31(8)
C(11)-C(1)-C(8)-C(9)	-8.62(8)
N(1)-C(1)-C(8)-C(13)	107.78(8)
N(2)-C(1)-C(8)-C(13)	-12.29(9)
C(11)-C(1)-C(8)-C(13)	-129.22(7)
C(7)-C(2)-C(3)-C(4)	1.46(15)
N(1)-C(2)-C(3)-C(4)	179.77(10)
N(1)-C(1)-C(11)-C(10)	121.86(9)
N(2)-C(1)-C(11)-C(10)	-106.79(9)
C(8)-C(1)-C(11)-C(10)	5.00(8)
N(1)-C(1)-C(11)-C(12)	-59.18(11)
N(2)-C(1)-C(11)-C(12)	72.17(10)
C(8)-C(1)-C(11)-C(12)	-176.04(7)
C(7)-C(8)-C(9)-C(10)	-101.98(9)
C(13)-C(8)-C(9)-C(10)	122.99(9)
C(1)-C(8)-C(9)-C(10)	9.00(8)
C(12)-C(11)-C(10)-C(9)	-177.96(8)
C(1)-C(11)-C(10)-C(9)	0.93(10)
C(8)-C(9)-C(10)-C(11)	-6.53(10)
C(2)-C(7)-C(6)-C(5)	0.75(16)
C(8)-C(7)-C(6)-C(5)	178.87(10)
C(4)-C(5)-C(6)-C(7)	-0.21(17)
C(6)-C(5)-C(4)-C(3)	0.31(18)
C(2)-C(3)-C(4)-C(5)	-0.91(17)
C(1)-N(2)-C(14)-C(13)	31.66(11)
S(1)-N(2)-C(14)-C(13)	-134.48(8)
N(2)-C(14)-C(13)-C(8)	-38.03(11)
C(7)-C(8)-C(13)-C(14)	141.74(10)
C(9)-C(8)-C(13)-C(14)	-83.39(11)
C(1)-C(8)-C(13)-C(14)	31.15(10)
C(19)-C(20)-C(15)-C(16)	-0.85(17)
C(19)-C(20)-C(15)-S(1)	175.44(9)

O(2)-S(1)-C(15)-C(16)	-6.95(11)
O(1)-S(1)-C(15)-C(16)	121.80(9)
N(2)-S(1)-C(15)-C(16)	-123.47(9)
O(2)-S(1)-C(15)-C(20)	176.71(9)
O(1)-S(1)-C(15)-C(20)	-54.55(10)
N(2)-S(1)-C(15)-C(20)	60.19(10)
C(20)-C(15)-C(16)-C(17)	0.61(17)
S(1)-C(15)-C(16)-C(17)	-175.71(9)
C(15)-C(20)-C(19)-C(18)	0.50(17)
C(15)-C(16)-C(17)-C(18)	-0.01(18)
C(16)-C(17)-C(18)-C(19)	-0.33(18)
C(16)-C(17)-C(18)-C(21)	-179.16(12)
C(20)-C(19)-C(18)-C(17)	0.09(17)
C(20)-C(19)-C(18)-C(21)	178.90(12)

Symmetry transformations used to generate equivalent atoms.

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Chapter 2. Introduction

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1. Indole Containing Natural Products

Indole chemistry began to develop with the study of the dye indigo. This was converted first to isatin (1*H*-indole-2,3-dione) and then to oxindole. Later, in 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust.[1] In 1869, he proposed the formula for indole shown in Figure 1.[2]

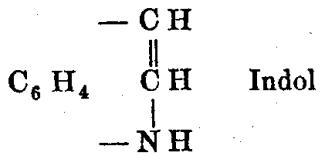


Figure 1. Baeyer's original structure for indole

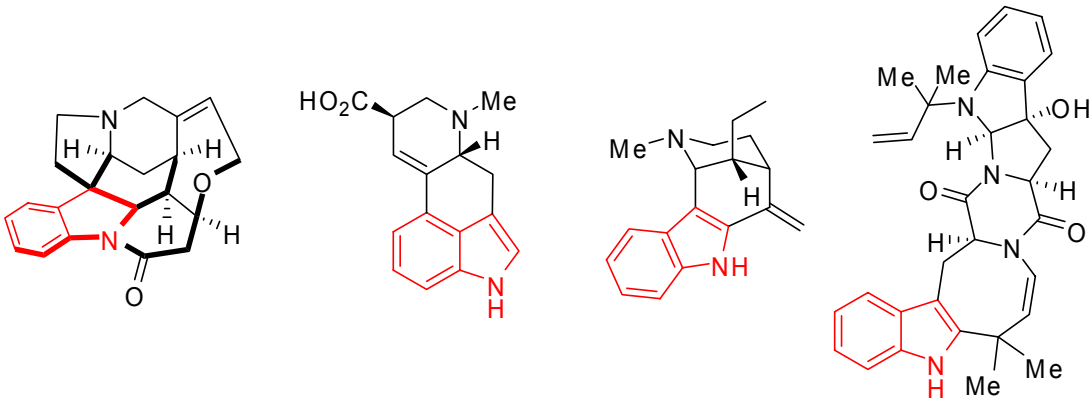
Certain indole derivatives were important dyes until the end of the 19th century. Indigo is still used nowadays as dye for the jeans. In the 1930s, interest in indole intensified when it became known that the indole moiety is present in many important alkaloids, as well as in tryptophane and auxins, and it remains an active area of research

1 Baeyer, A. *Justus Liebigs Ann. der Chem.* **1866**, *140*, 295-313.

2 Baeyer, A.; Emmerling, A. *Chem. Ber.* **1869**, *2*, 679-682.

today. Actually, indole is one of the most occurring structures among natural products and pharmaceutically important compounds.[3]

(-)-Strychnine was one of the first alkaloids to be isolated and it is known as a very powerful poison (Figure 2). The first total synthesis of this compound was accomplished by Woodward in 1954.[4] He also designed a total synthesis for lysergic acid,[5] precursor of the popular psychedelic drug of the 60s and 70s LSD, although the first synthesis of LSD was done by Hofmann in 1939. A large number of other indole alkaloids with a wide range of properties, *e.g.* antitumor or insecticidal, have been isolated and synthesized more recently, like the ones shown in Figures 2 and 3.



(-)-Strychnine | Lysergic acid | 20-Epiuleine[6] | Okaramine N[7]

Figure 2

3 (a) Joule, J. A. *Science of Synthesis* (*Houben-Weyl, Methods of Molecular Transformations*); Georg Thieme Verlag: Stuttgart, **2000**; Vol. 10, pp 361-652. (b) Bonjoch, J.; Bosch, J. *Alkaloids* **1996**, *48*, 75-189. (c) Sundberg, R. J. *Indoles*; Academic Press: London, **1996**. (d) Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Academic Press: New York, **1994**; 25, Part IV. (e) Döpp, H.; Döpp, U.; Langer, U.; Gerding, B. *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, **1994**; Vol. E6b$_1$, pp 546-848; Vol. E6b$_2$. (f) Chadwick, D. J.; Jones, R. A.; Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, **1984**; Vol. 4, pp 155-376.

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

5 Kornfield, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. H.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1954**, *76*, 5256-5257.

6 Amat, M.; Perez, M.; Llor, N.; Escolano, C.; Luque, J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681-8693.

7 Baran, P.; Guerrero, C.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.

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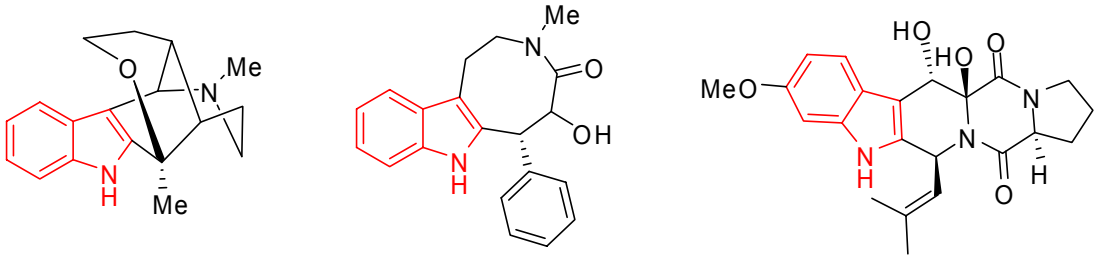

(-)-Gilbertine[8] Balusabramide[9] Cyclotryprostatin A[10]

Figure 3

Plants of the genus *Kopsia* (Figure 4), growing in South and Southeast Asia, have proven to be rich sources of novel alkaloids with intriguing carbon skeletons as well as interesting biological activities.[11]

Figure 4. *Kopsia fruticosa*

Some examples of these new indole alkaloids isolated from the *Kopsia* plants include lundurines A-D (Figure 5).[12] These novel dihydroindole derivatives are characterized by the presence of a cyclopropyl moiety embedded within a hexacyclic ring system and by the presence of an indoloazocine ring unit. Lundurines B and D have showed appreciable *in vitro* cytotoxicity towards B16 melanoma cells, being lundurine

8 Jiricek, J.; Blechert, S. *J. Am. Chem. Soc*. **2004**, *126*, 3534-3538.

9 Riemer, B.; Hofer, O.; Greger, H. *Phytochemistry* **1997**, *45*, 337-341.

10 Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59-72.

11 Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109-9122 and references therein.

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

B the one displaying the highest potency (IC_{50} 2.8 μg/mL). The total synthesis of these compounds has not been described yet.

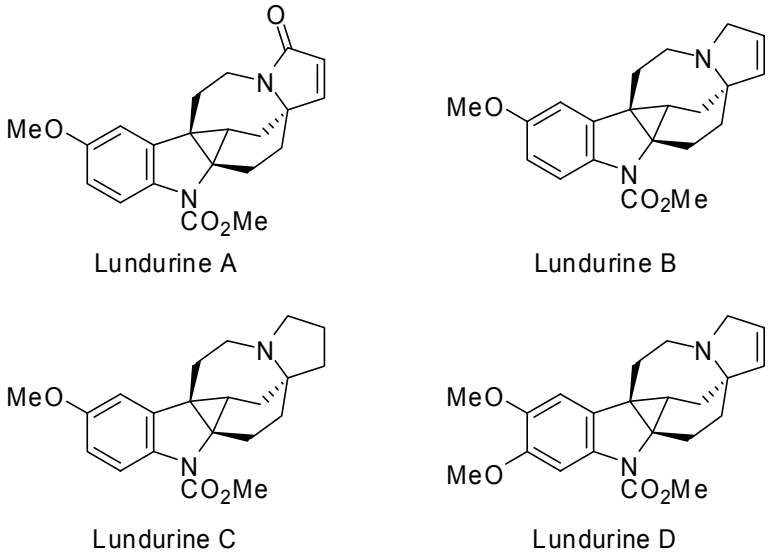

Figure 5

Another indoloazocine containing alkaloids isolated from these plants are the lapidilectines (Figure 6),[13] from which (+)-lapidilectine B has been synthesized by Pearson and coworkers in 23 linear steps.[11]

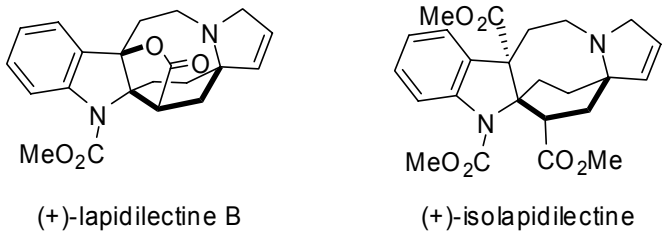

Figure 6

The indoloazocine structures that we obtained by the gold (III) catalyzed intramolecular reaction between indoles and alkynes (see Chapter 1) are related to these types of natural products.

13 Awang, K.; Sévenet, T.; Hadi, A. H. A.; David, B.; Païs, M. *Tetrahedron Lett.* **1992**, *33*, 2493-2496.

11 Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109-9122.

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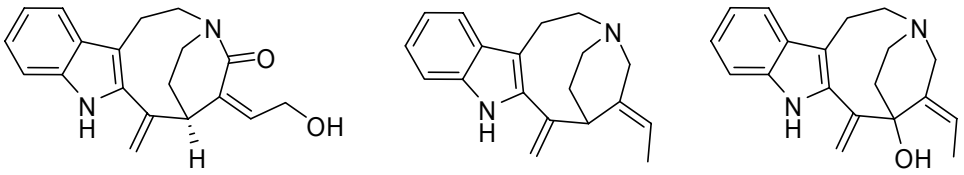
Pericidine (**1**) was also obtained from the stem-bark of *Kopsia Arborea* and its structure was determined by comparison with the known alkaloid pericine (**2**) (Figure 7).[14] Pericine (**2**) was first isolated in 1982 from *Picralina nitida* cell suspension cultures[15] and later, in 2002, under the name subincanadine E,[16] from *Aspidosperma subincanum*, from which an oxidized derivative, subincanadine D (**3**), was also obtained. Particularly interesting is **2**, which exhibits cytotoxicity against murine lymphoma L1210 cells (IC_{50} 0.3 μg/mL) and human epidermoid carcinoma KB cells (IC_{50}, 4.4 μg/mL). Pericidine (**1**) represents the third member belonging to this small group of tetracyclic indoles characterized by the presence of an exocyclic double bond. These compounds are also related to the compounds that we obtained by the gold(I) catalyzed intramolecular reaction between indoles and alkynes (see Chapter 1). The total synthesis of these natural products has not been described.



1 **2** **3**

Figure 7

2. Gold Catalysis in Total Synthesis

Despite all the new gold-catalyzed reactions that have been developed in the last few years and the applications found for new gold catalysts, only a few examples of gold-catalyzed total syntheses of natural compounds have been reported up to now.

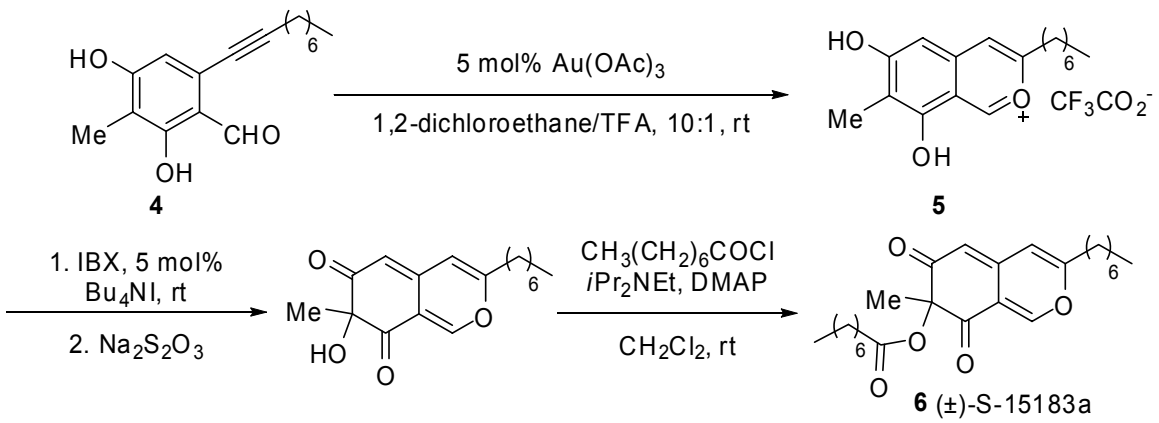
One example is the synthesis of a range of azaphilones, a structurally diverse family of natural products containing a highly oxygenated bicyclic core and a quaternary center. These compounds have been obtained by isolation of the oxonium species **5**, which is formed when the unprotected aldehyde **4** is treated with a gold

14 (a) Lim, K.; Low, Y.; Kam, T. *Tetrahedron Lett.* **2006**, *47*, 5037-5039. (b) Lim, K.; Kam, T. *Helv. Chim. Acta* **2007**, *90*, 31-35.

15 Arens, H.; Borbe, H. O.; Ulbrich, B.; Stockigt, J. *Planta Med.* **1982**, *46*, 210-214.

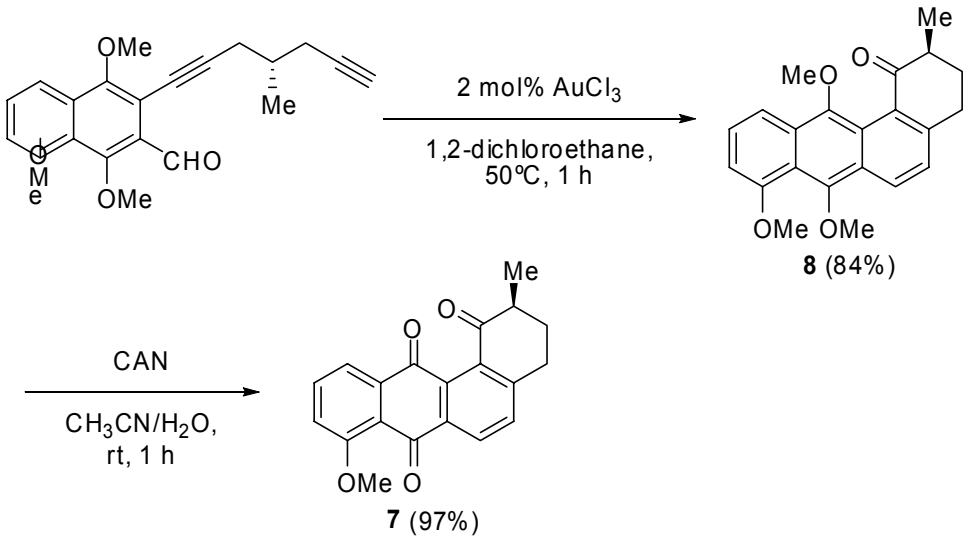
16 Kobayashi, J.; Sekiguchi, M.; Shimamoto, H.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449-6455.

catalyst in the presence of trifluoroacetic acid (Scheme 1).[17] Subsequent oxidation of **5** with IBX under phase-transfer conditions, followed by esterification, completed the synthesis of (±)-*S*-15183a (**6**), which acts as a potent sphingosine kinase inhibitor.



Scheme 1

The $AuCl_3$-catalyzed intramolecular formal [4+2] benzannulation of *o*-alkynylbenzaldehydes was utilized as the key step in the synthesis of (+)-rubiginone B_2 (**7**), a member of the angucyclinone family of natural products (Scheme 2).[18] After the efficient formation of the tetracyclic core, oxidation of the dihydrotetraphenone derivative **8** yields the target natural product.



Scheme 2

17 Zhu, J.; Germain, A. R.; Porco Jr., J. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1239-1243.

18 Sato, K.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 8977-8981.

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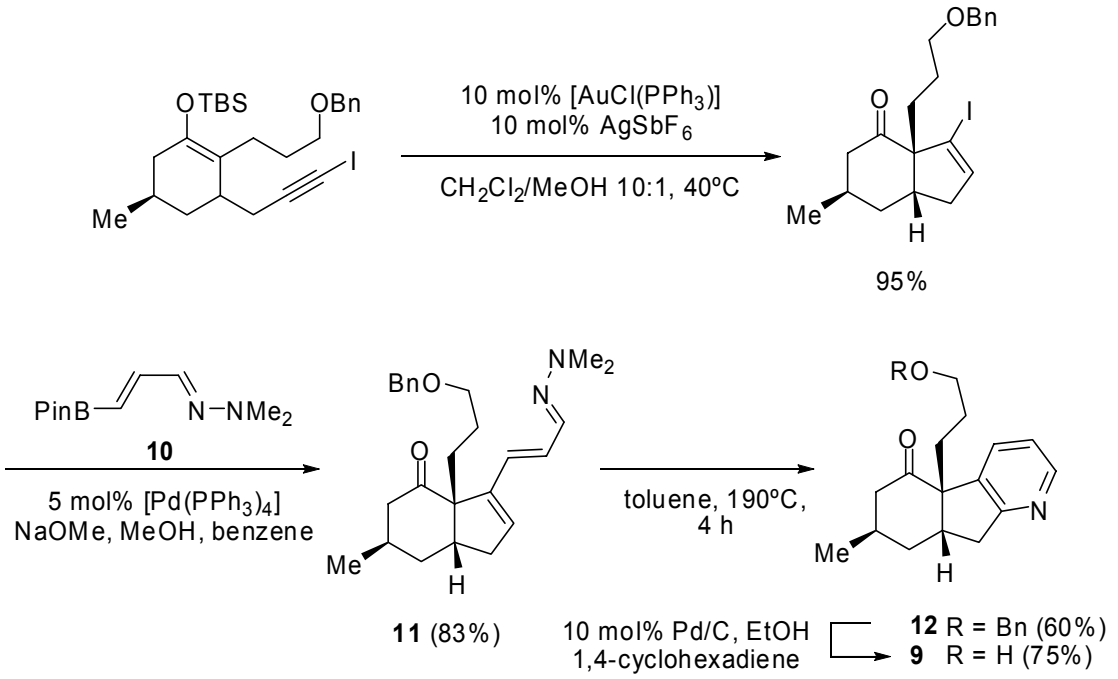
The reaction of a silyl enol ether as the nucleophile with an alkyne activated by a gold catalyst has been used for the construction of the hydrindanone core of the cytotoxic alkaloid (+)-lycopladine A (**9**) (Scheme 3).[19,20] A Suzuki reaction between boronic ester **10** and the vinyl iodide formed after the 5-*endo-dig* cyclization yielded compound **11**. Then, heating of **11** promoted a cascade sequence involving double-bond isomerization, 6π electrocyclization and elimination of dimethylamine to generate pyridyl-fused compound **12**. (+)-Lycopladine A (**9**) was obtained after deprotection of the hydroxyl group.



Scheme 3

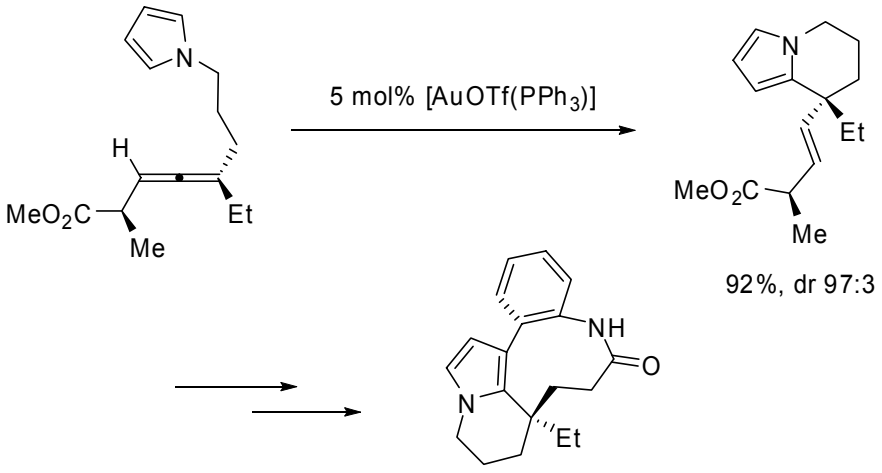
The hydroarylation of enantioenriched allenes catalyzed by gold has also been applied to the enantioselective total synthesis of (-)-rhazinilam (**13**) (Scheme 4).[21] The introduction of the quaternary carbon center proceeds with high diastereoselectivity by efficient transfer of chiral information from the allene. Whilst the cationic gold complex

19 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.

20 For a more recent related total synthesis: Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673.

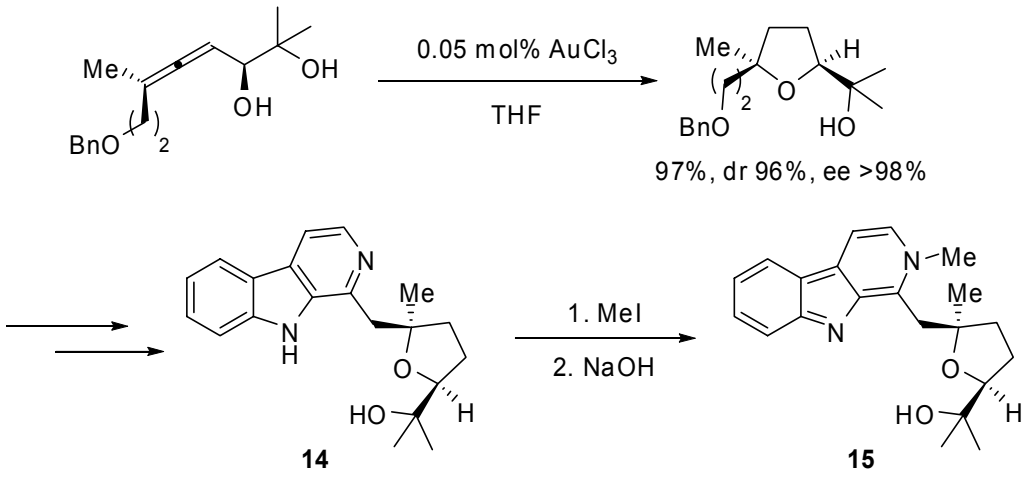
21 Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352-10353.

[AuOTf(PPh_3)] was shown to be the most effective, simpler cationic gold salts also were effective catalysts.



Scheme 4

Another example of chirality transfer from an allene to a carbon stereocenter has been described more recently by Krause and coworkers in the enantioselective total synthesis of the β-carboline alkaloids (-)-isocyclocapitelline (**14**) and (-)-isochrysotricine (**15**) by gold-catalyzed allene cycloisomerization (Scheme 5).[22]



Scheme 5

22 Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519-1521.

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Chapter 2. Objectives

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Our objective was to apply the methodology that we developed for the intramolecular reaction of indoles with alkynes to the synthesis of a more complex molecule. In particular, we wanted to investigate if the $AuCl_3$-catalyzed reaction of indole with alkynes leading to indoloazocines could be used in the synthesis of lundurines A-D (Figure 8).

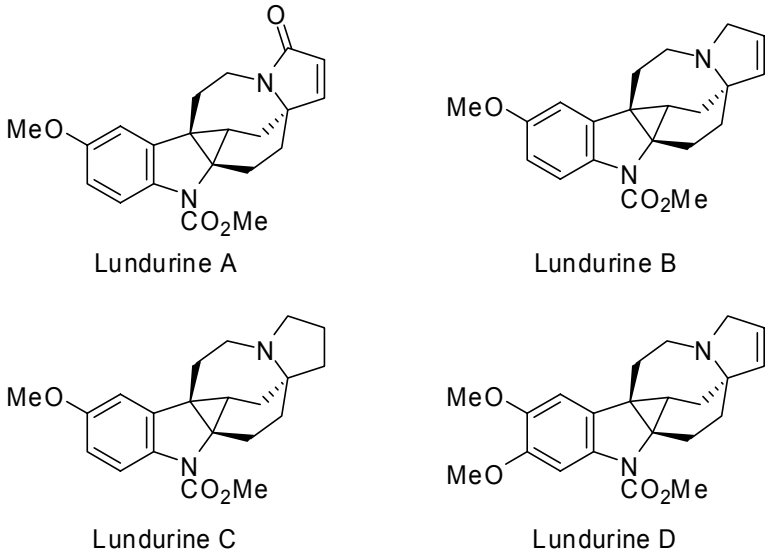

Figure 8

As an exploratory investigation, we wanted to test the feasibility of such syntheses on a model system (Figure 9). The product obtained in this cyclization reaction (**16**) has the same scaffold as the lundurines shown in Figure 8, but lacks the substituents on the phenyl ring and the bridgehead cyclopropane above the eight-membered ring. We expect that if compounds of type **16** could be prepared using $AuCl_3$ as catalyst, also natural products like the lundurines should be accessible using Au(III)-catalyzed cyclization reactions of indoles with alkynes.

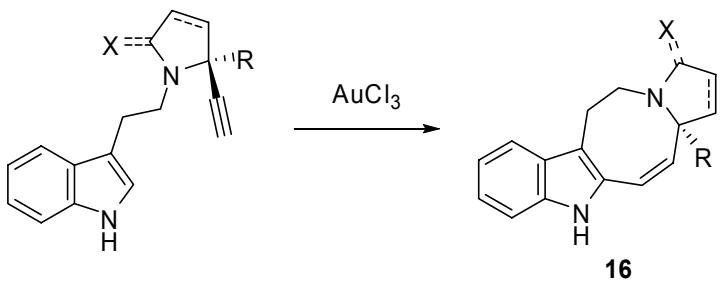

Figure 9

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Chapter 2. Results and discussion

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1. Exploratory Studies towards the Synthesis of the Lundurines

The first member of the lundurines of which we decided to study the gold-catalyzed synthesis was lundurine C. The retrosynthetic analysis that we envisioned for the synthesis of this compound is depicted in Figure 10.

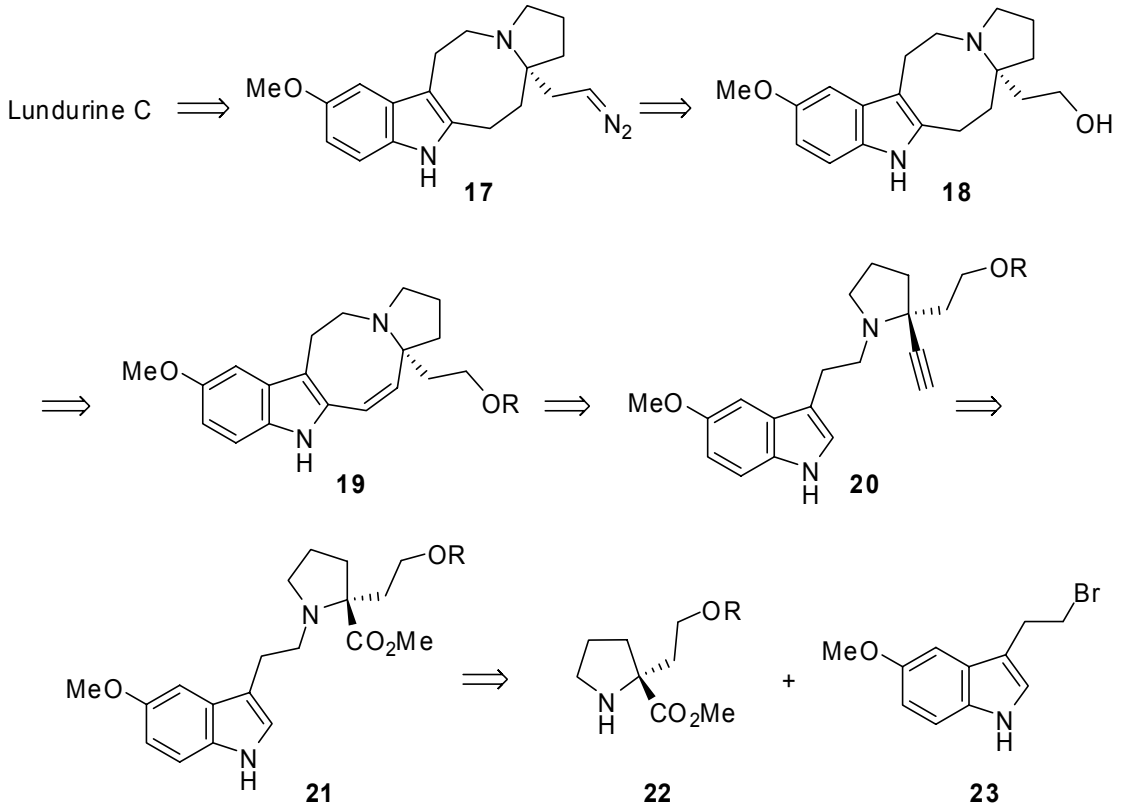


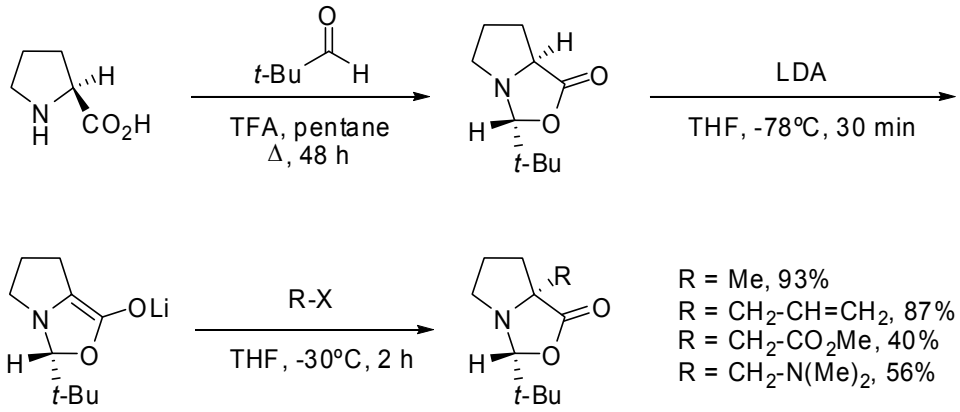
Figure 10

In this retrosynthetic analysis, the cyclopropane ring is formed by an intramolecular cyclopropanation of intermediate **17**,[23] derived from compound **18**, which is obtained from **19** after hydrogenation. Compound **19** is formed by the gold(III)-catalyzed cyclization of **20,** which arises from **21** upon converting the ester group into a homologated alkyne. Compound **21** is assembled from enantiomerically pure proline derivative **22** and indole derivative **23**.

23 For some recent examples of cyclopropanation of indoles: (a) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45,* 4277-4280. (b) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Quin, Y. *Org. Lett.* **2006**, *8,* 2187-2190. (c) Eis, M. J.; Lutz, M.; Spek, A. L.; Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **2007**, *63,* 1689-1694.

The main objective was to see whether the key-step, namely the formation of the eight-membered cycle, could be accomplished. Therefore, instead of using compound **23**, which is the starting indole in the envisioned synthesis of lundurine C, we decided to start our synthetic studies with the more simple, but very similar, 3-(2-bromoethyl)-1*H*-indole, the indole derivative with an unsubstituted phenyl ring.

For the synthesis of proline derivative **22**, we followed the procedure described by Germanas and coworkers for the enantioselective alkylation of proline.[24] This procedure was based on a method reported by Seebach,[25] in which proline is condensed with pivalaldehyde to give a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.3]octan-4-one that is deprotonated with LDA to give a chiral enolate that can be alkylated with an electrophile (Scheme 6).



Scheme 6

Germanas described the condensation of proline with chloral instead of pivalaldehyde to give the more stable oxazolidinone **24** (Scheme 7). We tried to alkylate **24** using LDA and commercially available ((2-bromoethoxy)methyl)benzene, but the reaction only lead to decomposition products. When we converted ((2-bromoethoxy)methyl)benzene into ((2-iodoethoxy)methyl)benzene, the alkylation worked, although only 33% of slightly impure **25** was isolated, while 60% of the alkylating agent was recovered.

24 Wang, H.; Germanas, J. P. *Synlett* **1999**, 33-36.

25 Seebach, D.; Boes, M.; Naef, R.; Schweizer, B. *J. Am. Chem. Soc.* **1983**, *105*, 5390-5389.

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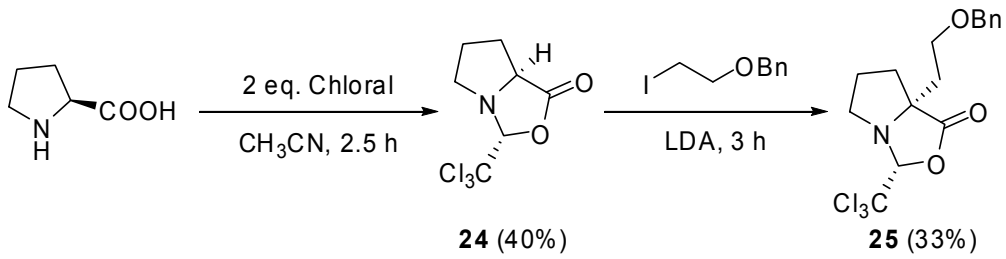


24 (40%) **25** (33%)

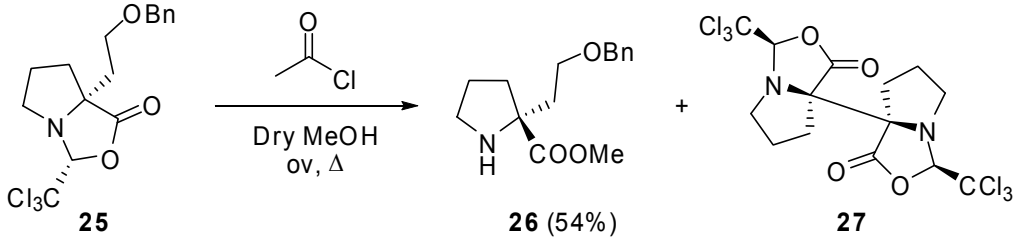
Scheme 7

Attempts to improve the yield, summarized in Table 1, were unsuccessful and only led to decomposition and lower or similar yields when the reaction was left for longer time or at higher temperature.

Table 1. Conditions for the alkylation of **24**

Conditions	Observations
KDA, 3 h, -78ºC	Decomposition
LDA, HMPA, 3 h, -78ºC	Decomposition
LDA, quinuclidine *N*-oxide, 2 h, -78ºC	Decomposition
LDA, 3 days, -78ºC	30%
LDA, 3 h, -40ºC	24%

Hydrolysis of the *N,O*-acetal function was effected under the acidic conditions described by Germanas.[24] In the hydrolysis of compound **25**, together with the expected proline derivative **26**, bis-proline **27** was also isolated (Scheme 8).



25 **26** (54%) **27**

Scheme 8

The structure of compound **27** was confirmed by X-ray crystallography (Figure 11). Apparently, **27** was already formed in the previous alkylation step. A similar

dimeric structure was described by Johnson and coworkers[26] when they tried to alkylate Seebach oxazolidinone with dibromoethane to obtain C2-linked bi-oxazolidinone **28** (Scheme 9).

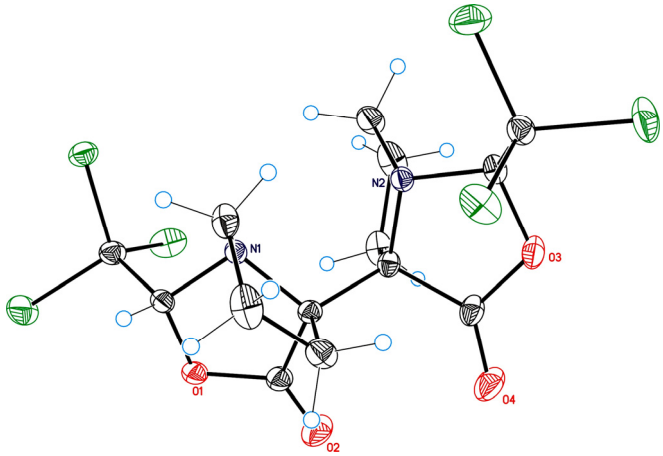
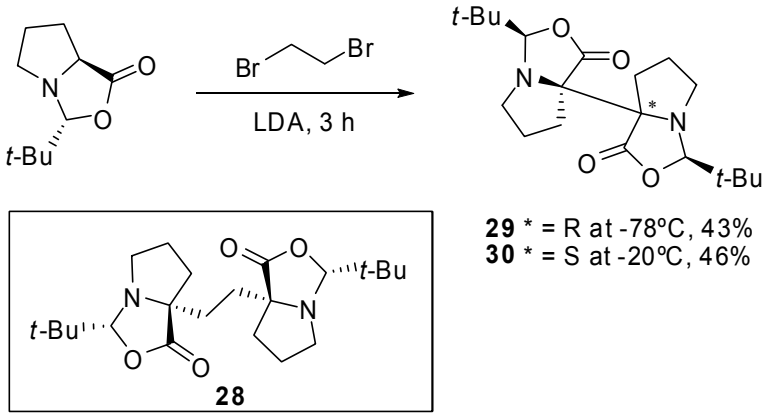


Figure 11. X-Ray structure of **27**

Instead of obtaining **28**, however, they observed the formation of dimers **29** and **30**. Running the reaction at -20ºC resulted primarily in the formation of **30** while subsequent runs at -78ºC yielded **29** as the major diastereomer. The involvement of radical intermediates in this dimerization was experimentally excluded.



Scheme 9

The next step was the alkylation of proline derivative **26** with 3-(2-bromoethyl)-1*H*-indole under standard conditions. The alkylated product **31** was obtained in only 23% yield, together with spiro[cyclopropane-1,3'-indole] (**32**) (Scheme 10). This

26 Vartak, A. P.; Young, V. G.; Johnson, R. L. *Org. Lett.* **2005**, *7*, 35-38.

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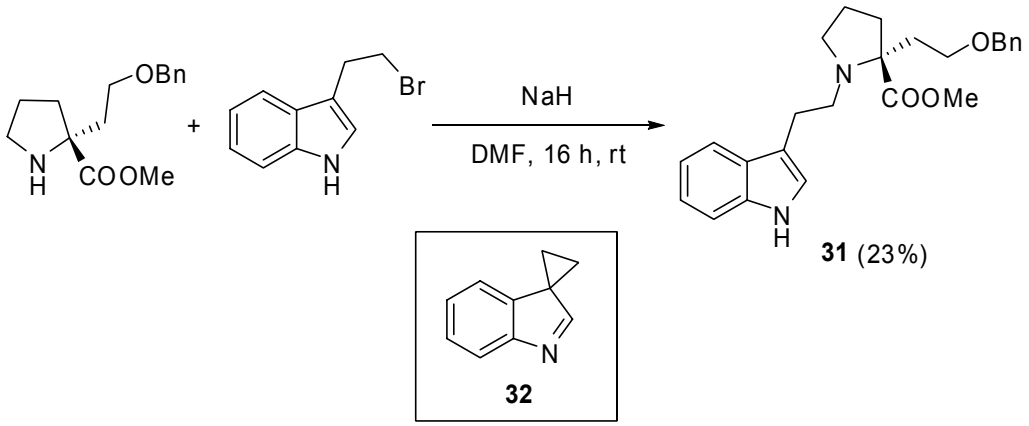
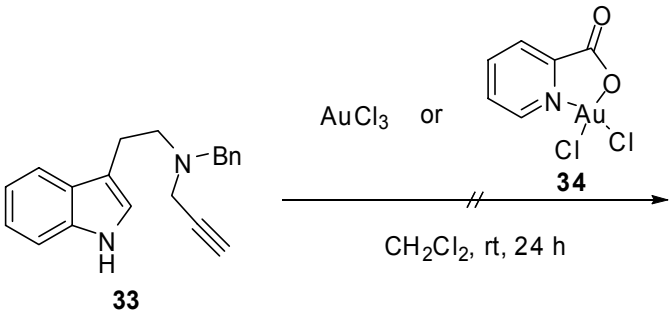
compound was previously obtained by Rapoport in the alkylation of 2,3-piperidinedicarboxylate with 3-(2-bromoethyl)-1*H*-indole.[27]



Scheme 10

In the work of Rapoport $NaHCO_3$ led to a more efficient alkylation, but in our case the use of $NaHCO_3$ only gave unchanged starting material. Using *N*-Boc protected indole derivative[28] for the alkylation was also unsuccessful.

Since most of the steps in the synthetic route towards **31** were low yielding, alternative ways of preparation were needed. Before starting a new synthesis of **31**, however, we decided to first investigate whether the gold-catalyzed reaction between an indole and an alkyne would work in the presence of an amine. For this purpose we synthesized model compound **33** and subjected it to our reactions conditions (Scheme 11).



Scheme 11

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

28 Yang, J.; Song, H.; Xiao, X.; Wang, J.; Quin, Y. *Org. Lett.* **2006**, *8*, 2187-2190.

Unfortunately, no reaction was observed when $AuCl_3$ or **34** was used as catalyst. Protonation of the amine using trifluoroacetic acid prior to the addition of the catalyst to prevent coordination to the gold was also ineffective.

Given the apparent incompatibility of the envisioned cyclization reaction in the presence of an amine in the synthetic pathway to lundurine C, we decided to change our strategy and focused our efforts on the synthesis of lundurine A, which contains an amide function instead of an amine. We thought about using (L)-methyl pyroglutamate (**35**) instead of using proline derivative **22** for the synthesis of compound **36**, which would be alkylated[29] before the cyclization and then converted into lundurine A (Figure 12).

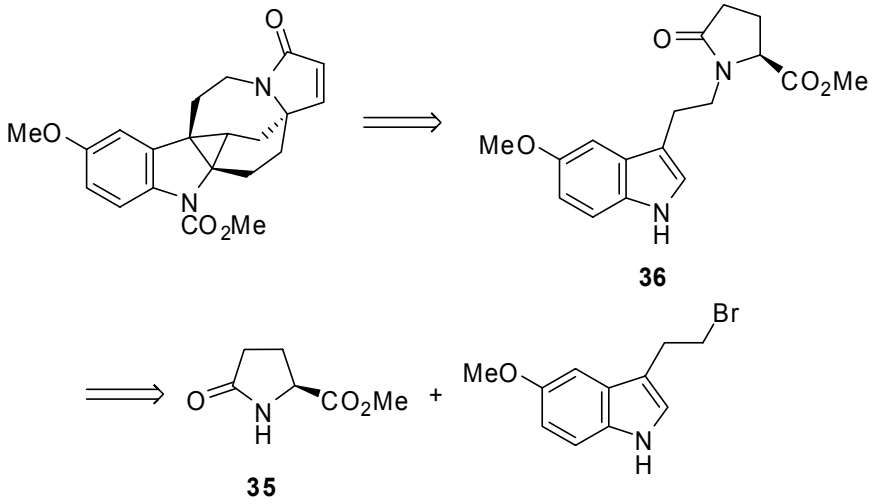


Figure 12

For the alkylation of **35**, we wanted to apply the methodology developed by Rigo and coworkers[30] in which methyl *N*-(trimethylsilyl)pyroglutamate reacts in the presence of a catalyst (typically triflic acid) with benzhydryl bromides or with trimethylsilyl benzhydryl ethers to give methyl *N*-(benzhydryl)pyroglutamates in nearly quantitative yields (Scheme 12).

29 Braña, M. F.; Garranzo, M.; Pascual-Teresa, B.; Pérez-Castells, J.; Torres, M. R. *Tetrahedron* **2002**, *58*, 4825-4836.

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

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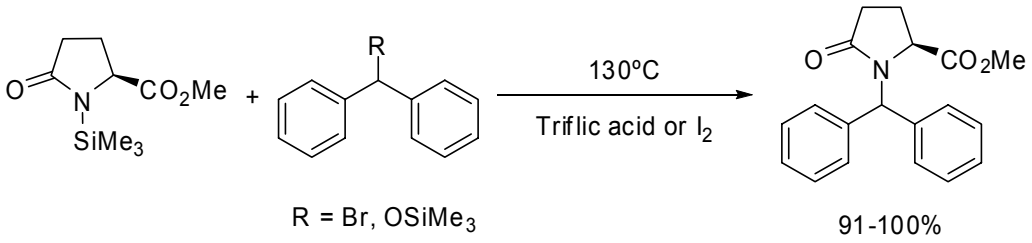
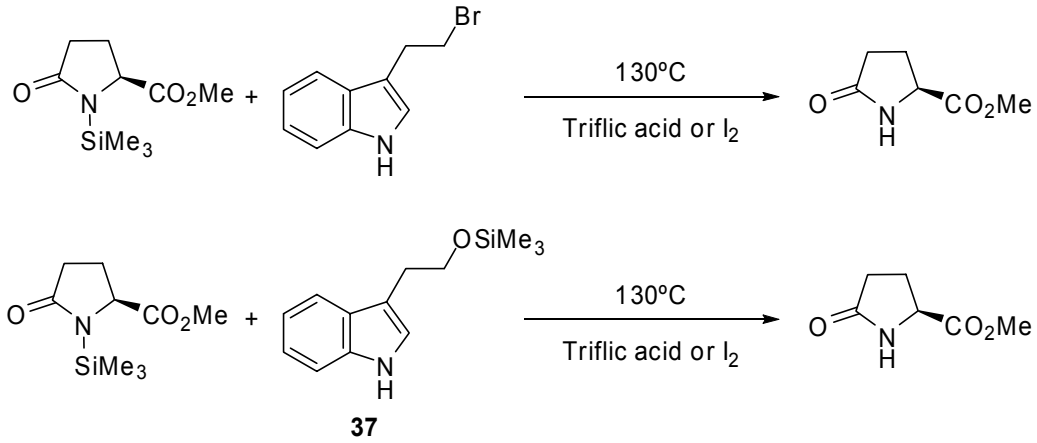


Scheme 12

The reaction of *N*-(trimethylsilyl)pyroglutamate with 3-(2-bromoethyl)-1*H*-indole or with 3-(2-(trimethylsilyloxy)ethyl)-1*H*-indole (**37**) under the conditions described by Rigo only led to desilylated (L)-methyl pyroglutamate (Scheme 13).



Scheme 13

Given these unsuccessful alkylation attempts with the *N*-(trimethylsilyl) pyroglutamate, we formulated a new retrosynthetic approach for lundurine A (Figure 13). In this new proposal, the formation of the cyclopropane is an intermolecular process that will take place preferentially at only one face of the indole due to the stereogenic center present in the molecule. Formation of a silyloxypyrrole followed by alkylation will form the bridge.[31] Compound **36** is formed via reductive amination between enantiomerically pure (L)-dimethyl glutamate (**39**) and aldehyde **38,** followed by lactamization.

31 Hunter, R.; Rees-Jones, S. C. M.; Su, H. *Tetrahedron Lett.* **2007**, *48*, 2819-2822.

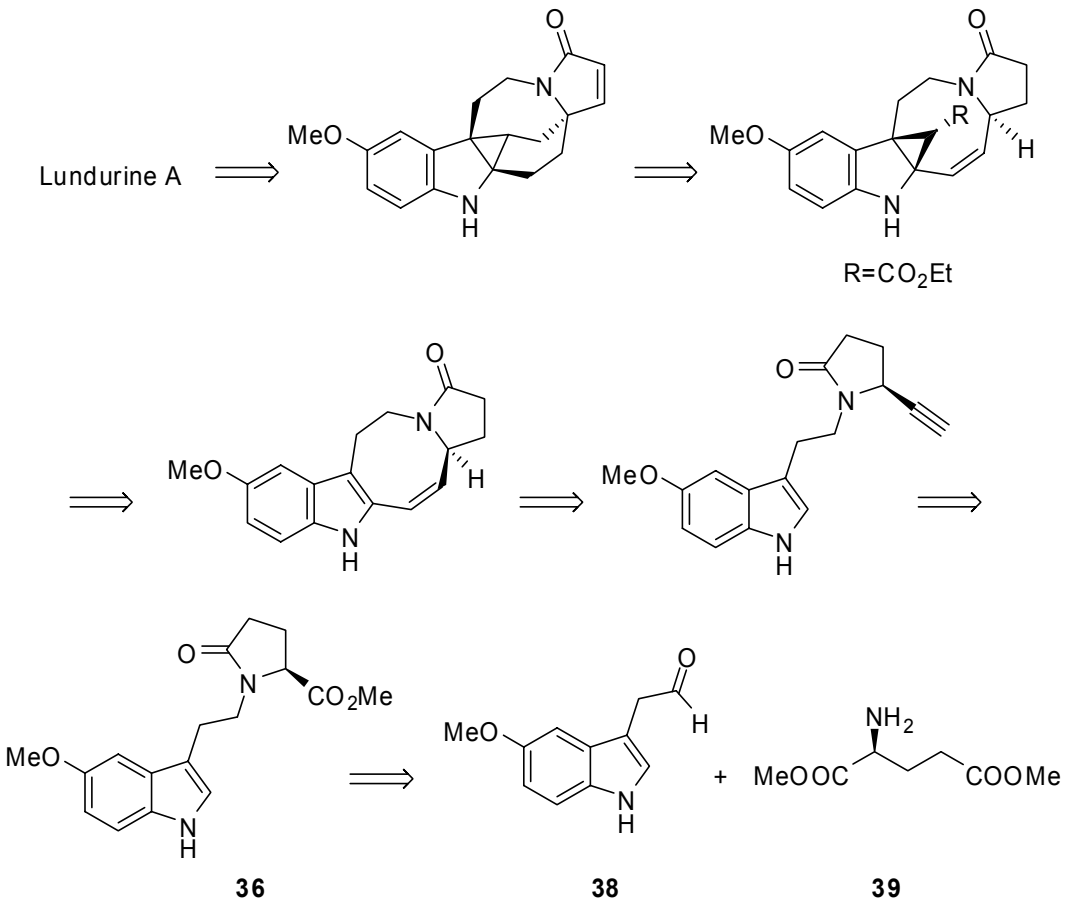


Figure 13

As in the case of the lundurine C, we used the simpler but very similar indole derivative lacking the phenyl substituent as a starting point of our exploratory synthetic investigation. Methyl 2-(1*H*-indol-3-yl)acetate was protected as a carbamate using $(Boc)_2O$[32] and the ester group was reduced with DIBAL at low temperature to give aldehyde **40** (Scheme 14). When we carried out the reductive amination of this aldehyde with (L)-dimethyl glutamate and sodium triacetoxyborohydride, we were pleased to see that lactam **41** was obtained in good yield.

32 Davies, H. M. L.; Towsend, R. J. *J. Org. Chem.* **2001**, *66*, 6565-6603.

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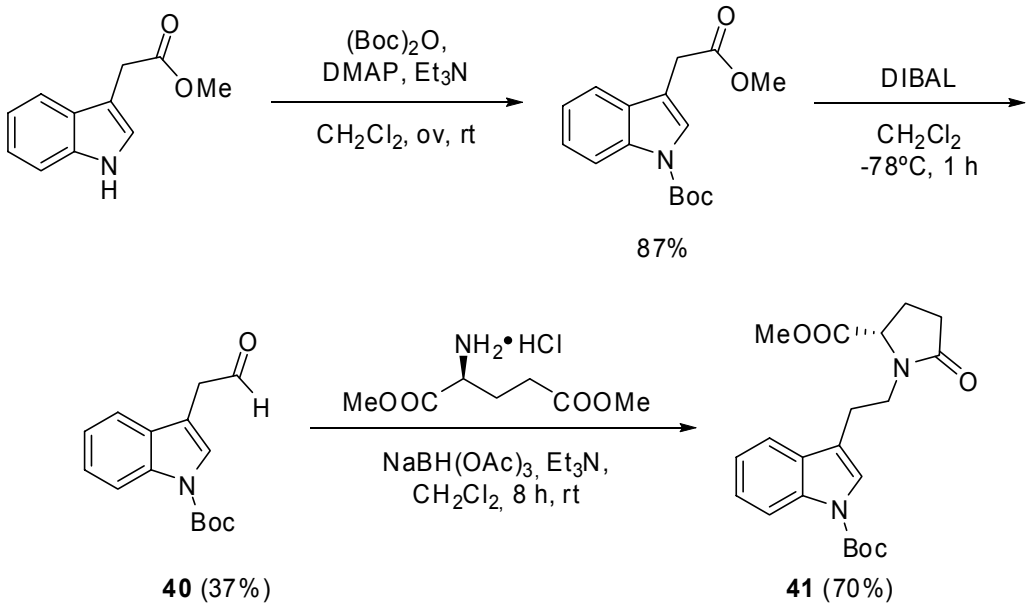


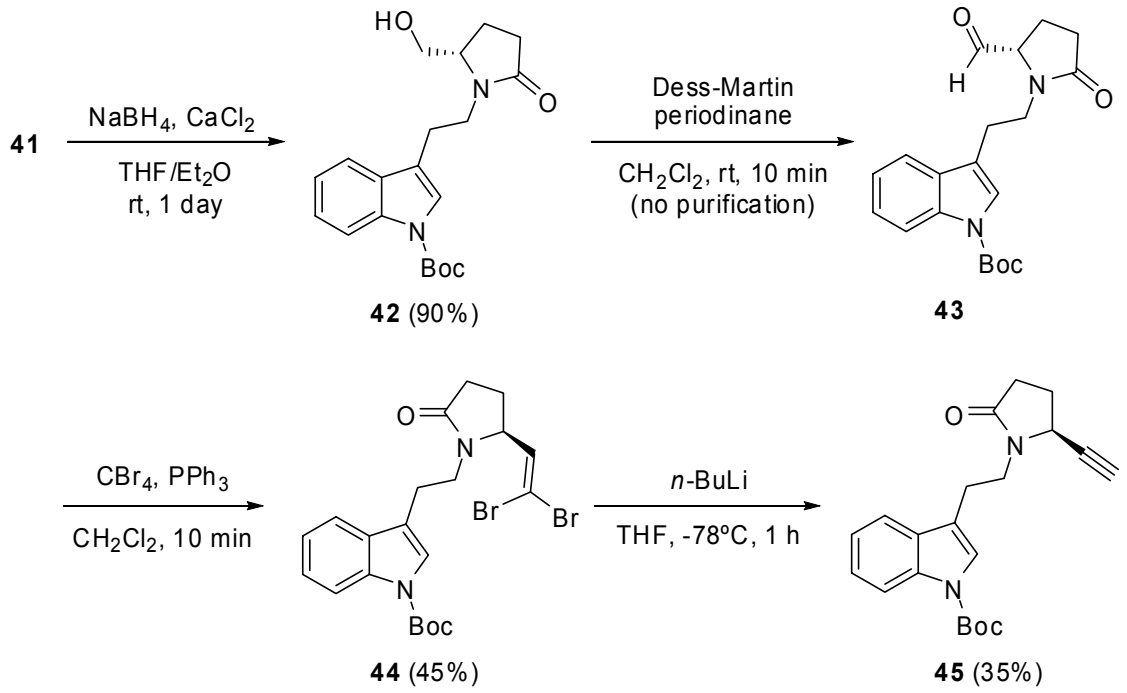
Scheme 14

Ester **41** was reduced to alcohol **42** in a very good yield using sodium borohydride and calcium chloride (Scheme 15). When lithium aluminum hydride was used, both reduction of the ester and the lactam were observed, even at low temperature. Dess-Martin oxidation of alcohol **42** gave aldehyde **43**, which was used in the next step without further purification.

Aldehyde **43** was converted into homologated alkyne **45** using the Corey-Fuchs reaction.[33] Treatment of dibromoalkene **44** with *n*-BuLi only gave low yields of alkyne **45**, probably due to the presence of enolizable protons on the molecule. An alternative method for this transformation would be to use the Bestmann-Ohira reagent.[34]

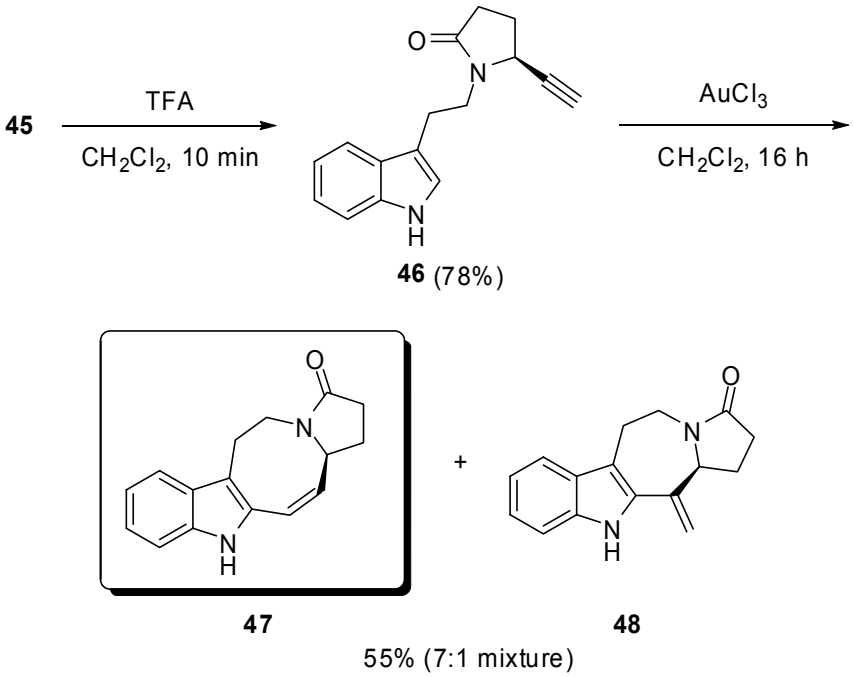
33 Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769-3762.

34 (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H.-J. *Synlett* **1996**, 521-522. (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59-62.



Scheme 15

Deprotection of the nitrogen of the indole ring using trifluoroacetic acid led to compound **46** (Scheme 16). We were very pleased to observe that compound **46** cyclized in the presence of $AuCl_3$ at room temperature to give indoloazocine **47** as the major product, which contains the tetracyclic core present in the lundurine A. A small amount of the regioisomeric **48** was also obtained.



Scheme 16

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Compounds **47** and **48** could be separated by HPLC chromatography. The ^{1}H-NMR-spectrum of indoloazocine **47** is shown in Figure 14 and the MM2-minimized structure for this compound is shown in Figure 15. This minimized structure is also supported by a NOE experiment and shows that the two faces of the indole ring are different. Compound **47** exhibits a very high value for the optical rotation ($[\alpha]_D$ = 478.5 (c = 0.46, $CHCl_3$)).

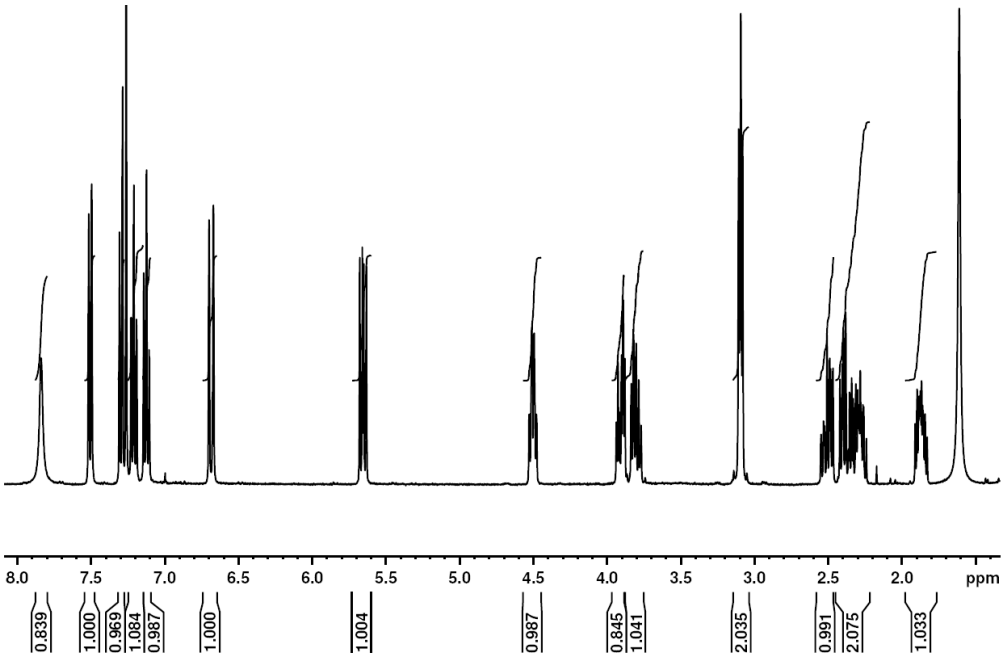

Figure 14. ^{1}H-NMR-Spectrum of **47**

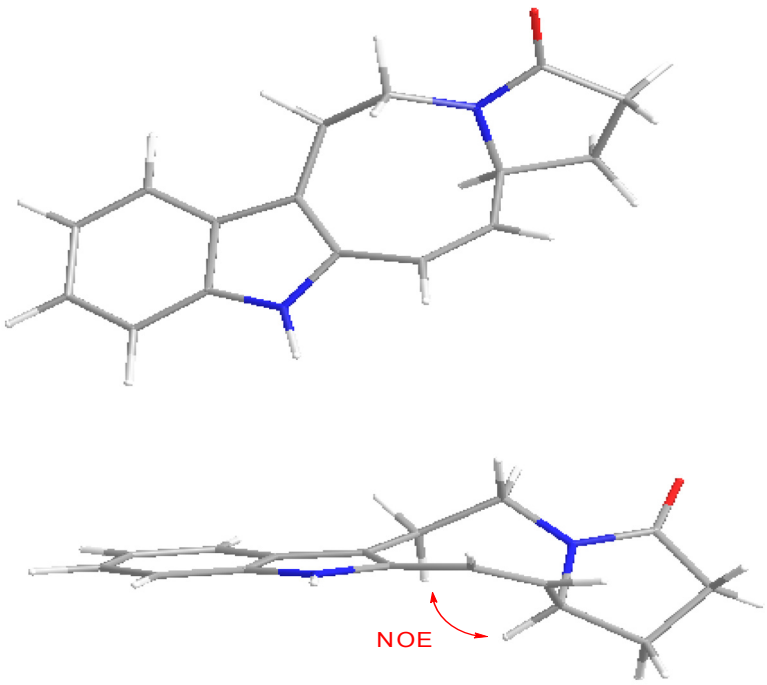

Figure 15. MM2-Minimized structure of **47**

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Chapter 2. Conclusions

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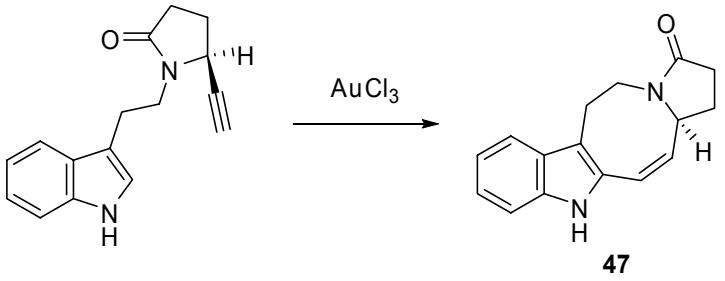
We have demonstrated that the methodology developed for the reaction between indoles and alkynes can be applied to the preparation of more complex molecules. In particular, we have been able to synthesize the tetracyclic core present in the family of natural products lundurines A-D (Scheme 17).

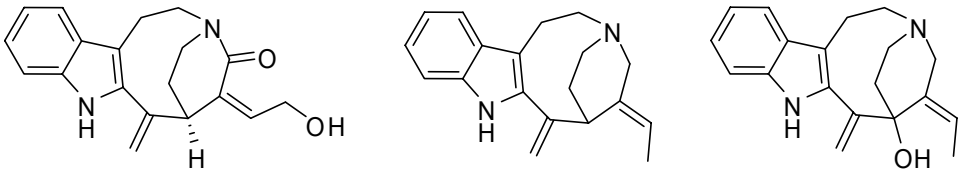
Compound **47** has been obtained in 9 steps starting from commercially available methyl 2-(1*H*-indol-3-yl)acetate and enantiomerically pure (L)-dimethyl glutamate. The reductive amination of aldehyde **40** with (L)-dimethyl glutamate leads to the formation of lactam **41** in one step and in good yield. Compound **47** could be further functionalized by cyclopropanation to give lundurine A. If the intermolecular cyclopropanation of **47** occurs at the undesired side of the indole, the required enantiomer of lundurine A could be obtained by reacting **40** with commercially available (D)-dimethyl glutamate. Reduction of the amide group in this molecule would lead to the formation of the other members of this family of natural products.



47

Scheme 17

In a similar way, the preparation of pericidine (**1**), pericine (**2**) and subincanadine D (**3**) (Figure 16) could be also accessible using the gold(I)-catalyzed intramolecular reaction of indoles with alkynes.



1 **2** **3**

Figure 16

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Chapter 2. Experimental section

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Experimental Section: Index

1. General Methods

All reactions were carried out under N_2 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.

2. Preparation of Substrates

tert-Butyl 3-(2-bromoethyl)-1*H*-indole-1-carboxylate,[28] complex **53**,[35] *N*-(trimethylsilyl)piroglutamate,[30] and *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate[32] were prepared according to the described procedures. Spiro[cyclopropane-1,3'-indole] (**32**)[27] showed spectroscopic data consistent with that described.

28 Yang, J.; Song, H.; Xiao, X.; Wang, J.; Quin, Y. *Org. Lett.* **2006**, *8*, 2187-2190.

35 (a) Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc., Dalton Trans.* **1992**, 1907-1913. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545-6547.

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

32 Davies, H. M. L.; Towsend, R. J. *J. Org. Chem.* **2001**, *66*, 6565-6603.

27 Vartak, A. P.; Young, V. G.; Johnson, R. L. *Org. Lett.* **2005**, *7*, 35-38.

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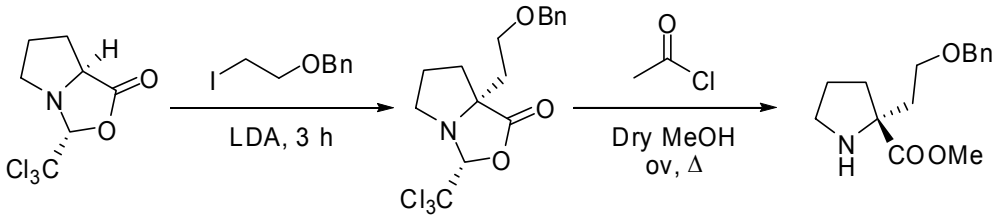
(*R*)-Methyl 2-(2-(benzyloxy)ethyl)pyrrolidine-2-carboxylate (26)



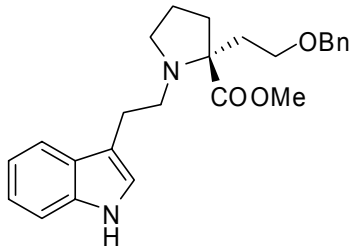
24 **25** **26**

An ice cold solution of LDA (0.86 mL diisopropylamine/2.45 mL *n*-butyl lithium, 6.13 mmol) was added dropwise to a solution of **24**[24] (1.00 g, 4.09 mmol) in THF (20 mL) at -78ºC. After 30 min ((2-iodoethoxy)methyl)benzene (1.18 g, 4.5 mmol) was added and it was stirred at this temperature for 3 h. Then, the reaction was quenched with MeOH and it was allowed to warm up to room temperature. The resulting mixture was portioned between chloroform and water, the organic layer dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel chromatography (10:1 hexane-EtOAc) to give **25** (510 mg, 33%) as a slightly impure oil.

To a solution of **25** (1.42 g, 3.75 mmol) in MeOH (16 mL) was added a solution of acetyl chloride (0.60 mL, 8.36 mmol) in MeOH (8 mL). The mixture was heated at reflux overnight. Then, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was made basic and then it was extracted again with CH_2Cl_2. Dimer **27** was isolated when EtOAc was used as the solvent for the extraction. The residue was purified by silica gel chromatography eluting with EtOAc to give **26** as a colorless oil (540 mg, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 4.42 (s, 2H), 3.60 (s, 3H), 3.53 (dd, J = 6.8, 5.3 Hz, 2H), 3.04-2.93 (m, 2H), 2.27 (dd, J = 13.9, 6.9 Hz, 1H), 2.17-2.10 (m, 1H), 1.84-1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 177.58 (C), 138.32 (C), 128.27 (CH, 2C), 127.79 (CH, 2C), 127.52 (CH), 73.22 (CH_2), 67.36 (C), 67.16 (CH_2), 52.15 (CH_3), 46.59 (CH_2), 39.59 (CH_2), 36.79 (CH_2), 24.88 (CH_2). Anal calcd for $C_{15}H_{21}NO_3 \cdot 1/2\ H_2O$: C, 66.15; H, 8.14; N, 5.14; found: C, 66.59; H, 7.87; N, 5.74. HRMS-ESI *m/z* calcd for $C_{15}H_{22}NO_3$: 264.1600; found: 264.1600 [M^++H].

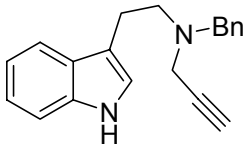
24 Wang, H.; Germanas, J. P. *Synlett* **1999**, 33-36.

Methyl 1-(2-(1*H*-indol-3-yl)acetyl)-2-(2-(benzyloxy)ethyl)pyrrolidine-2-carboxylate (31)



To a solution of sodium hydride (60% in mineral oil, 8 mg, 0.79 mmol) in DMF (1 mL) was added **26** (50 mg, 0.79 mmol) at 0ºC, the mixture was allowed to stir for 15 minutes. Then, 3-(2-bromoethyl)-1*H*-indole (43 mg, 0.79 mmol) was added and the reaction was stirred at room temperature for 16 hours. The mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na_2SO_4, filtered and evaporated. The residue was purified by chromatography (4:1 hexane-EtOAc) to give **31** as a colorless oil (18 mg, 23%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.35-7.27 (m, 6H), 7.17 (t, J = 7.4 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 4.39 (s, 2H), 3.59 (s, 3H), 3.50 (ddd, J = 9.4, 8.2, 6.3 Hz, 1H), 3.43 (ddd, J = 9.3, 7.9, 5.6 Hz, 1H), 3.32-3.27 (m, 1H), 3.03-2.97 (m, 1H), 2.93 (dd, J = 9.7, 4.2 Hz, 1H), 2.86-2.79 (m, 1H), 2.71-2.66 (m, 1H), 2.60-2.55 (m, 1H), 2.25 (ddd, J = 14.0, 7.7, 6.4 Hz, 1H), 2.19-2.14 (m, 1H), 1.94-1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.50 (C), 138.61 (C), 136.19 (C), 128.31 (CH, 2C), 127.63 (C), 127.57 (CH, 2C), 127.44 (CH), 121.88 (CH), 121.50 (CH), 119.22 (CH), 118.89 (CH), 111.01 (CH), 103.47 (C), 72.88 (CH_2), 69.45 (C), 66.99 (CH_2), 51.27 (CH_2), 51.01 (CH_3), 50.06 (CH_2), 34.38 (CH_2), 34.05 (CH_2), 25.52 (CH_2), 21.97 (CH_2). HRMS-ESI *m/z* calcd for $C_{25}H_{31}N_2O_3$: 407.2335; found: 407.2316 [M^++H].

***N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*-benzylprop-2-yn-1-amine (33)**



To a solution of sodium hydride (60% in mineral oil, 186 mg, 4.65 mmol) in THF (10 mL) was added *N*-benzyl-2-(1*H*-indol-3-yl)ethanamine (970 mg, 3.87 mmol) at 0ºC. The mixture was allowed to stir for 15 minutes and propargyl bromide (0.41 mL, 4.65 mmol) was added. The reaction was stirred at room temperature for 24 hours. Then, the mixture was washed with water and extracted with EtOAc. The organic layer

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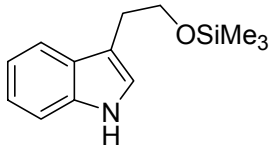
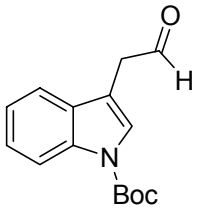
was dried over Na_2SO_4, filtered and evaporated. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **33** as a colorless oil (163 mg, 15%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.38-7.27 (m, 6H), 7.19 (td, J = 7.6, 1.1 Hz, 1H), 7.10 (td, J = 7.3, 1.0 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 3.73 (s, 2H), 3.44 (d, J = 2.3 Hz, 2H), 3.02-2.98 (m, 2H), 2.95-2.90 (m, 2H), 2.26 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 138.75 (C), 136.21 (C), 129.17 (CH, 2C), 128.40 (C), 128.32 (CH, 2C), 127.13 (CH), 121.94 (CH), 121.56 (CH), 119.21 (CH), 118.92 (CH), 114.41 (C), 111.05 (CH), 78.66 (C), 73.22 (CH), 57.96 (CH_2), 53.93 (CH_2), 41.46 (CH_2), 23.67 (CH_2). Anal calcd for $C_{20}H_{20}N_2 \cdot 1/3\ H_2O$: C, 81.60; H, 7.08; N, 9.52; found: C, 81.52; H, 7.68; N, 10.10. HRMS-ESI *m/z* calcd for $C_{20}H_{21}N_2$: 289.1705; found: 289.1693 [M^++H].

3-(2-(Trimethylsilyloxy)ethyl)-1*H*-indole (37)



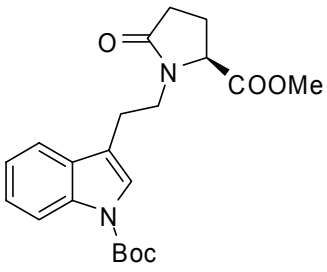
To a solution of tryptophol (1.00 g, 6.20 mmol) in THF (30 mL) was added hexamethyldisilazane (6.10 mL, 29.15 mmol) and then trimethylsilylchloride (1.60 mL, 13.02 mmol). The mixture was stirred for 20 h and then the solvent was evaporated. Saturated sodium bicarbonate was added to the residue until a basic reaction was obtained. The aqueous solution was extracted with ether and the organic phase was washed with water and dried over Na_2SO_4. After evaporation of the solvent, **37** was obtained as a brown solid (1.40 g, 97%): mp 50-52ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 3.88 (t, J = 7.5 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 136.40 (C), 127.69 (C), 122.02 (CH), 121.93 (CH), 119.27 (CH), 118.91 (CH), 113.00 (C), 111.10 (CH), 63.26 (CH_2), 28.95 (CH_2), -0.42 (CH_3, 3C). Anal calcd for $C_{13}H_{19}NOSi$: C, 66.90; H, 8.21; N, 6.00; found: C, 67.18; H, 7.68; N, 6.49. HRMS-ESI *m/z* calcd for $C_{13}H_{19}NOSiNa$: 256.1134; found: 256.1131 [M^++Na].

tert-Butyl 3-(2-Oxoethyl)-1*H*-indole-1-carboxylate (40)



To a solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (7.10 g, 24.54 mmol) in CH_2Cl_2 (300 mL) at -78ºC was added DIBAL (1 M solution in CH_2Cl_2, 49.1 mL, 49.10 mmol). The solution was allowed to stir for 1.5 hours at this temperature and then it was quenched with MeOH at -78ºC and warmed up to room temperature for 2 hours. The mixture was diluted with EtOAc and washed with a Na/K tartrate saturated solution, the organic layer dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by chromatography (10:1 hexane-EtOAc) to give **40** as a yellow oil (2.20 g, 37%): ^{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 198.51 (CH), 149.52 (C), 135.52 (C), 130.11 (C), 124.84 (CH), 124.78 (CH), 122.81 (CH), 118.69 (CH), 115.43 (CH), 110.95 (C), 83.91 (C), 40.03 (CH_2), 28.20 (CH_3, 3C). HRMS-ESI *m/z* calcd for $C_{16}H_{21}NO_4Na$: 314.1368; found: 314.1369 [M^++MeOH+Na].

(S)-_tert_-Butyl 3-(2-(2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (41)



To a solution of **40** (2.16 g, 8.33 mmol) and L-glutamic acid methyl ester hydrochloride (1.93 g, 9.16 mmol) in CH_2Cl_2 (35 mL), was added Et_3N (2.3 mL, 16.65 mmol) and then it was treated with sodium triacetoxyborohydride (2.64 g, 12.49 mmol). The mixture was stirred at room temperature for 8 hours and after extractive workup (EtOAc/ $NaHCO_3$ saturated solution) it was purified by chromatography (2:1 hexane-EtOAc) to give **41** as a yellow oil (2.25 g, 70%): $[\alpha]_D$ = -6.6 (c = 1.2, $CHCl_3$). ^{1}H NMR

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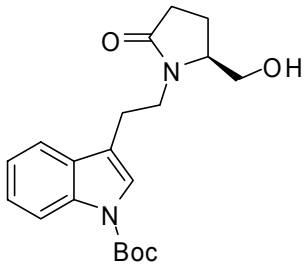
(400 MHz, $CDCl_3$) δ 8.20 (br d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.41 (s, 1H), 7.31 (td, J = 7.4, 1.2 Hz, 1H), 7.24 (td, J = 7.3, 1.0 Hz, 1H), 4.08 (dd, J = 9.0, 3.1 Hz, 1H), 4.00 (ddd, J = 13.9, 9.0, 5.6 Hz, 1H), 3.73 (s, 3H), 3.24 (ddd, J = 13.9, 8.6, 6.7 Hz, 1H), 3.00 (dddd, J = 14.5, 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 175.28 (C), 172.48 (C), 149.66 (C), 135.49 (C), 130.32 (C), 124.52 (CH), 123.04 (CH), 122.52 (CH), 118.82 (CH), 117.51 (C), 115.31 (CH), 83.59 (C), 60.22 (CH), 52.49 (CH_3), 42.13 (CH_2), 29.51 (CH_2), 28.23 (CH_3, 3C), 23.08 (CH_2, 2C). HRMS-ESI *m/z* calcd for $C_{21}H_{26}N_2O_5Na$: 409.1739; found: 409.1741 [M^++Na].

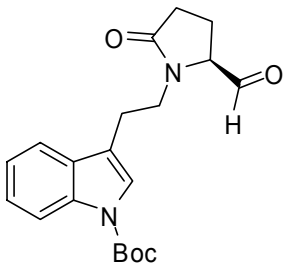
(*S*)-*tert*-Butyl 3-(2-(2-(Hydroxymethyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (42)



To a solution of **41** (1.53 g, 3.96 mmol) and calcium chloride (879 mg, 7.92 mmol) in a mixture of THF (60 mL) and Et_2O (40 mL) was added sodium borohydride (600 mg, 15.83 mmol) at 0ºC. The reaction was allowed to warm up to room temperature and it was left to stir for 1 day. Then the equivalents of water necessary to react with the $NaBH_4$ were added and also $MgSO_4 \cdot 7H_2O$, the mixture was stirred until the evolution of gas ceased and then it was filtered through a path of celite. After evaporation of the solvent, **42** was obtained as a colorless oil (1.29 g, 90%): $[\alpha]_D$ = 13.4 (c = 1.0, $CHCl_3$). ^{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 175.96 (C), 149.71 (C), 135.48 (C), 130.40 (C), 124.49 (CH), 123.11 (CH), 122.53 (CH), 118.90 (CH), 117.72 (C), 115.30 (CH), 83.58 (C), 63.46 (CH_2), 59.62

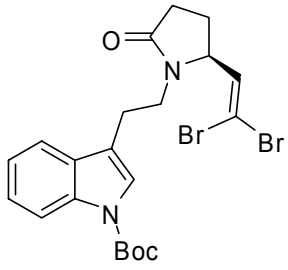
(CH), 41.30 (CH_2), 30.38 (CH_2), 28.23 (CH_3, 3C), 23.29 (CH_2), 21.26 (CH_2). HRMS-ESI *m/z* calcd for $C_{20}H_{26}N_2O_4Na$: 381.1790; found: 381.1773 [M^++Na].

(*S*)-*tert*-Butyl 3-(2-(2-Formyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (43)



To a solution of **42** (1.23 g, 3.43 mmol) in CH_2Cl_2 (30 mL) was added the Dess-Martin periodinane (1.60 g, 3.77 mmol). The reaction mixture was stirred at room temperature for 20 minutes and then saturated aqueous $Na_2S_2O_3$ was slowly added. 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 afford aldehyde **43** 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 198.57 (CH), 175.30 (C), 149.63 (C), 136.12 (C), 135.49 (C), 124.61 (CH), 123.16 (CH), 122.62 (CH), 118.78 (CH), 117.25 (C), 115.34 (CH), 83.66 (C), 66.10 (CH), 42.56 (CH_2), 29.28 (CH_2), 28.23 (CH_3, 3C), 23.34 (CH_2), 19.39 (CH_2).

(*S*)-*tert*-Butyl 3-(2-(2-(2,2-Dibromovinyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (44)



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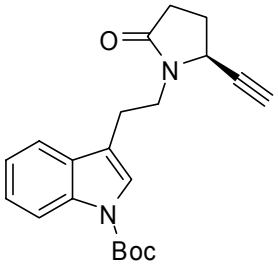
Triphenylphosphine (1.91 g, 7.29 mmol) was added at 0ºC to a solution of carbon tetrabromide (1.21 g, 3.65 mmol) in CH_2Cl_2 (30 mL). At the same temperature, aldehyde **43** (650 mg, 1.82 mmol) dissolved in CH_2Cl_2 (10 mL), was dropped slowly into the reaction mixture and then it was stirred at room temperature for 10 minutes. After extractive workup (CH_2Cl_2) and chromatography (2:1 hexane-EtOAc) **44** was obtained as a light yellow oil (420 mg, 45%): $[\alpha]_D$ = 37.5 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1H), 7.27-7.23 (m, 1H), 6.22 (d, *J* = 8.9 Hz, 1H), 4.26 (ddd, *J* = 8.9, 8.0, 5.3 Hz, 1H), 3.81 (ddd, *J* = 13.9, 8.9, 6.1 Hz, 1H), 3.23 (ddd, *J* = 13.8, 8.6, 6.2 Hz, 1H), 3.00 (dddd, *J* = 14.3, 8.9, 6.1, 0.8 Hz, 1H), 2.88 (dddd, *J* = 14.3, 8.7, 6.1, 0.8 Hz, 1H), 2.48-2.33 (m, 2H), 2.26-2.16 (m, 1H), 1.76-1.69 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.75 (C), 149.68 (C), 137.58 (CH), 135.50 (C), 130.42 (C), 124.52 (CH), 123.28 (CH), 122.60 (CH), 118.87 (CH), 117.44 (C), 115.33 (CH), 92.98 (C), 83.56 (C), 60.73 (CH), 41.66 (CH_2), 29.92 (CH_2), 28.25 (CH_3, 3C), 24.20 (CH_2), 23.32 (CH_2). HRMS-ESI *m/z* calcd for $C_{21}H_{24}N_2O_3NaBr_2$: 533.0051; found: 533.0070 [M^++Na].

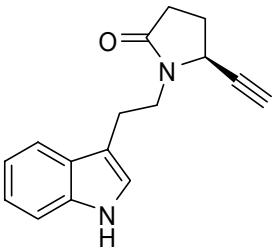
(*S*)-*tert*-Butyl 3-(2-(2-Ethynyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate (45)



To a solution of **44** (100 mg, 0.19 mmol) in THF (5 mL) at -78ºC was added *n*-BuLi (0.41 mmol). The reaction was kept at this temperature for 1 h, then it was quenched with MeOH and it was allowed to warm up to room temperature overnight. After extractive workup (EtOAc), the residue was purified by chromatography (2:1 hexane-EtOAc) to give **45** as a colorless oil (25 mg, 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),

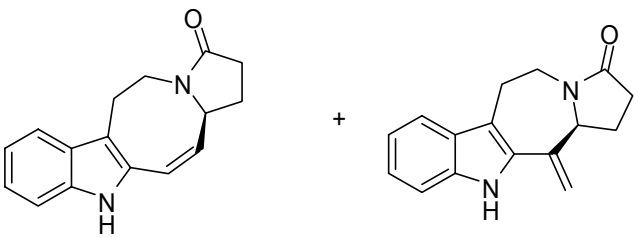
1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.21 (C), 149.71 (C), 135.50 (C), 130.43 (C), 124.46 (CH), 123.11 (CH), 122.50 (CH), 118.91 (CH), 117.53 (C), 115.28 (CH), 83.52 (C), 81.60 (CH), 73.51 (C), 49.47 (CH), 41.14 (CH_2), 29.86 (CH_2), 28.24 (CH_3, 3C), 26.30 (CH_2), 23.14 (CH_2). HRMS-ESI *m/z* calcd for $C_{21}H_{24}N_2O_3Na$: 375.1685; found: 375.1686 [M^++Na].

(*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-5-ethynylpyrrolidin-2-one (46)



A solution of **45** (90 mg, 0.25 mmol) in TFA/CH_2Cl_2 (2/0.5 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. Compound **46** was obtained as a colorless oil (50 mg, 78%): $[\alpha]_D$ = -20.2 (c = 0.9, $CHCl_3$). ^{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 174.28 (C), 136.24 (C), 127.48 (C), 122.08 (CH), 121.82 (CH), 119.39 (CH), 118.69 (CH), 112.90 (C), 111.15 (CH), 81.65 (C), 73.37 (CH), 49.30 (CH), 41.45 (CH_2), 29.95 (CH_2), 26.22 (CH_2), 23.13 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1168 [M^++Na].

Compound 47 and Compound 48



To a solution of **46** (45 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added $AuCl_3$ (3 mg, 0.008 mmol) and the mixture was stirred at room temperature for 16 hours. The

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residue was purified by chromatography (2:1 hexane-EtOAc) to give an isomer 7:1 mixture of **47** and **48** (25 mg, 55%)**.** The mixture 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 **48**; 16.35 min, compound **47**.

Compound 47: $[\alpha]_D$ = 478.5 (c = 0.5, $CHCl_3$). ^{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 174.08 (C), 136.11 (C), 131.13 (CH), 129.73 (C), 128.59 (C), 124.58 (CH), 123.12 (CH), 119.81 (CH), 118.65 (CH), 113.57 (C), 110.57 (CH), 56.36 (CH), 37.82 (CH_2), 30.43 (CH_2), 29.70 (CH_2), 26.28 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1164 [M^++Na].

Compound 48: ^{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 (100 MHz, $CDCl_3$, DEPT) δ 174.30 (C), 160.93 (C), 142.17 (C), 135.85 (C), 128.85 (C), 123.34 (CH), 119.91 (CH), 119.07 (CH_2), 113.24 (C), 112.85 (CH), 110.55 (CH), 65.15 (CH), 39.78 (CH_2), 30.90 (CH_2), 27.93 (CH_2), 25.12 (CH_2). HRMS-ESI *m/z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1156 [M^++Na].

3. X-Ray Structure of Dimer 27

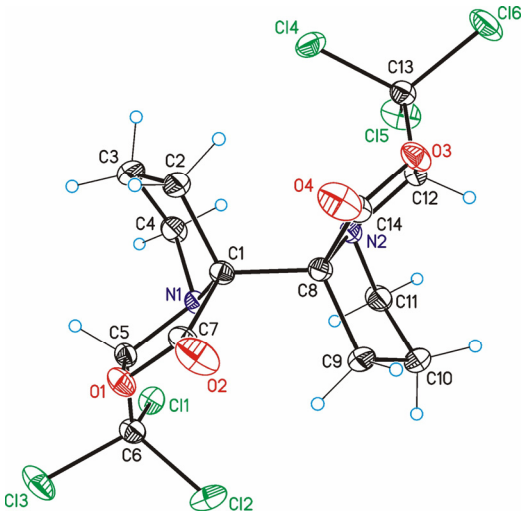

Table 1. Crystal data and structure refinement for **27**.

Empirical formula	C7 H7 Cl3 N O2	
Formula weight	243.49	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.6043(4) Å	α= 90°.
	b = 13.3378(5) Å	β= 90°.
	c = 14.8580(6) Å	γ = 90°.
Volume	1903.31(13) $Å^3$	
Z	8	
Density (calculated)	1.699 Mg/m^3	
Absorption coefficient	0.926 mm^{-1}	
F(000)	984	
Crystal size	0.30 x 0.10 x 0.03 mm^3	
Theta range for data collection	2.95 to 39.47°.	
Index ranges	-7<=h<=16, -23<=k<=23, -26<=l<=26	
Reflections collected	39128	
Independent reflections	10349 [R(int) = 0.0426]	
Completeness to theta = 39.47°	96.7 %	
Absorption correction	SADABS (Bruker-Nonius)	
Max. and min. transmission	0.9727 and 0.7686	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10349 / 0 / 235	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0795	
R indices (all data)	R1 = 0.0378, wR2 = 0.0827	
Absolute structure parameter	-0.01(3)	
Largest diff. peak and hole	0.720 and -0.319 $e.Å^{-3}$	

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Table 2. Bond lengths [Å] and angles [°] for **27**.

Cl(1)-C(6)	1.7622(10)	N(1)-C(1)-C(7)	103.01(7)
N(1)-C(5)	1.4583(12)	N(1)-C(1)-C(8)	110.16(8)
N(1)-C(1)	1.4760(12)	C(7)-C(1)-C(8)	112.67(9)
N(1)-C(4)	1.4841(14)	N(1)-C(1)-C(2)	106.35(9)
C(1)-C(7)	1.5216(13)	C(7)-C(1)-C(2)	108.91(9)
C(1)-C(8)	1.5546(15)	C(8)-C(1)-C(2)	114.90(8)
C(1)-C(2)	1.5665(17)	C(7)-O(1)-C(5)	110.49(7)
O(1)-C(7)	1.3709(13)	C(12)-N(2)-C(11)	112.98(9)
O(1)-C(5)	1.4229(12)	C(12)-N(2)-C(8)	107.60(7)
Cl(2)-C(6)	1.7576(13)	C(11)-N(2)-C(8)	106.91(8)
N(2)-C(12)	1.4517(12)	C(3)-C(2)-C(1)	105.14(9)
N(2)-C(11)	1.4809(16)	C(4)-C(3)-C(2)	103.55(10)
N(2)-C(8)	1.4826(12)	C(14)-O(3)-C(12)	110.51(8)
C(2)-C(3)	1.5393(18)	N(1)-C(4)-C(3)	104.83(9)
O(2)-C(7)	1.1954(13)	O(1)-C(5)-N(1)	107.43(7)
Cl(3)-C(6)	1.7833(11)	O(1)-C(5)-C(6)	107.43(8)
C(3)-C(4)	1.527(2)	N(1)-C(5)-C(6)	112.97(9)
O(3)-C(14)	1.3627(14)	C(5)-C(6)-Cl(2)	111.69(7)
O(3)-C(12)	1.4232(13)	C(5)-C(6)-Cl(1)	109.34(7)
Cl(4)-C(13)	1.7676(13)	Cl(2)-C(6)-Cl(1)	109.78(6)
O(4)-C(14)	1.1994(14)	C(5)-C(6)-Cl(3)	107.92(8)
Cl(5)-C(13)	1.7567(11)	Cl(2)-C(6)-Cl(3)	108.90(6)
C(5)-C(6)	1.5496(15)	Cl(1)-C(6)-Cl(3)	109.15(6)
Cl(6)-C(13)	1.7732(11)	O(2)-C(7)-O(1)	121.53(9)
C(8)-C(14)	1.5177(14)	O(2)-C(7)-C(1)	130.17(10)
C(8)-C(9)	1.5666(16)	O(1)-C(7)-C(1)	108.22(8)
C(9)-C(10)	1.531(2)	N(2)-C(8)-C(14)	102.73(7)
C(10)-C(11)	1.534(2)	N(2)-C(8)-C(1)	111.63(8)
C(12)-C(13)	1.5533(15)	C(14)-C(8)-C(1)	111.65(9)
C(5)-N(1)-C(1)	106.70(7)	N(2)-C(8)-C(9)	106.11(9)
C(5)-N(1)-C(4)	112.07(9)	C(14)-C(8)-C(9)	111.51(9)
C(1)-N(1)-C(4)	105.79(8)	C(1)-C(8)-C(9)	112.65(8)

C(10)-C(9)-C(8)	105.29(9)	Cl(5)-C(13)-Cl(4)	108.82(6)
C(9)-C(10)-C(11)	103.17(11)	C(12)-C(13)-Cl(6)	108.58(7)
N(2)-C(11)-C(10)	104.51(10)	Cl(5)-C(13)-Cl(6)	109.71(6)
O(3)-C(12)-N(2)	107.54(8)	Cl(4)-C(13)-Cl(6)	109.10(6)
O(3)-C(12)-C(13)	107.27(9)	O(4)-C(14)-O(3)	121.10(10)
N(2)-C(12)-C(13)	112.90(9)	O(4)-C(14)-C(8)	129.58(10)
C(12)-C(13)-Cl(5)	109.04(8)	O(3)-C(14)-C(8)	109.31(9)
C(12)-C(13)-Cl(4)	111.58(8)		

Symmetry transformations used to generate equivalent atoms.

Table 3. Torsion angles [°] for **27**.

C(5)-N(1)-C(1)-C(7)	20.24(12)
C(4)-N(1)-C(1)-C(7)	139.75(10)
C(5)-N(1)-C(1)-C(8)	140.65(8)
C(4)-N(1)-C(1)-C(8)	-99.85(10)
C(5)-N(1)-C(1)-C(2)	-94.24(9)
C(4)-N(1)-C(1)-C(2)	25.26(11)
N(1)-C(1)-C(2)-C(3)	-3.07(11)
C(7)-C(1)-C(2)-C(3)	-113.46(10)
C(8)-C(1)-C(2)-C(3)	119.08(10)
C(1)-C(2)-C(3)-C(4)	-19.39(11)
C(5)-N(1)-C(4)-C(3)	77.72(10)
C(1)-N(1)-C(4)-C(3)	-38.19(11)
C(2)-C(3)-C(4)-N(1)	35.30(11)
C(7)-O(1)-C(5)-N(1)	5.88(13)
C(7)-O(1)-C(5)-C(6)	127.72(10)
C(1)-N(1)-C(5)-O(1)	-16.90(12)
C(4)-N(1)-C(5)-O(1)	-132.25(10)
C(1)-N(1)-C(5)-C(6)	-135.20(9)
C(4)-N(1)-C(5)-C(6)	109.45(11)
O(1)-C(5)-C(6)-Cl(2)	-49.18(10)
N(1)-C(5)-C(6)-Cl(2)	69.13(9)
O(1)-C(5)-C(6)-Cl(1)	-170.90(7)
N(1)-C(5)-C(6)-Cl(1)	-52.59(11)
O(1)-C(5)-C(6)-Cl(3)	70.49(10)

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N(1)-C(5)-C(6)-Cl(3)	-171.20(7)
C(5)-O(1)-C(7)-O(2)	-175.60(13)
C(5)-O(1)-C(7)-C(1)	7.28(14)
N(1)-C(1)-C(7)-O(2)	166.08(15)
C(8)-C(1)-C(7)-O(2)	47.41(19)
C(2)-C(1)-C(7)-O(2)	-81.30(18)
N(1)-C(1)-C(7)-O(1)	-17.13(13)
C(8)-C(1)-C(7)-O(1)	-135.80(10)
C(2)-C(1)-C(7)-O(1)	95.49(11)
C(12)-N(2)-C(8)-C(14)	15.13(12)
C(11)-N(2)-C(8)-C(14)	136.77(10)
C(12)-N(2)-C(8)-C(1)	134.89(9)
C(11)-N(2)-C(8)-C(1)	-103.47(10)
C(12)-N(2)-C(8)-C(9)	-102.03(9)
C(11)-N(2)-C(8)-C(9)	19.61(10)
N(1)-C(1)-C(8)-N(2)	45.73(10)
C(7)-C(1)-C(8)-N(2)	160.13(8)
C(2)-C(1)-C(8)-N(2)	-74.34(10)
N(1)-C(1)-C(8)-C(14)	160.09(8)
C(7)-C(1)-C(8)-C(14)	-85.51(10)
C(2)-C(1)-C(8)-C(14)	40.02(11)
N(1)-C(1)-C(8)-C(9)	-73.54(10)
C(7)-C(1)-C(8)-C(9)	40.86(11)
C(2)-C(1)-C(8)-C(9)	166.40(9)
N(2)-C(8)-C(9)-C(10)	3.76(11)
C(14)-C(8)-C(9)-C(10)	-107.37(11)
C(1)-C(8)-C(9)-C(10)	126.18(10)
C(8)-C(9)-C(10)-C(11)	-24.49(11)
C(12)-N(2)-C(11)-C(10)	82.62(10)
C(8)-N(2)-C(11)-C(10)	-35.56(11)
C(9)-C(10)-C(11)-N(2)	36.92(11)
C(14)-O(3)-C(12)-N(2)	5.33(13)
C(14)-O(3)-C(12)-C(13)	127.04(10)
C(11)-N(2)-C(12)-O(3)	-130.99(10)
C(8)-N(2)-C(12)-O(3)	-13.21(12)
C(11)-N(2)-C(12)-C(13)	110.88(11)
C(8)-N(2)-C(12)-C(13)	-131.35(10)
O(3)-C(12)-C(13)-Cl(5)	-178.74(7)

N(2)-C(12)-C(13)-Cl(5)	-60.45(11)
O(3)-C(12)-C(13)-Cl(4)	-58.52(10)
N(2)-C(12)-C(13)-Cl(4)	59.77(11)
O(3)-C(12)-C(13)-Cl(6)	61.76(10)
N(2)-C(12)-C(13)-Cl(6)	-179.95(8)
C(12)-O(3)-C(14)-O(4)	-175.88(13)
C(12)-O(3)-C(14)-C(8)	4.60(14)
N(2)-C(8)-C(14)-O(4)	168.29(14)
C(1)-C(8)-C(14)-O(4)	48.54(18)
C(9)-C(8)-C(14)-O(4)	-78.45(18)
N(2)-C(8)-C(14)-O(3)	-12.24(13)
C(1)-C(8)-C(14)-O(3)	-131.99(10)
C(9)-C(8)-C(14)-O(3)	101.01(11)

Symmetry transformations used to generate equivalent atoms.

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Chapter 3. Introduction

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1. Cycloisomerization of 1,6-Enynes

The transition metal catalyzed enyne cycloisomerization is among the most important strategies for the synthesis of functionalized carbo- and heterocyclic structures.[1] From a wide range of transition metal complexes capable of catalyzing this reaction, gold and platinum complexes are particularly powerful as they can lead to a diverse range of cyclic products under mild conditions and with excellent chemoselectivity.[2]

Some different types of products obtained in the cycloisomerization of 1,6-enynes are shown in Figure 1. The diversity of cyclic structural motifs that can be efficiently accessed from a common enyne precursor **1** is remarkable.

1 For reviews see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067-2096. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1-16. (c) Lloyd- Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215-236. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813-834. (e) Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405-2412. (f) Ojima, I.; Tzamarioudaki, M.; Li, Z. Y. R.; Donovan, J. *Chem. Rev.* **1996**, *96*, 635-662. (g) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev*. **2004**, *33*, 431-436.

2 For reviews see: (a) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 200-203. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.-Eur. J.* **2006**, *11*, 5916-5923. (c) Zhang, L.; Sunm, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271-2296.

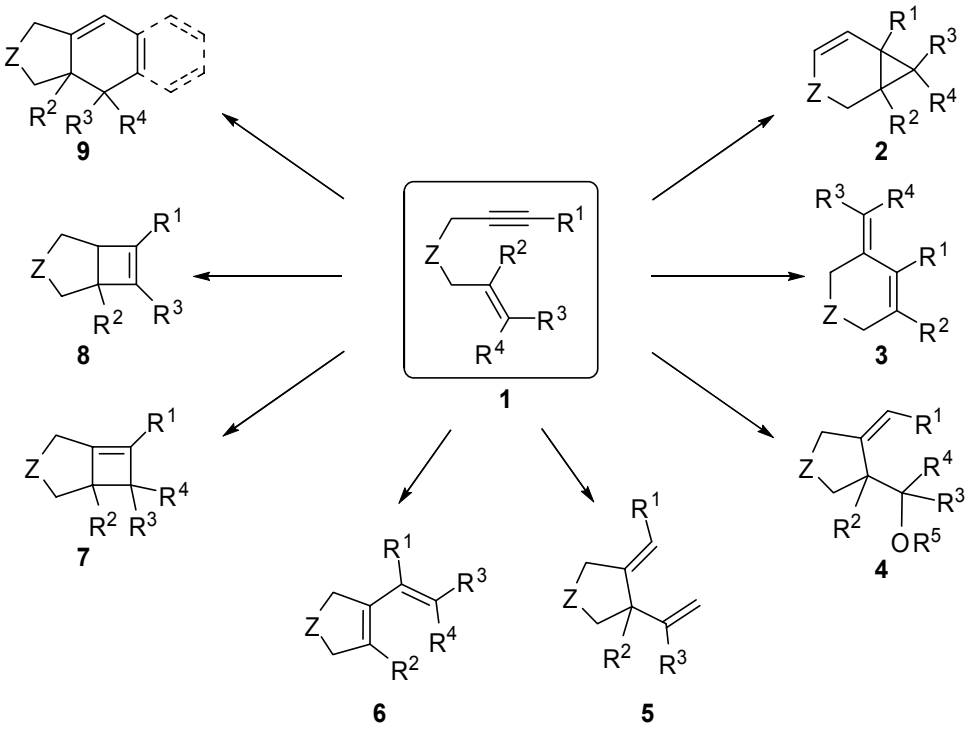

Figure 1

This reaction can furnish the six-membered carbocyclic or heterocyclic products **2** and **3**. In the presence of a nucleophile, compounds of type **4** are obtained in a hydroxy- or alkoxycyclization process. Alternatively, the cycloisomerization provides an efficient access to five-membered dienes **5** when the reaction is an Alder-ene-type,[3,4] or **6** in the so-called skeletal rearrangement.[5] Highly strained bicyclo[3.2.0]alkenes **7** or

3 Pd: (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781-1783. (b) Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887-4890. (c) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053-6054. (d) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268-5270. (e) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. S.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636-644. (f) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc*. **1994**, *116*, 4255-4267.

4 Cycloisomerization with other metals: Co: (a) Kraft, M. E.; Wilson, A. M.; Dasse, O. A.; Bonaga, L. V. R.; Cheung, Y. Y.; Fu, Z.; Shao, B.; Scott, I. L. *Tetrahedron Lett.* **1998**, *39*, 5911-5914. (b) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem*. **1996**, *61*, 2699-2708 and references therein. (c) Buisine, O.; Aubert, C.; Malacria, M. *Chem. Eur. J.* **2001**, *7*, 3517-3525. Ti: (d) Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976-1977. Ru: (e) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714-715. Rh: (f) Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* **2000**, *39,* 4104-4106.

5 (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050. (b) Chatani, N.; Furukawa. N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901-903. (c)

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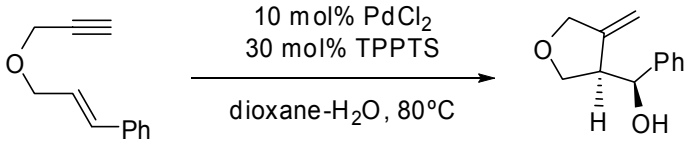
8 can also be obtained as a result of this transformation.[6] Incorporation of arene and alkene groups at the terminal alkyne position (R^1) provides access to bicyclic and tricyclic products **9** as a result of a formal [4+2] cycloaddition.[7] The substitution pattern of the starting enyne, as well as the catalyst, influences significantly the outcome of the cycloisomerization process.

Formation of compounds of type **2**, **3**, and **4** will be discussed in more detail in this introduction.

1.1 Hydroxy- and alkoxycyclization reactions: metal cyclopropyl carbenes

Genêt and coworkers were the first to report the Pd(II)-catalyzed enyne alkoxycyclization in the presence of the water-soluble phosphine TPPTS (*m*-sulfonated triphenyl phosphine).[8] Five-membered rings with a hydroxyl group were obtained as a result of a *5-exo-dig* cyclization, in a homogeneous mixture of dioxane and water (Scheme 1). The authors proposed a mechanism based on Pd(0)-Pd(II) intermediates, invoking alkyne hydropalladation, and proposed the configuration shown in Scheme 1 based on this mechanism.[8a]



Scheme 1

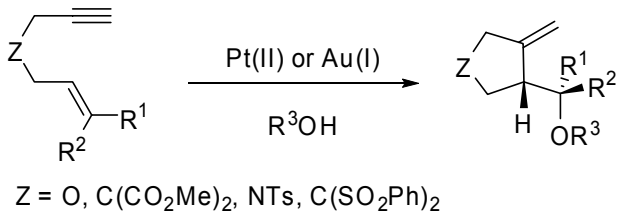
Chatani, N.; Kataoka. K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105. (d) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294-10295. (e) Ho-Oh, C.; Youn-Bang, S.; Yun-Rhim, C. *Bull. Korean Chem. Soc.* **2003**, *24*, 887-888. (f) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

6 (a) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294-5295. (b) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, *8*, 824-832. (c) 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. (d) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244-8245.

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

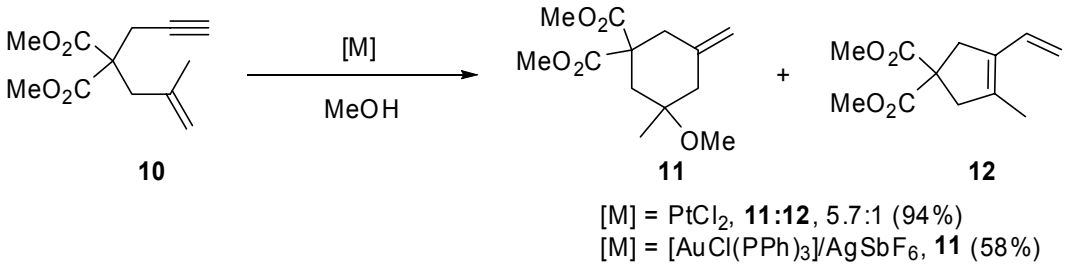
8 (a) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 8695-8698. (b) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 5137-5148.

A similar reaction was developed in our group catalyzed by Pt(II)[9] and Au(I)[5f,10] (Scheme 2).



Scheme 2

In some cases, instead of a five-membered ring, a six-membered ring was obtained as a result of a 6-*exo-dig* process (Scheme 3). Thus, when enyne **10** was treated with $PtCl_2$ in the presence of MeOH, carbocycle **11** was obtained as the major product, along with diene **12**. When the reaction was carried out with a gold(I) catalyst, **11** was the only product obtained.



Scheme 3

During the study of this reaction, a mechanistic proposal was made based on DFT calculations and experimental data (Scheme 4). The key step in this cyclization is the coordination of the metal to the alkyne affording the corresponding (η^2-alkyne)metal complex **13**. This coordination favours the nucleophilic attack of the

9 (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549-11550. (b) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511-10520. (c) Muñoz, M. P.; Méndez, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Synthesis* **2003**, 2898-2902.

5 (f) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

10 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.

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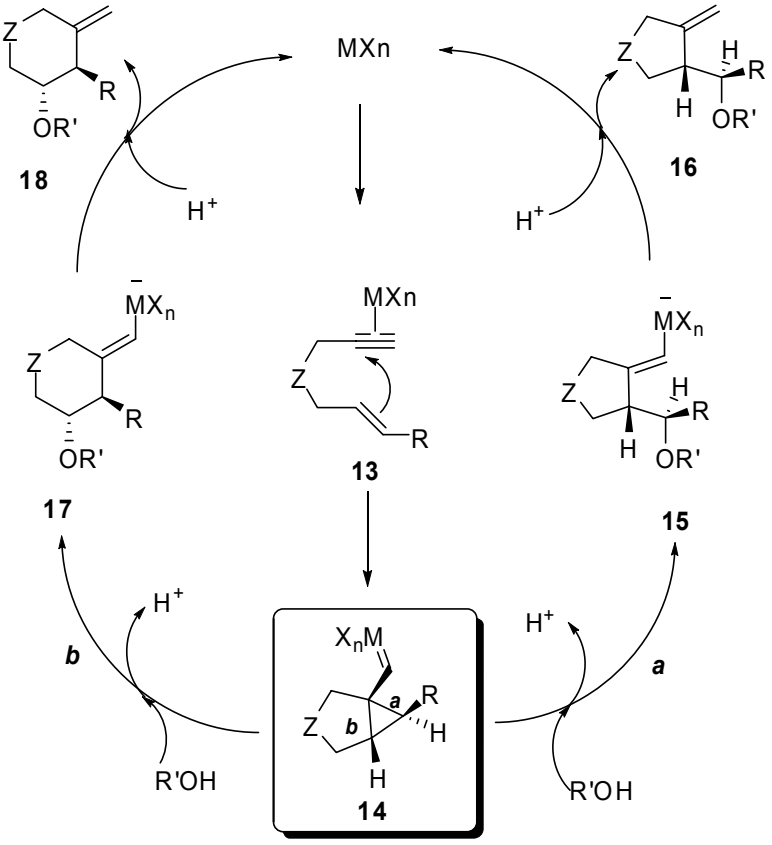
alkene to form the metal cyclopropyl carbene **14**. This intermediate can suffer the nucleophilic attack of the solvent at position *a*, giving rise to **15**. Subsequent demetalation gives five-membered ring **16**. Alternatively, when the attack of the nucleophile occurs at position *b* intermediate **17** is formed, which after demetalation affords six-membered ring **18**.



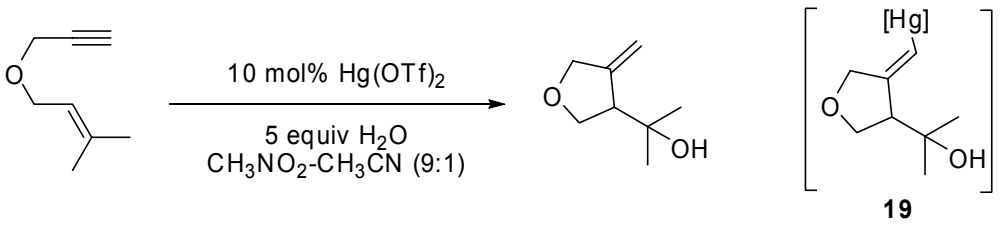
Scheme 4

In a collaboration between the group of Genêt and our group it was concluded that the hydroxycyclization reaction that was proposed to be catalyzed by Pd(0) was actually catalyzed by Pd(II) and involves the same type of cyclopropyl carbene intermediates.[11] In addition, the configuration of the hydroxycyclized compounds, originally misassigned by Genêt,[8a] was corrected.

11 Nevado, C.; Charrualult, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz. M. P.; Méndez, M.; Rager, M. -N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706-713.

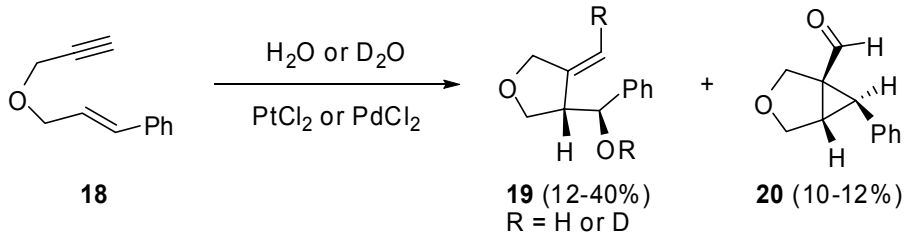
8 (a) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 8695-8698.

Nishizawa and coworkers reported the hydroxycyclization of 1,6-enynes using $Hg(OTf)_2$ as catalyst. Vinyl mercury **19** was proposed as the key intermediate for this process (Scheme 5).[12]



Scheme 5

Cyclopropyl derivatives have been obtained as secondary products in hydroxycyclization reactions of enynes. Thus, reaction of cinnamyl propargyl ether **18** using $PtCl_2$ or $PdCl_2$ as catalyst leads to cyclopropane **20**, in addition to the expected alcohol **19** (Scheme 6).[11]



Scheme 6

These results support the involvement of **14** (Scheme 4) as the actual intermediate in the intramolecular reaction of alkenes with alkynes catalyzed by electrophilic MX_n. Additional support was obtained by the group of Murai in the cyclization of **21** to give tetracycle **22**, in which a Ru-carbene is intramolecularly trapped by the terminal alkene (Scheme 7).[13] Geranyl derivatives such as **23** also yield tetracycles **24** using Au(I) cationic complexes.[5f,14]

12 Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609-1611.

11 Nevado, C.; Charrualult, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz. M. P.; Méndez, M.; Rager, M. -N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706-713.

13 Chatani, N.; Kataoka, K.; Sakurai, H.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105.

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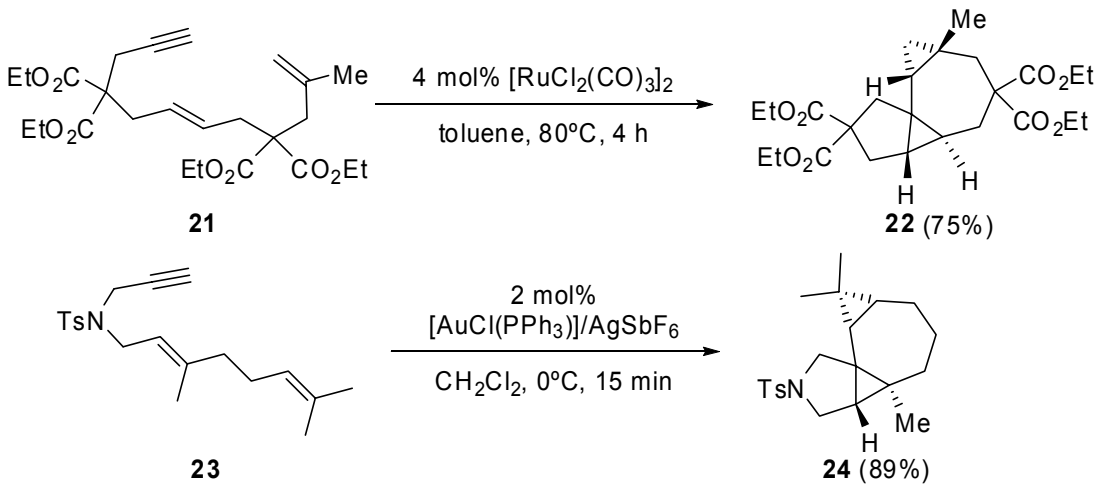
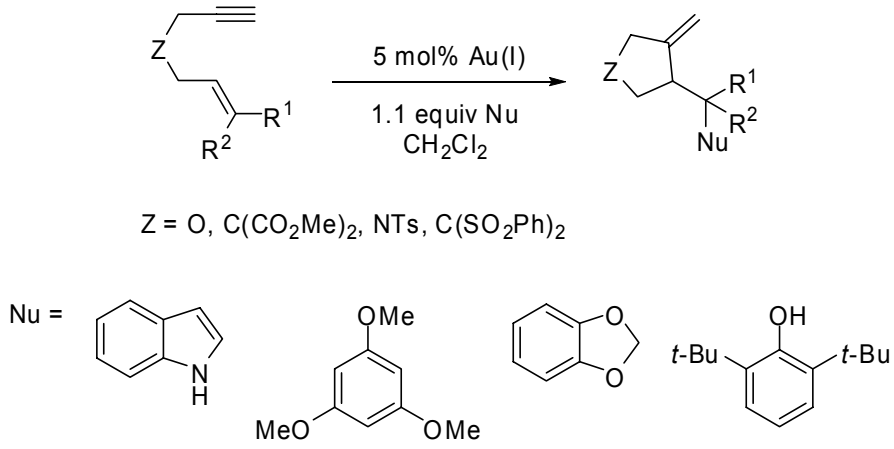


21 **22** (75%)

23 **24** (89%)

Scheme 7

Recently, the attack of electron-rich arenes and heteroarenes to the cyclopropyl metal carbene **14** giving rise to C-C bond formation has been described almost simultaneously by the group of Genêt and by our group (Scheme 8).[15]



Scheme 8

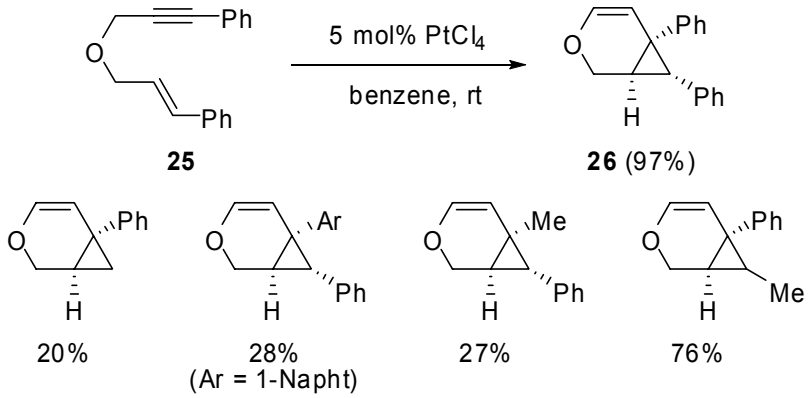
5 (f) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

14 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.

15 (a) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698-700. (b) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt J.-P.; Michelet, V. *Angew. Chem. Int. Ed*. **2006**, *45*, 7427-7430.

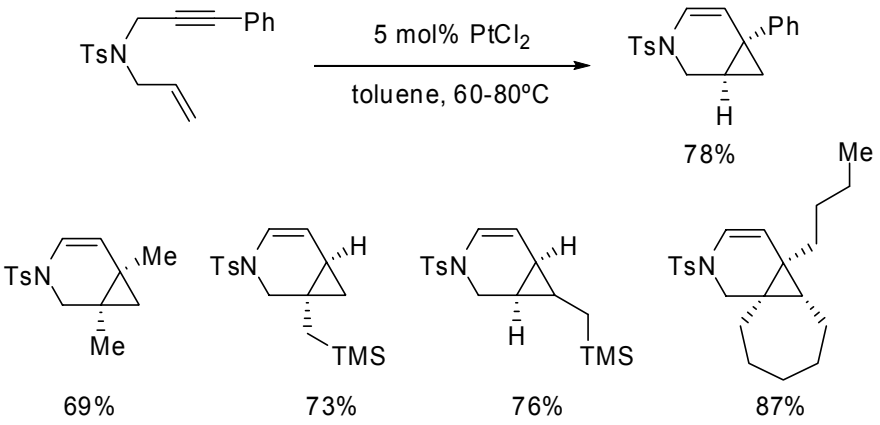
1.2 Formation of bicyclo[4.1.0]heptenes

In 1995, Blum and coworkers reported that treatment of enyne **25** with 5 mol% of $PtCl_4$ resulted in the formation of oxabicyclo[4.1.0]heptene **26** (Scheme 9).[16] The product was obtained as a single diastereomer. Yields, however, were rather low in most of the examples.



Scheme 9

Later on, the group of Fürstner found that treatment of enyne-containing sulfonamides in the presence of a catalytic amount of $PtCl_2$ at elevated temperature resulted in the assembly of the corresponding azabicyclo[4.1.0]heptenes (Scheme 10).[17] Mono-, di-, and tri-substituted alkenes efficiently participated in this process.



Scheme 10

16 Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567-5569.

17 (a) Fürtsner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc*. **2000**, *122*, 6785-6786. (b) Fürstner, A.; Szillat, H.; Stelzer F. *J. Am. Chem. Soc*. **2001**, *123*, 11863-11869.

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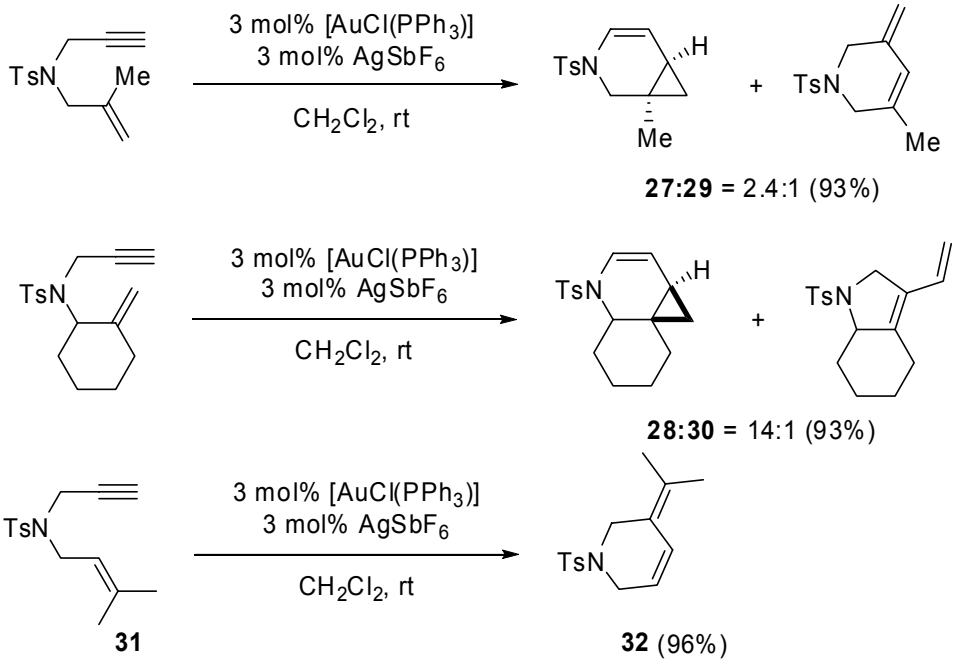
Our group has described two examples of gold-catalyzed formation of azabicyclo[4.1.0]heptenes **27** and **28**, in which the corresponding dienes **29** and **30** were obtained as minor products (Scheme 11).[5f] In the case of the enyne **31**, with a trisubstituted olefin, diene **32** was the only product obtained in the reaction. The mild reaction conditions and excellent efficiency of these reactions are noteworthy.

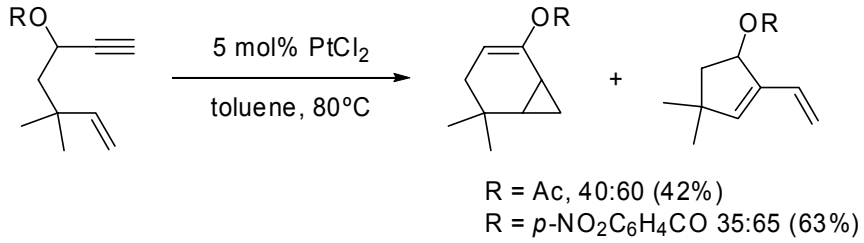


Scheme 11

Malacria extended this reaction to 1,6-enynes with carbon as tether, instead of oxygen or nitrogen, using Pt(II) as catalyst (Scheme 12).[18] The reaction only works when a gem-dimethyl is present in the molecule and a propargyl acetate, giving a mixture of rearrangement product and bicyclo[4.1.0]heptene, of which the bicyclic one is the minor product.

5 (f) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

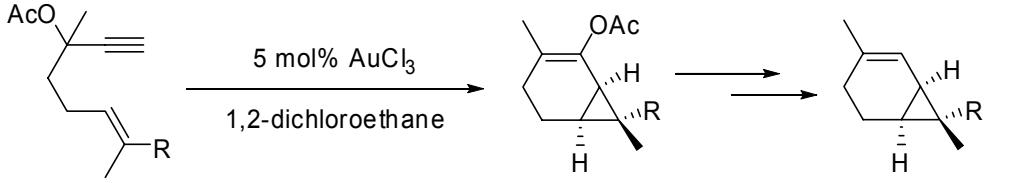
18 (a) Mainetti, E.; Mouries, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2132-2135. (b) Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745-9755. (c) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656-8657.



R = Ac, 40:60 (42%)
R = *p*-$NO_2C_6H_4CO$ 35:65 (63%)

Scheme 12

Fürstner and coworkers applied this methodology to the synthesis of carene terpenoids products using $AuCl_3$ as catalyst (Scheme 13).[19] Bicyclo[4.1.0] heptene was the only product obtained when gold was used as catalyst for this transformation.

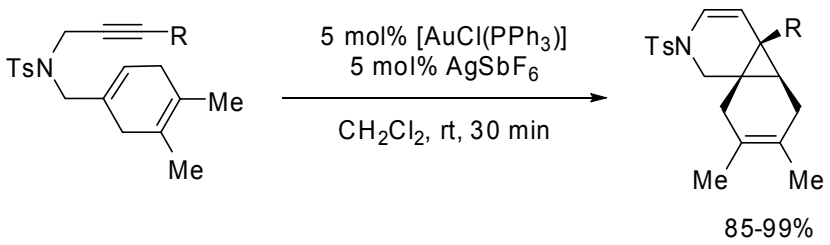


R = Me (99%)
R = $CH_2CH_2CH{=}C(CH_3)_2$ (87%)

R = Me, (+)-carene
R = $CH_2CH_2CH{=}C(CH_3)_2$, (-)sesquicarene

Scheme 13

Gold(I)-catalyzed cyclization of enynes containing an olefinic cycle to give fused polycyclic compounds has been developed more recently by Chung and coworkers (Scheme 14).[20] They also found that when the reaction is catalyzed by $GaCl_3$ instead of Au(I), eight-membered rings are obtained.[21]



85-99%

Scheme 14

19 (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546-2547. (b) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006-3019.

20 Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Lett.* **2006**, *71*, 9366-9372.

21 Kim, S. M.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2006**, *8*, 5425-5427.

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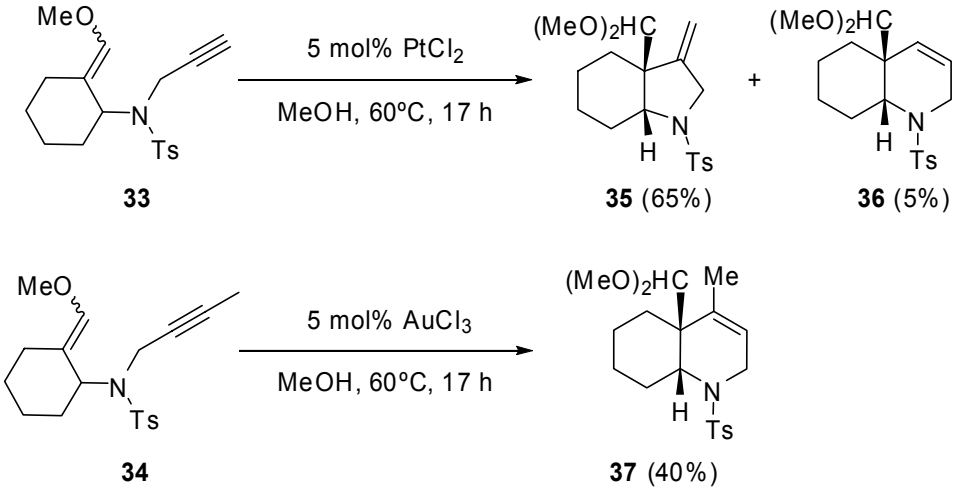
In our group, the formation of a new type of product in the methoxycyclization of enol ethers **33** and **34** has been described (Scheme 15).[22] The cyclization of **33** with $PtCl_2$ gave a mixture of acetals **35** and **36** in 70% yield. Interestingly, substrate **34** with a methyl substituent on the alkyne led selectively to *endo-dig* cyclization using $AuCl_3$ as catalyst. In this case, **37** was the only product isolated in 40% yield.



Scheme 15

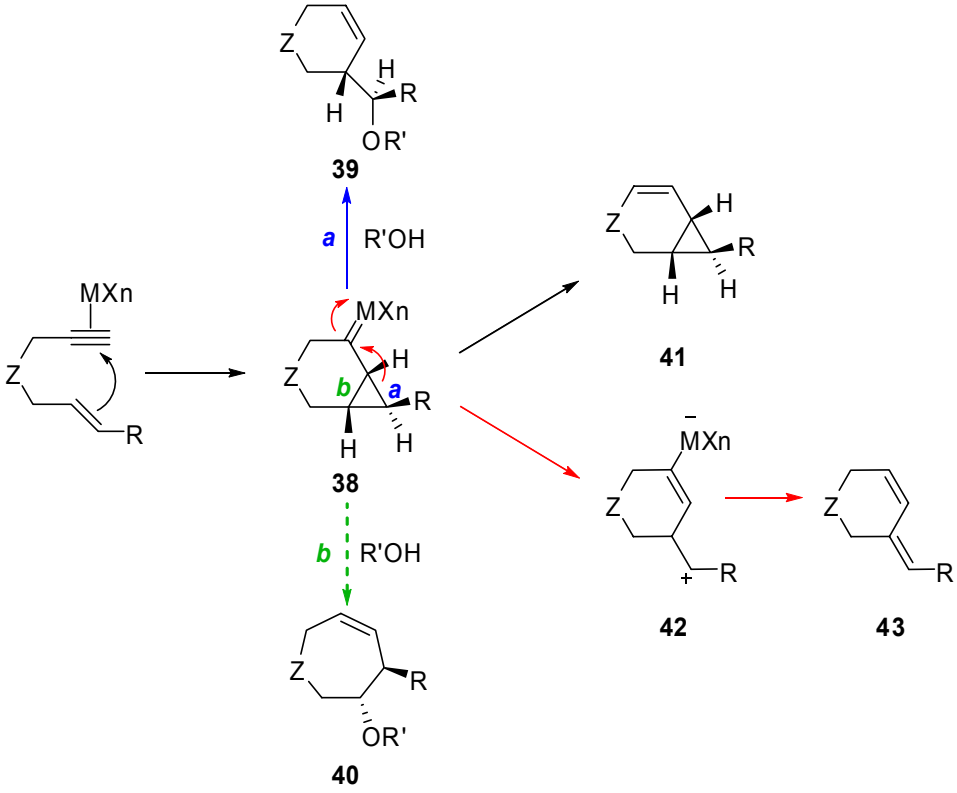
Octahydroquinolines **36** and **37** result from *endo* cyclization,[23] a type of reaction that has been found in the cyclization *ω*-acetylenic silyl enol ethers with $W(CO)_6$, from which tungsten vinylidene complexes were proposed as intermediates.[24] The formation of **37** from methyl substituted **34,** however, excludes the involvement of a similar platinum or gold vinylidene complex in the cyclization.

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

23 *Endo* cyclizations have been observed in the reaction of allyl silanes with alkynes catalyzed by the strong Lewis acid $HfCl_4$: (a) Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4874-4875. (b) Yoshikawa, E.; Gevorgyan, V.; Asao, N.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6781-6786. (c) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339-5340. (d) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071-1087. (e) Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123,* 10899-10902.

24 (a) Iwasawa, N.; Maeyama, K. *J. Org. Chem.* **1999**, *64*, 1344-1346. (b) Iwasawa, N.; Miura, T. *J. Am. Chem. Soc.* **2002**, *124*, 518-519.

A mechanism explaining the formation of these compounds (**36** and **37**), as well as the bicyclo[4.1.0]heptenes and the exocyclic dienes (Scheme 11) is depicted in Scheme 16.[22]



Scheme 16

Analogous to the mechanism proposed in Scheme 4, if attack of the double bond occurs at the terminal carbon of the alkyne instead of the internal carbon, cyclopropyl metal carbene intermediate **38** is formed. In the presence of a nucleophile this intermediate can suffer attack on carbon *a* giving rise to compound **39**, the same kind of compound **36** and **37** observed in Scheme 15. Attack of the nucleophile could also occur at carbon *b*, forming compounds of type **40**. This kind of reactivity, however, has not been described yet. Alternatively, β-hydrogen elimination from intermediate **38** yields bicyclo[4.1.0]heptenes **41**. Compound **38** could also evolve via **42**, which after loss of a proton and protodemetalation would form diene **43**.

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

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Chapter 3. Objectives

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CYCLIZATION OF INDOLES AND ENOL ETHERS WITH ALKYNES CATALYZED BY PLATINUM AND GOLD
Catalina Ferrer Llabrés
ISBN:978-84-691-1870-2 / D.L.: T.304-2008

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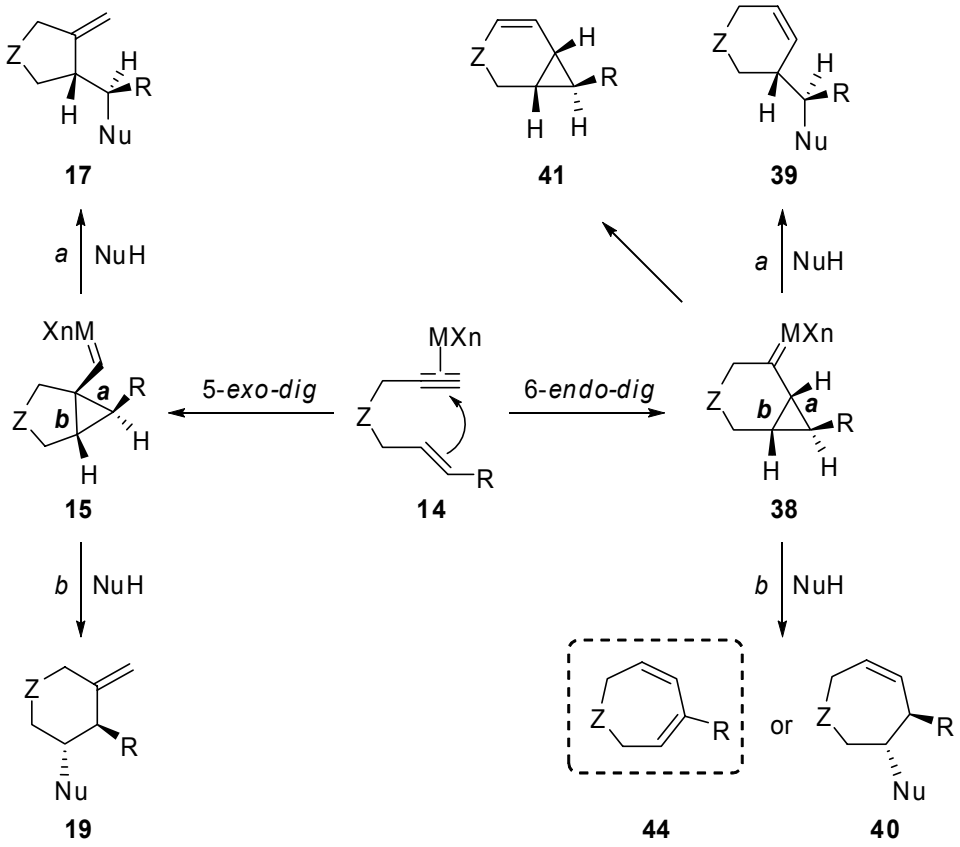
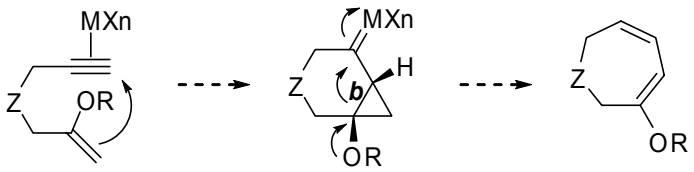
The general mechanistic scheme of metal-catalyzed reactions between alkynes and alkenes has been demonstrated in the context of 1,6-enyne cyclization. Herein, two general manifolds upon coordination of the metal fragment to the alkyne, have been identified: a 5-*exo-dig* via cyclopropyl metal carbenes **15** to give products **17** or **19**, and the relatively less common 6-*endo-dig* cyclization via **38** (Scheme 17). Intermediate **38** can evolve to give cyclopropanes **41**, addition products **39**, or the corresponding *endo* skeletal rearrangement derivatives **44**. However, formation of seven-membered ring compounds **40** or **44** from **38** by cleavage of bond *b* has not been observed before this work.



Scheme 17

The objective of this part of the Thesis was to study the intramolecular reaction of enol ethers with alkynes catalyzed by gold and platinum complexes. In particular, we expected that in compounds of type **45** (Scheme 18) the presence of a OR group would allow the cleavage of bond *b* via intermediate **46** to form seven-membered rings **40** or **44**.



45 **46**

Scheme 18

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Chapter 3. Results and discussion

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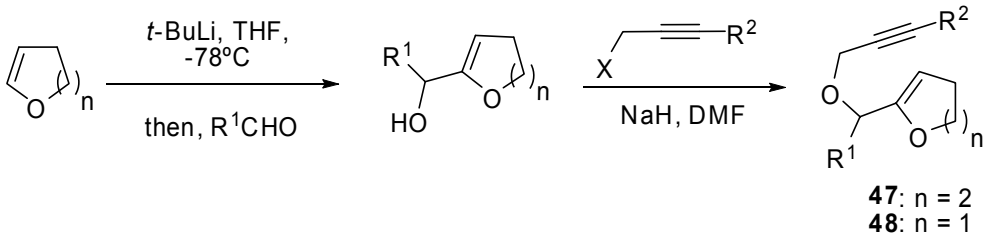
1. Reactions of Enol Ethers with Alkynes Catalyzed by Gold(I) and Platinum(II)[25,26]

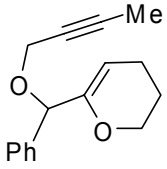
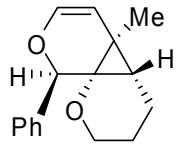
Enynes **47** and **48** are readily available substrates that are assembled in a modular way in two steps by the addition of α-lithiated enol ethers to aldehydes, followed by propargylation of the resulting secondary alcohols (Scheme 19).



Scheme 19

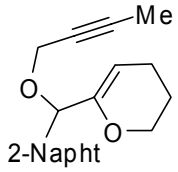
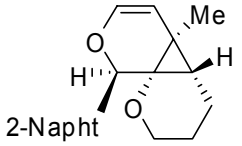
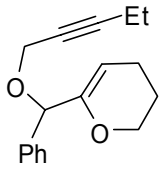
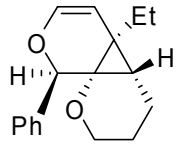
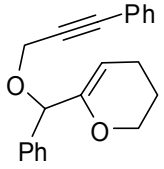
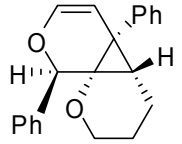
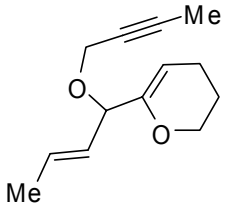
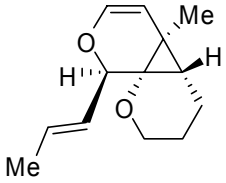
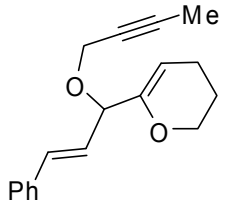
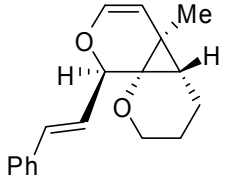
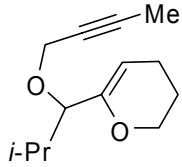
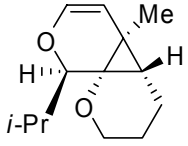
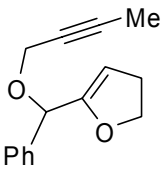
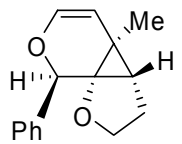
Cyclization of **47-48** was cleanly carried out with 5 mol% $PtCl_2$ in toluene to give bicyclo[4.1.0]heptenes **49-50** (Table 1). No skeletal rearrangement was observed under these conditions. Although the cyclizations were performed routinely in toluene at 80°C, some of these reactions also proceed at much lower temperatures (0-50°C, Table 1, entries 2, 3, 6, and 8), what proved to be particularly convenient for substrates such as **47f** that decomposed at higher temperatures.

Table 1. Cyclization of enynes **47** and **48** catalyzed by $PtCl_2$.[a]

Entry	Enyne	T (°C)	t (h)	Product (yield)
1	 **47a**	80	6	 **49a** (84%)

25 Taken from: Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 31391-3194 and Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

26 This work has been done in collaboration with Cristina Nevado (UAM, 2003-2004) and Mihai Raducan (ICIQ, 2006-2007).

Entry	Enyne	T (°C)	t (h)	Product (yield)
2	 **47b**	50	2	 **49b** (97%)
3	 **47c**	45	4	 **49c** (79%)
4	 **47d**	80	12	 **49d** (72%)
5	 **47e**	80	48	 **49e** (52%)
6	 **47f**	0	17	 **49f** (61%)
7	 **47g**	80	4	 **49g** (74%)
8	 **48a**	50	24	 **50a** (58%)

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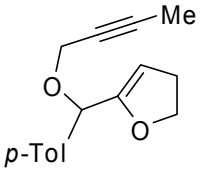
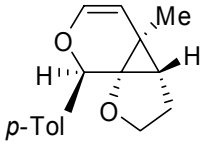
Entry	Enyne	T (°C)	t (h)	Product (yield)
9	 **48b**	80	1	 **50b** (70%)

(a) Reactions carried out with 5 mol% of $PtCl_2$ in toluene.

The reactions of **47-48** proceeded with total regiocontrol by 6-*endo-dig* cyclization, as a result of the terminal substitution at the alkyne and the electronegative character of the tether. In addition, these reactions are highly stereoselective. Thus, in all cases a single stereoisomer was isolated. The configuration of cyclopropane derivatives **49-50** was assigned by ^{1}H-NMR and by X-ray diffraction of **49b** (Figure 2).

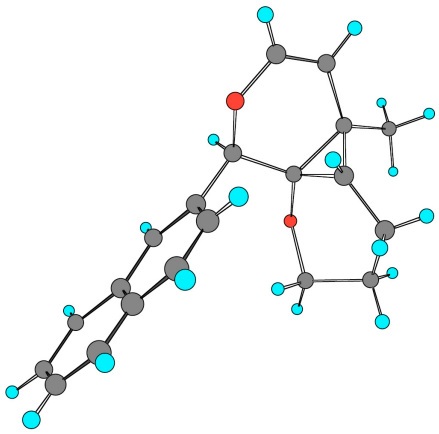
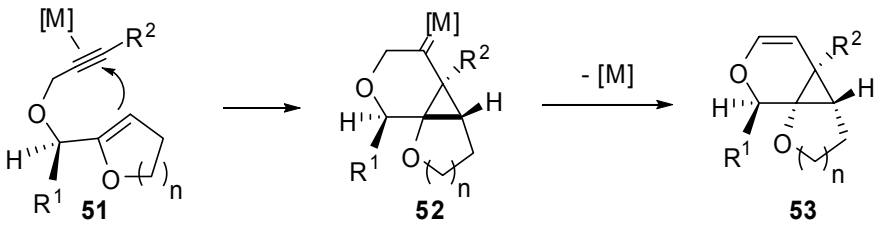


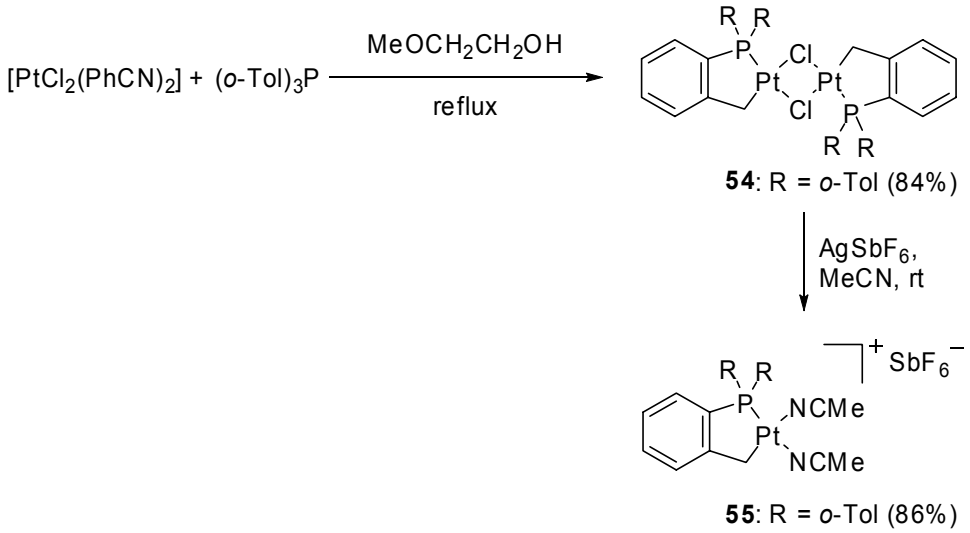
Figure 2. Chem3D drawing of **49b** based on the X-ray crystallographic data.

The cyclization presumably proceeds via η^2-alkyne-$PtCl_2$ complex **51**, by formation of two carbon-carbon bonds from the face of the alkene opposite to the R^2 substituent (Scheme 20). Platinum carbene **52** then evolves by a β-hydrogen elimination to give enol ether **53**.



Scheme 20

Almost identical results were obtained when $PtCl_4$ was used as catalyst,[27] which suggests that Pt(IV) is reduced to Pt(II) under the reaction conditions. In search for a more active platinum catalyst, we have previously found that a combination of $PtCl_2$ and bulky phosphine $(o\text{-Tol})_3P$ provided a catalytic system that outperformed $PtCl_2$.[28] Although the exact nature of the active catalyst is not known, we reasoned that under the reaction conditions known dimeric complex **54** could be formed (Scheme 21).[29] Indeed, complex **54** is readily prepared from $[PtCl_2(PhCN)_2]$ as an insoluble solid by the procedure of Fornies *et al*. Cleavage of the chloride bridges of dimeric **54** with $AgSbF_6$ in acetonitrile provided new Pt-complex **55** in good yield as a white solid.[30] This cationic platinum complex is soluble in CH_2Cl_2 and partially soluble in toluene at room temperature. Complex **55** displays a ^{31}P resonance at δ 19.8 ($CDCl_3$) coupled to ^{195}Pt ($^1J_{PtP}$ = 4600 Hz).



Scheme 21

27 Skeletal rearrangement of enynes catalyzed by $PtCl_4$: Oh, C. H.; Bang, S. Y.; Rhim, C. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 887-888.

28 Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

29 Fornies, J.; Martin, A.; Navarro, R.; Sicilia, V.; Villarroya, P. *Organometallics* **1996**, *15*, 1826-1833.

30 Complex **55** was prepared by Mihai Raducan (ICIQ, 2007).

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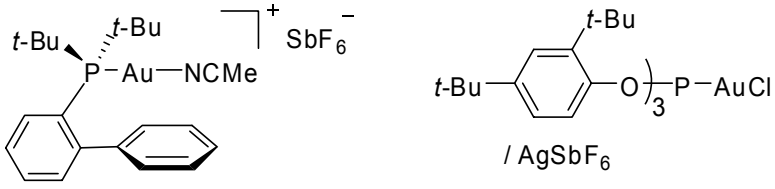
Complex **55** catalyzes the skeletal rearrangement of simple 1,6-enynes.[25] In addition to new Pt(II) complex **55**, we also assayed the cyclizations of substrates **47** and **48** with Au(I) catalysts **56** and **57** (Figure 3). Complex **56**[31] proved to be the best Au(I) catalyst, whereas **57**[32] led to poorer results, probably due to its higher electrophilicity, which led to decomposition of the acid-sensitive enol ethers used as substrates.



56 **57**

Figure 3

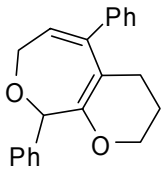
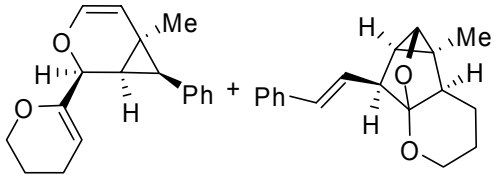
Enynes **47a-c** are cyclized with catalysts **55** and **56** to give tricyclic compounds **49a-c** (Table 2, entries 1-5). Best yields are obtained with Au(I) catalyst **56** (Table 2, entries 2, 4, and 5). Reaction of enynes **47d** with catalyst **56** provided 3,4,7,9-tetrahydro-2*H*-pyrano[2,3-*c*]oxepine **58**, in addition to the expected cyclopropane derivative **49d** (Table 2, entry 6). Catalyst **55** led only to cyclopropane **49d** and catalyst **57** to oxepine **58**, albeit in low yield in both cases (Table 2, entries 7 and 8). Interestingly, whereas reaction of dienyne **47f** with $PtCl_2$ proceeded selectively between the acetylene and the more electron-rich enol ether to give **49f** (Table 1, entry 6), reaction of **47f** with catalyst **56** afforded a mixture of regioisomeric cyclopropane **59** (25%) and tetracyclic acetal **60** (45%) (Table 2, entry 9).

25 Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

31 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694-1702. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 5455-5459.

32 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032.

Table 2. Cyclizations of enynes **47a-f** (see Table 1) with catalysts **55**, **56** or **57**.[a]

Entry	Enyne	Catalyst	Solvent	t (h)	Product (yield)
1	**47a**	**55**	toluene	2	**49a** (41%)
2	**47a**	**56**	CH_2Cl_2	0.2	**49a** (75%)
3	**47b**	**55**	CH_2Cl_2	0.7	**49b** (77%)
4	**47b**	**56**	CH_2Cl_2	0.5	**49b** (78%)
5	**47c**	**56**	CH_2Cl_2	0.5	**49c** (80%)
6	**47d**	**56**	CH_2Cl_2	0.3	**49d** (45%) +  **58** (14%)
7	**47d**	**55**	CH_2Cl_2	1	**49d** (38%)
8	**47d**	**57**	CH_2Cl_2	5	**58** (12%)
9	**47f**	**56**	CH_2Cl_2	0.2	 **59** (25%) **60** (45%)

(a) Reactions carried out with 5 mol% catalyst at room temperature.

The structure of the unexpected rearrangement product **60** was confirmed by X-ray diffraction (Figure 4).

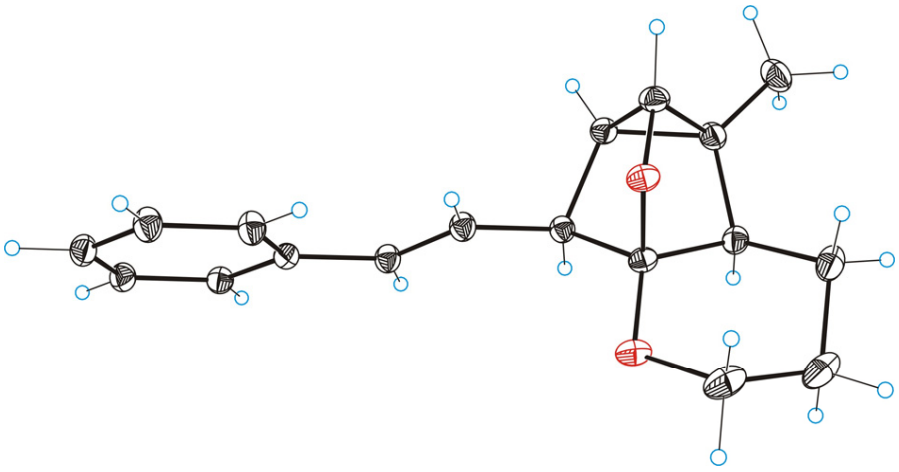


Figure 4. X-Ray structure of **60**

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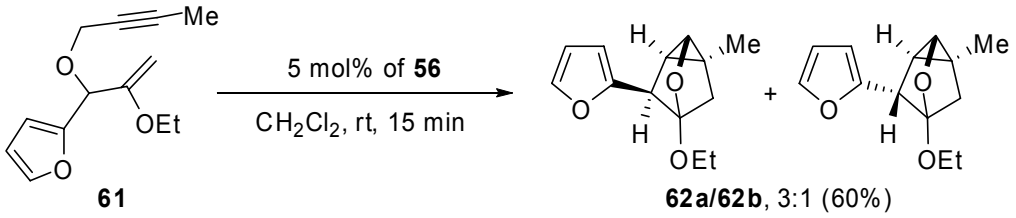
Reaction of derivative **61,** with a non-cyclic enol ether and a 2-furyl substituent, with catalyst **56** led to cyclic acetals **62a-b**, as a 3:1 mixture of epimers with a cage structure similar to that of compound **60** (Scheme 22).

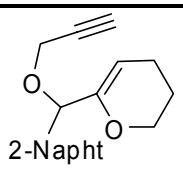
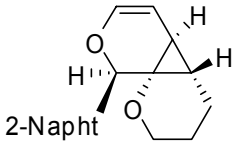
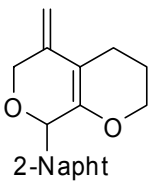


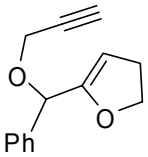
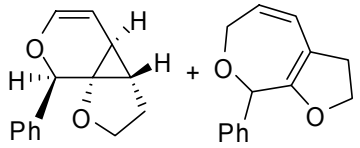
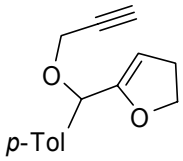
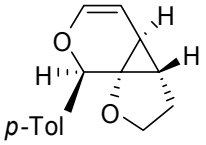
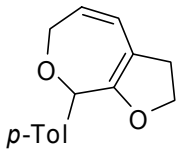
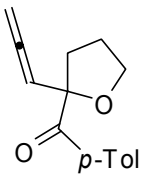
61 **62a/62b**, 3:1 (60%)

Scheme 22

An interesting difference in the reactivity of Pt(II) and Au(I) catalysts was found in the reaction of substrate **47h**. Thus, whereas its reaction with catalyst **55** led to **49h** in low yield, Au(I) catalysts **56** and **57** gave bicyclic **63** (Table 3, entries 1-3). Seven-membered ring derivatives **64** and **65** were also obtained in the reactions of **48c** and **48d** (Table 3, entries 4-6 and 8). Oxepine derivatives **58**, **64**, and **65** are labile and suffer extensive decomposition in the reaction mixture, during chromatographic purification on silica gel or even upon storage at low temperatures (< 0°C). Reaction of compounds **47h** and **48c-d** in methanol only led to decomposition or complex mixtures. A totally different reactivity was found in the reaction of substrate **48d** with AuCl as catalyst (Table 3, entry 9). In this case, allene **66** was obtained in 60% yield.

Table 3. Cyclizations of enynes **47h** and **48c-d** with catalysts **55**, **56** or **57**.[a]

Entry	Enyne	Catalyst	Solvent	t (h)	Product (yield)
1	 **47h**	**55**	toluene	0.2	 **49h** (29%)
2	**47h**	**56**	CH_2Cl_2	0.1	 **63** (66%)
3	**47h**	**57**	CH_2Cl_2	0.2	**63** (50%)

Entry	Enyne	Catalyst	Solvent	t (h)	Product (yield)
4	 **48c**	**55**	toluene	0.2	 **50c** (78%) **64** (17%)
5	**48c**	**56**	CH_2Cl_2	0.1	**64** (20%)
6	**48c**	**57**	CH_2Cl_2	0.1	**64** (10%)
7	 **48d**	**55**	toluene	0.5	 **50d** (5%)
8	**48d**	**56**	CH_2Cl_2	0.1	 **65** (20%)
9	**48d**	AuCl	CH_2Cl_2	16	 **66** (60%)

(a) Reactions carried out with 5 mol% catalyst at room temperature.

Allene **66** is presumably formed by gold-catalyzed isomerization of **48d** to **67**, followed by Claisen rearrangement that is probably also catalyzed by gold (Scheme 23). Interestingly, related allene **68** had been obtained before in the reaction of **47a** with $AuCl_3$ as catalyst,[33] which points to formation of the same catalytic gold species in reactions with AuCl and $AuCl_3$.

33 Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735-9744.

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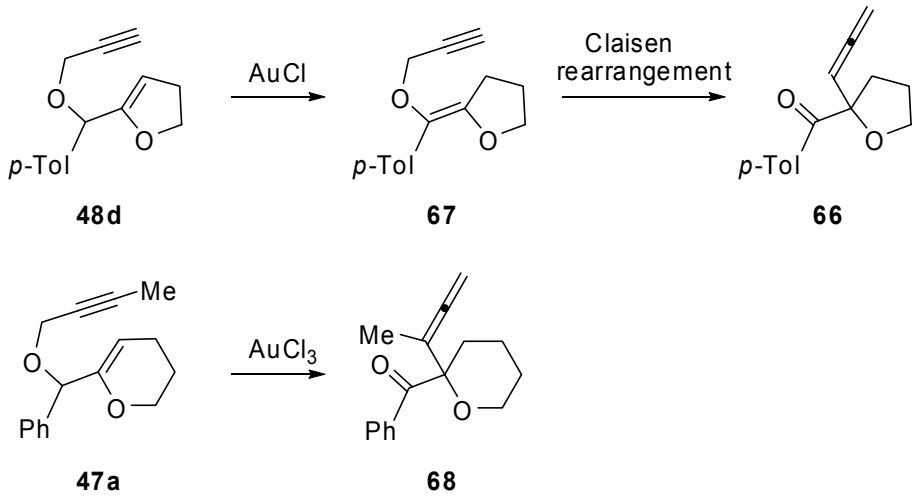
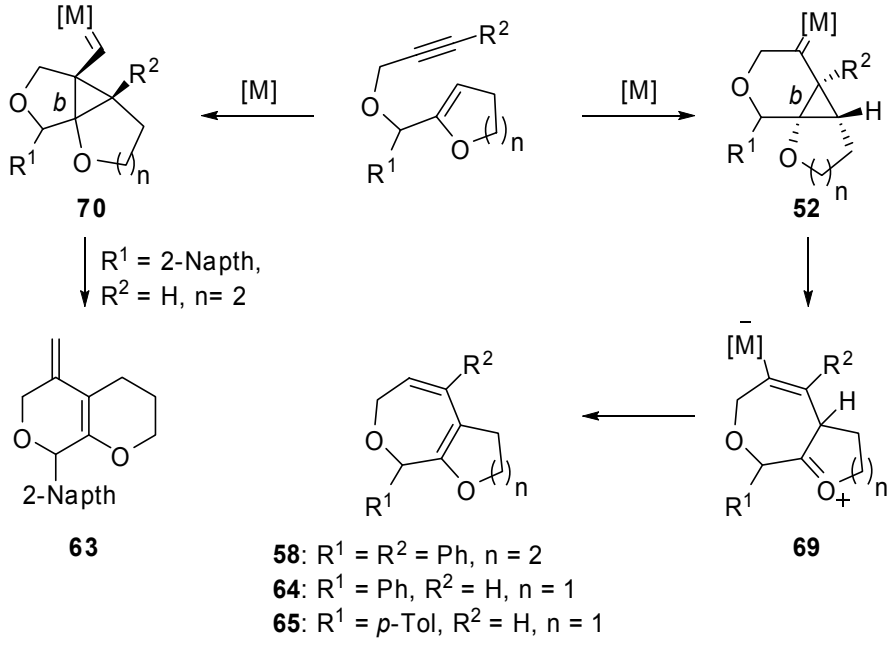


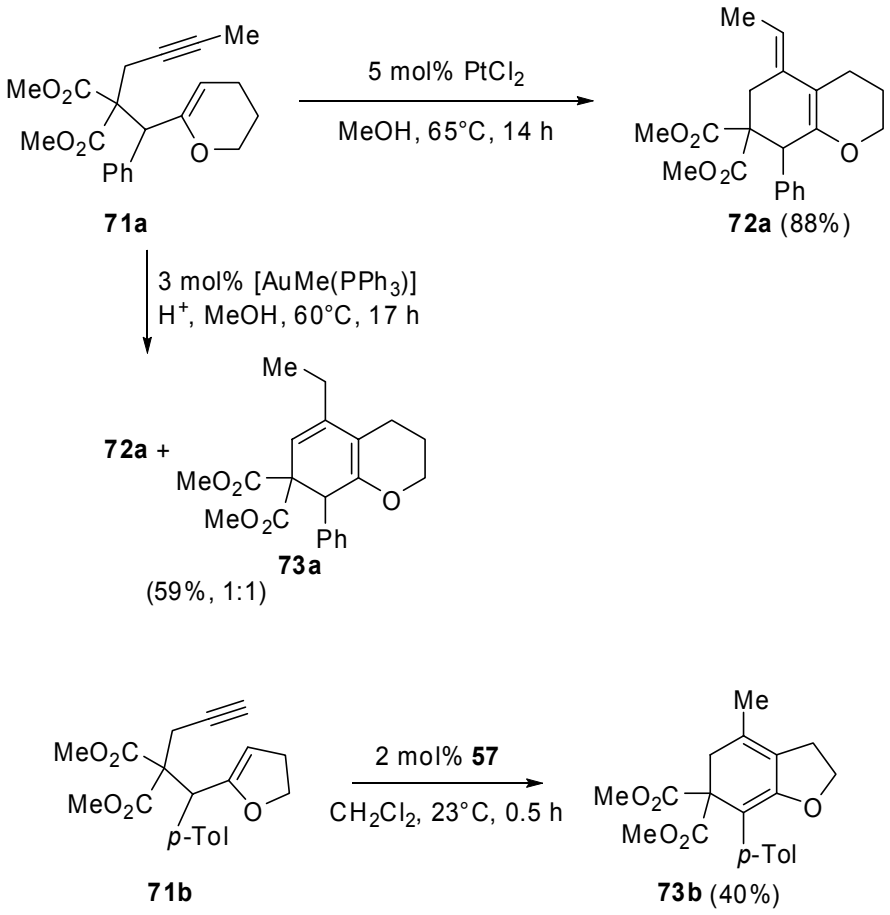
Scheme 23

Oxepines **58**, **64** and **65** are formed by an initial 6-*endo-dig* cyclization to give intermediates of type **52**, which suffer cleavage at bond *b* (see Scheme 17) leading to **69** (Scheme 24). Intermediates **69** undergo proton-loss and a final proto-demetalation to afford **58**, **64** and **65**. The formation of **63** from **47h** (Table 3, entry 2) can be explained by an initial 5-*exo-dig* cyclization *via* intermediate **70**, followed by cleavage at bond *b* to give compound **63**.



Scheme 24

We also observed the formation of compounds related to **63** in the reaction of malonates **71a**[34] and **71b** with Pt(II) or Au(I) catalysts (Scheme 25). Thus, reaction of **71a** with $PtCl_2$ in MeOH provided **72a** in 88% yield. Reaction of **71a** with a cationic Au(I) catalyst generated *in situ* by reaction of [AuMe(PPh_3)] with phosphotungstic acid led to a 1:1 mixture of **72a** and **73a** in 59% yield. On the other hand, treatment of **71b** with catalyst **57** in CH_2Cl_2 led to **73b** in 40% yield.



Scheme 25

These reactions probably take place through intermediates of type **70**, which open initially to give **74**. Gold- or proton-catalyzed isomerization of the exocyclic olefin of **74** then gives products **73a-b** (Scheme 26).

34 Cristina Nevado, Doctoral Thesis (UAM, 2004).

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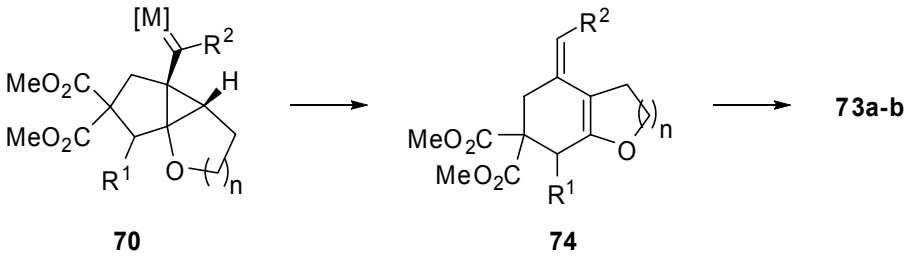
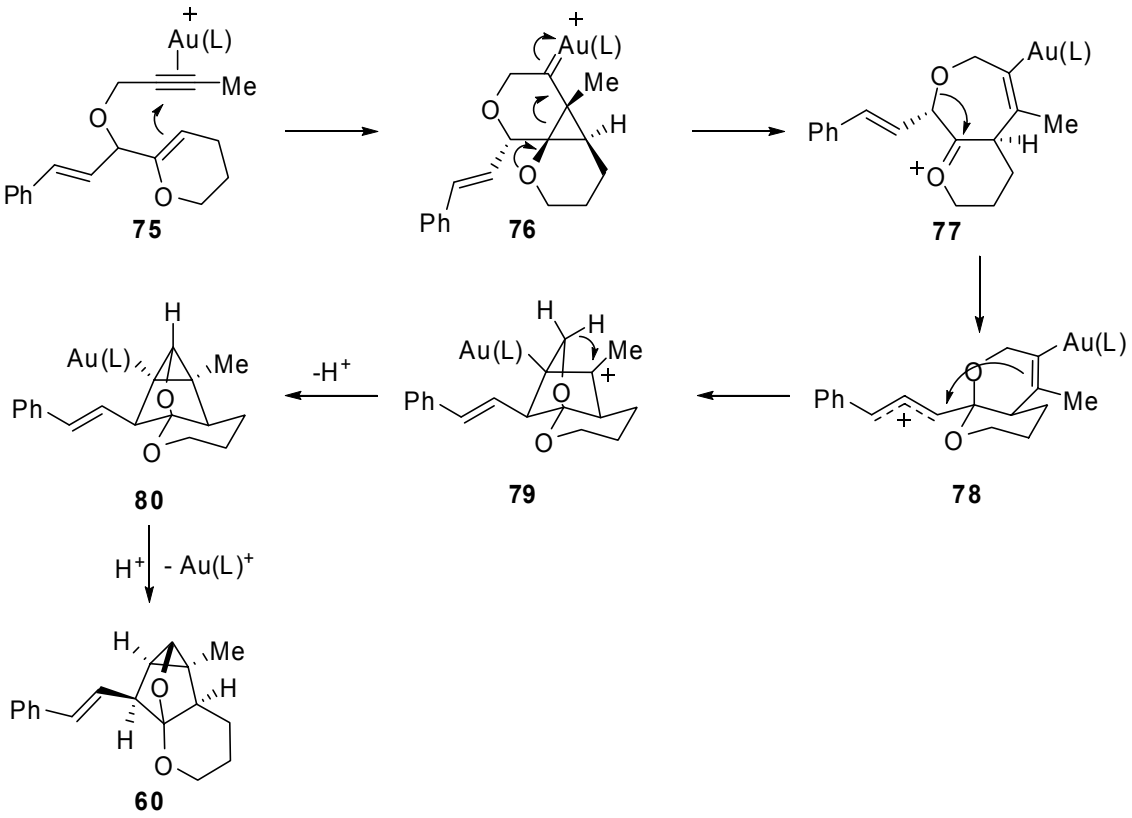


Scheme 26

Formation of rearranged compounds **60** and **62** probably proceeds also via seven-membered ring intermediates. For simplicity the proposed mechanism is shown for the formation of acetal **60** (Scheme 27). Accordingly, 6-*endo-dig* cyclization of **75** gives gold(I) carbene **76**, whose opening affords oxonium cation **77**. In this case, instead of the loss of a proton, a ring contraction from **77** leads to carbocation **78**, which reacts with the alkenyl-gold to give **79**. The cyclopropane ring is formed as shown to give **80**, from which a protodemetalation then affords **60**. A similar series of transformation could also explain the formation of acetals **62**.



Scheme 27

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Chapter 3. Conclusions

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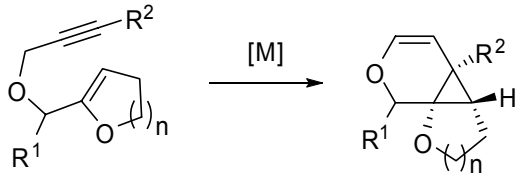
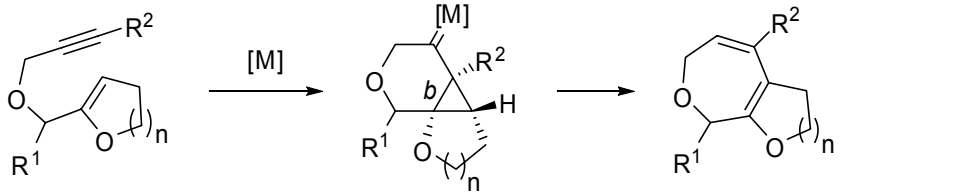
A new platinum and gold catalyzed cyclization of ω-acetylenic enol ethers has been developed. 3-Oxa-bicyclo[4.1.0]hept-4-ene derivatives are obtained when the tether between the alkyne and the enol ether is an oxygen atom by the intramolecular Pt(II)- and Au(I)-catalyzed cyclopropanation of enol ethers by alkynes (Scheme 28).



Scheme 28

As predicted by the mechanistic scheme originally proposed for the Pt(II)-catalyzed nucleophilic additions to 1,6-enynes, the cyclopropyl metal carbene formed in the 6-*endo-dig* cyclization may evolve to form seven-membered ring intermediates by cleavage of bond *b* (Scheme 29). This has been realized by using more electrophilic platinum(II) and gold(I) complexes as catalysts.



58: $R^1 = R^2 = Ph$, n = 2
64: $R^1 = H$, $R^2 = Ph$, n = 1
65: $R^1 = H$, $R^2 = p$-Tol, n = 1

Scheme 29

Gold(I) also trigger a remarkable rearrangement leading in a single step to complex cyclic systems bearing up to six stereogenic centers from starting compounds with only one stereogenic center (Figure 5).

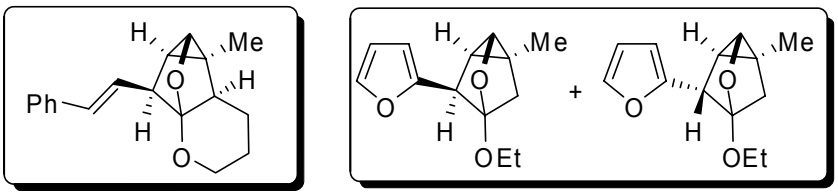
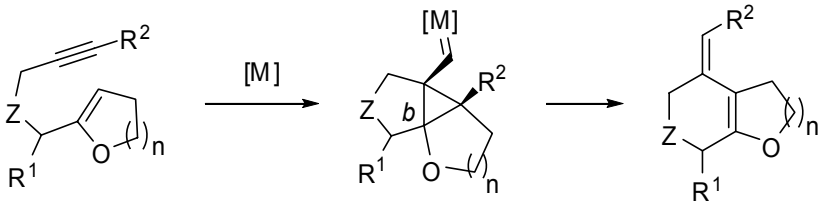


Figure 5

Cleavage of bond *b* in cyclopropyl metal carbene formed in the 5-*exo*-*dig* cyclization has also been observed in the formation of compound **63**, **72a** and **73a-b** (Scheme 30).



63: Z = O, R^1 = 2-Napht, R^2 = H, n = 2
72a: Z = $C(CO_2Me)_2$, R^1 = Ph, R^2 = Me, n = 2
73b: Z = $C(CO_2Me)_2$, R^1 = *p*-Tol, R^2 = H, n = 1

Scheme 30

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Chapter 3. Experimental section

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1. General methods

All reactions were carried out under N_2 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).

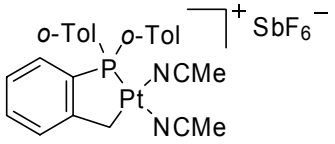
NMR spectra were recorded at 23°C on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus.

Mass spectra were recorded on a 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.

2. Catalysts

The following complexes and salts were used as received: $PtCl_2$ (Johnson Mattey PLC), AuCl and $AgSbF_6$ (Aldrich). Complexes **56**[31] and **57**[32] were prepared according to the described procedures.

Synthesis of [Pt{*o*-$CH_2C_6H_4$P(*o*-tolyl)$_2$-C,P}$(CH_3CN)_2$][SbF_6] (55)[30]



31 (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694-1702. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 5455-5459.

32 López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032.

30 Complex **55** was prepared by Mihai Raducan (ICIQ, 2007).

(a) $PtCl_2$ (0.508 g, 1.901 mmol) in benzonitrile (30 mL) was heated at 180 ºC. After 15 min, the mixture was cooled to room temperature. The solvent was partially evaporated to *ca.* 1/3 of the original volume (9 mbar, 55 ºC). Hexane (20 mL) was added and the precipitate was filtered and washed with hexane (3x10 mL) to yield $[Pt(PhCN)_2Cl_2]$ (cis and trans mixture) as a yellow powder (0.81 g, 90%).

(b) A mixture of $[PtCl_2(PhCN)_2]$ (*cis* + *trans*, 0.49 g, 1.04 mmol) and tri-*o*-tolylphosphine (0.325 mg, 1.04 mmol) in 2-methoxyethanol (6 mL) was refluxed for 30 min. The initial suspension dissolved to give a clear pale yellow solution, and then a white crystalline solid was deposited. After cooling, the solid was filtered off, washed with methanol and Et_2O to yield **54** as a pale yellow insoluble solid (0.468 g, 84%).

(c) $[Pt\{o\text{-}CH_2C_6H_4P(o\text{-tolyl})_2\text{-}C,P\}(\mu\text{-}Cl)]_2$ (0.468 g, 0.44 mmol) and $AgSbF_6$ (0.307 g, 0.876 mmol) were stirred in acetonitrile (10 mL) in the absence of light for 23 h. The mixture was filtered and evaporated. The residue was dissolved in CH_2Cl_2 then filtered through silica and evaporated to yield a colorless oil that solidified on addition of a few drops of Et_2O. Complex **55** was obtained as a white solid (0.615 g, 86%): ^1H NMR (500 MHz, $CDCl_3$, 50ºC) δ 7.45 (tt, J = 7.3, 1.6 Hz, 2H), 7.39-7.30 (m, 4H), 7.20 (t, J = 7.2 Hz, 2 H), 7.08 (td, J = 7.2, 2.7 Hz, 1 H), 6.93 (dd, J = 10.4, 7.7 Hz, 1H), 3.42 (br s, 2H, Pt satellites J = 100 Hz), 2.58 (br s, 6H), 2.46 (d, J = 1.0 Hz, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 ºC) δ 156.95 (d, $J_{P,C}$ = 26 Hz, C), 142.04 (d, $J_{P,C}$ = 9 Hz, C sp^2), 133.32 (s, C), 133.17 (d, $J_{P,C}$ = 10 Hz, CH), 132.76 (s, C), 132.37 (d, $J_{P,C}$ = 10 Hz, CH), 132.31 (s, CH), 131.93 (b, CH), 131.32 (d, $J_{P,C}$ = 5 Hz, CH), 128.27 (d, $J_{P,C}$ = 17 Hz, CH), 126.35 (d, $J_{P,C}$ = 14 Hz, CH), 126.27 (d, $J_{P,C}$ = 13 Hz, CH), 119.70 (s, CN), 119.55 (s, CN), 22.75 (d, $J_{P,C}$ = 8 Hz, CH_3), 12.20 (s, CH_2, Pt satellites J = 702 Hz), 2.86 (d, $J_{P,C}$ = 1 Hz, CH_3), 2.45 (s, CH_3); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ 19.8 (s, Pt satellites 4600 Hz).

3. General procedure for the preparation of alcohol precursors of compounds 47, 48 and 61

A solution containing 1.2 equiv of the corresponding enol ether in dried THF (volume of THF necessary to make the concentration of enol ether 2 M) was cooled to -78ºC and 1 equiv of *t*-BuLi was added dropwise. The mixture was warmed up to -5ºC and then stirred at that temperature for 5 h. The solution was then cooled again to -78ºC

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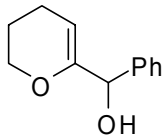
and 1.0 equiv of the aldehyde was slowly added. The mixture was warmed up to room temperature overnight and then quenched with 4 mL of a saturated NH_4Cl solution. The mixture was extracted with 3 x 20 mL of Et_2O and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (15:1 hexane-EtOAc containing 5% Et_3N). Reactions were carried out in a 15-30 mmol scale.

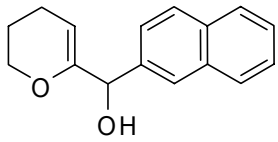
Because of its lability, the alcohol precursor of compound **47f** was not purified and was used in the alkylation without further purification after extractive work-up and evaporation of the solvent.

(3,4-Dihydro-2*H*-pyran-6-yl)(phenyl)methanol (precursor of 47a, 47c and 47d)[35]



Yield: 66% (4.50 g, 23.60 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.44 (m, 5H), 5.02 (d, J = 4.8 Hz, 1H), 4.77 (t, J = 3.6 Hz, 1H), 3.97-4.00 (m, 2H), 2.58 (d, J = 5.3 Hz, 1H), 2.01-2.07 (m, 2H), 1.75-1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.99, 141.94, 128.86, 128.25, 127.22, 98.79, 75.12, 67.17, 22.94, 20.64.

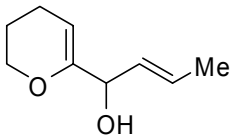
(3,4-Dihydro-2*H*-pyran-6-yl)(naphthalen-2-yl)methanol (precursor of 47b)



Yield: 75% (5.80 g, 24.20 mmol). Pale yellow solid: mp 61-63°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 0.8 Hz, 1H), 7.86-7.91 (m, 3H), 7.59 (dd, J = 8.5, 1.6 Hz, 1H), 7.55-7.49 (m, 2H), 5.26 (s, 1H), 4.88 (t, J = 3.6 Hz, 1H), 4.06 (t, J = 8.9 Hz, 2H), 2.75 (br s, 1H), 2.10-2.14 (m, 2H), 1.82-1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 155.08 (C), 139.44 (C), 133.92 (C), 133.69 (C), 128.79 (CH), 128.51 (CH), 128.31 (CH), 126.64 (CH), 126.47 (CH), 125.99 (CH), 125.44 (CH), 99.00 (CH), 75.27 (CH), 67.24 (CH_2), 22.98 (CH_2), 20.66 (CH_2). HRMS-EI *m/z* calcd for $C_{16}H_{16}O_2$: 240.1150; found: 240.1147 [M^+].

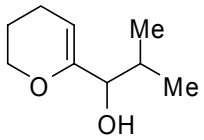
35 Lebouc, A.; Delaunay, J.; Riobe, O. *Synthesis* **1979**, 610-613.

(*E*)-1-(3,4-Dihydro-2*H*-pyran-6-yl)but-2-en-1-ol (precursor of 47e)



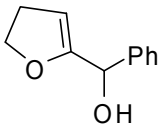
Yield: 59% (3.20 g, 20.10 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (dqd, J = 15.4, 6.5, 0.8 Hz, 1H), 5.59 (ddq, J = 15.4, 6.7, 1.5 Hz, 1H), 4.77 (t, J = 3.8 Hz, 1H), 4.38 (br m, 1H), 4.15-3.97 (m, 2H), 2.05-2.00 (m, 2H), 1.85-1.77 (m, 2H), 1.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.22 (C), 130.49 (CH), 128.43 (CH), 96.88 (CH), 73.26 (CH), 66.45 (CH_2), 22.33 (CH_2), 19.88 (CH_2), 17.76 (CH_3). HMRS-EI *m/z* calcd for $C_9H_{14}O_2$: 154.0993; found: 154.0992 [M^+].

1-(3,4-Dihydro-2*H*-pyran-6-yl)-2-methylpropan-1-ol (precursor of 47g)[36]



Yield: 67% (3.70 g, 23.70 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 3.84, 3.84 Hz, 1H), 4.05-3.91 (m, 2H), 3.48 (t, J = 7.8 Hz, 1H), 2.04-1.99 (m, 2H), 1.86-1.66 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.49, 98.32, 79.51, 66.85, 32.42, 23.15, 20.58, 19.89, 19.01.

(4,5-Dihydrofuran-2-yl)(phenyl)methanol (precursor of 48a and 48c)



Yield: 60% (2.50 g, 14.20 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (dd, J = 7.9, 1.4 Hz, 2H), 7.38-7.27 (m, 3H), 5.25 (br s, 1H), 4.78 (td, J = 2.4, 0.8 Hz, 1H), 4.37 (t, J = 9.3 Hz, 2H), 2.65 (d, J = 4.4 Hz, 1H), 2.64 (tdd, J = 9.3, 2.3, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 158.88, 140.56, 128.26, 127.93, 126.56, 96.89, 70.53, 70.22, 29.78. HRMS-EI *m/z* calcd for $C_{11}H_{12}O_2$: 176.0837; found: 176.0833 [M^+].

36 Ley, S. V.; Lygo, B. K.; Sternfeld, F.; Wonnacott, A. *Tetrahedron* **1986**, *42*, 4333-4342.

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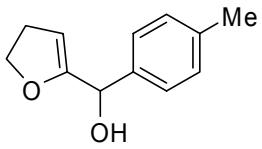
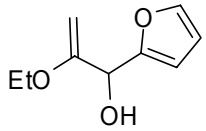
(4,5-Dihydrofuran-2-yl)(*p*-tolyl)methanol (precursor of 48b and 48d)



Yield: 50% (4.00 g, 21.00 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 5.23 (br s, 1H), 4.80 (ddd, J = 2.7, 2.7, 1.1 Hz, 1H), 4.38 (t, J = 9.4 Hz, 2H), 2.70-2.58 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.74, 138.36, 129.70, 127.20, 97.39, 71.26, 70.82, 30.48, 21.82 (one C signal was not observed due to overlapping). HMRS-EI *m/z* calcd for $C_{12}H_{14}O_2$: 190.0994; found: 190.0997 [M^+].

2-Ethoxy-1-(furan-2-yl)prop-2-en-1-ol (precursor of 61)



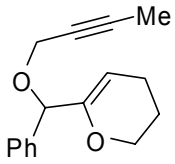
Yield: 53% (2.50 g, 14.90 mmol). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (dd, J = 1.8, 0.8 Hz, 1H), 6.36 (dd, J = 3.2, 1.8 Hz, 1H), 6.33 (dt, J = 3.2, 0.8 Hz, 1H), 5.15 (d, J = 6.1 Hz, 1H), 4.29 (d, J = 2.6 Hz, 1H), 4.15 (d, J = 2.6 Hz, 1H), 3.85 (q, J = 7.1 Hz, 2H), 2.83 (d, J = 6.1 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 Hz, DEPT) δ 161.12 (C), 154.94 (C), 142.78 (CH), 110.90 (CH), 107.72 (CH), 83.55 (CH_2), 69.64 (CH), 64.02 (CH_2), 14.89 (CH_3). Anal calcd for $C_9H_{12}O_2$: C, 64.27; H, 7.19; found: C, 64.06; H, 7.19.

4. General procedure for the preparation of compounds 47, 48 and 61

A solution containing 1.2 equiv of NaH (60% in mineral oil) in dried DMF (volume of DMF necessary to make the concentration of NaH 1.0 M) was cooled to 0°C. A 1.0 equiv solution of the corresponding benzylic alcohol in DMF (volume of DMF necessary to make the concentration of the alcohol 1.0 M) was added dropwise. The mixture was warmed up to room temperature and stirred for 20 min and 1.0 equiv of the alkylating agent was added. The reaction was stirred at 23ºC for 4 h and then quenched with a water-ice mixture and diluted with Et_2O. The organic layer was washed several times with water and then dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (100:1

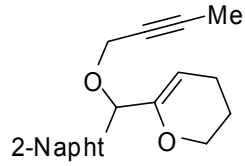
hexane-EtOAc containing 5% Et_3N). All reactions were carried out in a 1-30 mmol scale.

6-((But-2-ynyloxy)(phenyl)methyl)-3,4-dihydro-2*H*-pyran (47a)



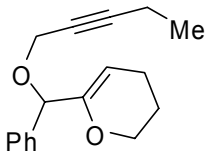
Yield: 63% (1.20 g, 4.96 mmol). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.44 (m, 2H), 7.24-7.36 (m, 3H), 4.91 (t, J = 3.8 Hz, 1H), 4.89 (s, 1H), 4.17 (dq, J = 15.4, 2.4 Hz, 1H), 4.10 (dq, J = 15.4, 2.4 Hz, 1H), 3.91-4.03 (m, 2H), 2.04-2.09 (m, 2H), 1.84 (t, J = 2.4 Hz, 3H), 1.75-1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.78, 140.42, 128.73, 128.56, 128.12, 113.59, 74.07, 69.99, 64.87, 25.63, 22.95, 21.95, 16.15, 13.05. HMRS-EI *m/z* calcd for $C_{16}H_{18}O_2$: 242.1301; found: 242.1296 [M^+].

6-((But-2-ynyloxy)(naphthalen-1-yl)methyl)-3,4-dihydro-2*H*-pyran (47b)



Yield: 89% (2.90 g, 9.90 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 1.0 Hz, 1H), 7.95-7.88 (m, 3H), 7.65 (dd, J = 8.5, 1.8 Hz, 1H), 7.57-7.49 (m, 2H), 5.17 (s, 1H), 5.07 (t, J = 3.8 Hz, 1H), 4.33 (dq, J = 12.9, 2.2 Hz, 1H), 4.27 (dq, J = 12.9, 2.2 Hz, 1H), 4.09-3.99 (m, 2H), 2.18-2.12 (m, 2H), 1.94 (t, J = 2.2 Hz, 3H), 1.89-1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 153.03 (C), 137.38 (C), 133.91 (C), 133.81 (C), 128.81 (CH), 128.52 (CH), 128.33 (CH), 126.97 (CH), 126.63 (CH), 126.51 (CH), 125.90(CH), 100.56 (CH), 83.36 (C), 80.92 (CH), 75.83 (C), 67.14 (CH_2), 57.03 (CH_2), 22.99 (CH_2), 20.86 (CH_2), 4.46 (CH_3). Anal calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89; found: C, 82.08; H, 6.95. HMRS-EI *m/z* calcd for $C_{20}H_{20}O_2$: 292.1463; found: 292.1468 [M^+].

6-((Pent-2-ynyloxy)(phenyl)methyl)-3,4-dihydro-2*H*-pyran (47c)



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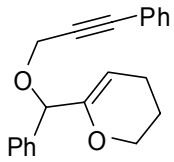
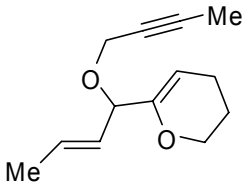
Yield: 90% (5.30 g, 20.60 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.34 (m, 2H), 7.28-7.19 (m, 3H), 4.58-4.83 (m, 2H), 4.12 (dt, J = 15.3, 2.2 Hz, 1H), 4.07 (dt, J = 15.3, 2.2 Hz, 1H), 3.95-3.85 (m, 2H), 2.15 (qt, J = 7.6, 2.2 Hz 2H), 2.02-1.97 (m, 2H), 1.75-1.68 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 152.22 (C), 139.21 (C), 128.06 (CH, 2C), 127.58 (CH), 127.25 (CH, 2C), 99.62 (CH), 88.42 (C), 79.97 (CH), 75.17 (C), 66.37 (CH_2), 56.25 (CH_2), 22.27 (CH_2), 20.11 (CH_2), 13.78 (CH_3), 12.50 (CH_2). MS-EI *m/z* calcd for $C_{15}H_{15}O_2$: 227.1; found: 227.0 [M^+-C_2H_5].

6-(Phenyl(3-phenylprop-2-ynyloxy)methyl)-3,4-dihydro-2*H*-pyran (47d)



Yield: 57% (1.80 g, 6.00 mmol). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.30 (m, 10H), 5.05 (s, 1H), 5.01 (t, J = 4.0 Hz, 1H), 4.52 (d, J = 15.8 Hz, 1H), 4.44 (d, J = 15.8 Hz, 1H), 4.11-3.99 (m, 2H), 2.17-2.09 (m, 2H), 1.90-1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 152.78 (C), 139.71 (C), 132.43 (CH), 128.98 (CH), 128.88 (CH), 128.81 (CH), 128.37 (CH), 127.97 (CH), 123.47 (C), 100.65 (CH), 87.01 (C), 85.84 (C), 81.04 (CH), 67.10 (CH_2), 57.16 (CH_2), 22.93 (CH_2), 20.80 (CH_2). HMRS-EI *m/z* calcd for $C_{21}H_{20}O_2$: 304.1463; found: 304.1461 [M^+].

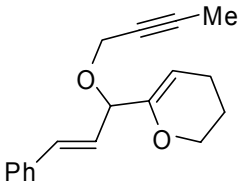
(*E*)-6-(1-(But-2-ynyloxy)but-2-enyl)-3,4-dihydro-2*H*-pyra (47e)



Yield: 73% (943 mg, 4.60 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (dq, J = 15.4, 6.5 Hz, 1H), 5.53 (ddq, J = 15.4, 7.5, 1.4 Hz, 1H), 4.81 (t, J = 3.6 Hz, 1H), 4.20 (d, J = 7.5 Hz 1H), 4.07 (q, J = 2.3 Hz, 2H), 4.04-3.94 (m, 2H), 2.06-2.01 (m, 2H), 1.82 (t, J = 2.2 Hz, 3H), 1.83-1.76 (m overlapped, 2H), 1.71 (dd, J = 6.23, 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 152.21 (C), 129.73 (CH), 128.37 (CH), 98.97 (CH), 82.07 (C), 79.37 (CH), 75.29 (C), 66.34 (CH_2), 55.38 (CH_2), 22.30 (CH_2),

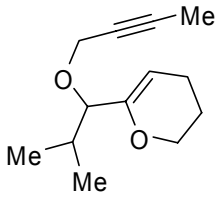
20.30 (CH_2), 17.79 (CH_3), 3.62 (CH_3). HMRS-EI *m/z* calcd for $C_{13}H_{18}O_2$: 206.1306; found: 206.1297 [M^+].

(*E*)-6-(1-(But-2-ynyloxy)-3-phenylallyl)-3,4-dihydro-2*H*-pyran (47f)



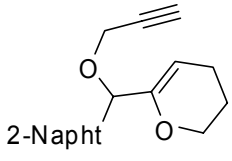
Yield: 19% (353 mg, 1.30 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.32-7.19 (m, 3H), 6.64 (d, J = 16.2 Hz, 1H), 6.25 (dd, J = 16.2, 7.3 Hz, 1H), 4.89 (t, J = 5.0 Hz, 1H), 4.45 (d, J = 7.3 Hz, 1H), 4.15 (q, J = 2.8 Hz, 2H), 4.07-3.96 (m, 2H), 2.08-2.02 (m, 2H), 1.84 (t, J = 2.8 Hz, 3H), 1.81-1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 152.50 (C), 137.33 (C), 133.42 (CH), 129.10 (CH), 128.35 (CH), 127.43 (CH), 127.29 (CH), 100.28 (CH), 83.10 (C), 80.03 (CH), 75.79 (C), 67.09 (CH_2), 56.35 (CH_2), 22.91 (CH_2), 20.73 (CH_2), 4.36 (CH_3). HMRS-EI *m/z* calcd for $C_{18}H_{19}O_2$: 267.1385; found: 267.1378 [M^+-H].

6-(1-(But-2-ynyloxy)-2-methylpropyl)-3,4-dihydro-2*H*-pyran (47g)



Yield: 70% (561 mg, 2.70 mmol). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (t, J = 3.6 Hz, 1H), 4.21-4.13 (m, 2H), 4.05-3.91 (m, 2H), 3.27 (d, J =8.5 Hz, 1H), 2.07-1.75 (m, 8H), 0.98 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.39, 101.25, 85.84, 82.18, 82.05, 76.42, 66.74, 56.64, 30.81, 23.13, 20.81, 19.91, 19.84. HMRS-EI *m/z* calcd for $C_{13}H_{20}O_2$: 208.1463; found: 208.1459 [M^+].

6-(Naphthalen-2-yl(prop-2-ynyloxy)methyl)-3,4-dihydro-2*H*-pyran (47h)



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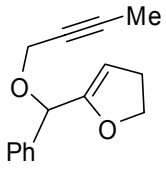
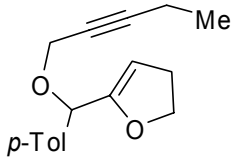
Yield: 71% (372 mg, 1.13 mmol). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.85-7.81 (m, 3H), 7.54 (d, J = 8.6 Hz, 1H), 7.84-7.43 (m, 2H), 5.09 (s, 1H), 4.99 (t, J = 3.6 Hz, 1H), 4.88 (dd, J = 15.6, 2.3 Hz, 1H), 4.20 (dd, J = 15.6, 2.3 Hz, 1H), 4.03-3.93 (m, 2H), 2.45 (t, J = 2.3 Hz, 1H), 2.11-2.07 (m, 2H), 1.83-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 152.00 (C), 136.27 (C), 133.18 (C), 133.14 (C), 128.13 (CH), 127.88 (CH), 127.63 (CH), 126.31 (CH), 125.95 (CH), 125.88 (CH), 125.11 (CH), 100.26 (CH), 80.40 (CH), 79.71 (C), 74.65 (CH), 66.50 (CH_2), 55.69 (CH_2), 22.27 (CH_2), 20.17 (CH_2). HRMS-ESI *m/z* calcd for $C_{19}H_{18}O_2Na$: 301.1204; found: 301.1205 [M^++Na].

5-((But-2-ynyloxy)(phenyl)methyl)-2,3-dihydrofuran (48a)



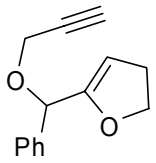
Yield: 69% (7.60 g, 35.40 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.9, 1.4 Hz, 2H), 7.39-7.29 (m, 3H), 5.14 (br s, 1H), 4.87 (td, J = 2.4, 0.8 Hz, 1H), 4.37 (t, J = 9.5 Hz, 2H), 4.18 (dq, J = 15.3, 2.4 Hz, 1H), 4.06 (dq, J = 15.3, 2.4 Hz 1H), 2.62 (tdd, J = 9.5, 2.4, 1.2 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.98, 138.33, 128.23, 128.03, 127.45, 98.39, 82.77, 75.49, 74.76, 70.44, 56.41, 29.69, 3.62. Anal calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; found: C, 78.86; H, 7.07. HMRS-EI *m/z* calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1143 [M^+].

5-((Pent-2-ynyloxy)(phenyl)methyl)-2,3-dihydrofuran (48b)



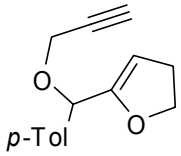
Yield: 59% (1.20 g, 4.70 mmol). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1Hz, 2H), 5.12 (br s, 1H), 4.88 (td, J = 2.4, 1.0 Hz, 1H), 4.40-4.33 (m, 2H), 4.18 (dt, J = 4.5, 2.2, 1H), 4.06 (dt, J = 4.5, 2.2 Hz, 1H), 2.66-2.59 (m, 2H), 2.34 (s, 3H), 2.24 (qt, J = 7.7, 2.2 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.90, 138.44, 135.98, 129.63, 128.14, 98.74, 89.29, 75.99, 75.65, 71.13, 56.99, 30.37, 21.82, 14.42, 13.15. HMRS-EI *m/z* calcd for $C_{17}H_{19}O_2$: 255.1385; found: 255.1373 [M^+-H].

5-(Phenyl(prop-2-ynyloxy)methyl)-2,3-dihydrofuran (48c)



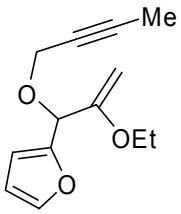
Yield: 69% (7.58 g, 35.38 mmol). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.29 (m, 5H), 5.19 (s, 1H), 4.91 (td, J = 2.5, 0.8 Hz, 1H), 4.37 (td, J = 9.4, 1.8 Hz, 2H), 4.25 (dd, J = 15.8, 2.3 Hz, 1H), 4.12 (dd, J = 15.6, 2.4 Hz, 1H), 2.63 (tdd, J = 9.4, 2.5, 1.2 Hz, 2H), 2.45 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 156.51 (C), 137.84 (C), 128.16 (CH), 128.05 (CH, 2C), 127.29 (CH, 2C), 98.61 (CH), 79.25 (C), 75.52 (CH), 74.69 (CH), 70.33 (CH_2), 55.63 (CH_2), 29.54 (CH_2). HRMS-ESI *m/z* calcd for $C_{14}H_{14}O_2$: 214.0993; found: 214.0985 [M^+].

5-((Prop-2-ynyloxy)(*p*-tolyl)methyl)-2,3-dihydrofuran (48d)



Yield: 78% (940 mg, 4.11 mmol). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 5.14 (s, 1H), 4.89 (t, J = 2.4 Hz, 1H), 4.41-4.32 (m, 2H), 4.22 (dd, J = 15.7, 2.3 Hz, 1H), 4.08 (dd, J = 15.7, 2.4 Hz, 1H), 2.65-2.61 (m, 2H), 2.43 (t, J = 2.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 156.89 (C), 138.01 (C), 134.92 (C), 129.08 (CH, 2C), 127.48 (CH, 2C), 98.53 (CH), 79.51 (C), 75.57 (CH), 74.73 (CH), 70.55 (CH_2), 55.68 (CH_2), 29.74 (CH_2), 21.22 (CH_3). HRMS-ESI *m/z* calcd for $C_{15}H_{16}O_2Na$: 251.1048; found: 251.1042 [M^++Na].

2-(1-(But-2-ynyloxy)-2-ethoxyallyl)furan (61)



Yield: 47% (800 mg, 3.29 mmol). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 1.8, 0.6 Hz, 1H), 6.37 (d, J = 3.2 Hz, 1H), 6.33 (dd, J = 3.2, 1.8 Hz, 1H), 5.02 (s, 1H), 4.39 (d, J = 2.3 Hz, 1H), 4.18 (d, J = 2.3 Hz, 1H), 4.17-4.15 (m, 2H), 3.38-3.76 (m, 2H), 1.85 (t, J = 2.3 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz,

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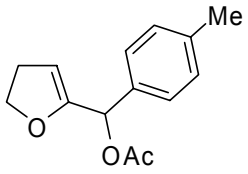
$CDCl_3$, DEPT) δ 158.50 (C), 152.27 (C), 142.43 (CH), 110.22 (CH), 108.69 (CH), 84.00 (CH_2), 82.93 (C), 74.67 (C), 73.93 (CH), 63.28 (CH_2), 56.50 (CH_2), 14.26 (CH_3), 3.72 (CH_3). HRMS-ESI *m/z* calcd for $C_{13}H_{16}O_3Na$: 243.0997; found: 243.0985 [M^++Na].

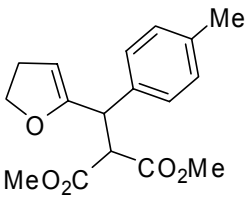
5. Preparation of Compound 71b

(4,5-Dihydrofuran-2-yl)(*p*-tolyl)methyl acetate



A mixture of (4,5-dihydrofuran-2-yl)(p-tolyl)methanol (4.00 g, 21.06 mmol), DMAP (128 mg, 1.05 mmol), and DIPEA (4.4 mL, 25.25 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 ºC. Then, Ac_2O (2.3 mL, 25.23 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was diluted with CH_2Cl_2, washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (10:1 hexane-EtOAc with 5% Et_3N) to give the title compound as a colorless oil. Yield: 66% (3.22 g, 13.86 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.31 (br s, 1H), 4.85 (td, J = 2.4, 1.0 Hz, 1H), 4.38 (td, J = 9.3, 1.2 Hz, 2H), 2.63 (tdd, J = 9.4, 2.4, 1.5 Hz, 2H), 2.34 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 168.85 (C), 155.95 (C), 138.25 (C), 138.11 (C), 129.10 (CH, 2C), 127.33 (CH, 2C), 98.67 (CH), 70.94 (CH), 70.73 (CH_2), 29.74 (CH_2), 21.21 (CH_3), 21.16 (CH_3). HRMS-ESI *m/z* calcd for $C_{14}H_{16}O_3Na$: 255.0997; found: 255.0998 [M^++Na].

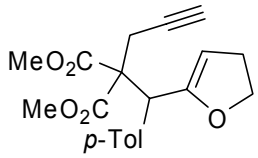
Dimethyl 2-((4,5-Dihydrofuran-2-yl)(*p*-tolyl)methyl)malonate



A mixture of the above acetate (200 mg, 0.86 mmol), triphenylphosphine (23 mg, 0.08 mmol), and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) was mixed in THF (3 mL). In a separate flask, dimethyl malonate (0.4 mL, 3.44 mmol) was slowly added to a

suspension of NaH (60% in mineral oil, 138 mg, 3.44 mmol) in THF (9 mL) and stirred for 20 min. The resulting solution was added in one portion to the former and the combined mixture stirred at 80ºC for 16 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O and water, the aqueous phase was extracted with ether, and the ether extracts were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography (30:1 hexane-EtOAc with 5% Et_3N) to give the corresponding product as a white solid. Yield: 38% (100 mg, 0.33 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 4.74 (t, J = 2.5 Hz, 1H), 4.33-4.22 (m, 3H), 4.03 (d, J = 11.3 Hz, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 2.60-2.54 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 168.19 (C), 167.68 (C), 157.43 (C), 137.00 (C), 135.17 (C), 129.15 (CH, 2C), 128.08 (CH, 2C), 95.90 (CH), 70.27 (CH_2), 55.85 (CH), 52.72 (CH_3), 52.42 (CH_3), 44.52 (CH), 29.88 (CH_2), 21.09 (CH_3). HRMS-ESI *m/z* calcd for $C_{17}H_{20}O_5Na$: 327.1208; found: 327.1198 [M^++Na].

Dimethyl 2-((4,5-dihydrofuran-2-yl)(*p*-tolyl)methyl)-2-(prop-2-ynyl)malonate (71b)



To a suspension of NaH (60% in mineral oil, 79 mg, 1.97 mmol) in DMF (5 mL) at 0 ºC, a solution of dimethyl 2-((4,5-dihydrofuran-2-yl)(p-tolyl)methyl)malonate (500 mg, 1.64 mmol) in DMF (2 mL) was added. The mixture was stirred for 5 min and propargyl bromide (0.21 mL, 1.97 mmol) was then added. The reaction was stirred for 3 h at room temperature and then quenched with an ice-water mixture and extracted with Et_2O. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by chromatography (100:1 hexane-EtOAc with 5% Et_3N) to give **71b** as a colorless oil. Yield: 99% (560 mg, 1.63 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.76 (br s, 1H), 4.43 (s, 1H), 4.33-4.24 (m, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 2.79 (dd, J = 16.8, 2.5 Hz, 1H), 2.66 (dd, J = 16.8, 2.8 Hz, 1H), 2.56-2.52 (m, 2H), 2.31 (s, 3H), 1.99 (t, J = 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 169.96 (C), 169.70 (C), 156.34 (C), 137.25 (C), 133.57 (C), 130.01 (CH, 2C), 128.72 (CH, 2C), 98.85 (CH), 79.76 (C), 71.01 (CH), 70.31 (CH_2), 60.20 (C), 52.55 (CH_3), 52.48 (CH_3), 48.46 (CH), 29.88 (CH_2), 25.00

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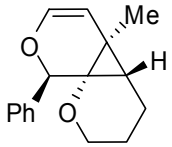
(CH_2), 21.10 (CH_3). HRMS-ESI *m/z* calcd for $C_{20}H_{22}O_5Na$: 365.1365; found: 365.1359 [M^++Na].

6. General procedure for the cyclization of substrates 47, 48, 61 and 71b (Tables 1, 2, 3 and Schemes 21 and 24)

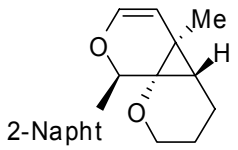
A mixture of enyne (0.5 mmol, 1 equiv) and the stated catalyst ($PtCl_2$, **55**, **56** or **57**) (0.05 equiv) was dissolved in toluene or CH_2Cl_2 (2.5 mL). The solution was stirred under conditions stated in Tables 1-3 and Scheme 21 and then filtered through a short path of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (100:1 hexane-EtOAc containing 5% Et_3N) to yield the corresponding product.

Tricycle 49a



White solid: mp 58-59°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.39-7.28 (m, 3H), 6.14 (d, J = 5.7 Hz, 1H), 5.13 (d, J = 5.7 Hz, 1H), 4.56 (s, 1H), 3.31 (ddd, J = 10.9, 4.4, 2.4 Hz, 1H), 2.27 (ddd, J = 12.4, 10.9, 2.4 Hz, 1H), 1.82-1.74 (m, 2H), 1.45-1.26 (m, 2H), 1.19 (s, 3H), 1.18-1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 140.41 (C), 140.40 (CH), 128.73 (CH), 128.56 (CH), 128.12 (CH), 113.59 (CH), 74.07 (CH), 69.99 (C), 64.87 (CH_2), 25.63 (CH), 22.95 (CH_2), 21.95 (C), 16.14 (CH_2), 13.05 (CH_3). Anal calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49; found: C, 79.06; H, 7.36.

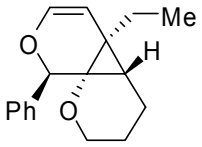
Tricycle 49b



White solid: mp 103-105ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.94-7.89 (m, 3H), 7.64 (dd, J = 8.5, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 6.25 (d, J = 5.6 Hz, 1H), 5.23 (d, J = 5.6 Hz, 1H), 4.81 (s, 1H), 3.32 (ddd, J = 10.9, 4.4, 2.4 Hz, 1H), 2.28

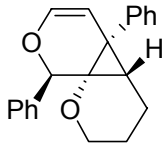
(ddd, J = 12.1, 10.9, 2.4 Hz, 1H), 1.87-1.80 (m, 2H), 1.46-1.30 (m, 1H), 1.28 (s, 3H), 1.20-1.11 (m, 1H), 0.94-0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.41, 138.26, 133.80 (2 x C), 128.78, 128.37, 128.32, 127.25, 126.60, 126.49, 125.99, 113.69, 74.25, 69.94, 64.95, 25.78, 22.85, 21.96, 16.11, 13.03. Anal calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89; found: C, 81.94; H, 7.03. HMRS-EI *m/z* calcd for $C_{20}H_{20}O_2$: 292.1463; found: 292.1469 [M^+].

Tricycle 49c



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.39-7.31 (m, 3H), 6.23 (d, J = 5.6 Hz, 1H), 5.19 (d, J = 5.6 Hz, 1H), 4.59 (s, 1H), 3.33-3.29 (m, 1H), 2.32-2.26 (m, 1H), 1.82-1.77 (m, 2H), 1.63-1.57 (m, 2H), 1.46-1.33 (m, 2H), 1.26-1.11 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.78, 140.23, 128.03, 127.87, 127.49, 110.41, 73.89, 69.72, 63.95, 26.80, 25.67, 22.48, 19.98, 15.75, 11.35. Anal calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86; found: C, 79.78; H, 7.92.

Tricycle 49d



White solid: mp 107-109ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.5, 2.0 Hz, 2H), 7.48-7.37 (m, 7H), 7.32-7.27 (m, 1H), 6.26 (d, J = 5.7 Hz, 1H), 5.25 (d, J = 5.7 Hz, 1H), 4.84 (s, 1H), 3.23-3.17 (m, 1H), 2.33 (ddd, J = 12.5, 10.9, 2.0 Hz, 1H), 1.99 (m, 2H), 1.88 (ddt, J = 14.1, 12.1, 6.9 Hz, 1H), 0.86 (m, 1H), 0.48-0.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 140.97 (C), 140.77 (CH), 140.02 (C), 131.93 (CH), 129.44 (CH), 129.25 (CH), 129.17 (CH), 128.71 (CH), 127.55 (CH), 114.12 (CH), 75.23 (CH), 71.64 (C), 65.45 (CH_2), 31.34 (C), 29.41 (CH), 22.64 (CH_2), 19.31 (CH_2). Anal calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62; found: C, 82.56; H, 6.66. HMRS-EI *m/z* calcd for $C_{21}H_{20}O_2$: 304.1463; found: 304.1466 [M^+].

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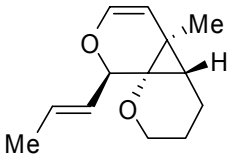
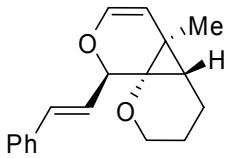
Tricycle 49e



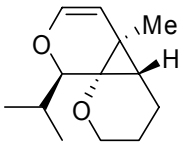
Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 5.8 Hz, 1H), 5.95 (dqd, J = 15.4, 6.5, 0.8 Hz, 1H), 5.64 (ddq, J = 15.4, 7.7, 1.6 Hz, 1H), 5.06 (d, J = 5.8 Hz, 1H), 4.11 (d, J = 7.7 Hz, 1H), 3.73-3.67 (m, 1H), 3.36 (ddd, J = 11.1, 11.1, 3.2 Hz, 1H), 2.05-1.81 (m, 2H), 1.83 (dd, J = 6.5, 1.6 Hz, 3H), 1.60-1.56 (m, 2H), 1.26 (dd, J = 7.7, 1.2 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.88, 130.07, 128.09, 112.42, 72.67, 67.04, 64.64, 24.09, 22.53, 20.18, 17.95, 15.66, 12.40. Anal calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; found: C, 75.74; H, 8.90. HMRS-EI *m/z* calcd for $C_{13}H_{18}O_2$: 206.1306; found: 206.1304 [M^+].

Tricycle 49f



Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.14 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.14 (dd, J = 16.0, 9.7 Hz, 1H), 5.90 (d, J = 5.7 Hz, 1H), 5.07 (d, J = 5.7 Hz, 1H), 4.22 (d, J = 9.7 Hz, 1H), 3.90 (m, 1H), 3.35 (m, 1H), 2.18 (d, J = 9.7 Hz, 1H), 2.00-1.95 (m, 1H), 1.87-1.73 (m, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.85, 136.79, 132.21, 128.40, 126.75, 125.88, 123.57, 111.02, 70.75, 67.62, 67.09, 38.73, 26.83, 25.32, 24.82, 12.40. HMRS-EI *m/z* calcd for $C_{18}H_{20}O_2$: 268.1463; found: 268.1467 [M^+].

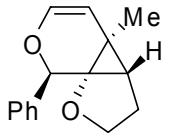
Tricycle 49g



Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 5.6 Hz, 1H), 4.94 (d, J = 5.6 Hz, 1H), 3.74 (ddd, J = 10.9, 4.0, 2.4 Hz, 1H), 3.49 (d, J = 1.6 Hz, 1H), 3.34 (ddd, J = 12.1, 10.9, 3.2 Hz, 1H), 2.27 (septet d, J = 7.3, 1.6 Hz, 1H), 1.87 (m, 3H), 1.46 (m, 1H), 1.19 (m, 1H), 1.13 (s, 3H), 1.08 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H); ^{13}C

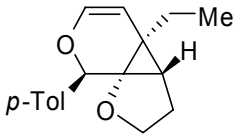
NMR (75 MHz, $CDCl_3$, DEPT) δ 140.39 (CH), 113.00 (CH), 76.25 (CH), 66.29 (C), 65.03 (CH_2), 28.84 (CH), 26.21 (CH), 23.20 (CH_2), 21.44 (CH_3), 16.33 (CH_2), 16.28 (CH_3), 13.08 (CH_3). One C signal is missed due to overlapping. Anal calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; found: C, 74.94; H, 8.70.

Tricycle 50a



White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 6.20 (d, J = 5.9 Hz, 1H), 5.07 (dd, J = 5.9, 0.6 Hz, 1H), 4.91 (s, 1H), 3.78-3.71 (m, 1H), 3.59-3.50 (m, 1H), 2.12-2.01 (m, 1H), 1.93-1.82 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 140.85 (CH), 139.78 (C), 128.08 (CH), 127.92 (CH), 127.29 (CH), 109.82 (CH), 78.72 (C), 75.45 (CH_2), 71.28 (CH), 34.37 (CH), 27.48 (C), 26.30 (CH_2), 11.22 (CH_3). Anal calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; found: C, 79.05; H, 7.68. HMRS-EI *m/z* calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1143 [M^+].

Tricycle 50b



Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.30 (d, J = 6.1 Hz, 1H), 5.11 (d, J = 6.1 Hz, 1H), 4.91 (s, 1H), 3.85-3.78 (m, 1H), 3.64-3.56 (m, 1H), 2.40 (s, 3H), 2.16-2.06 (m, 1H), 1.98-1.87 (m, 2H), 1.54 (q, J = 7.3 Hz, 2H), 1.09 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.65 (CH), 138.24 (C), 137.57 (C), 129.46 (CH), 127.92 (CH), 108.15 (CH), 79.90 (C), 76.56 (CH_2), 72.35 (CH), 35.61 (CH or CH_3), 33.86 (C), 27.19 (CH_2), 21.86 (CH or CH_3), 19.14 (CH_2), 12.03 (CH or CH_3). HMRS-EI *m/z* calcd for $C_{17}H_{20}O_2$: 256.1463; found: 256.1462 [M^+].

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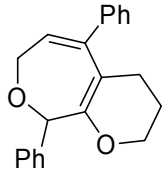
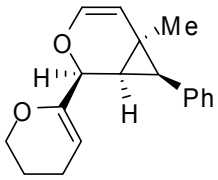
(4a*E*,5*Z*)-5,9-Diphenyl-3,4,7,9-tetrahydro-2*H*-pyrano[2,3-*c*]oxepine (58)



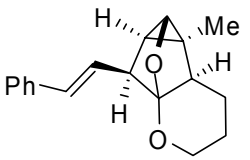
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.34-7.29 (m, 5H), 7.24-7.20 (m, 3H), 6.15 (t, J = 6.8 Hz, 1H), 5.26 (s, 1H), 4.26 (dd, J = 11.2, 6.8 Hz, 1H), 4.14 (overlapped dd, J = 11.2, 6.8 Hz, 1H), 4.13-4.08 (overlapped m, 1H), 4.03-3.98 (m, 1H), 2.15-2.08 (m, 1H), 2.02-1.94 (m, 1H), 1.89-1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 156.34 (C), 149.08 (C), 139.63 (C), 139.18 (C), 128.26 (CH, 2C), 127.92 (CH, 2C), 127.71 (CH, 2C), 127.63 (CH), 127.54 (CH, 2C), 127.19 (CH), 124.70 (CH), 111.35 (C), 77.85 (CH), 66.67 (CH_2), 62.41 (CH_2), 23.41 (CH_2), 22.19 (CH_2). HRMS-ESI *m/z* calcd for $C_{21}H_{20}O_2Na$: 327.1361; found: 327.1364 [M^++Na].

2-(3,4-Dihydro-2*H*-pyran-6-yl)-6-methyl-7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (59)



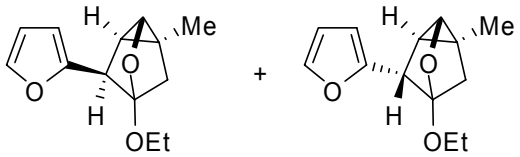
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.21-7.17 (m, 3H), 6.27 (d, J = 5.9 Hz, 1H), 5.18 (d, J = 5.9 Hz, 1H), 4.97 (t, J = 3.9 Hz, 1H), 4.17 (br s, 1H), 4.07 (dd, J = 5.9, 4.4 Hz, 2H), 2.47 (d, J = 5.7 Hz, 1H), 2.06-2.02 (m, 2H), 1.89 (dd, J = 5.7, 1.6 Hz, 1H), 1.87-1.81 (m, 2H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 152.99 (C), 140.78 (CH), 138.21 (C), 129.03 (CH, 2C), 128.09 (CH, 2C), 126.02 (CH), 111.51 (CH), 97.94 (CH), 70.62 (CH), 66.53 (CH_2), 34.99 (CH), 32.05 (CH), 22.40 (CH_2), 20.01 (CH_2), 19.87 (C), 17.95 (CH_3). HRMS-ESI *m/z* calcd for $C_{18}H_{20}O_2Na$: 291.1361; found: 291.1356 [M^++Na].

Tetramer 60



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.28-7.24 (m, 2H), 7.19-7.14 (m, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.16 (dd, J = 15.9, 8.5 Hz, 1H), 3.91-3.82 (m, 2H), 3.71 (d, J = 4.2 Hz, 1H), 2.60 (d, J = 8.3 Hz, 1H), 1.72-1.69 (m, 1H), 1.61-1.57 (m, 2H), 1.45-1.42 (m, 2H), 1.21 (dd, J = 4.3, 1.0 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 137.36 (C), 132.15 (CH), 128.29 (CH, 2C), 127.01 (CH), 126.32 (CH, 2C), 126.21 (CH), 103.61 (C), 65.20 (CH_2), 56.38 (CH), 48.51 (CH), 43.29 (CH), 24.73 (CH), 24.14 (C), 23.67 (CH_2), 20.77 (CH_2), 11.57 (CH_3). HRMS-ESI *m/z* calcd for $C_{18}H_{20}O_2Na$: 291.1361; found: 291.1358 [M^++Na].

Tricycle 62



Yellow oil, 3:1 isomer mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.36 (m, 1H, minor), 7.34 (dd, J = 1.7, 0.8 Hz, 1H, major), 6.33 (overlapped dd, J = 3.2, 1.8 Hz, 1H, minor), 6.32 (overlapped dd, J = 3.2, 1.8 Hz, 1H, major), 6.19 (d, J = 3.1 Hz, 1H, major), 6.13-6.12 (m, 1H, minor), 3.95-3.87 (m, 1H, minor), 3.84 (d, J = 4.2 Hz, 1H, major), 3.81-3.77 (overlapped m, 1H, minor), 3.78 (overlapped d, J = 4.9 Hz, 1H, minor), 3.63 (q, J = 7.1 Hz, 2H, major), 3.14 (s, 1H, major), 3.06 (s, 1H, minor), 1.74 (d, J = 10.1 Hz, 1H, major), 1.70 (d, J = 10.1 Hz, 1H, minor), 1.65 (d, J = 10.1 Hz, 1H, major), 1.40 (d, J = 10.2 Hz, 1H, minor), 1.38 (overlapped d, J = 3.2 Hz, 1H, minor), 1.36 (overlapped d, J = 4.4 Hz, 1H, major), 1.30 (s, 3H, minor), 1.26 (s, 3H, major), 1.24 (t, J = 7.1 Hz, 3H, minor), 1.15 (t, J = 7.1 Hz, 3H, major); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 153.34 (C, minor), 152.36 (C, major), 141.77 (CH, minor), 141.30 (CH, major), 110.36 (CH, major), 110.13 (CH, minor), 107.25 (C, minor), 106.86 (CH, minor), 106.78 (CH, major), 106.53 (C, major), 62.30 (CH_2, major), 62.18 (CH_2, minor), 57.55 (CH, minor), 57.42 (CH, major), 44.32 (CH, major), 43.56 (CH, minor), 38.18 (CH_2, major), 35.59 (CH_2, minor), 23.88 (CH, major), 23.29 (CH, minor), 20.97 (C, minor), 20.60 (C, major), 15.61 (CH_3, major), 15.48 (CH_3, minor), 14.19 (CH_3, major), 14.01 (CH_3, minor). HRMS-ESI *m/z* calcd for $C_{13}H_{16}O_3Na$: 243.0997; found: 243.1005 [M^++Na].

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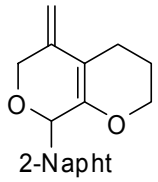
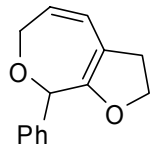
5-Methylene-8-(naphthalen-2-yl)-2,3,4,5,6,8-hexahydropyrano[3,4-*b*]pyran (63)



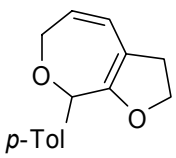
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.81 (m, 4H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.48-7.46 (m, 2H), 5.28 (s, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 4.32 (d, J = 13.3 Hz, 1H), 4.24 (d, J = 13.3 Hz, 1H), 4.06-3.97 (m, 2H), 2.36 (dt, J = 16.5, 6.5 Hz, 1H), 2.26 (dtd, J = 16.4, 6.6, 2.2 Hz, 1H), 2.02-1.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 151.45 (C), 140.63 (C), 135.94 (C), 133.37 (C), 133.14 (C), 128.18 (CH), 128.12 (CH), 127.79 (CH), 127.67 (CH), 126.22 (CH), 126.08 (CH), 125.98 (CH), 106.95 (C), 100.99 (CH_2), 76.59 (CH), 66.87 (CH_2), 66.36 (CH_2), 22.30 (CH_2), 19.21 (CH_2). HRMS-ESI *m/z* calcd for $C_{19}H_{18}O_2Na$: 301.1204; found: 301.1216 [M^++Na].

(*Z*)-8-Phenyl-2,3,6,8-tetrahydrofuro[2,3-*c*]oxepine (64)



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 6.04 (d, J = 10.5 Hz, 1H), 5.81 (dt, J = 10.5, 5.1 Hz, 1H), 5.51 (br s, 1H), 4.39-4.30 (m, 2H), 4.18 (dd, J = 15.3, 5.1 Hz, 1H), 4.08 (dd, J = 15.4, 5.3 Hz, 1H), 2.94-2.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 157.93 (C), 139.22 (C), 128.45 (CH, 2C), 128.43 (CH), 128.41 (CH, 2C), 127.10 (CH), 124.75 (CH), 109.72 (C), 80.31 (CH), 69.79 (CH_2), 64.95 (CH_2), 33.89 (CH_2). HRMS-ESI *m/z* calcd for $C_{14}H_{14}O_2Na$: 237.0891; found: 237.0897 [M^++Na].

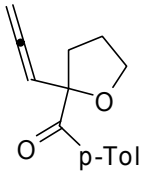
(*Z*)-8-*p*-Tolyl-2,3,6,8-tetrahydrofuro[2,3-*c*]oxepine (65)



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.03 (d, J = 10.5 Hz, 1H), 5.79 (dt, J = 10.5, 5.2 Hz, 1H), 5.47 (s, 1H), 4.38-4.30 (m, 2H), 4.18 (dd, J = 15.3, 5.1 Hz, 1H), 4.06 (dd, J = 15.4, 5.4 Hz, 1H),

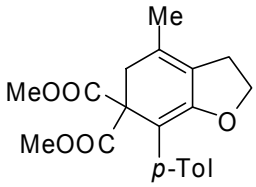
2.93-2.82 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 158.10 (C), 138.22 (C), 136.26 (C), 129.15 (CH, 2C), 128.39 (CH, 2C), 127.08 (CH), 124.66 (CH), 109.61 (C), 80.04 (CH), 69.78 (CH_2), 64.75 (CH_2), 33.90 (CH_2), 21.23 (CH_3). HRMS-ESI *m/z* calcd for $C_{15}H_{16}O_2Na$: 251.1048; found: 251.1044 [M^++Na].

(2-(Propa-1,2-dienyl)tetrahydrofuran-2-yl)(*p*-tolyl)methanone (66)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 5.49 (t, J = 6.6 Hz, 1H), 4.90 (dd, J = 11.3, 6.6 Hz, 1H), 4.84 (dd, J = 11.3, 6.3 Hz, 1H), 4.02 (dt, J = 14.3, 7.6 Hz, 1H), 3.87 (dt, J = 14.3, 7.6 Hz, 1H), 2.70-2.62 (m, 1H), 2.39 (s, 3H), 2.14-2.07 (m, 1H), 2.01-1.95 (m, 1H), 1.90-1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 207.21 (C), 198.81 (C), 143.47 (C), 132.14 (C), 130.52 (CH, 2C), 128.75 (CH, 2C), 94.99 (CH), 89.34 (C), 78.72 (CH_2), 68.91 (CH_2), 34.75 (CH_2), 24.99 (CH_2), 21.65 (CH_3). HRMS-ESI *m/z* calcd for $C_{15}H_{16}O_2Na$: 251.1048; found: 251.1038 [M^++Na].

Dimethyl 4-methyl-7-*p*-tolyl-2,3-dihydrobenzofuran-6,6(5*H*)-dicarboxylate (73b)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 4.26 (t, J = 7.4 Hz, 2H), 3.60 (s, 6H), 3.00 (s, 2H), 2.66 (br s, 2H), 2.29 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 172.55 (2C), 152.86 (C), 135.63 (C), 133.36 (C), 128.83 (CH, 2C), 128.48 (CH, 2C), 127.63 (C), 126.53 (C), 100.17 (C), 70.47 (CH_2), 61.48 (C), 52.62 (CH_3, 2C), 39.16 (CH_2), 26.61 (CH_2), 21.18 (CH_3), 19.60 (CH_3). HRMS-ESI *m/z* calcd for $C_{20}H_{22}O_5Na$: 365.1365; found: 365.1356 [M^++Na].

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7. X-Ray Structure of Tricycle 49b

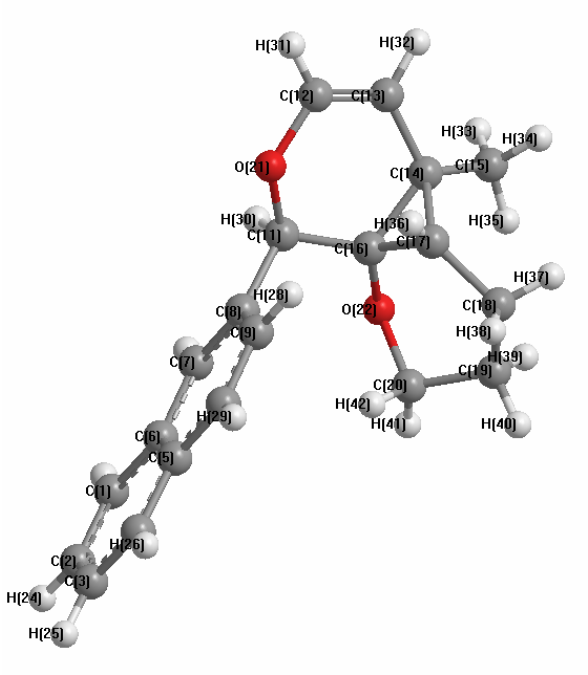

Table 1. Crystal data and structure refinement for **49b**

Empirical formula	C20 H20 O2	
Formula weight	292.36	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.37920(10) Å	α = 90°.
	b = 6.09700(10) Å	β = 94.1530(10)°.
	c = 16.8579(2) Å	γ = 90°.
Volume	756.462(18) $Å^3$	
Z	2	
Density (calculated)	1.284 Mg/m^3	
Absorption coefficient	0.640 mm-1	
F(000)	312	
Crystal size	0.19 x 0.09 x 0.03 mm^3	
Theta range for data collection	2.63 to 70.54°.	
Index ranges	-7<=h<=9, -6<=k<=7, -19<=l<=19	

Reflections collected	4895
Independent reflections	2330 [R(int) = 0.0174]
Completeness to theta = 70.54°	94.5 %
Absorption correction	YES, SADABS v. 2.03
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2330 / 1 / 280
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0825
R indices (all data)	R1 = 0.0326, wR2 = 0.0839
Absolute structure parameter	0.0(2)
Extinction coefficient	0.0004(7)
Largest diff. peak and hole	0.156 and -0.155 e.$Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for **49b**.

C(1)-C(2)	1.370(2)	C(10)-H(10)	0.97(2)
C(1)-C(6)	1.421(2)	C(11)-O(1)	1.4404(19)
C(1)-H(1)	0.99(2)	C(11)-C(16)	1.523(2)
C(2)-C(3)	1.406(3)	C(11)-H(11)	1.01(2)
C(2)-H(2)	1.00(2)	C(12)-C(13)	1.323(3)
C(3)-C(4)	1.369(2)	C(12)-O(1)	1.379(2)
C(3)-H(3)	1.016(19)	C(12)-H(12)	0.96(2)
C(4)-C(5)	1.422(2)	C(13)-C(14)	1.479(3)
C(4)-H(4)	0.94(2)	C(13)-H(13)	0.98(2)
C(5)-C(6)	1.417(2)	C(14)-C(15)	1.508(2)
C(5)-C(10)	1.420(2)	C(14)-C(16)	1.511(2)
C(6)-C(7)	1.425(2)	C(14)-C(17)	1.547(3)
C(7)-C(8)	1.366(2)	C(15)-H(15A)	0.98(4)
C(7)-H(7)	0.99(2)	C(15)-H(15B)	1.01(2)
C(8)-C(9)	1.423(3)	C(15)-H(15C)	1.00(3)
C(8)-C(11)	1.509(2)	C(16)-O(2)	1.4024(19)
C(9)-C(10)	1.372(2)	C(16)-C(17)	1.503(2)
C(9)-H(9)	0.990(18)	C(17)-C(18)	1.514(3)

C(17)-H(17)	0.99(2)	C(10)-C(9)-C(8)	120.67(15)
C(18)-C(19)	1.536(3)	C(10)-C(9)-H(9)	119.7(11)
C(18)-H(18A)	0.99(2)	C(8)-C(9)-H(9)	119.6(11)
C(18)-H(18B)	0.96(3)	C(9)-C(10)-C(5)	120.67(16)
C(19)-C(20)	1.514(3)	C(9)-C(10)-H(10)	120.1(10)
C(19)-H(19A)	0.97(2)	C(5)-C(10)-H(10)	119.2(10)
C(19)-H(19B)	1.01(3)	O(1)-C(11)-C(8)	107.16(13)
C(20)-O(2)	1.439(2)	O(1)-C(11)-C(16)	112.46(13)
C(20)-H(20A)	0.97(2)	C(8)-C(11)-C(16)	111.83(14)
C(20)-H(20B)	1.008(19)	O(1)-C(11)-H(11)	108.8(10)
C(2)-C(1)-C(6)	119.91(17)	C(8)-C(11)-H(11)	110.5(11)
C(2)-C(1)-H(1)	122.7(10)	C(16)-C(11)-H(11)	106.1(11)
C(6)-C(1)-H(1)	117.4(10)	C(13)-C(12)-O(1)	124.09(16)
C(1)-C(2)-C(3)	121.07(16)	C(13)-C(12)-H(12)	123.2(11)
C(1)-C(2)-H(2)	119.1(13)	O(1)-C(12)-H(12)	112.6(11)
C(3)-C(2)-H(2)	119.8(13)	C(12)-C(13)-C(14)	122.42(16)
C(4)-C(3)-C(2)	120.30(16)	C(12)-C(13)-H(13)	119.1(12)
C(4)-C(3)-H(3)	120.0(11)	C(14)-C(13)-H(13)	118.3(12)
C(2)-C(3)-H(3)	119.7(11)	C(13)-C(14)-C(15)	117.05(15)
C(3)-C(4)-C(5)	120.37(17)	C(13)-C(14)-C(16)	112.90(15)
C(3)-C(4)-H(4)	119.2(11)	C(15)-C(14)-C(16)	121.19(14)
C(5)-C(4)-H(4)	120.4(11)	C(13)-C(14)-C(17)	115.36(15)
C(6)-C(5)-C(10)	118.91(15)	C(15)-C(14)-C(17)	118.70(16)
C(6)-C(5)-C(4)	119.12(15)	C(16)-C(14)-C(17)	58.88(11)
C(10)-C(5)-C(4)	121.96(16)	C(14)-C(15)-H(15A)	115.5(17)
C(5)-C(6)-C(1)	119.22(15)	C(14)-C(15)-H(15B)	108.5(13)
C(5)-C(6)-C(7)	119.03(14)	H(15A)-C(15)-H(15B)	107(2)
C(1)-C(6)-C(7)	121.75(16)	C(14)-C(15)-H(15C)	111.5(14)
C(8)-C(7)-C(6)	121.22(16)	H(15A)-C(15)-H(15C)	106(3)
C(8)-C(7)-H(7)	120.4(11)	H(15B)-C(15)-H(15C)	108(2)
C(6)-C(7)-H(7)	118.3(11)	O(2)-C(16)-C(17)	118.09(14)
C(7)-C(8)-C(9)	119.51(15)	O(2)-C(16)-C(14)	117.79(13)
C(7)-C(8)-C(11)	120.59(16)	C(17)-C(16)-C(14)	61.75(12)
C(9)-C(8)-C(11)	119.82(15)	O(2)-C(16)-C(11)	111.12(13)

C(17)-C(16)-C(11)	121.90(14)	C(20)-C(19)-C(18)	111.39(15)
C(14)-C(16)-C(11)	118.22(14)	C(20)-C(19)-H(19A)	106.2(13)
C(16)-C(17)-C(18)	119.55(15)	C(18)-C(19)-H(19A)	113.5(12)
C(16)-C(17)-C(14)	59.37(11)	C(20)-C(19)-H(19B)	111.1(13)
C(18)-C(17)-C(14)	123.68(14)	C(18)-C(19)-H(19B)	109.2(13)
C(16)-C(17)-H(17)	112.8(13)	H(19A)-C(19)-H(19B)	105.3(18)
C(18)-C(17)-H(17)	116.3(13)	O(2)-C(20)-C(19)	109.41(15)
C(14)-C(17)-H(17)	112.8(13)	O(2)-C(20)-H(20A)	104.0(13)
C(17)-C(18)-C(19)	114.44(16)	C(19)-C(20)-H(20A)	110.9(11)
C(17)-C(18)-H(18A)	110.6(12)	O(2)-C(20)-H(20B)	106.9(11)
C(19)-C(18)-H(18A)	108.8(11)	C(19)-C(20)-H(20B)	113.5(11)
C(17)-C(18)-H(18B)	104.2(15)	H(20A)-C(20)-H(20B)	111.6(14)
C(19)-C(18)-H(18B)	109.5(14)	C(12)-O(1)-C(11)	115.44(13)
H(18A)-C(18)-H(18B)	109(2)	C(16)-O(2)-C(20)	111.72(13)

Symmetry transformations used to generate equivalent atoms.

Table 3. Torsion angles [°] for **49b**.

C(6)-C(1)-C(2)-C(3)	0.2(2)
C(1)-C(2)-C(3)-C(4) -	0.8(2)
C(2)-C(3)-C(4)-C(5)	0.7(2)
C(3)-C(4)-C(5)-C(6)	0.0(2)
C(3)-C(4)-C(5)-C(10)	178.82(14)
C(10)-C(5)-C(6)-C(1)-	179.40(15)
C(4)-C(5)-C(6)-C(1)	-0.5(2)
C(10)-C(5)-C(6)-C(7)-	0.3(2)
C(4)-C(5)-C(6)-C(7)	178.56(15)
C(2)-C(1)-C(6)-C(5)	0.4(2)
C(2)-C(1)-C(6)-C(7)	-178.66(14)
C(5)-C(6)-C(7)-C(8)	-0.1(2)
C(1)-C(6)-C(7)-C(8)	178.94(14)
C(6)-C(7)-C(8)-C(9)	0.4(2)
C(6)-C(7)-C(8)-C(11)	177.20(14)

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C(7)-C(8)-C(9)-C(10)-	0.3(2)
C(11)-C(8)-C(9)-C(10)	-177.11(14)
C(8)-C(9)-C(10)-C(5)	-0.1(2)
C(6)-C(5)-C(10)-C(9)	0.4(2)
C(4)-C(5)-C(10)-C(9)-	178.40(15)
C(7)-C(8)-C(11)-O(1)	135.32(16)
C(9)-C(8)-C(11)-O(1)	-47.9(2)
C(7)-C(8)-C(11)-C(16)	-101.01(18)
C(9)-C(8)-C(11)-C(16)	75.73(18)
O(1)-C(12)-C(13)-C(14)	-1.3(3)
C(12)-C(13)-C(14)-C(15)	159.9(2)
C(12)-C(13)-C(14)-C(16)	12.0(3)
C(12)-C(13)-C(14)-C(17)	-53.1(3)
C(13)-C(14)-C(16)-O(2)	144.53(16)
C(15)-C(14)-C(16)-O(2)	-1.9(3)
C(17)-C(14)-C(16)-O(2)	-108.72(17)
C(13)-C(14)-C(16)-C(17)	-106.75(18)
C(15)-C(14)-C(16)-C(17)	106.9(2)
C(13)-C(14)-C(16)-C(11)	6.4(2)
C(15)-C(14)-C(16)-C(11)	-140.03(19)
C(17)-C(14)-C(16)-C(11)	113.10(17)
O(1)-C(11)-C(16)-O(2)	-174.25(15)
C(8)-C(11)-C(16)-O(2)	65.12(19)
O(1)-C(11)-C(16)-C(17)	39.1(2)
C(8)-C(11)-C(16)-C(17)	-81.50(18)
O(1)-C(11)-C(16)-C(14)	-33.5(2)
C(8)-C(11)-C(16)-C(14)	-154.11(15)
O(2)-C(16)-C(17)-C(18)	-5.6(2)
C(14)-C(16)-C(17)-C(18)	-113.90(17)
C(11)-C(16)-C(17)-C(18)	138.77(16)
O(2)-C(16)-C(17)-C(14)	108.25(16)
C(11)-C(16)-C(17)-C(14)	-107.33(17)
C(13)-C(14)-C(17)-C(16)	102.52(17)
C(15)-C(14)-C(17)-C(16)	-111.05(17)

C(13)-C(14)-C(17)-C(18)	-150.37(17)
C(15)-C(14)-C(17)-C(18)	-3.9(2)
C(16)-C(14)-C(17)-C(18)	107.11(18)
C(16)-C(17)-C(18)-C(19)	0.2(2)
C(14)-C(17)-C(18)-C(19)	-70.8(2)
C(17)-C(18)-C(19)-C(20)	-26.7(2)
C(18)-C(19)-C(20)-O(2)	60.6(2)
C(13)-C(12)-O(1)-C(11)	-28.9(3)
C(8)-C(11)-O(1)-C(12)	167.45(16)
C(16)-C(11)-O(1)-C(12)	44.2(2)
C(17)-C(16)-O(2)-C(20)	39.25(19)
C(14)-C(16)-O(2)-C(20)	110.27(17)
C(11)-C(16)-O(2)-C(20)	-108.77(16)
C(19)-C(20)-O(2)-C(16)	-67.51(18)

Symmetry transformations used to generate equivalent atoms.

8. X-Ray Structure of Tetracycle 60

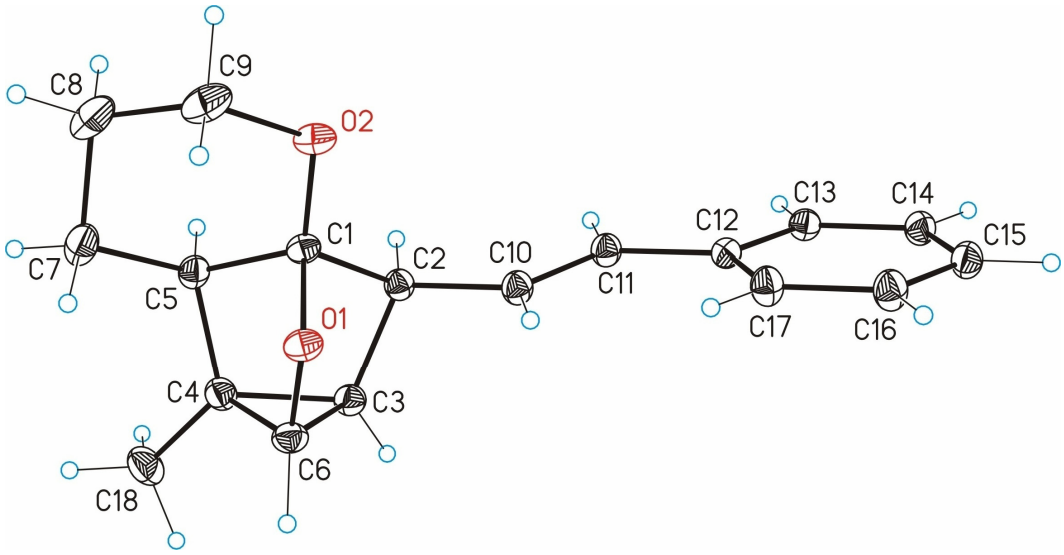

Table 1. Crystal data and structure refinement for **60**.

Empirical formula	C18 H20 O2

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Formula weight	268.34	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.6053(11) Å	α= 90°.
	b = 9.2113(8) Å	β= 90.260(2)°.
	c = 13.2192(12) Å	γ = 90°.
Volume	1413.1(2) $Å^3$	
Z	4	
Density (calculated)	1.261 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	576	
Crystal size	0.40 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.70 to 39.58°.	
Index ranges	-17<=h<=17, -10<=k<=16, -23<=l<=19	
Reflections collected	21754	
Independent reflections	6835 [R(int) = 0.0237]	
Completeness to theta = 39.58°	80.1 %	
Absorption correction	SADABS (Bruker-Nonius)	
Max. and min. transmission	0.9841 and 0.9685	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6835 / 0 / 182	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.1190	
R indices (all data)	R1 = 0.0466, wR2 = 0.1257	
Largest diff. peak and hole	0.528 and -0.251 $e.Å^{-3}$	

Table 2. Bond lengths [Å] and angles [°] for **60**.

O(1)-C(6)	1.4202(7)	O(1)-C(1)	1.4559(8)

C(1)-O(2)	1.3730(7)	C(3)-C(2)-C(1)	94.15(4)
C(1)-C(5)	1.5433(7)	C(1)-O(2)-C(9)	112.01(5)
C(1)-C(2)	1.5453(7)	C(6)-C(3)-C(2)	104.39(4)
C(2)-C(10)	1.4949(7)	C(6)-C(3)-C(4)	59.31(4)
C(2)-C(3)	1.5306(9)	C(2)-C(3)-C(4)	108.40(4)
O(2)-C(9)	1.4579(8)	C(18)-C(4)-C(6)	123.92(6)
C(3)-C(6)	1.5197(9)	C(18)-C(4)-C(5)	123.42(5)
C(3)-C(4)	1.5382(8)	C(6)-C(4)-C(5)	103.65(4)
C(4)-C(18)	1.5019(9)	C(18)-C(4)-C(3)	123.43(5)
C(4)-C(6)	1.5131(8)	C(6)-C(4)-C(3)	59.73(4)
C(4)-C(5)	1.5185(9)	C(5)-C(4)-C(3)	105.42(5)
C(5)-C(7)	1.5237(8)	C(4)-C(5)-C(7)	117.77(6)
C(7)-C(8)	1.5314(11)	C(4)-C(5)-C(1)	95.98(4)
C(8)-C(9)	1.5249(11)	C(7)-C(5)-C(1)	110.14(5)
C(10)-C(11)	1.3381(9)	O(1)-C(6)-C(4)	109.33(5)
C(11)-C(12)	1.4737(7)	O(1)-C(6)-C(3)	108.06(5)
C(12)-C(13)	1.4010(8)	C(4)-C(6)-C(3)	60.95(4)
C(12)-C(17)	1.4045(8)	C(5)-C(7)-C(8)	107.69(6)
C(13)-C(14)	1.3957(8)	C(9)-C(8)-C(7)	111.03(5)
C(14)-C(15)	1.3911(9)	O(2)-C(9)-C(8)	112.35(5)
C(15)-C(16)	1.3943(9)	C(11)-C(10)-C(2)	124.48(5)
C(16)-C(17)	1.3906(8)	C(10)-C(11)-C(12)	125.92(5)
C(6)-O(1)-C(1)	98.32(4)	C(13)-C(12)-C(17)	118.19(5)
O(2)-C(1)-O(1)	111.49(4)	C(13)-C(12)-C(11)	119.43(5)
O(2)-C(1)-C(5)	117.67(4)	C(17)-C(12)-C(11)	122.37(5)
O(1)-C(1)-C(5)	102.86(5)	C(14)-C(13)-C(12)	120.94(5)
O(2)-C(1)-C(2)	116.75(5)	C(15)-C(14)-C(13)	120.04(6)
O(1)-C(1)-C(2)	102.68(4)	C(14)-C(15)-C(16)	119.76(5)
C(5)-C(1)-C(2)	103.48(4)	C(17)-C(16)-C(15)	120.12(6)
C(10)-C(2)-C(3)	113.22(5)	C(16)-C(17)-C(12)	120.94(6)
C(10)-C(2)-C(1)	114.13(4)		

Symmetry transformations used to generate equivalent atoms.

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Table 3. Torsion angles [°] for **60**.

C(6)-O(1)-C(1)-O(2)	179.43(4)
C(6)-O(1)-C(1)-C(5)	52.43(5)
C(6)-O(1)-C(1)-C(2)	-54.81(5)
O(2)-C(1)-C(2)-C(10)	57.89(7)
O(1)-C(1)-C(2)-C(10)	-64.38(6)
C(5)-C(1)-C(2)-C(10)	-171.15(5)
O(2)-C(1)-C(2)-C(3)	175.65(5)
O(1)-C(1)-C(2)-C(3)	53.38(5)
C(5)-C(1)-C(2)-C(3)	-53.39(5)
O(1)-C(1)-O(2)-C(9)	-67.39(6)
C(5)-C(1)-O(2)-C(9)	51.06(7)
C(2)-C(1)-O(2)-C(9)	175.05(5)
C(10)-C(2)-C(3)-C(6)	87.48(5)
C(1)-C(2)-C(3)-C(6)	-31.02(5)
C(10)-C(2)-C(3)-C(4)	149.45(5)
C(1)-C(2)-C(3)-C(4)	30.95(5)
C(6)-C(3)-C(4)-C(18)	-112.89(7)
C(2)-C(3)-C(4)-C(18)	150.95(6)
C(2)-C(3)-C(4)-C(6)	-96.16(5)
C(6)-C(3)-C(4)-C(5)	97.04(5)
C(2)-C(3)-C(4)-C(5)	0.88(6)
C(18)-C(4)-C(5)-C(7)	60.99(8)
C(6)-C(4)-C(5)-C(7)	-87.04(6)
C(3)-C(4)-C(5)-C(7)	-148.94(5)
C(18)-C(4)-C(5)-C(1)	177.50(6)
C(6)-C(4)-C(5)-C(1)	29.47(6)
C(3)-C(4)-C(5)-C(1)	-32.43(5)
O(2)-C(1)-C(5)-C(4)	-174.45(5)
O(1)-C(1)-C(5)-C(4)	-51.50(5)
C(2)-C(1)-C(5)-C(4)	55.14(6)
O(2)-C(1)-C(5)-C(7)	-51.95(8)

O(1)-C(1)-C(5)-C(7)	71.00(6)
C(2)-C(1)-C(5)-C(7)	177.64(5)
C(1)-O(1)-C(6)-C(4)	-32.17(6)
C(1)-O(1)-C(6)-C(3)	32.57(5)
C(18)-C(4)-C(6)-O(1)	-147.47(6)
C(5)-C(4)-C(6)-O(1)	0.35(6)
C(3)-C(4)-C(6)-O(1)	100.43(6)
C(18)-C(4)-C(6)-C(3)	112.10(6)
C(5)-C(4)-C(6)-C(3)	-100.08(5)
C(2)-C(3)-C(6)-O(1)	0.56(5)
C(4)-C(3)-C(6)-O(1)	-102.54(5)
C(2)-C(3)-C(6)-C(4)	103.10(5)
C(4)-C(5)-C(7)-C(8)	160.21(5)
C(1)-C(5)-C(7)-C(8)	51.64(7)
C(5)-C(7)-C(8)-C(9)	-56.66(8)
C(1)-O(2)-C(9)-C(8)	-52.87(8)
C(7)-C(8)-C(9)-O(2)	57.49(9)
C(3)-C(2)-C(10)-C(11)	115.31(7)
C(1)-C(2)-C(10)-C(11)	-138.51(6)
C(2)-C(10)-C(11)-C(12)	-178.82(5)
C(10)-C(11)-C(12)-C(13)	172.13(6)
C(10)-C(11)-C(12)-C(17)	-7.76(9)
C(17)-C(12)-C(13)-C(14)	1.07(9)
C(11)-C(12)-C(13)-C(14)	-178.82(5)
C(12)-C(13)-C(14)-C(15)	-0.78(9)
C(13)-C(14)-C(15)-C(16)	0.14(10)
C(14)-C(15)-C(16)-C(17)	0.19(10)
C(15)-C(16)-C(17)-C(12)	0.12(10)
C(13)-C(12)-C(17)-C(16)	-0.74(9)
C(11)-C(12)-C(17)-C(16)	179.15(6)

Symmetry transformations used to generate equivalent atoms.

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Chapter 4. Introduction

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1. Synthesis of Pyrroles

Pyrroles are very important heterocycles found as structural motifs in a number of naturally occurring biologically active compounds,[1] such as marine pyrrole-based alkaloids[2] and pyrrole-imidazole alkaloids.[3] Pyrroles, especially polypyrroles for their conducting properties,[4] are as well used in materials science.[5]

Pyrroles have also gained importance in the field of medicinal chemistry. Pyrrole derivatives, of which some are shown in Figure 1, have very interesting therapeutic activities.[6] For example, atorvastatin is a totally synthetic drug used to

1 Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Pergamon Press: Oxford, **1996**, Vol. *2*, 149.

2 Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54-62.

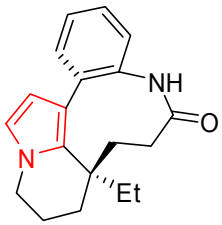
3 Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237-243.

4 (a) MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27-34. (b) *Handbook of Conducting Polymers*; 2nd ed.; Skotheim, T. A.; Elsenbaumer, R. L.; Reynolds, J. R.; Eds.; Marcel Dekker: New York, **1998**.

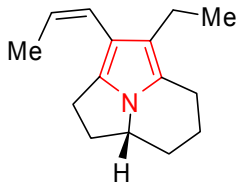
5 Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992-4993 and references therein.

6 (a) Gossauer, A. *Pyrrole*; Thieme: Stuttgart, **1994**. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817-2825. (c) Sayah, B.; Pelloux-Léon, N.; Vallée, Y. *J. Org. Chem.* **2000**, *65*,

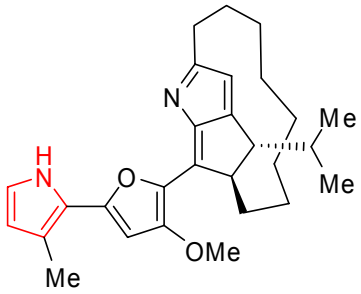
reduce cholesterol levels in blood. This compound inhibits the enzyme HMG-CoA reductase that plays a crucial role in cholesterol biosynthesis.[7] In addition to antitumor activity,[8] pyrroles are also known to possess antifungal,[9] anti-inflammatory[10] and immunosuppressant activity.[11] Certain highly substituted pyrroles show antibacterial, antiviral and antioxidant activities and inhibit cytokine-mediated diseases.[12]



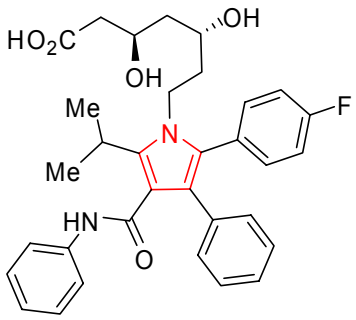
Rhazinilam (Tubulin polymerization-depolymerization inhibitor)



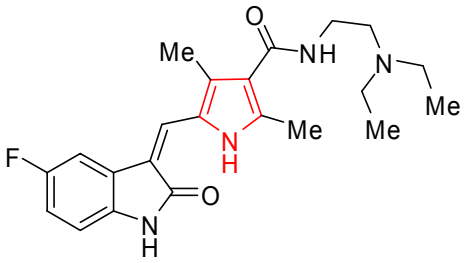
Myrmicarin 215-A (Poison isolated from African ants)



Roseophilin A (Antibiotic)



Atorvastatin (Reduction of cholesterol levels in blood)



Sunitinib (Treatment of gastrointestinal tumor)

Figure 1

2824-2826. (d) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587-3595.

7 Corey, E. J.; Czakó, B.; Kürti, L. In *Molecules and Medicine*; Wiley VCH: Weinheim, **2007**.

8 Cozzi, P.; Mongell, N. *Current Pharm. Des.* **1998**, *4*, 181-201.

9 (a) Castro, J.; Coteron, J. M.; Fraile, M. T.; Garcia-Ochoa, S.; Gómez de las Heras, F.; Martin-Cuesta, A. *Tetrahedron Lett.* **2002**, *43*, 1851-1854. (b) Tafi, A.; Costi, R.; Botta, M.; Santo, R. D.; Correlli, F.; Massa, S.; Ciacci, A.; Manetti, F.; Artico, M. *J. Med. Chem.* **2002**, *45*, 2720-2732.

10 Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109-135.

11 Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305-8314.

12 Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297-3300 and references therein.

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Pyrroles can be synthesized in a number of ways; which are summarized in Figure 2.

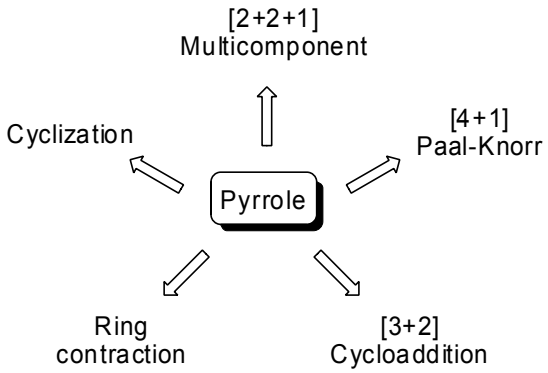
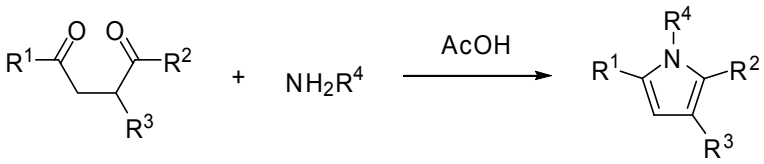


Figure 2

1.1. Paal-Knorr pyrrole synthesis

The Paal-Knorr[1,13] pyrrole synthesis is the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to give a pyrrole (Scheme 1). The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at pH < 3 lead to furans as main products.



Scheme 1

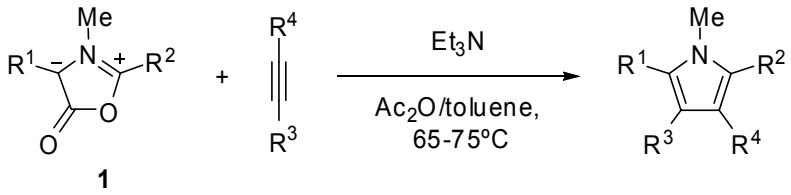
1.2. 1,3-Dipolar cycloaddition

The cycloaddition process consists of the reaction of azomethine ylides (1,3-dipole) with alkenes or alkynes (dipolarophile) to give five-membered ring

1 Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Pergamon Press: Oxford, **1996**, Vol. *2*, 149.

13 (a) Paal, C. *Chem. Ber*. **1884**, *17*, 2756-2767. (b) Knorr, L. *Chem. Ber*. **1884**, *17*, 2863-2870. (c) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, Heidelberg, New York, **1974**. (d) Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R., Ed.; G. Thieme Verlag: Stuttgart, **1994**; Bd. E6a, p 556.

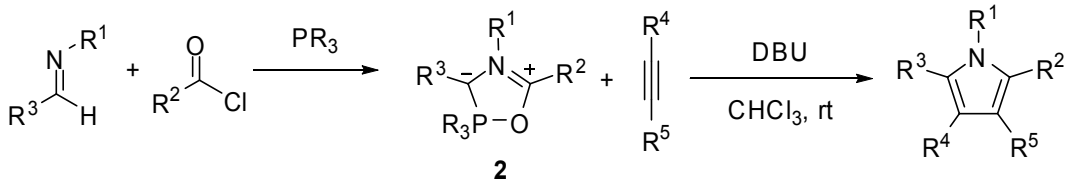
heterocycles.[14] One useful class of 1,3-dipoles is 1,3-oxazolium-5-oxides, commonly known as münchnones (**1**). The cycloaddition of **1** is usually followed by CO_2-loss and provides an efficient route to pyrroles (Scheme 2).[15]



Scheme 2

1.3. Multicomponent reactions

Multicomponent reactions in which the 1,3-dipole is generated *in situ* have also been developed.[16] In a recent example, the reaction of stabilized azomethine ylides of type **2** with alkynes to give rise to a wide variety of substituted pyrroles has been described (Scheme 3).[17] Azomethine ylide **2** is formed *in situ* by the reaction of simple imines and acid chlorides in the presence of a phosphine



Scheme 3

1.4. Ring contraction

In the ring contraction process a larger ring opens under specific reaction conditions. This is followed by a rearrangement and then the resulting acyclic moiety

14 Joule, J. A.; Mills, K. *Heterocyclic Chemistry,* 4th ed.; Blackwell Sciences Ltd: Oxford, **2000**.

15 (a) Gribble, G. W. In *The Chemistry of Heterocyclic Compounds*; Padwa, A., Ed.; Wiley: New York, **2002**; Vol. 59, p 681. (b) Coppola, B. P.; Noe, M. C.; Schwartz, D. J.; Abdon, R. L.; Trost, B. M. *Tetrahedron* **1994**, *50*, 93-116.

16 (a) Ranu, B. C.; Dey, S. S. *Tetrahedron Lett.* **2003**, *44*, 2865-2868. (b) Dhavan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468-469.

17 Cyr, D. J. St.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366-12367.

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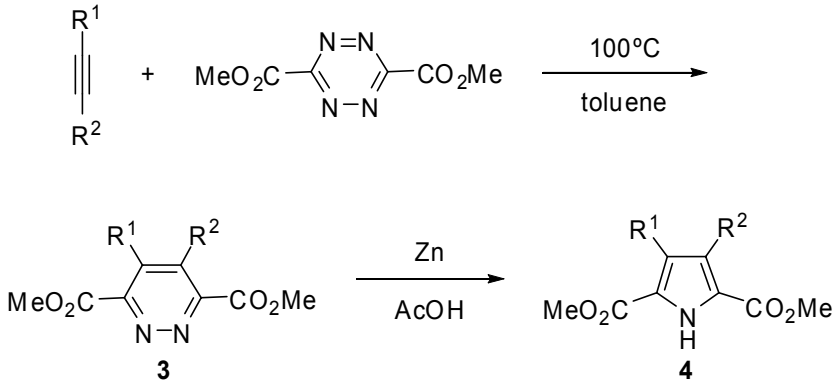
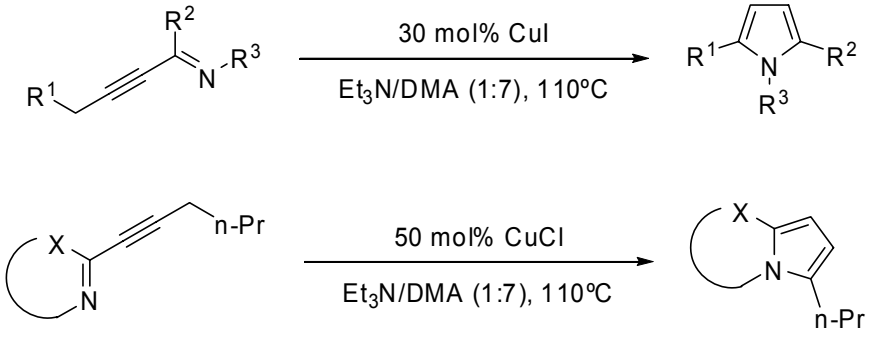
cyclizes to give a pyrrole derivative. In this process, an atom or group of atoms is totally extruded or remains as a substituent on the final pyrrole ring.[18] One example described by Boger and coworkers[19] involves [4+2] addition of an alkyne with a tetrazine, which decomposes with the release of nitrogen to give **3**. Diazine **3** is then converted into pyrrole **4** by ring reductive contraction (Scheme 4).



Scheme 4

1.5. Cyclization

Gevorgyan and co-workers have developed a novel copper(I)-catalyzed cyclization of alkynyl imines for the synthesis of pyrroles as well as fused aromatic heterocycles containing a pyrrole ring (Scheme 5).[20]



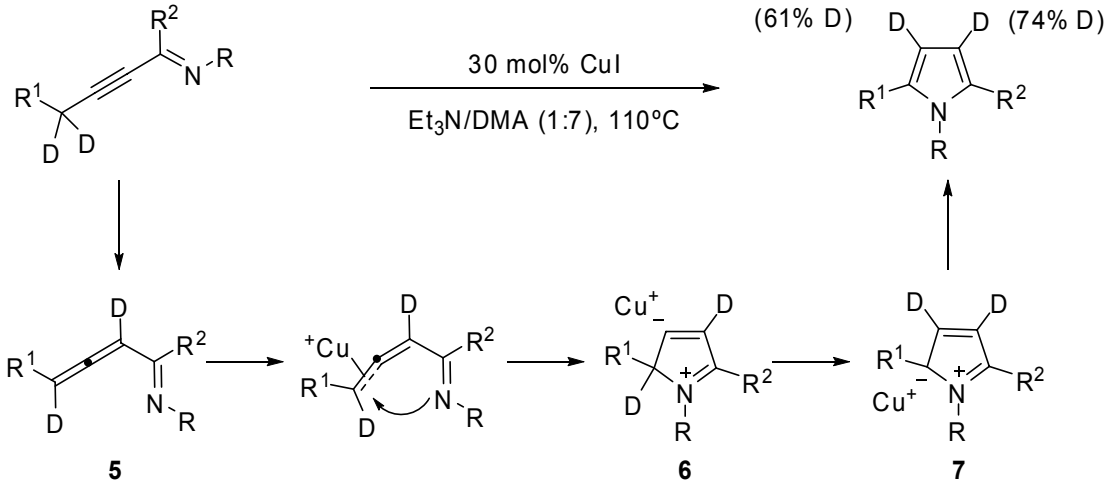
Scheme 5

18 Joshi, U.; Pipelier, M.; Naud, S.; Dubreuil, D. *Current Org. Chem.* **2005**, *9*, 261-288.

19 Boger, D. L., Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54-62.

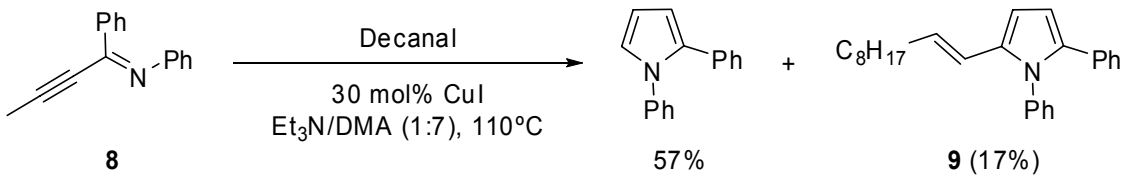
20 Kel'in, A. V.; Sromek A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074-2075.

The proposed mechanism for this transformation involves a base-induced propargyl-allenyl isomerization to form **5** (Scheme 6). Then, coordination of copper to the terminal double bound of the allene makes it susceptible to intramolecular nucleophilic attack to give **6**, which isomerizes to the more stable **7**. Pyrrole is formed after rearomatization of **7**. Deuterium labelling studies were claimed to support this proposal. In this Scheme, intermediate **7** is depicted as a zwitterion. However, this is actually just a resonance form of the final pyrrole.



Scheme 6

The group of Gevorgyan also obtained support for the involvement of intermediate **7** when they carried out the reaction of substrate **8** in the presence of decanal (Scheme 7). Along with the expected pyrrole product, they also isolated compound **9**, which is formed after the addition of an intermediate of type **7** to the aldehyde, in 17% yield.



Scheme 7

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Chapter 4. Objectives

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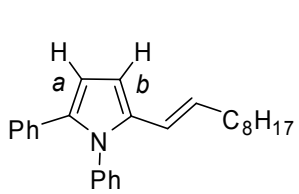
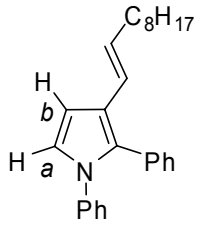
We were interested in the copper-catalyzed synthesis of pyrroles developed by Gevorgyan for its potential to obtain substituted pyrroles by trapping the copper intermediate of type **7** proposed in the mechanism (Scheme 6). Based on the spectroscopic data of compound **9**,[20] however, we believed that this compound was misassigned. The chemical shifts for the unsubstituted carbons of the pyrrole are δ = 106.1 and 123.5 ppm respectively. This large difference of *ca*. 17 ppm suggests that the downfield carbon corresponds to C-5. Subsequently, the structure of this compound is **10** instead of **9** (Figure 3). This would also mean that their mechanistic proposal for this transformation is incorrect.



9

	Protons:	Carbons:
a	H = 6.92	C = 123.5
b	H = 6.58	C = 106.1



10

	Protons:	Carbons:
a	H = 6.92	C = 123.5
b	H = 6.58	C = 106.1

Figure 3

The objective of this part of the Thesis is to study the Cu(I)-catalyzed cyclization of alkynyl imines and to determine whether the compound isolated in the reaction of alkynyl imine **8** (Scheme 7) in the presence of decanal is **9** or **10**. In the case the formed product is **10**, an alternative mechanism for this reaction has to be proposed. Additionally, in this chapter the possibility to obtain a variety of substituted pyrroles by trapping the anionic intermediate of type **7** by reaction with different electrophiles will be described.

20 Kel'in, A. V.; Sromek A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074-2075.

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Chapter 4. Results and discussion

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To establish the identity of the compound (**9** or **10**) obtained in the copper catalyzed reaction of alkynyl imine **8** in the presence of decanal (Scheme 7), we first repeated the synthesis following the procedure described by Gevorgyan[20] and studied the obtained product in detail by NMR-spectroscopy.

Based on the HMBC experiment we could distinguish between the protons of the two phenyl rings, marked as pink and green in Figure 4. In the NOESY experiment we identified three NOE-contacts indicating that pyrrole was substituted at positions 2,3 and not at positions 2,5. These data were more consistent with structure **10** than **9**.

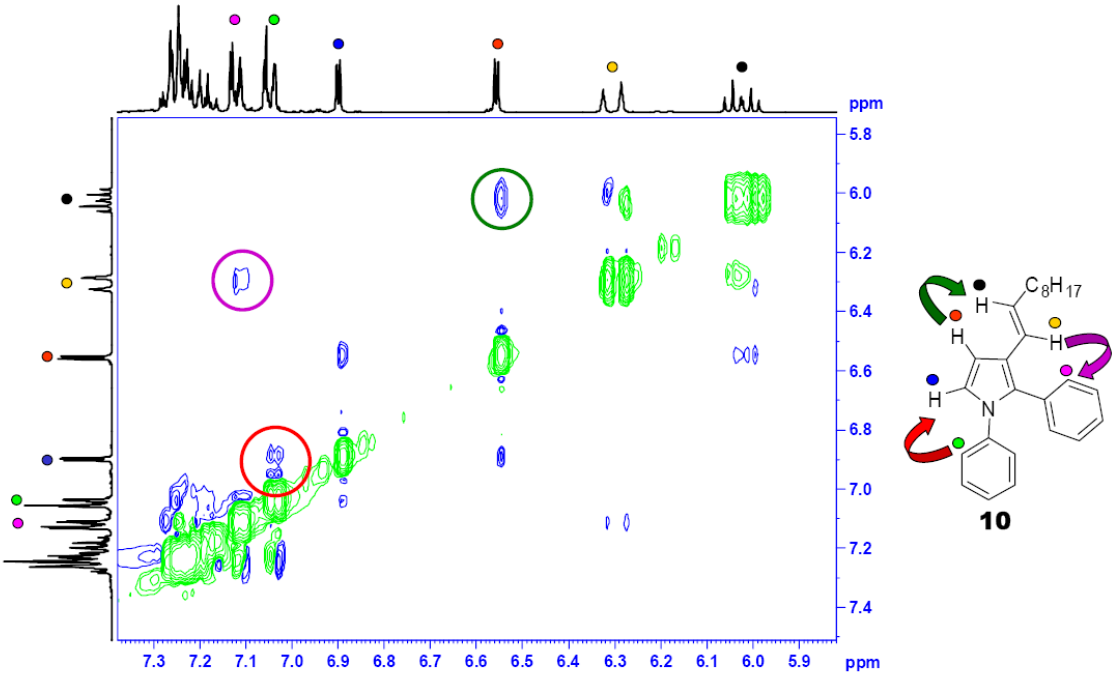
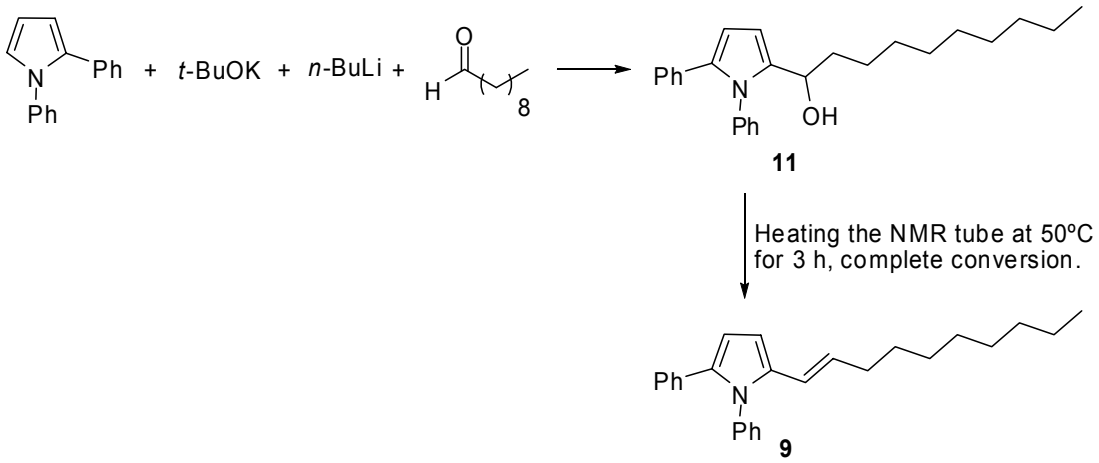


Figure 4

Then, we decided to synthesize compound **9** via an alternative route. We applied the methodology developed by Schlosser[21] for the selective α-monolithiation of *N*-phenylpyrrole. Thus, when 1,2-diphenyl-1*H*-pyrrole was treated with a mixture of *n*-BuLi/*t*-BuOK and decanal, alcohol **11** was obtained selectively (Scheme 8). Upon standing in the NMR tube with $CDCl_3$ elimination of water to give product **9** was observed. After heating the NMR tube for 3 hours complete conversion into product **9** was achieved.

20 Kel'in, A. V.; Sromek A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074-2075.

21 Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271-10278.



Scheme 8

Comparison between the ^{1}H-NMR-spectrum of compound **9** obtained via α-lithiation and the compound obtained in the reaction of alkynyl imine **8** in the presence of decanal catalyzed by copper (Scheme 7), clearly showed that the two compounds are different (Figure 5). This confirms that **10**, and not **9**, is the compound obtained in the copper-catalyzed reaction of **8** in the presence of decanal (Scheme 9).

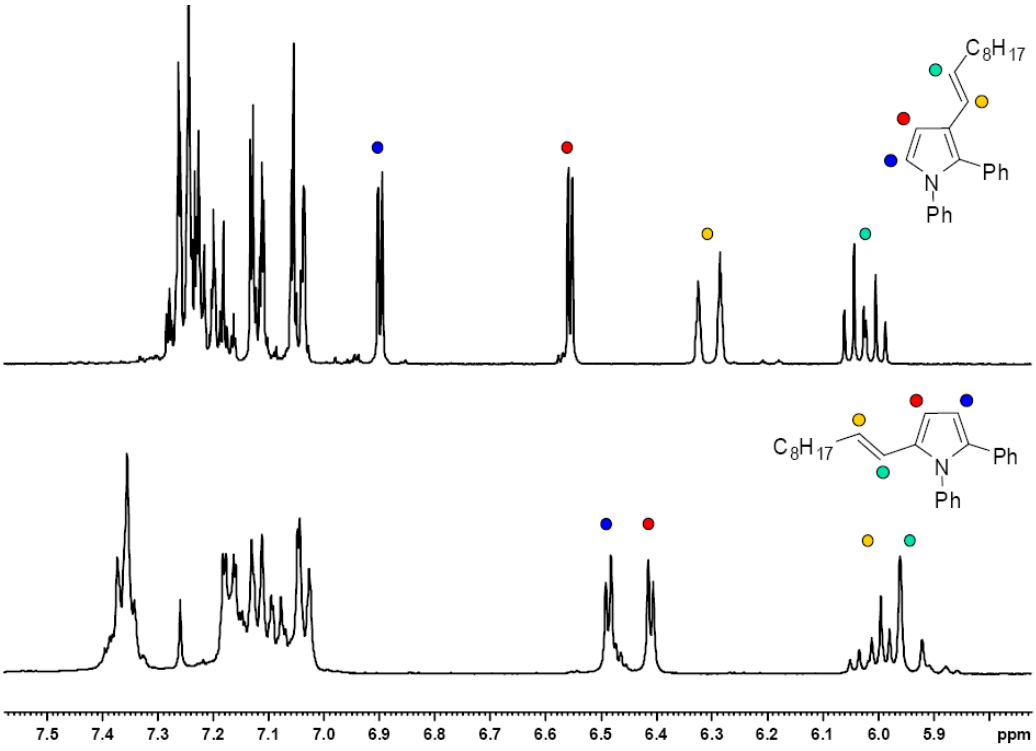


Figure 5

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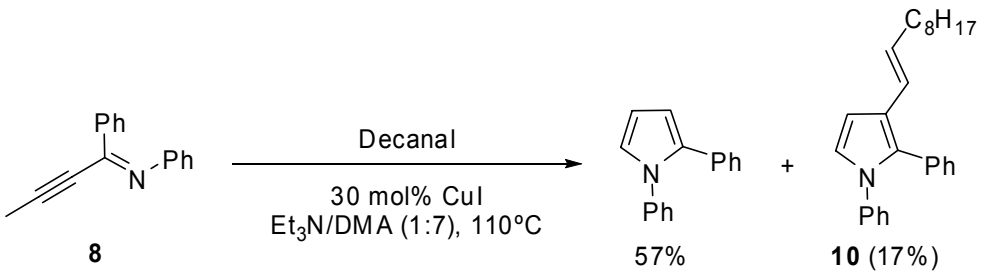
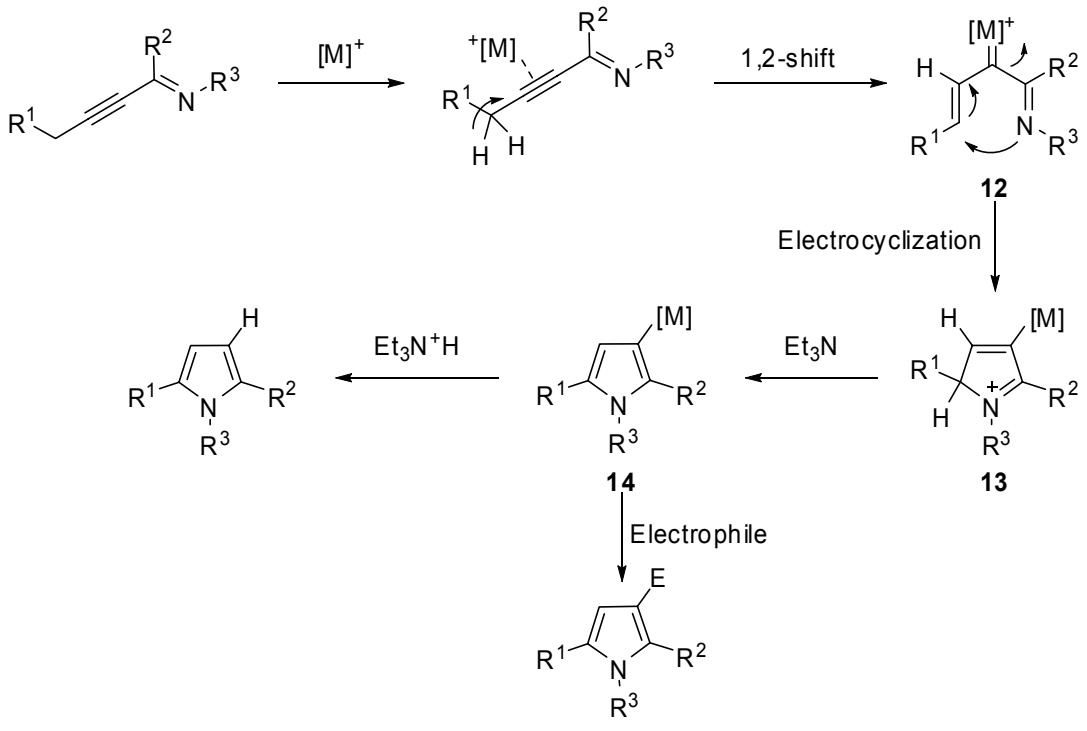


Scheme 9

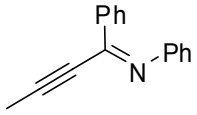
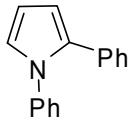
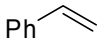
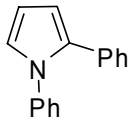
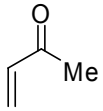
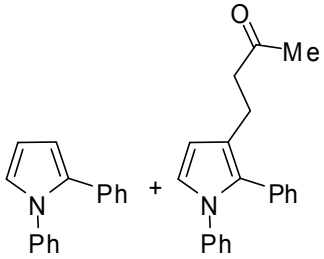
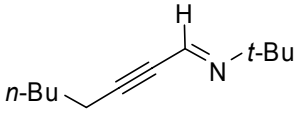
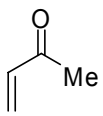
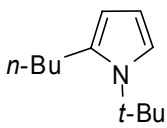
In the copper-catalyzed cyclization of alkynyl imines to form pyrroles, the Cu-C bond is formed in the 3-position and not in the 2-position (see above). Therefore, the mechanism proposed by Gevorgyan for this reaction is incorrect. The alternative mechanism that we propose for this transformation is shown in Scheme 10. After activation of the alkyne by the metal, a 1,2-proton shift forms the metal carbene intermediate **12**. This intermediate undergoes a Nazarov-type electrocyclization to give **13**, which after deprotonation forms pyrrolyl-copper complex **14**. Compound **14** can evolve by protodemetalation to yield the final observed pyrroles. Alternatively, in the presence of an electrophile, **14** reacts to form 3-substituted pyrroles, like in the example of the reaction in the presence of decanal. This proposal is in agreement with the deteuration experiments carried out by Gevorgyan.



Scheme 10

After having demonstrated that the mechanism of Gevorgyan was incorrect, we focused on preparing 3-substituted pyrroles by trapping the anionic intermediate of the reaction. The results obtained in the copper-catalyzed cyclization of different alkynyl imines in the presence of electrophiles are summarized in Table 1. Cyclization of alkynyl imine **8** in the presence of benzaldehyde or styrene resulted in the formation of the corresponding 1,2-disubstituted pyrrole without the addition of the electrophile (Table 1, entries 1 and 2). When the reaction was carried out in the presence of methyl vinyl ketone 1,2,3-trisubstituted pyrrole **15** was obtained along with the expected pyrrole, albeit in low yield (Table 1, entry 3). Reaction of compound **16** in the presence of methyl vinyl ketone only gave the 1,2-disubstituted pyrrole product and in the case of alkynyl imine **17** no reaction was observed (Table 1, entries 4 and 5).

Table 1. Copper-catalyzed cyclization of alkynyl imines in the presence of electrophiles.[a]

Entry	Alkynyl imine	Cat.	Electrophile	t (h)	Product (yield)
1	 **8**	CuI	PhCHO	4	
2	**8**	CuI		4	
3	**8**	CuI		4	 (37%) **15** (26%)
4	 **16**	CuI		7	

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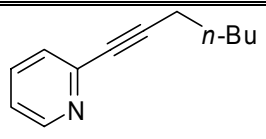
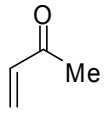
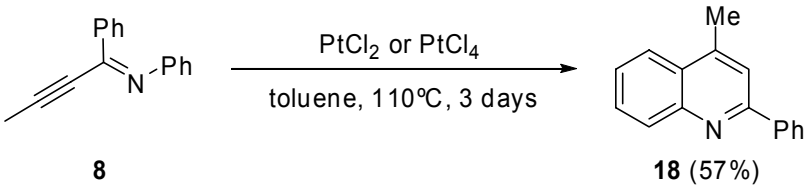
Entry	Alkynyl imine	Cat.	Electrophile	t (h)	Product (yield)
5	 **17**	CuCl		7	-

(a) Reactions carried out in DMA at 110ºC, with 30 mol% of catalyst, 4.5 equiv of Et_3N and 3 equiv of the electrophile.

In order to improve these results, other copper salts, like CuBr, CuCl or CuCN, were tested in the reaction of alkynyl imine **8** with methyl vinyl ketone as electrophile. In all cases the 3-substituted pyrrole was obtained as a minor product along with the expected 1,2-disubstituted pyrrole. When the reaction was carried out using gold or silver catalysts only starting material was recovered.

Then we tried to use platinum as catalyst for this transformation. Reaction of alkynyl imine **8** with $PtCl_2$ or $PtCl_4$ led to the formation of quinoline **18** as the only product (Scheme 11). When the reaction was done in the presence of a phosphine ligand, mixtures of quinoline **18** and 1,2-diphenyl-1*H*-pyrrole were observed.

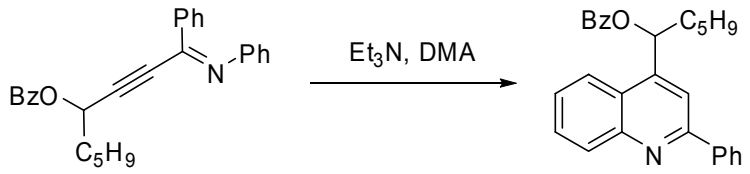


8 **18** (57%)

Scheme 11

Quinoline **18** has been previously isolated by Gevorgyan and coworkers when they performed in one pot the preparation of alkynyl imine **8** via a Sonogashira coupling, followed by a copper-catalyzed cyclization.[22] They also observed that this reaction can be carried out without a metal. Actually, by heating alkynyl imine **19** in the presence of Et_3N and DMA, quinoline **20** is formed (Scheme 12). They proposed for this transformation a Friedel-Crafts-type reaction between the phenyl ring and the alkyne.

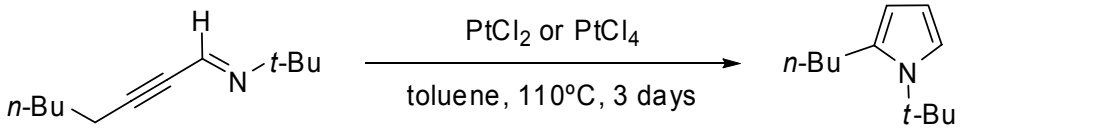
22 Sromek, A. W.; Rheingold, A. L.; Wink, D. J.; Gevorgyan, V. *Synlett* **2006**, *14*, 2325-2328.



19 **20** (87%)

Scheme 12

Reaction of alkynyl imine **16** with $PtCl_2$ or $PtCl_4$ led to the formation of the 1,2-disubstitued pyrrole product (Scheme 13). When the reaction was carried out in the presence of methyl vinyl ketone, the formation of 1,2,3-trisubstituted pyrrole was not observed. Alkynyl imine **17** did not react under these conditions.



16 (Complete conversion by NMR)

Scheme 13

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Chapter 4. Conclusions

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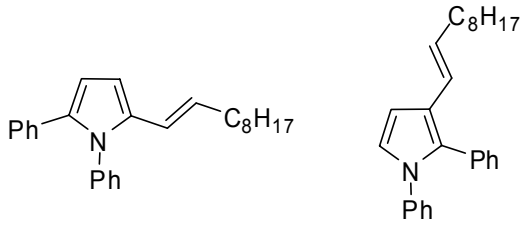
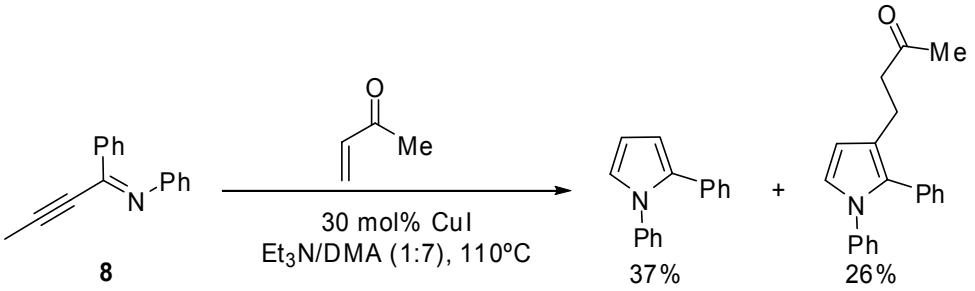
We have independently synthesized pyrrole **9**, which was assigned by Gevorgyan to be the product in the Cu-catalyzed reaction of alkynyl imine **8** in the presence of decanal (Scheme 7). By repeating the reaction described by Gevorgyan and comparing the NMR data of the obtained product with that of **9**, we have demonstrated that instead of the 1,2,5-trisubstituted pyrrole **9**, the 1,2,3-trisubstituted pyrrole **10** is formed (Figure 6). To account for the formation of **10**, we have proposed an alternative mechanism for the Cu-catalyzed cyclization of alkynyl imines.



9 **10**

Figure 6

We succeeded in trapping the anionic intermediate formed in the course of this reaction when alkynyl imine **8** was reacted in the presence of methyl vinyl ketone (Scheme 14). Gold and silver catalysts proved to be ineffective for this transformation. Platinum catalysts led to the formation of quinoline **18** when the imine is substituted with a phenyl ring, by a Friedel-Crafts-type process (Scheme 11).



8 37% 26%

Scheme 14

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Chapter 4. Experimental section

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Experimental Section: Index

1. General Methods

All reactions were carried out under N_2 in solvents dried using a Solvent Purification System (SPS). Anhydrous DMA under nitrogen was purchased from Aldrich. 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.

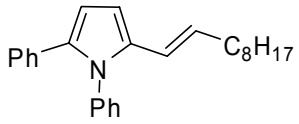
Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm).

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 (CI) spectrometers.

2. Preparation of Substrates

The following known compounds showed spectroscopic data consistent with those described: alkynyl imines **8**,[20] **16**,[20] and **17**,[20] 1,2-diphenyl-1*H*-pyrrole,[20] 1-*tert*-butyl-2-butyl-1*H*-pyrrole,[20] and quinoline **18**.[22]

(*E*)-2-(Dec-1-enyl)-1,5-diphenyl-1*H*-pyrrole (9)



Potassium *tert*-butoxide (51 mg, 0.45 mmol) and *n*-butyl lithium (0.18 mL of a 2.5 M solution, 0.45 mmol) were mixed at room temperature in 1 mL of hexane. Then, this mixture was added to a solution of 1,2-diphenyl-1*H*-pyrrole (100 mg, 0.45 mmol) in 1 mL of THF at -78ºC. After 90 min at -78ºC, decanal (0.08 mL, 0.45 mmol) was added and the reaction was allowed to stir at -78ºC for another hour. Then it was allowed to warm up slowly to room temperature overnight. A small amount of 1-(1,5-diphenyl-1H-pyrrol-2-yl)decan-1-ol (**11**) was formed after this time. The reaction was

20 Kel'in, A. V.; Sromek A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074-2075.

22 Sromek, A. W.; Rheingold, A. L.; Wink, D. J.; Gevorgyan, V. *Synlett* **2006**, *14*, 2325-2328.

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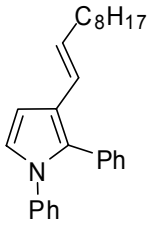
quenched with water and extracted with EtOAc. The residue was purified by silica gel chromatography (15:1 hexane-EtOAc) to give **11** as a colorless oil. After standing overnight in a NMR tube, a significant amount of **9** had formed. Then the NMR tube was heated at 50ºC for 3 h and **9** was then the only product observed by NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 3H), 7.18-7.02 (m, 7H), 6.48 (d, J = 3.7 Hz, 1H), 6.41 (d, J = 3.7 Hz, 1H), 6.01 (dt, J = 15.6, 6.6 Hz, 1H), 5.93 (d, J = 15.8 Hz, 1H), 2.05 (q, J = 6.7 Hz, 2H), 1.37-1.25 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 138.74 (C), 134.85 (C), 134.59 (C), 133.18 (C), 129.62 (CH, alkene), 128.92 (CH, 2C), 128.87 (CH, 2C), 127.92 (CH, 4C), 127.54 (CH), 125.84 (CH), 119.43 (CH, alkene), 109.93 (CH, pyrrole), 105.43 (CH, pyrrole), 33.14 (CH_2), 31.88 (CH_2), 29.46 (CH_2), 29.44 (CH_2), 29.30 (CH_2), 29.11 (CH_2), 22.67 (CH_2), 14.11 (CH_3). HRMS-CI *m/z* calcd for $C_{26}H_{32}N$: 358.2535; found: 358.2530 [M^++H].

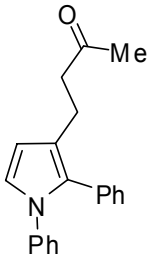
(*E*)-3-(Dec-1-enyl)-1,2-diphenyl-1*H*-pyrrole (10)



To a flask under nitrogen, copper iodide (70 mg, 0.37 mmol), anhydrous DMA (6 mL) and (*Z*)-*N*-(1-phenylbut-2-ynylidene)aniline (270 mg, 1.23 mmol) were added successively. After copper iodide dissolved, anhydrous triethylamine (0.77 mL, 5.54 mmol) and decanal (0.69 mL, 3.69 mmol) were added and the flask was placed in a heating block preheated to 110ºC. The mixture was stirred at this temperature protected from the light for 4 h. Then it was cooled to room temperature, poured into water and extracted with hexane. The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography (2:1 hexane-toluene) to give the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.16 (m, 6H), 7.13-7.10 (m, 2H), 7.05-7.03 (m, 2H), 6.86 (d, J = 3.1 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 6.02 (dt, J = 15.7, 6.9 Hz, 1H), 2.12 (q, J = 6.9 Hz, 2H), 1.45-1.37 (m, 2H), 1.30-1.27 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 140.30 (C), 131.97 (C), 130.68 (CH, 2C), 130.44 (C), 128.81 (CH, 2C), 128.28 (CH, alkene), 127.94 (CH, 2C), 126.69 (CH), 126.15 (CH), 125.40 (CH, 2C), 123.54 (CH, pyrrole), 122.45 (C), 122.28 (CH,

alkene), 106.06 (CH, pyrrole), 33.21 (CH_2), 31.92 (CH_2), 29.83 (CH_2), 29.53 (CH_2), 29.34 (CH_2), 29.25 (CH_2), 22.69 (CH_2), 14.12 (CH_3).

4-(1,2-Diphenyl-1*H*-pyrrol-3-yl)butan-2-one (15)



Compound **15** was prepared following the procedure described above and was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.19 (m, 6H), 7.12-7.10 (m, 2H), 7.08-7.05 (m, 2H), 6.91 (d, J = 2.9 Hz, 1H), 6.92 (d, J = 2.9 Hz, 1H), 2.85-2.81 (m, 2H), 2.71-2.67 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 208.75 (C), 140.45 (C), 132.36 (C), 130.35 (CH, 2C), 130.14 (C), 128.77 (CH, 2C), 128.07 (CH, 2C), 126.67 (CH, 2C), 126.06 (CH), 125.37 (CH), 122.37 (CH, pyrrole), 122.28 (C), 109.24 (CH, pyrrole), 33.21 (CH_2), 45.14 (CH_2), 29.90 (CH_3), 20.79 (CH_2). HRMS-ESI *m/z* calcd for $C_{20}H_{19}NONa$: 312.1364; found: 312.1363 [M^++Na].