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TESIS DOCTORAL

SÍNTESIS Y ESTUDIO DE CARBENOS ACÍCLICOS DE ORO(I): UNA ALTERNATIVA A LOS CARBENOS HETEROCÍCLICOS COMO CATALIZADORES EN TRANSFORMACIONES ORGÁNICAS DE INTERÉS

Presentada por Zoraida Rosa Ramiro Mangas

para optar al grado de doctora

por la Universidad de Valladolid

Dirigida por:

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AUTORIZACIÓN DE LOS DIRECTORES DE LA TESIS

(Art. 2.1. c de la Normativa para la presentación y defensa de la Tesis Doctoral en la UVa)

Dr. Pablo Espinet Rubio, con D.N.I. nº 17176361F, Catedrático de Química Inorgánica del Departamento de Química Física y Química Inorgánica de la Universidad de Valladolid y **Dra. Mª del Camino Bartolomé Albistegui**, con D.N.I. nº 9324689Y, Profesora contratada doctora de Química Inorgánica del Departamento de Química Física y Química Inorgánica de la Universidad de Valladolid, como directores de la Tesis Doctoral titulada ***SÍNTESIS Y ESTUDIO DE CARBENOS ACÍCLICOS DE ORO(I): UNA ALTERNATIVA A LOS CARBENOS HETEROCÍCLICOS COMO CATALIZADORES EN TRANSFORMACIONES ORGÁNICAS DE INTERÉS*** y presentada por Zoraida Rosa Ramiro Mangas, alumna del programa "*Doctorado en Química: Química de síntesis, métodos de separación, catálisis, materiales avanzados*" impartido por el Instituto CINQUIMA, autorizan la presentación de la misma considerando que la doctoranda ha desarrollado un trabajo experimental original, ha cumplido las diferentes etapas de formación y ha conseguido los objetivos propuestos.

Valladolid, 8 de Mayo de 2015

Los Directores de la Tesis,

Pablo Espinet Rubio Mª del Camino Bartolomé Albistegui

Esta tesis se ha elaborado gracias a la financiación económica de los proyectos: INTECAT Consolider Ingenio 2010 (Grant CSD2006-0003), CTQ2007-67411, la Junta de Castilla y León (GR169, VA117A06 y VA256U13), Ministerio de Economía y Competitividad MINECO (CTQ2013-48406-P), AGUR (proyectos 2005 SGR00993 y 2009 SGR47).

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Este trabajo se presenta para su consideración como Tesis Doctoral como compendio de publicaciones. La normativa de la Universidad de Valladolid, establece que los requisitos a cumplir son (BOCYL nº 243, página 76918, Artículo 3):

1. Siempre que merezcan la consideración de trabajo original de investigación elaborado por el candidato, las tesis doctorales podrán presentarse como compendio de al menos tres artículos en revistas científicas con factor de impacto, aceptados para su publicación con posterioridad al inicio de los estudios de doctorado. Las tesis presentadas por este procedimiento deberán incluir una introducción, de al menos veinte páginas, que justifique la relación temática de las publicaciones y contenga los objetivos perseguidos, la metodología empleada, los resultados obtenidos y las conclusiones más relevantes.

2. Los artículos incluidos deberán figurar completos, con la referencia precisa de la publicación y con los nombres y filiación de todos sus autores. Cada artículo en coautoría deberá acompañarse de un escrito, firmado por todos los coautores, en el que consten la contribución del doctorando y la renuncia a incluir el artículo en otra tesis doctoral.

De acuerdo con la normativa establecida, en este trabajo se incluyen seis artículos, cinco de los cuales, en el momento de la presentación de la Memoria ante la comisión de Doctorado, ya estaban aceptados y publicados:

Artículo I. **Gold(I) Complexes with Hydrogen-Bond Supported Heterocyclic Carbenes as Active Catalysts in Reactions of 1,6-Enynes**

Publicado en *Inorganic Chemistry* 2008, **47**, 11391–11397

Índice de impacto: 4.794

Número de citas (a fecha 15/05/2015): 48

Artículo II. **Nitrogen Acyclic Gold(I) Carbenes: Excellent and Easily Accessible Catalysts in Reactions of 1,6-Enynes**

Publicado en *Organometallics*, 2010, **29**, 951–956

Índice de impacto: 4.253

Número de citas (a fecha 15/05/2015): 71

Artículo III. **Exploring the Scope of Nitrogen Acyclic Carbenes (NACs) in Gold-Catalyzed Reactions**

Publicado en *Organometallics*, 2010, **29**, 3589–3592

Índice de impacto: 4.253

Número de citas (a fecha 15/05/2015): 36

Artículo IV. **Synthesis and Catalytic Activity of Gold Chiral Nitrogen Acyclic Carbenes and Gold Hydrogen Bonded Heterocyclic Carbenes in Cyclopropanation of Vinyl Arenes and in Intramolecular Hydroalkoxylation of Allenes**

Publicado en *Inorganic Chemistry*, 2010, **49**, 9758–9764

Índice de impacto: 4.794

Número de citas (a fecha 15/05/2015): 35

Artículo V. **Protection of the Gold(I) Catalyst by $AsPh_3$ in Reactions of Enynes**

Publicado en *European Journal of Inorganic Chemistry* **2014**, 5499–5506

Índice de impacto: 2.965

Número de citas (a fecha 15/05/2015): 0

Por último aunque no se incluya dentro de la Memoria., dentro del periodo de trabajo doctoral se realizó otro trabajo con un artículo ya publicado en relación a una de las dos estancias breves realizadas:

Artículo VI. **Pt^{II}-Catalyzed Hydrophenylation of α‑Olefins: Variation of Linear/Branched Products as a Function of Ligand Donor Ability**

Publicado en *ACS Catalysis* **2014**, *4*, 1607–16015

Índice de impacto (a fecha 15/05/2015): 7.572

Número de citas (a fecha 15/05/2015): 3

Índice

Introducción

INTRODUCCIÓN

Durante siglos, el oro había sido considerado como un metal fundamentalmente inerte. Tras los primeros resultados publicados sobre su uso en catálisis homogénea,[1] y en concreto sobre su capacidad para activar alquinos,[2] los sistemas basados en complejos de oro(I) han resultado ser los más adecuados en reacciones de activación electrofílica de enlaces C–C insaturados.

A partir de entonces, su uso en catálisis homogénea ha crecido de forma espectacular en las últimas décadas.[3] Aunque muchas sales de oro(I) o de oro(III) han resultado ser catalizadores activos en diferentes reacciones orgánicas de interés, en la mayoría de los trabajos publicados se utilizan complejos de oro(I) del tipo [AuXL] en presencia de un extractor de haluro (generalmente una sal de plata). De este modo, se forma un "desnudo de oro" que actúa como electrófilo, por lo que se requiere que el ligando auxiliar L del complejo catiónico tenga unas determinadas características que estabilicen al sistema en las condiciones en las que se produce la reacción catalítica.

Los complejos [AuXL] utilizados en catálisis necesitan un ligando σ-dador fuerte para estabilizar al centro metálico. Los ligandos L más comunes son fosfinas o carbenos N-heterocíclicos, aunque también se han utilizado fosfitos o arsinas.

Los sistemas catiónicos $[AuLL']^+$ contienen un átomo de oro(I) coordinado a dos ligandos neutros, donde L es un ligando σ-dador fuerte (típicamente una fosfina o un carbeno N-heterocíclico) y L' un ligando débilmente coordinado[4] (por lo general es una molécula de disolvente, como acetonitrilo, tolueno o *p*-xileno, que pueden ser desplazados fácilmente por el sustrato durante la reacción de catálisis). Aunque en muchos de estos casos moléculas sencillas como MeCN o PhCN pueden coordinarse

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[1] Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

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

[3] Revisiones sobre oro(I) en catalisis homogénea: (a) Chiarucci, M.; Bandini, M. *Beilstein J. Org. Chem.* **2013**, *9*, 2586–2614. (b) *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F.D. Toste), WILEY-VCH, Weinheim, **2012**. (c) Hashmi, A. S. K. *Chem. Rev,* **2007**, *107*, 3180–3211. (d) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936. Catálisis heterogénea (e) Stratakis, M.; Garcia, H. *Chem.Rev.* **2012***, 112,* 4469−4506.

[4] a) Blanco Jaimes, M. C.; Rominger, F.; Pereira, M. M.; Carrilho, R. M. B.; Carabineiro, S. A. C.; Hashmi, A. S. K. *Chem. Commun.* **2014**, *50*, 4937–4940. (b) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun*. **2011**, *47*, 218–220. (c) Odabachian, Y.; Le Goff, X. F.; Gagosz, F. *Chem. Eur. J*. **2009**, *15*, 8966–8970. (d) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed*. **2007**, *46*, 1141–1144. (e) de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun*. **2006**, 2045–2047. (f) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 5455–5459.

como L', el ligando trimetoxibenzonitrilo incrementa considerablemente la estabilidad de estos sistemas catiónicos.[5] Todos estos complejos poseen también un anión no coordinante (por lo general SbF_6^- o PF_6^-).

Alternativamente se han utilizado sistemas neutros del tipo [AuYL], donde Y^- es un buen grupo saliente (NTf_2^-, bis(trifluorometanosulfonil)amiduro,[6] u otros aniones débilmente coordinantes), o incluso el [Au(OH)(IPr)],[7] desarrollado por Nolan. El complejo [Au(NTf_2)(PPh_3)], con fosfina como L principal, o [Au(NTf_2)(NHC)],[8] donde L es un carbeno heterocíclico, han resultado ser excelentes catalizadores en multitud de transformaciones orgánicas.

En el Figura 1 se han representado algunos de los complejos de oro(I) neutros [AuXL] y [AuYL] además de catiónicos $[AuLL']^+$ habitualmente utilizados en catálisis.

Como se puede observar, los sistemas más utilizados hasta el momento generalmente se basan en fosfinas o en ligandos carbeno heterocíclico (NHC's). Una desventaja inherente a los ligandos fosfina es su posible oxidación en determinadas condiciones, lo que conduciría a la descomposición del sistema catalítico y por tanto a su inactividad.[9] Por su parte, los carbenos NHC's no presentan el problema asociado a los sistemas con fosfinas terciarias, por lo que su uso en catálisis homogénea se ha incrementado enormemente en los últimos años.

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[5] Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem*. **2008**, *73*, 7721–7730.
[6] Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett*. **2005**, *7*, 4133–4136.
[7] (a) Ramón, R. S.; Gaillard, S.; Poater, A.; Cavallo, L.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J*. **2011**, *17*, 1238–1246. (b) Boogaerts, I. I. F.; Nolan, S. P. *Chem. Commun*. **2011**, *47*, 3021–3024. (c) Gaillard, S.; Bosson, J.; Ramón, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J.* **2010**, *16*, 13729–13740. (d) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc*. **2010**, *132*, 8858–8859. (e) Nun, P.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun*. **2010**, *46*, 9113–9115.
[8] Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.
[9] (a) Rogers, M. M.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *21*, 21–46. (b) Zinn, F. K.; Viciu, M. S.; Nolan, S. P. *Annu. Rep. Progr. Chem. Sect. B: Org. Chem*. **2004**, *100*, 231–249. (c) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309. (d) Huang, J.; Jafarpour, L.; Hillier, A.C.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 2878–2882. (e) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev*. **2000**, *100*, 39–91.

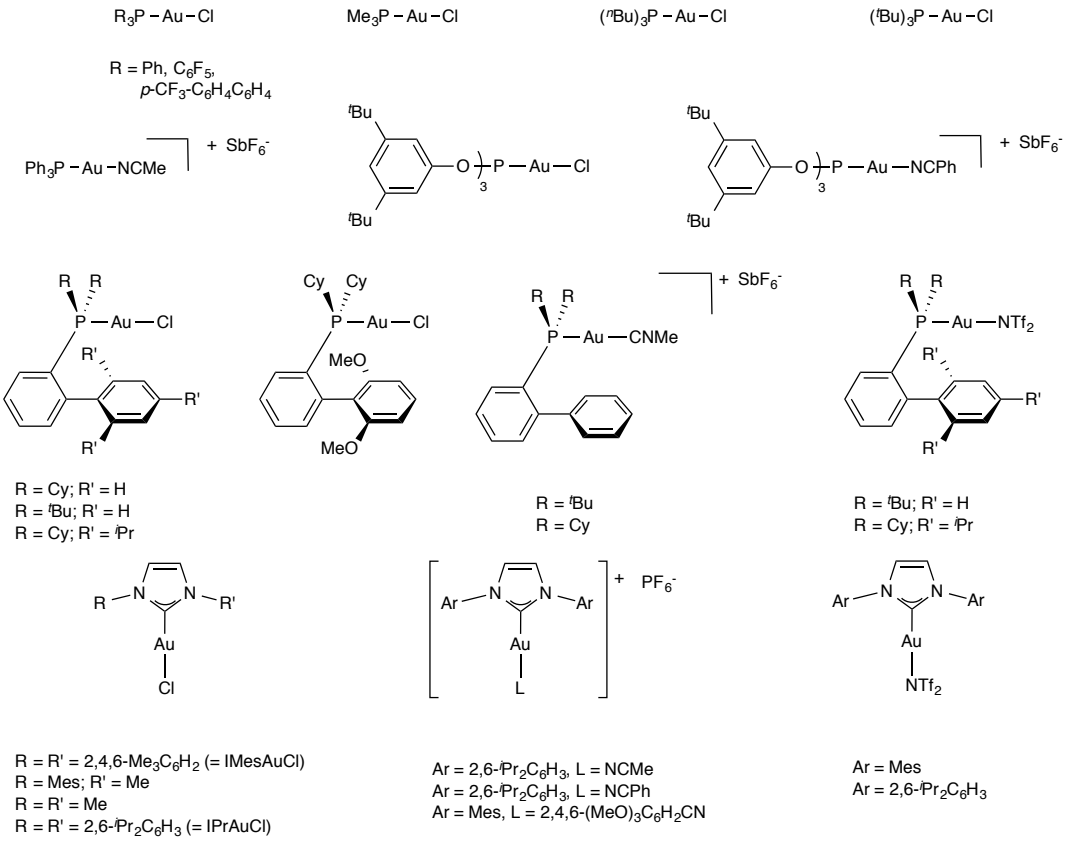

Figura 1. Algunos de los complejos de oro(I) más utilizados en catálisis

Aunque los complejos de oro con carbenos heterocíclicos NHC son bien conocidos desde hace más de tres décadas,[10] en los últimos años han cobrado enorme importancia debido a sus aplicaciones catalíticas en síntesis orgánica.[3c,11] Paralelamente al desarrollo de sistemas de oro(I) basados en carbenos heterocíclicos NHC's, Bertrand ha descrito la actividad de otro tipo de carbenos cíclicos, también de cinco eslabones, en concreto alquilaminocarbenos (Cyclic Alkyl-Amino Carbenes, CAAC) en diferentes transformaciones orgánicas.[12]

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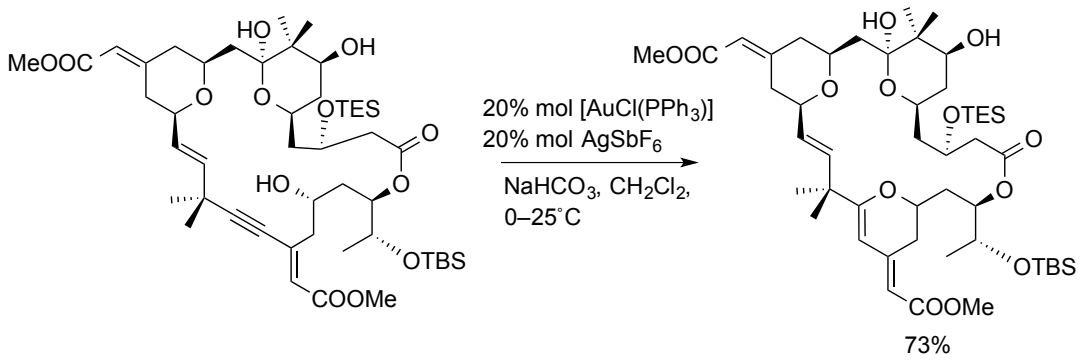
[10] (a) Bonati, F.; Burini, A.; Pietroni, B. R.; Bovio, B. *J. Organomet. Chem.* **1991**, *408*, 271–280. (b) Minghetti, G.; Bonati, F. *J. Organomet. Chem.* **1973**, *54*, C62–C63. Bonati, F.; Burini, A.; Pietroni, B. R.; Bovio, B. *J. Organomet. Chem.* **1991**, *408*, 271–280.

[11] Revisiones de carbenos heterocíclicos de diferentes metales utilizados en catálisis: Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009,** *109,* 3612–3676. Revisiones específicas de carbenos heterocíclicos de oro en catálisis: (a) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Re*v. **2008**, *108*, 3351–3378 (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Re*v. **2008**, *108*, 3326–3265. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.(e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346.

[12] (a) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 942–945.
(b) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem Eur. J.* **2009**, *15*, 3056–3060; (c) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690–8696. (d) Xiaoming Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166–3169. (e) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5224–5228.

Existen ejemplos muy relevantes de transformaciones orgánicas catalizadas por sistemas de oro(I) con fosfinas o carbenos heterocíclicos. En muchos casos la participación de estos catalizadores permite reducir de forma drástica el número de pasos necesarios para la síntesis de productos biológicamente activos. Por ejemplo, una de las etapas clave en la síntesis de la Briostatina 16 es una reacción hidroalcoxilación de un grupo alquino catalizada por [AuCl(PPh_3)] en presencia de una sal de plata (Esquema 1). Esta ruta sintética, desarrollada por Trost,[13] ha permitido reducir de 40 a 28 pasos la síntesis total de este compuesto con actividad anticancerígena y potencialmente activo en el tratamiento del Alzheimer.



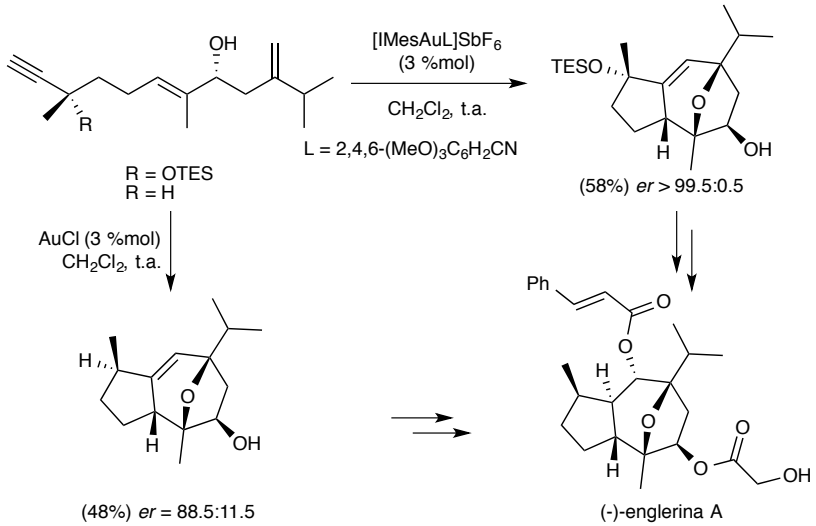
Esquema 1. Paso clave en la síntesis de Briostatina 16

Una de las etapas de la síntesis total del sesquiterpeno (–)-Englerina A[14] (Esquema 2), principio activo con propiedades antitumorales (inhibe las células cancerígenas de origen renal), consiste en una cicloadición a partir de un alcohol desprotegido. Los mejores resultados en rendimiento y estereoselectividad se han obtenido utilizando el carbeno de oro(I) catiónico [Au(IMes)L](SbF_6) (IMes = *N*,*N*-bis(2,4,6-trimetilfenil)imidazol-2-ilideno); L = 2,4,6-trimetoxifenilbenzonitrilo).

(f) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13569–13573.

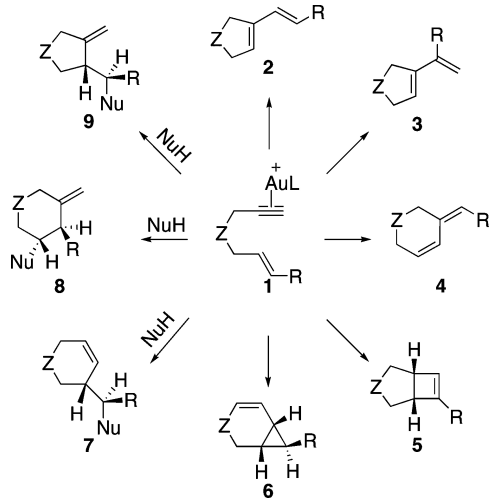
[13] (a) Trost, B. M.; Dong, G. *J. Am. Chem. Soc*. **2010**, *132*, 16403−16416. (b) Trost, B. M.; Dong, G. *Nature*, **2008**, *456*, 485–488.

[14] (a) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2010**, *49*, 3517−3519. (b) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513−3516.



Esquema 2. Síntesis de (-)-Englerina A

Una de las múltiples transformaciones catalizadas por carbenos de oro(I) heterocíclicos es la activación de alquinos,[15] y, más en concreto, de alquenos con alquinos.[11,16] Como se puede observar en el Esquema 3, la activación de 1,6-eninos a través de un η^2-alquino (**1**) puede dar una amplia variedad de compuestos.



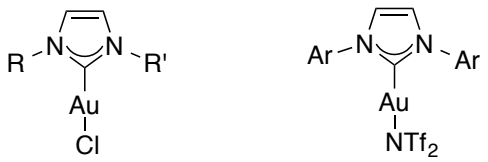
Esquema 3. Productos derivados de la ciclación de 1,6-eninos catalizada por complejos de oro(I)

[15] Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015** DOI: 10.1021/cr500691k. (b) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16–28.

[16](a) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res*. **2014**, *47*, 902–912. (b) Jiménez-Nuñez, E.; Echavarren, A. M. *Chem. Rev*. **2008**, *108*, 3326–3350. (c) 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. (d) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916–5923. (e) 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. (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.

En ausencia de nucleófilos, los eninos dan lugar a dienos **2** y/o **3** como resultado de la transposición de esqueleto. También es posible aislar los productos de transposición endocíclica **4**,[16,17] ciclobutenos **5**[16] y productos bicíclicos por ciclopropanación intramolecular **6**.[18] En presencia de nucleófilos, se pueden formar los aductos **7-9** en procesos estereoespecíficos.[16,19,20,21,22] Se han descrito transformaciones mucho más complejas cuando se utilizan eninos más funcionalizados.[23]

Existen en la bibliografía varios ejemplos de carbenos heterocíclicos de oro(I) que son precatalizadores en reacciones de ciclación de eninos.[23a,24] El catalizador se forma en disolución tras la adición de una sal de plata como extractor del ligando cloruro (Figura 2). Se ha estudiado además la actividad de complejos análogos a los anteriores con NTf_2^- como ligando muy lábil,[8,25] y complejos catiónicos derivados de los correspondientes [AuCl(NHC)].[4e]



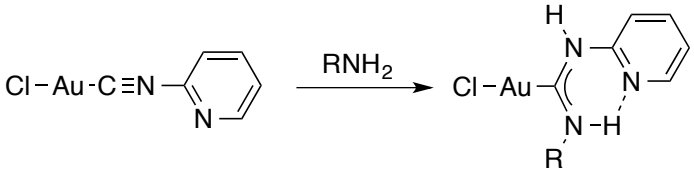
R = R' = 2,4,6-$Me_3C_6H_2$
R = Mes, R' = Me
R = R' = Me
R = R' = 2,6-$^i Pr_2C_6H_3$

Ar = Mes
Ar= 2,6-$^i Pr_2C_6H_3$

Figura 2. Carbenos de oro(I) utilizados como catalizadores en transposiciones de esqueleto de 1,n-eninos

[17] Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, *421*, 7–4223.
[18] Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191–3194.
[19] (a) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627–2635. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316.
[20] Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J. P.; Michelet, V. *Synlett* **2007**, 1780–1784.
[21] Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427–7430.
[22] Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698–700.
[23] (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033. (b) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour,C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (c) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263–2266. (d) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 2605–2607. (e) Kim, S. M.; Park, J. H.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6172–6175. (f) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimana, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207–2209. (g) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.
[24] (a) Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048–2050. (b) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411–2418.
[25] Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.

Como alternativa a los carbenos de oro(I) heterocíclicos convencionales, nuestro grupo de investigación había publicado la síntesis de carbenos de oro(I) del tipo [AuCl{C(NRH)(NHPy-2)}] (Py-2 = 2-piridilo) por adición nucleófila de aminas primarias a [AuCl(CNPy-2)] (Esquema 4).[26]



Esquema 4. Síntesis de [AuCl{C(NRH)(NHPy-2)}]

Los espectros de RMN de protón de los carbenos de oro(I) sintetizados, registrados a la temperatura ambiente, revelan la existencia de un único isómero de entre los cuatro posibles confórmeros (Figura 3).

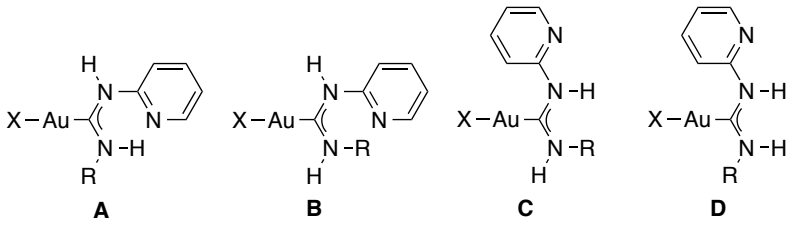


Figura 3. Confórmeros posibles en carbenos obtenidos por ataque nucleofílico con RNH_2

El desapantallamiento al que se ve sometido el hidrógeno de uno de los N–H es consistente con la existencia de un fuerte enlace de hidrógeno intramolecular entre dicho protón y el nitrógeno del grupo 2-piridilo (Figura 2, A). Esta interacción de hidrógeno da lugar a un ciclo de seis miembros que parece ser muy estable en disolución, lo que hace a este tipo de carbenos estructuralmente similares a los heterocíclicos, aunque con distinto número de eslabones en el ciclo (Figura 4).

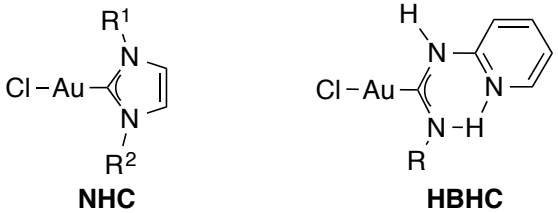


Figura 4. Carbenos de oro(I) heterocíclicos del tipo NHC y HBHC

[26] Bartolomé, C.; Carrasco-Rando, M.; Coco, S.; Cordovilla, C.; Martín-Álvarez, J. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 1616–1624.

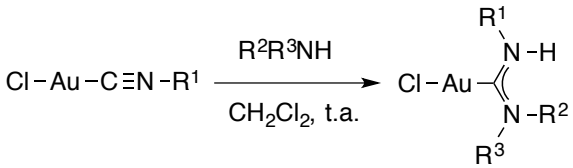
El método de preparación de estos carbenos, que hemos denominado HBHC's (Hydrogen Bond supported Heterocyclic Carbenes), permite modular de una forma muy sencilla sus características electrónicas o estéricas modificando el sustituyente R de la amina que actúa como nucleófilo, lo que supone una gran ventaja frente a los carbenos heterocíclicos convencionales.

Con estos antecedentes bibliográficos se decidió estudiar la actividad de los complejos de oro con carbenos HBHC como catalizadores en algunas transformaciones orgánicas de gran interés, y comparar los resultados con los obtenidos utilizando carbenos heterocíclicos del tipo NHC como catalizadores.

Aprovechando que en el grupo de investigación en el que he realizado mi tesis doctoral participaba en el proyecto CONSOLIDER INGENIO 2010 *"Diseño de Catalizadores para una Química Sostenible: Una Aproximación Integrada"* (INTECAT), mi trabajo se centró en diseñar catalizadores originales para la creación de enlaces carbono-carbono o carbono-heteroátomo (N, O, S) como parte de uno de los *deliverables* (objetivos específicos) del proyecto. Se decidió como punto de partida estudiar tanto la síntesis de nuevos HBHC de oro(I) como su actividad en reacciones de reorganización de esqueleto de 1,n-eninos, reacciones en las que el grupo de Antonio M. Echavarren, otro de los investigadores participantes en este proyecto, tiene una amplia experiencia.

Por otro lado, y como se verá en el resumen de los resultados conseguidos en este trabajo, se observó que en alguna de estas reacciones, en concreto, en las alcoxiciclaciones de 1,6-eninos, la interacción de hidrógeno intramolecular del ligando HBHC no se mantiene en disolución, pero el sistema sigue siendo activo. Se decidió entonces extender el estudio a carbenos de oro(I) acíclicos, con el fin de comparar los resultados con los obtenidos tanto con carbenos HBHC como con NHC.

La síntesis de estos carbenos acíclicos, que hemos denominado NAC (Nitrogen Acyclic Carbenes), consiste de nuevo en un ataque nucleofílico de una amina a un isocianoderivado de oro(I) (Esquema 5). En este caso, la adecuada elección tanto de la amina como del isocianuro coordinado al metal aumenta enormemente la versatilidad de estos sistemas.



Esquema 5. Síntesis de carbenos NAC de oro(I)

Además de confirmar que los carbenos NAC son activos en reacciones de reorganización de esqueleto de 1,n-eninos, análogamente a los HBHC, se estudió su actividad en diferentes reacciones de ciclación tanto intra como intermoleculares, tal y como se comentará en el resumen de los resultados. La simplicidad sintética de la mayoría de estos carbenos acíclicos de oro permite modular a voluntad las características tanto estéricas como dadoras del carbeno coordinado al centro metálico, lo que ha dado pie a grupos de investigación expertos en catálisis con oro(I) a adoptar este sistema.[27]

Como ya se ha comentado anteriormente, el uso de complejos de oro(I) como catalizadores en transformaciones orgánicas viene siendo muy habitual desde hace más de una década. Sin embargo, la aplicación de este tipo de complejos en catálisis enantioselectiva es relativamente reciente.[28] La mayoría de los sistemas de oro(I) descritos son μ-(P-P)[AuX]$_2$ (con P-P = difosfina quiral[29]), fosforamidatos quirales[29b,c] o incluso aniones quirales.[30] Una posible explicación a este hecho puede tener que ver con el modo de coordinación del oro(I), que da lugar a complejos con índice de coordinación 2, lineales,[31] de manera que la molécula susceptible de transformarse se sitúa muy lejos del ligando quiral. El modo de coordinación lineal del oro(I) además excluye en muchos casos la posibilidad de utilizar ligandos bidentados basados en bisfosfinas quirales y otros ligandos análogos que actualmente son la piedra angular de

[27] (a) Blanco Jaimes, M. C.; Boehling, C. R. N.; Serrano-Becerra, J. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 7963–7966. (b) Hashmi, A. S. K. *Top. Organomet. Chem.* **2013**, *44*, 143–164. (c) Boyarskiy, V. P.; Luzyanin, K. V.; Kukushkin, V. Y. *Coordination Chemistry Reviews* **2012**, *256*, 2029–2056. (d) Slaughter, L. M. *ACS Catal*. **2012**, *2,* 1802−1816. (e) Hashmi, A. S. K.; Hengst, T.; Lothschütz, C.; Rominger, F. *Adv. Synth. Catal*. **2010**, *8*, 1315–1337. (f) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846–9854.

[28] Catálisis enantioselectiva de oro(I): (a) Gu, P.; Xu, Q.; Shi, M. *Tetrahedron Letters*, **2014**, *55*, 577–584. (b) Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889–901. (c) Cera, G.; Bandini, M. *Israel Journal of Chemistry*, **2013**, *53*, 11–12. (d) Toste, F. D. *Chem. Sci*. **2012**, *3*, 2899–2919. (e) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, 14, 5382–5391. (f) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *Chem. Commun.* **2005**, 3451–3453. (g) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300. (h) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**; Chapter 7.2, p 367. Watson, I. D. G.

[29] (a) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5175–5178. (b) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1949–1953. (c) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*,13020–13030.

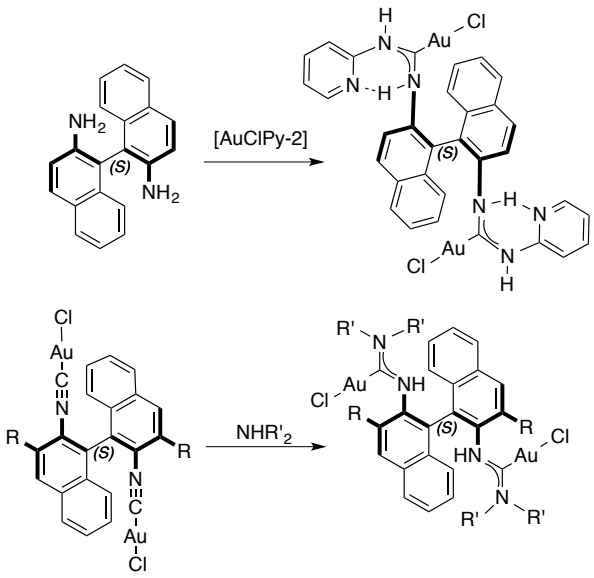
[30] (a) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 598–601. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007,** *317*, 496–499.

[31] (a) Schwerdtfeger, P.; Hermann, H. L.; Schmidbaur, H. *Inorg. Chem.* **2003**, *42*, 1334–1342. (b) Carvajal, M. A.; Novoa, J. J.; Alvarez, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465–1477. (c) Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522.

la catálisis enantioselectiva en complejos de metales de transición con índices de coordinación cuatro, cinco o seis.[32] Además, los catalizadores basados en fosfinas tienen la desventaja de que, en las condiciones de catálisis, los ligandos fosfina pueden oxidarse fácilmente.[9]

Por estos motivos, el intentar desarrollar un proceso catalítico enantioselectivo utilizando catalizadores de oro(I) supone un reto en catálisis homogénea. Por tanto, otro de los objetivos de este trabajo se centró en extender el estudio de la actividad catalítica de carbenos heterocíclicos soportados por enlace de hidrógeno así como de carbenos acíclicos en síntesis enantioselectiva. Para ello, se sintetizaron carbenos del tipo [AuCl{C(NRH)(NHPy-2)}] y [AuCl{C(NHR)(NR'$_2$)}], donde o R o R' fueran sustituyentes quirales.

La mayoría de los carbenos quirales que hemos sintetizado se basan en el sistema binaftilo con dos grupos NH_2 en posiciones 2 y 2' o alternativamente dos grupos isocianuro en las posiciones 2 y 2' (Esquema 6).



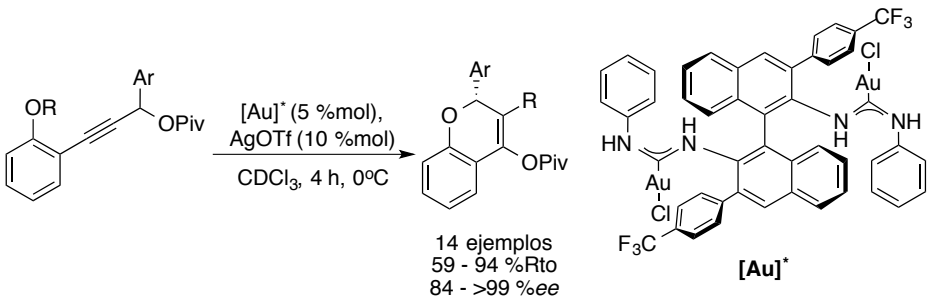
Esquema 6. Carbenos quirales HBHC y NAC sintetizados en este trabajo

Este sistema posee un enorme requerimiento estérico, que impide el giro entorno al enlace C-C de los dos grupos naftilo. El resultado de esta restricción en el giro es que posee quiralidad axial, lo que le hace ser un buen candidato si se utiliza como ligando auxiliar de catalizadores en síntesis enantioselectiva.

[32] (a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd. ed., Wiley-VCH, Weinheim, **2000**. (b) *Comprehensive Asymmetric Catalysis Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

Se eligieron dos transformaciones enantioselectivas para estudiar la actividad de dichos catalizadores: reacciones de hidrofuncionalización de alenos y, más en concreto, de hidroalcoxilación de alenos y reacciones de ciclopropanación de olefinas. Como se analizará en el resumen de los resultados obtenidos, aunque todos los carbenos quirales sintetizados son activos en ambas reacciones, la enantioselectividad que inducen es baja. A pesar de ello, demuestran que el sistema está bien diseñado estructuralmente, aunque hace preciso realizar modificaciones que induzcan excesos enantioméricos muy superiores a los obtenidos en el sondeo inicial. Estas modificaciones demandan mucho trabajo, relativamente repetitivo, de síntesis, prueba y nueva modificación, que es accesible a grupos más potentes y numerosos pero se escapa un tanto del planteamiento del grupo de investigación, que se mueve más en la línea de prueba de conceptos. La confirmación de lo acertado de nuestro diseño vino muy poco después de la publicación de nuestros resultados, de la mano de grupos potentes en catálisis con oro(I) que desarrollaron nuevos sistemas modificados utilizando como esqueleto nuestros complejos con ligandos HBHC y NAC quirales, aumentando muy considerablemente los excesos enantioméricos.[33]

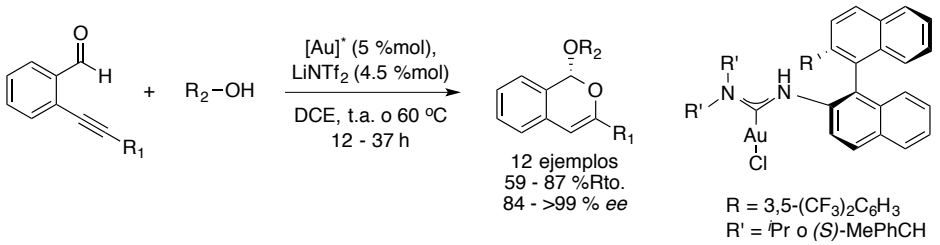
Así, Toste abordó la reorganización asimétrica de ésteres propargílicos utilizando como catalizador un carbeno HBHC análogo a nuestros carbenos quirales pero modificando el sustituyente en posición 3,3' del binaftilo (Esquema 7).[34]



Esquema 7. Reorganización asimétrica de ésteres propargílicos catalizada por HBHC quirales de oro(I)

Por su parte, Slaughter modificó nuestros carbenos NAC quirales utilizando 2-isociano-1,1'-binaftilos con un sustituyente voluminoso en la posición 2' (Esquema 8). Este sistema es activo en la ciclación enantioselectiva de alquinilbenzaldehído.[35]

[33] Barbazanges, M.; Fensterbank, L. *ChemCatChem* **2012**, *4*, 1065–1066.
[34] Wang, Y.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972–12975.
[35] Handa, S.; Slaughter, L. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2912–2915.



Esquema 8. Ciclación enantioselectiva de alquinilbenzaldehido catalizada por NAC quirales de oro(I)

La especie activa en los procesos catalizados por oro(I) suele ser un complejo catiónico. De este modo, el centro metálico puede activar un doble o triple enlace C–C. Estas especies catiónicas se generan por extracción de un haluro de complejos del tipo [AuXL], generalmente con una sal de plata. Algunos autores han sugerido que en ocasiones la presencia de sales de plata podría interferir en la catálisis,[36] por lo que parece conveniente diseñar sistemas que eviten la formación de la especie activa *in situ* con sales de plata.[37]

Algunos autores han conseguido solucionar este problema estabilizando los complejos catiónicos con ligandos neutros o alternativamente con ligandos aniónicos fácilmente desplazables.

Dado que en la mayoría de las catálisis con sistemas basados en oro(I) se observa descomposición a Au^0 parecía interesante estudiar en qué condiciones esta vía de desactivación del sistema catalítico se podía evitar, ya que esta ruta indeseada en algunos procesos podría ser perjudicial para el TON de un proceso catalítico o incluso para una posible reutilización del catalizador.[27a,38] Por tanto, conseguir estabilizar sistemas en los que se observa este tipo de descomposición a Au^0 constituye un reto en catálisis con oro.

Se había encontrado en otras líneas desarrolladas en el grupo que el ligando $AsPh_3$, no muy utilizado en sistemas catalíticos, muestra un interesante efecto estabilizador en catálisis bimetálica Pd/Au.[39] Este resultado nos animó a examinar la posibilidad de que la trifenilarsina fuese también un buen candidato para estabilizar sistemas catalíticos basados sólo en oro. Como se detalla en el resumen de los

[36] Homs, A.; Escofet, I.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 5782–5785.
[37] Schmidbaur, H.; Schier, A. Z. *Naturforsch* **2011**, *66b*, 329–350, y sus referencias.
[38] (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
[39] (a) delPozo, J.; Casares, J. A.; Espinet, P. *Chem Comm*. **2013**, *49*, 7246–7248. (b) delPozo, J.; Carrasco, D.; Pérez-Temprano, M. H.; García-Melchor, M.; Álvarez, R.; Casares, J. A.; Espinet, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2189–2193. (c) Pérez-Temprano, M. H.; Casares, J. A.; de Lera, Á. R.; Álvarez, R.; Espinet, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 4917–4920.

resultados obtenidos, se estudió el efecto de la presencia de cantidades estequiométricas o incluso subestequiométricas de $AsPh_3$ en las reacciones catalíticas. Sorprendentemente, la descomposición se reduce drásticamente o se inhibe por completo en la mayoría de los casos. La Figura 5 muestra de forma muy visual este efecto estabilizador de la $AsPh_3$. Este espectacular resultado nos animó a estudiar la posibilidad de recuperar y reutilizar el catalizador en alguna de las reacciones llevadas a cabo.

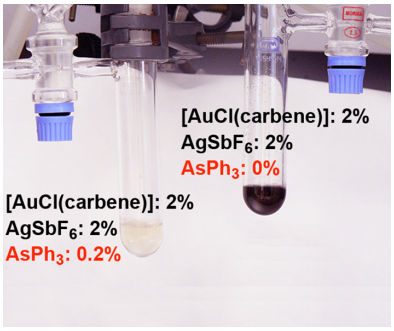


Figura 5. Catálisis llevadas a cabo con carbenos NAC de oro(I) en presencia (izquierda) y en ausencia (derecha) de cantidades subestequiométricas de $AsPh_3$

El resumen de los resultados publicados en los cinco artículos que se han derivado de esta tesis doctoral se divide en los siguientes bloques:

Por un lado se comenta la síntesis y caracterización de carbenos de oro(I) del tipo [AuCl{C(NRH)(NHPy-2)}] obtenidos por adición nucleófila de aminas primarias a [AuCl(CNPy-2)]. Dada su analogía estructural con los carbenos heterocíclicos tradicionales, se estudia su actividad catalítica en reacciones de ciclación de 1,n-eninos.

En una segunda parte se extiende la síntesis a carbenos acíclicos del tipo [AuCl{C(NHR)(NHR')}] y [AuCl{C(NHR)(NR'$_2$)}], así como su actividad catalítica en el mismo tipo de reacciones de ciclación, comparando los resultados de estas catálisis con los obtenidos con los carbenos heterocíclicos soportados por enlaces de hidrógeno [AuCl{C(NRH)(NHPy-2)}]. Se resume a continuación el alcance de la actividad catalítica de los carbenos NAC en diferentes tipos de ciclaciones intra e intermoleculares e incluso a reacciones de bencilación de arenos.

La tercera parte del resumen se centra en la síntesis y estudio de la actividad catalítica de los carbenos heterocíclicos y acíclicos quirales en las reacciones de hidroalcoxilación enantioselectiva de alenos y ciclopropanación enantioselectiva de olefinas.

A continuación se han incluido interesantes observaciones derivadas de la presencia de cantidades estequiométricas o subestequiométricas de ligandos estabilizadores, en concreto de $AsPh_3$. Se ha estudiado cómo afecta a la supervivencia del catalizador la presencia de este ligando en las condiciones habituales de catálisis.

Finaliza el resumen con las conclusiones derivadas del trabajo y con la metodología utilizada, es decir, algunos detalles sintéticos de los complejos aislados así como de las reacciones de catálisis llevadas a cabo y las técnicas utilizadas para la caracterización de todos los productos sintetizados.

Como apéndice, se incluye la publicación (*ACS Catal.* **2014**, *4,* 1607−1615) derivada del trabajo que desarrollé durante mi estancia en la Universidad de Virginia en 2012, acompañada de un breve resumen en español.

Objetivos

OBJETIVOS

El trabajo que se resume en esta memoria tiene tres objetivos muy claros:

-Por una lado, se ha abordado la síntesis de carbenos de oro(I) soportados por enlace de hidrógeno intramolecular (HBHC) y acíclicos (NAC) sintetizados por adición nucleofílica de diferentes aminas a isocianocomplejos de oro(I). Se estudia además su actividad catalítica en reacciones de activación de eninos, en concreto metoxiciclaciones y reacciones de transposición de esqueleto. Se compararán los resultados con los obtenidos para carbenos heterocíclicos convencionales del tipo NHC. Se extenderá el estudio de la actividad de ambos tipos de carbenos a otros tipos de reacciones de ciclación intra o intermoleculares.

-El segundo objetivo se ha centrado en la síntesis de carbenos de oro(I) quirales, tanto cíclicos, derivados del complejo [AuCl(CNPy-2)] por adición de aminas quirales, como acíclicos, por reacción con diferentes aminas no quirales del isocianocomplejo de oro(I) con 2,2'-diisociano-1,1'-binaftilo o 1,1'-binaftil-(3,3'-difenil)-2,2'-diisocianuro. Se estudia por último su actividad catalítica en la versión enantioselectiva de dos reacciones: hidroalcoxilación de alenos y ciclopropanación de olefinas.

- El último objetivo consiste en estabilizar los sistemas de oro(I) durante el proceso de catálisis mediante la adición de un ligando estabilizador, en concreto $AsPh_3$, que reduzca o inhiba por completo la indeseada y muy habitual reducción del Au^I a Au^0, que conduce a la desactivación del sistema catalítico.

Resumen de Resultados Obtenidos

Resumen de los resultados obtenidos

Se resumen a continuación los resultados más importantes, todos ellos recogidos en las cinco publicaciones a que ha dado lugar este trabajo. Para facilitar la lectura del resumen se ha mantenido la numeración de los compuestos que aparecen en cada uno de los artículos, precedida del número romano que se ha asignado a cada una de estas cinco aportaciones:

Artículo I

Gold(I) Complexes with Hydrogen-Bond Supported Heterocyclic Carbenes as Active Catalysts in Reactions of 1,6-Enynes; *Inorg. Chem.* **2008**, *47*, 11391–11397

Artículo II

Nitrogen Acyclic Gold(I) Carbenes: Excellent and Easily Accessible Catalysts in Reactions of 1,6-Enynes; *Organometallics* **2010**, *29*, 951–956

Artículo III

Exploring the Scope of Nitrogen Acyclic Carbenes (NACs) in Gold-Catalyzed Reactions; *Organometallics* **2010**, *29*, 3589–3592

Artículo IV

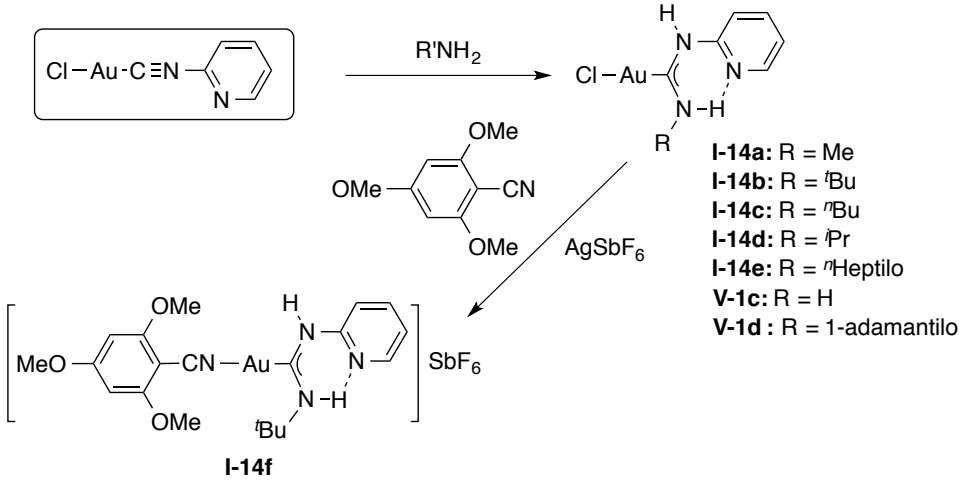
Synthesis and Catalytic Activity of Gold Chiral Nitrogen Acyclic Carbenes and Gold Hydrogen Bonded Heterocyclic Carbenes in Cyclopropanation of Vinyl Arenes and in Intramolecular Hydroalkoxylation of Allenes; *Inorg. Chem.* **2010**, *49*, 9758–9764

Artículo V

Protection of the Gold(I) Catalyst by $AsPh_3$ in Reactions of Enynes; *Eur. J. Inorg. Chem.* **2014**, 5499–5506

Síntesis de Carbenos HBHC de oro(I)

Como se ha comentado en la introducción, se sintetizaron nuevos carbenos del tipo [AuCl{C(NRH)(NHPy-2)}] con sustituyentes R de diferente requerimiento estéreo (Esquema 9) a partir de [AuCl(CNPy-2)] por ataque nucleofílico de aminas con diferentes características electrónicas o estéreas.



Esquema 9. Síntesis de carbenos HBHC´s

El espectro de RMN de ^{1}H registrado en $CDCl_3$ de todos los carbenos HBHC revela la existencia de un enlace de hidrógeno intramolecular entre el hidrógeno del grupo NRH de la amina y el nitrógeno del grupo 2-piridilo. Esta interacción de hidrógeno da lugar a un ciclo de seis miembros que parece ser muy estable en disolución, lo que hace a este tipo de carbenos estructuralmente parecidos a los carbenos heterocíclicos. La conformación observada en disoluciones de $CDCl_3$ o Me_2CO–d_6 se mantiene en estado sólido, como se puede observar en la Figura 6 que recoge las estructuras de Rayos X de [AuCl{C(NH^{t}Bu)(NHPy-2)}] (**I-14c**) y de AuCl{C(NH_2)(NHPy-2)}]$_3$ (**V-1c**).

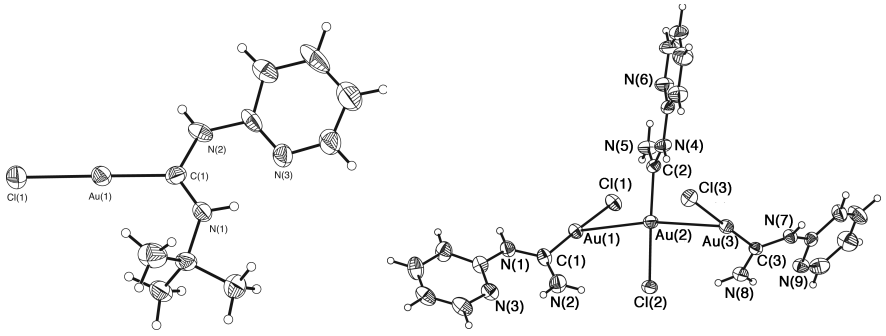
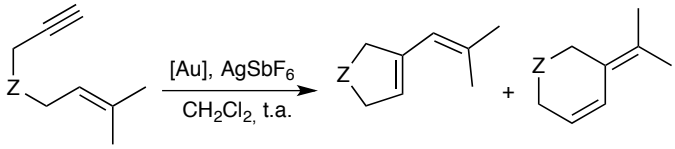


Figura 6. ORTEP de [AuCl{C(NH^{t}Bu)(NHPy-2)}] (**I-14c**) y AuCl{C(NH_2)(NHPy-2)}]$_3$ (**V-1c**)

Carbenos HBHC de oro(I) como catalizadores en ciclaciones de 1,6-eninos

Todos los carbenos sintetizados resultaron ser activos como precatalizadores en las reacciones de transposición de esqueleto de 1,6-eninos, resultado que no sorprende si se tiene en cuenta que en disolución el enlace de hidrógeno intramolecular se mantiene en las condiciones de reacción, por lo que estos carbenos son estructuralmente análogos a los carbenos heterocíclicos. La Tabla 1 recoge los resultados obtenidos utilizando 2-(3-metil-2-butenil)-2-(2-propinil)malonato de dimetilo (**I-16**).[40] Todas las reacciones se llevaron a cabo disolviendo el catalizador y el 1,6-enino en CH_2Cl_2 y añadiendo $AgSbF_6$ como extractor de cloruro, lo que favorece la coordinación del enino al centro metálico.

Tabla 1. Ciclación de **I-16a** catalizadas por carbenos de oro HBHC´s

Ensayo	**[Au]**	**tiempo**	**Producto** **Rendimiento, (%, ratio)**
			
	I-16a: Z = $C(CO_2Me)_2$		**I-17a** **I-18a**
1	**I-14a**	2 min	**I-17a** + **I-18a** (89, 30:1)
2	**I-14b**	2 min	**I-17a** + **I-18a** (93, 31:1)
3	**I-14c**	5 min	**I-17a** (88)
4	**I-14d**	5 min	**I-17a** (73)
5	**I-14e**	5 min	**I-17a** (89)
6[b]	**I-14f**	5 min	**I-17a** + **18a** (94, 46:1)

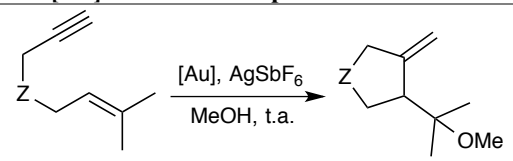
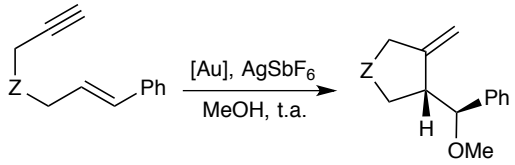
[a] Reacciones en CH_2Cl_2 con 2 mol% de [Au]. [b] Reacciones en ausencia de $AgSbF_6$.

Todas las reacciones son muy rápidas, obteniéndose una conversión total en pocos minutos, lo que indica la espectacular actividad de estos carbenos. La actividad del complejo catiónico **I-14f**, obtenido a partir de **I-14b** con $AgSbF_6$ en presencia de 2,4,6-trimetoxibenzonitrilo en exceso, es análoga a la observada utilizando como **I-14b** + $AgSbF_6$ (Tabla 1, ensayos 2 y 6) este resultado abre una interesante vía para desarrollar sistemas catalíticos de oro(I) en ausencia de sales de plata, evitando así la posibilidad de que tengan lugar durante la catálisis transformaciones promovidas por sales de plata.

[40] Los resultados de las ciclaciones de eninos con diferentes sustituyentes se encuentran recogidas en la publicación original. Ver Bartolomé, C.; Ramiro, Z.; Pérez-Galán, P.; Bour, C.; Raducan, M.; Echavarren, A. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 11391–11397.

Los carbenos de oro HBHC sintetizados son también activos en reacciones de metoxiciclación (Tabla 2).

Tabla 2. Metoxiciclaciones de 1,6-eninos catalizadas por carbenos de oro HBHC´s

Ensayo	[Au]	tiempo	Producto (%)
			
	I-16a: Z = $C(CO_2Me)_2$		**I-20a**
1	**I-14a**	3 h	**I-20a** (20)
2	**I-14b**	3 h	**I-20a** (70)
3	**I-14c**	2 h	**I-20a** (44)
4	**I-14d**	2 h	**I-20a** (33)
5	**I-14e**	2 h	**I-20a** (39)
6[b]	**I-14f**	2 h	**I-20a** (80)
			
	I-16c: Z = $C(CO_2Me)_2$		**I-20b**
8	**I-14a**	3 h	**I-20b** (55)
9	**I-14b**	3 h	**I-20b** (59)

[a] Reacciones en CH_2Cl_2 con 5 mol% de [Au].

Teniendo en cuenta que este tipo de reacciones se lleva a cabo en metanol, donde el enlace de hidrógeno no se mantiene (Figura 7), la especie activa es un carbeno acíclico.

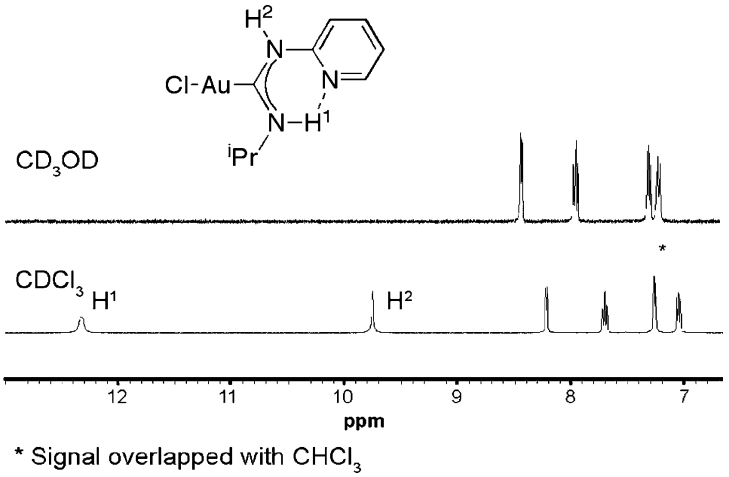


Figura 7. Espectro de ^{1}H RMN de la región aromática y de NH para [AuCl{C(NH^{i}Pr)(NHPy-2)}] (**I-14d**) en $CDCl_3$ y CD_3OD a temperatura ambiente

Este resultado nos animó a extender el estudio a carbenos acíclicos sintetizados de la misma manera que los HBHC´s, esto es, por ataque nucleofílico con aminas primarias o dietilamina a isocianocomplejos de oro(I).

Síntesis de Carbenos NAC de oro(I)

El hecho de que, a pesar de que la estructura cíclica de los carbenos HBHC se rompe en presencia de alcoholes, la actividad de estos carbenos no se altera en las reacciones de alcoxiciclación y abre la puerta a utilizar carbenos de oro(I) acíclicos, que se pueden sintetizar con muchísima facilidad a partir de cualquier tipo de isocianoderivados de oro(I) por reacción con aminas tanto primarias como secundarias. Se obtienen entonces carbenos acíclicos de oro, que hemos denominado NAC (Nitrogen Acyclic Carbene) (Figura 8).

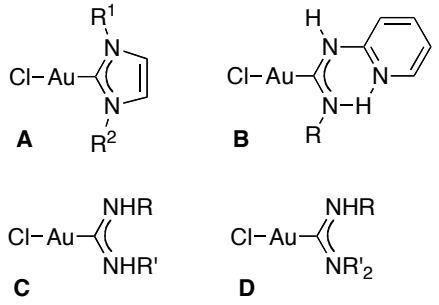
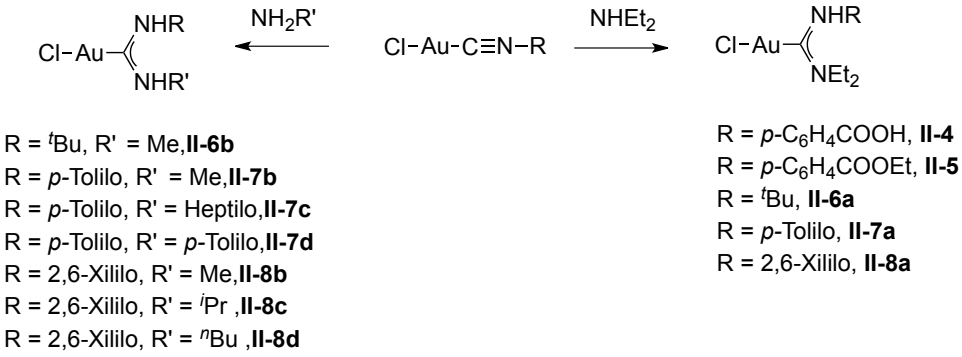


Figura 8. Carbenos de oro(I) NHC y HBHC cíclicos y NAC acíclicos

Los carbenos de oro(I) [AuCl{C(NHR)(NHR')}] y [AuCl{C(NHR)(NEt_2)}] han sido sintetizados por ataque nucleofílico a los isocianuros alquílicos o arílicos de oro [AuCl(CNR)] (R= *p*-C_6H_4COOH,[41] *t*Bu,[42] *p*-Tolilo,[43] 2,6-Xililo[44]) con aminas primarias de diferente impedimento o con la amina secundaria dietilamina (Esquema 10).

[41] Coco, S.; Espinet, E.; Espinet, P.; Palape, I. *Dalton Trans.* **2007**, 3267–3272.
[42] Elbjeirami, O.; Omary, M. A.; Stender M.; Balch, A. L. *Dalton Trans.* **2004**, 3173–3175.
[43] Bonati, F.; Minghetti, G. *Gazz. Chim. Ital.* **1973**, 373–386.
[44] Heathcote, R.; Howell, J. A. S.; Jennings, N.; Cartlidge, D.; Cobden, L.; Coles, S.; Hursthouse M. *Dalton Trans.* **2007**, 1309–1315.



Esquema 10. Síntesis de carbenos de oro acíclicos

Todos los isocianuros de oro habían sido previamente descritos, con la excepción de [AuCl(CN*p*-C_6H_4COOEt)], que fue obtenido a partir del correspondiente precursor con tetrahidrotiofeno [AuCl(tht)][45] por sustitución del tht con CN(*p*-C_6H_4COOEt),[41] procedimiento análogo al descrito para otros isocianocomplejos de oro.[46]

Como muestra la Figura 9, se podrían observar hasta cuatro isómeros en disolución para los complejos carbénicos, dependiendo de la disposición relativa de los grupos R y R' con el sustituyente de oro, para aminas primarias ($R'NH_2$), o solo dos para la amina secundaria Et_2NH.

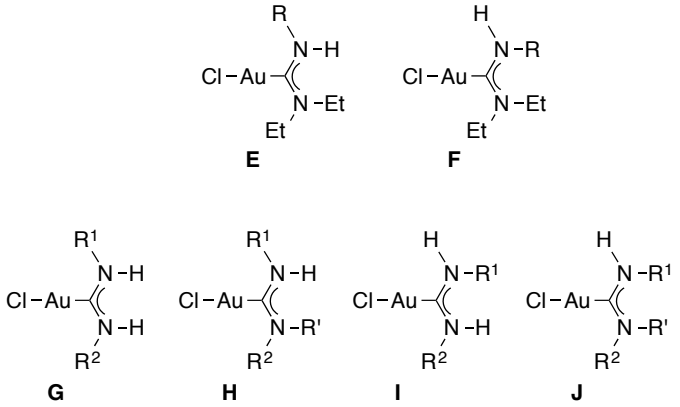


Figura 9. Posibles isómeros para complejos carbénicos derivados de $HNEt_2$ o RNH_2

Teniendo en cuenta el carácter doble parcial de los enlaces C–N, se puede proponer que la interconversión entre isómeros es suficientemente lenta como para no ser observada por RMN, ya que la barrera rotacional asociada al giro en torno a cualquiera de los dos enlaces C–N es alta. Por tanto, en los carbenos de oro(I) obtenidos

[45] Usón, R.; Laguna, A.; Laguna, M. *Inorg. Synth.* **1989**, *26*, 85–91.
[46] Bayón, R.; Coco, S.; Espinet, P.; Fernández-Mayordomo, C.; Martin-Alvarez, J. M. *Inorg. Chem.* **1997**, *36*, 2329–2334.

por tratamiento con Et_2NH, deberían observarse los dos posibles isómeros, *syn* (Figura 9, **E**) y *anti* (Figura 9, **F**). Sin embargo, en todos los casos se ha observado un único isómero en el espectro de ^1H de los carbenos [AuCl{C(NHR)(NEt_2)}] a temperatura ambiente. Experimentos NOE confirman que el confórmero menos impedido, es decir, el isómero *syn*, es el que está presente en disolución, análogamente a lo observado en estado sólido para [AuCl{(CNHPy-2)(NEt_2)}][26] y para los complejos derivados del 4-PyNC, [AuR{(CNHPy-4)(NEt_2)}],[47] (R = C_6F_5, 2,4,6-tris(trifluorometil)fenilo).

En los carbenos derivados de aminas primarias [AuCl{C(NHR^1)(NHR^2)}] se podrían formar hasta cuatro isómeros; los espectros de ^1H RMN en $CDCl_3$ a temperatura ambiente mostraron un número diferente de confórmeros dependiendo del requerimiento estérico de los sustituyentes R^1 y R^2. En el caso de los carbenos [AuCl{C(NH-2,6-Xilil)(NH^{i}Pr)}] (**II-8c**) y [AuCl{C(NH-2,6-Xilil)(NH^{n}Bu)}] (**II-8d**) se observa un único confórmero. La configuración del isómero mayoritario se asignó para todos los complejos mediante experimentos NOE (Figura 10).

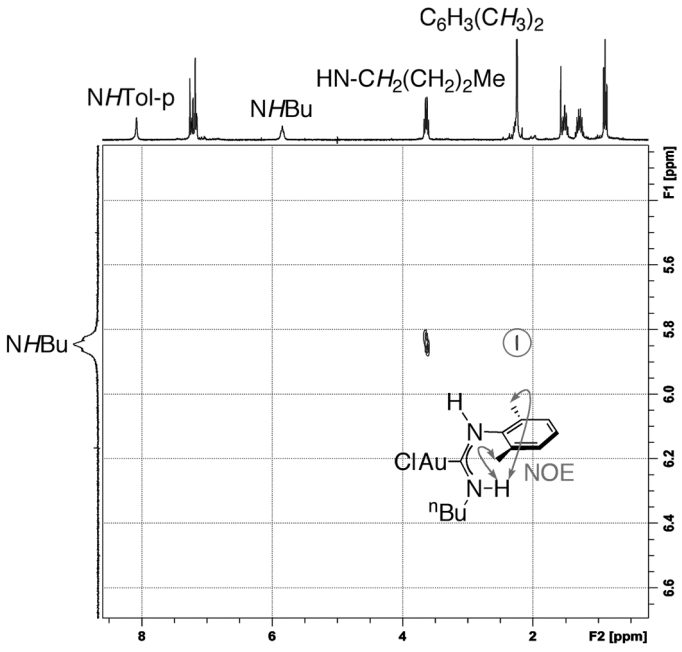


Figura 10. Espectro ^1H-^1H NOESY de **II-8d** (zona de N*H*Bu) registrado a 295K. El hidrógeno N*H*Bu muestra NOE con los hidrógenos metílicos del grupo 2,6-xililo a 2.24 ppm y con el grupo CH_2 de la cadena de ^{n}Bu

[47] Bartolomé, C.; Carrasco-Rando, M.; Coco, S.; Cordovilla, C.; Espinet, P.; Martín-Alvarez*, J. M. Dalton Trans.* **2007**, 5339–5345.

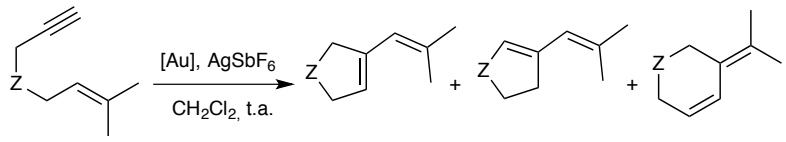
Como se puede observar en el experimento ^{1}H–^{1}H NOESY de **II-8d**, existe NOE entre el hidrógeno del grupo N*H*Bu y el singlete asignado a los Me del grupo 2,6-Xilil, lo que permite afirmar que el confórmero mayoritario es **I** (Figura 9), donde R^1 se sitúa *anti* con respecto al centro metálico; de hecho, este es el único isómero que se observa en los complejos **II-8c** y **II-8d**. El isómero mayoritario observado en el espectro de ^{1}H del complejo **II-6b** es **H** (Figura 9), donde el grupo ^{t}Bu se sitúa *syn* con respecto al oro.

Carbenos NAC de oro(I) como catalizadores en ciclaciones de 1,6-eninos

La actividad catalítica de los carbenos NAC de oro, se probó en reacciones de transposición de esqueleto y metoxiciclaciones de 1,6-eninos. Todos los experimentos de catálisis se llevaron a cabo en condiciones idénticas a las utilizadas con los carbenos del tipo HBHC previamente descritos. De nuevo, los carbenos sintetizados resultaron ser catalizadores activos en la reacción de transposición de esqueleto. Los rendimientos y conversiones en ambas reacciones varían dependiendo de los sustituyentes R y R' de los carbenos.

Los resultados obtenidos para la reacción de transposición de esqueleto de 1,6-eninos se resumen en la Tabla 3.

Tabla 3. Ciclación de **II-9a** catalizada por carbenos NAC de oro



II-9a: Z = $C(CO_2Me)_2$ **II-10a** **II-11a** **II-12a**

Ensayo	[Au]	Productos (Rendimiento, %)
1	**II-4**	**II-10a** (74) + **II-11a** (6) + **II-12a** (2)[b]
2	**II-5**	**II-10a** (51) + **II-11a** (12)
3	**II-6a**	**II-10a** (81) + **II-12a** (2)[b]
4	**II-6b**	**II-10a** (35) + **II-11a** (21) + **II-12a** (1)[b]
5	**II-7a**	**II-10a** (50) + **II-11a** (15)
6	**II-7b**	**II-10a** (85) + **II-12a** (3)
7	**II-7b**	**II-10a** + **II-12a** (30:1) (88)[c]
8	**II-7c**	**II-10a** (98)
9	**II-7d**	**II-10a** (61) + **II-11a** (12)
10	**II-8a**	**II-10a** (100)
11	**II-8b**	**II-10a** (100)
12	**II-8c**	**II-10a** (8) + **II-11a** (17)
13	**II-8d**	**II-10a** (5) + **II-11a** (8)

[a] Reacciones en CH_2Cl_2 con 2 mol% de [Au]. Rendimientos determinados por GC. [b]Rendimientos determinados por ^{1}H RMN. [c]Rendimiento del producto aislado.

Aunque todos los carbenos NAC de oro sintetizados catalizan esta reacción, la eficiencia observada depende de los sustituyentes del carbeno. Cuando la reacción da lugar a más de un producto, el porcentaje de los productos obtenidos depende del catalizador utilizado.

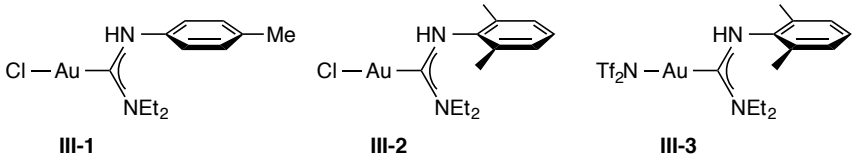
Así, de la reacción de transposición de esqueleto de **II-9a** se han obtenido hasta tres productos diferentes: el producto de ciclación exo **II-10a**, el producto de ciclación endo **II-12a** y, en algunas de las reacciones catalíticas, el dieno **II-11a** como producto de la isomerización del doble enlace endocíclico de **II-10a**. El dieno **II-11a** ya había sido observado en las ciclaciones de **II-9a** catalizadas por $FeCl_3$, y como producto minoritario en reacciones catalizadas por diferentes complejos de oro(I).[16a] Los catalizadores **II-7b**, **II-7c, II-8a** y **II-8b** conducen exclusivamente o casi exclusivamente al producto exo **10a** (Tabla 3, ensayos 6-8, y10-11).

El alcance de la actividad catalítica del sistema NAC de oro(I) se extendió a diferentes tipos de 1,6-eninos y 1,7-eninos. Asimismo, se llevaron a cabo reacciones de metoxiciclación y, al igual que lo observado para los sistemas HBHC anteriormente descritos, todos los carbenos NAC sintetizados resultaron ser activos.[48]

Alcance de la actividad catalítica de carbenos NAC de oro(I) en diferentes reacciones intra e intermoleculares

Los carbenos NAC de oro resultaron ser activos no sólo en reorganizaciones de esqueleto o alcoxiciclaciones de eninos sino que fueron también muy eficaces como catalizadores en diferentes transformaciones orgánicas de interés.

Se eligieron para este estudio diferentes reacciones tales como ciclaciones de homopropargilsulfóxido, exo-hidroaminaciones o hidroalcoxilaciones de alenos, hidroarilaciones intramoleculares de alquinos o incluso reacciones de bencilación de arenos. El Esquema 11 recoge los carbenos elegidos para llevar a cabo este estudio.



Esquema 11. Carbenos elegidos para analizar el alcance de la actividad de sistemas NAC

[48] Todos estos resultados están detallados en la publicación original. Ver Bartolomé, C.; Ramiro, Z.; García-Cuadrado, D.; Pérez-Galán, P.; Bour, C.; Raducan, M.; Echavarren, A. M.; Espinet, P. *Organometallics* **2010**, *29*, 951–956.

El complejo [Au(NTf_2){C(NEt_2)(NHXilil)}] (**III-3**) con el ligando aniónico bis(trifluorometilsulfonil)imidato se sintetizó a partir de **III-2** por reacción con $AgNTf_2$.[8]

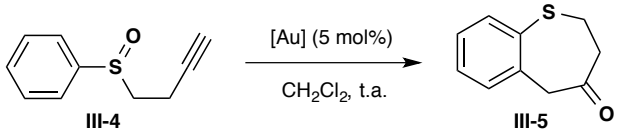
Estos tres carbenos acíclicos se utilizaron para examinar el alcance de su actividad como catalizadores en diferentes transformaciones comparando los resultados obtenidos con los mejores resultados publicados para ese tipo de reacciones catalizadas por otros sistemas de oro(I).

Reacciones intramoleculares:

Ciclación de homopropargilsulfóxido

Los complejos NAC de oro(I) en presencia de una sal de plata como extractor de haluro son activos en la reacción de reorganización de homopropargilsulfóxido (**III-4**), para dar 1-benzotiepin-4-ona (**III-5**) con buenos rendimientos (Tabla 4, ensayos 1-5).

Tabla 4. Ciclación de homopropargilsulfóxido catalizada por complejos NAC de oro

Ensayo	**[Au]**	**AgX**	**Rendimiento[a] [%]**
	 **III-4** **III-5**		
1	**III-1**	$AgSbF_6$	62
2	**III-1**	$AgNTf_2$	75
3	**III-2**	$AgNTf_2$	82
4	**III-2**	$AgSbF_6$	76
5	**III-3**	–	60
6	[AuCl(PPh_3)]	$AgSbF_6$	30 (34[b])
7	[AuCl(PPh_3)]	$AgNTf_2$	30
8	[AuCl(P(*p*-$CF_3C_6H_4)_3$)]	$AgSbF_6$	25[b]
9	[AuCl(IMes)]	$AgSbF_6$	76 (94[b])
10	[AuCl(IMes)]	$AgNTf_2$	77

[a] Rendimiento por ^{1}H NMR. [b]Rendimientos descritos (ver Ref.49)

Esta ciclación había sido descrita por Toste utilizando como catalizadores complejos de oro(I) con diferentes ligandos fosfina o carbeno NHC.[49] En este caso, los peores rendimientos se obtienen con fosfinas y, en concreto, con aquellas menos

[49] Shapiro, N. Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.

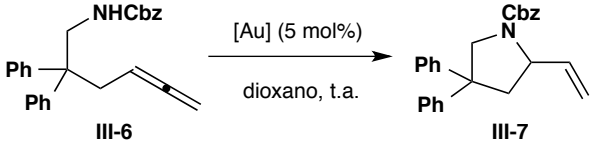
dadoras como P(*p*-$CF_3C_6H_4)_3$. Estos rendimientos mejoran considerablemente cuando el ligando principal es carbeno, resultado consistente con el hecho de que, en general, éstos son más dadores que las fosfinas.[50]

Ciclaciones intramoleculares de alenil alcoholes o alenil carbamatos

Dado que muchos sistemas tanto *N* como *O*-heterocíclicos forman parte del esqueleto de multitud de sistemas biológicamente activos, el diseño de catalizadores activos para este tipo de transformaciones es un campo de muchísimo interés en la actualidad.[51] Muchos de estos sistemas están basados en complejos de oro(I) con fosfinas o carbenos heterocíclicos como ligandos principales.[52]

Los complejos de oro **III-2** (y AgOTs como extractor de haluro) y **III-3** catalizan de forma muy eficaz la exo-hidroaminación del N-alenilcarbamato **III-6** para dar 2-vinylpirrolidina **III-7**, análogamente a lo descrito con [AuClP(^{t}Bu)$_2$(*o*-biphenyl)] y AgOTf en cantidades equimolares (Tabla 5).[53]

Tabla 5. *Exo*-hidroamination intramolecular de *N*-alenil carbamato catalizada por NAC de oro(I)

Ensayo	**[Au]**	**AgX**	**Rendimiento [%]**
			
1	**III-2**	AgOTs	92[a]
2	**III-3**	_	78[a]
3	[AuClP(^{t}Bu)$_2$(*o*-bifenil)]	AgOTf	95[b]

[a] Rendimiento del producto aislado. [b] Ref. 53

[50] (a) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717–8724. (b) Slaughter, L. M. Comments on *Inorg. Chem.* **2008**, *29*, 46–72.

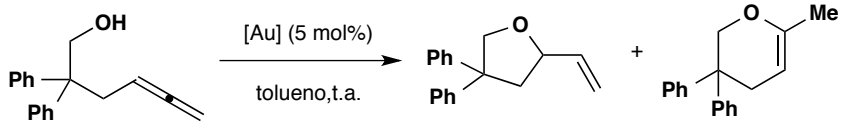
[51] Schafer, L. L.; Yim, J. C.-H.; Yonson, N. En *Metal-Catalyzed Cross-Coupling Reactions and More,* First Edition. Edited by Armin de Meijere, Stefan Bräse, and Martin Oestreich. ″2014 Wiley-VCH Verlag GmbH & Co. KGaA. Published 2014 by Wiley-VCH Verlag GmbH & Co. KGaA.

[52] Revisiones sobre ciclaciones de alenos catalizadas por oro(I): (a) Krause, N.; Winter, N. *Chem. Rev.* **2011**, *111*, 1994–2009. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (c) Ross A. Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563. Estudios mecanísticos sobre adiciones de alenos catalizadas por oro(I): (d) Wang, Z. J.; Benítez, D.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 13064–13071.

[53] Zhang, Z. Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073.

Los carbenos NAC también son activos en reacciones de *exo*-hidroalcoxilación intramolecular de alenos. Así, la reacción de 2, 2-difenil-4, 5-hexadienol **III-8** en presencia de **III-2** con AgOTs conduce selectivamente al tetrahidrofurano **III-9**, análogamente a lo observado con [AuClP(^{t}Bu)$_2$(*o*-bifenil)] y AgOTs (Tabla 6).

Tabla 6. Hidroalcoxilación intramolecular de 2, 2-difenil-4, 5-hexadienol catalizada por NAC de oro(I)

Ensayo	[Au]	AgX	Rendimiento [%]
			
	III-8	**III-9**	**III-10**
1	**III-2**	AgOTs	94/<1[a]
2	**III-3**	–	45/<1[a]
3	[AuClP(^{t}Bu)$_2$(*o*-bifenil)]	AgOTf	48/37[b]
4	[AuClP(^{t}Bu)$_2$(*o*-bifenil)]	AgOTs	91[c]

[a]Rendimiento del producto aislado. [b]Rendimiento calculado por GC con patrón interno (ver Ref. 53). [c]Rendimiento del producto aislado (Ref. 53).

A pesar de que la regioselectividad de esta reacción depende del anión que participa en el sistema catalítico (Tabla 6, ensayos 3 y 4),[53] el carbeno **III-3**, con el ligando fácilmente desplazable NTf_2, sigue siendo selectivo hacia el producto de exociclación, si bien el rendimiento disminuye considerablemente.

Reacciones intermoleculares

Hidroarilación intermolecular de alquinos

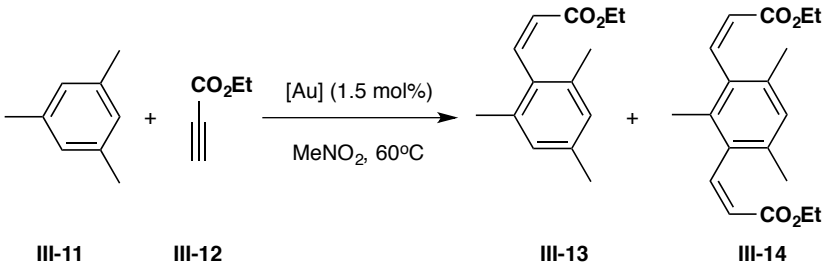
La formación de un enlace C–C por activación de un enlace C–H aromático es una interesante alternativa al uso de derivados halogenados. Existen multitud de trabajos publicados sobre hidratación o hidroaminación de alquinos; sin embargo no existen demasiados ejemplos en la bibliografía de hidroarilaciones de alquinos catalizadas por complejos de oro(I), a pesar del interés de este tipo de transformaciones ya que es muy difícil controlar su quimio, regio o estereoselectividad.[38a,54]

[54] (a) Hahn, C.; Cruz, L.; Villalobos, A.; Garza, L.; Adeosun, S. *Dalton Trans.* **2014**, *43*, 16300–16309. (b) Tubaro, C.; Baron, M.; Biffis, A.; Basato, M. *Beilstein J. Org. Chem.* **2013**, *9*, 246–256. (c) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644–661. (d) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671. (e) Reetz, M.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496.

Como se puede observar en la Tabla 7, los carbenos NAC muestran una alta selectividad hacia el producto de monoadición *Z* (**III-13**), aunque también se aísla en cantidades no despreciables el producto de la doble adición (**III-14**).

Tabla 7. Hidroarilación con propiolato de etilo, catalizada por carbenos NAC de oro(I)

Ensayo	[Au]	AgX	Rendimiento [a] [%]
1	**III-2**	$AgNTf_2$	76/7
2	**III-3**	–	78/7
3	$[AuCl(PEt_3)]$	AgOTf	67/20[b]
4	$[AuCl(PPh_3)_3)]$	$AgBF_4$	63/6 (57/16[c])
5	$[AuCl(PPh_3)_3)]$	$AgSbF_6$	77/7



III-11 III-12 III-13 III-14

[a] Nuestros resultados, % obtenido por ^{1}H NMR. [b] A 25 °C, 5% mol de [Au]. % determinado por GC con patrón interno (ver ref. 54). [c] A 60 °C 5% mol de [Au]. % determinado por GC con patrón interno (ver ref. 54).

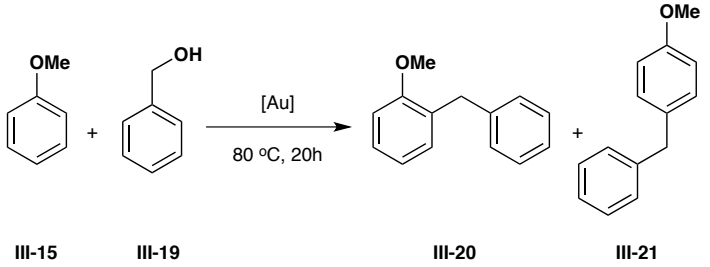
Aunque la selectividad observada mejora considerablemente los resultados publicados por Reetz, cuando hemos repetido estas catálisis con su sistema $[AuCl(PR_3)]$ (Tabla 7, ensayos 4 y 5) los resultados apenas difieren de los conseguidos con nuestros carbenos NAC.

Bencilación de arenos

Los carbenos NAC de oro **III-1** (en presencia de $AgNTf_2$) y **III-3** son también activos en reacciones de bencilación de anisol. Los complejos **III-1** (en presencia de $AgNTf_2$) y **III-3** son también activos en reacciones de bencilación de anisol. Si bien los resultados de la bencilación con acetato de 1-feniletilo obtenidos con los carbenos NAC son análogos a los descritos utilizando ácido tetracloroáurico, cuando se utiliza alcohol bencílico (Tabla 8) los rendimientos mejoran considerablemente con respecto a los descritos en la bibliografía.[55]

[55] Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691–695.

Tabla 8. Reacción de anisol con alcohol bencílico catalizada por complejos de oro(I) NAC

Ensayo	[Au]	AgX	Rendimiento[a] [%]
			
	III-15 III-19		III-20 III-21
1	**III-1**[b]	$AgNTf_2$	96 (40/60)
2	**III-1**[c]	$AgNTf_2$	91 (40/60)
3	**III-3**[b]	–	94 (40/60)
4	**III-3**[c]	–	66 (40/60)
5	$H[AuCl_4]$[b]	–	15 (33/67)

[a] Rendimiento obtenido por ^{1}H NMR. [b] 10 mol%. [c] 5 mol%.

Todos los experimentos de catálisis llevados a cabo los complejos de oro(I) con ligandos NAC resultan ser catalizadores tan activos como los sistemas carbeno heterocíclicos e incluso en algunos casos más activos que los complejos con fosfinas como ligando principal. Las tendencias observadas en todas estas reacciones están en consonancia con el orden de basicidad del ligando principal: PR_3 < NACs < NHCs.[50]

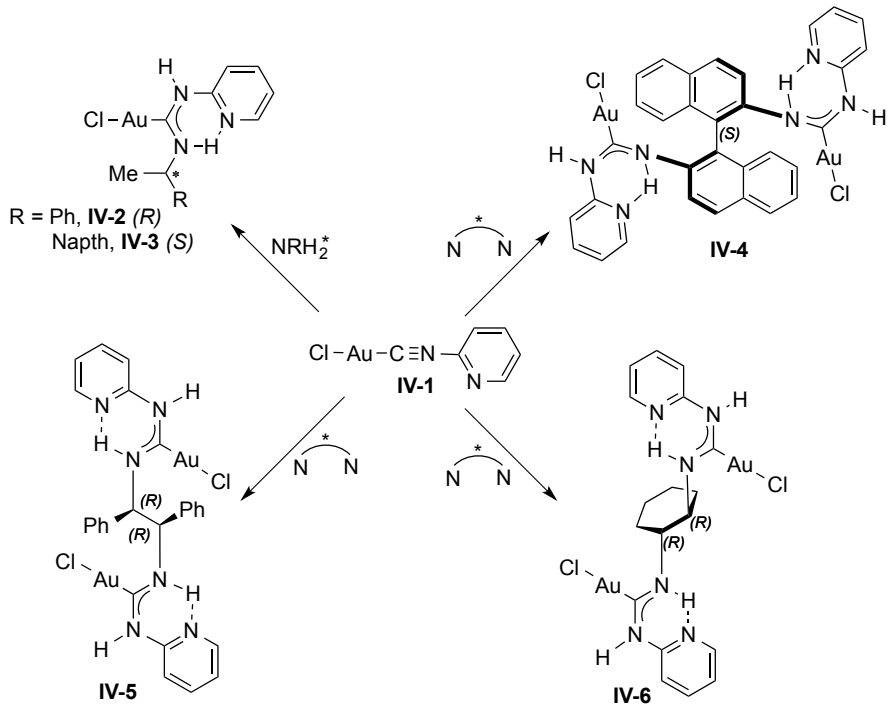
Carbenos HBHC y NAC quirales de oro(I). Estudio de su actividad catalítica

Como ya se comentó en la introducción, el uso de complejos de oro(I) en catálisis enantioselectiva es relativamente reciente.[28] La mayoría de los sistemas de oro(I) descritos son del tipo μ-(P-P)[$(AuX)_2$] (con P-P = difosfina quiral[29]), fosforamidatos quirales[29b,c] o aniones quirales.[30] Los catalizadores basados en fosfinas tienen la desventaja de que, en las condiciones de catálisis, pueden oxidarse fácilmente.[9] Con estos antecedentes, hemos llevado a cabo la síntesis de carbenos de oro(I) HBHC y NAC quirales que son resistentes a la oxidación y pueden ser una interesante alternativa.

Síntesis de carbenos quirales HBHC y NAC de oro(I)

La síntesis de los carbenos quirales se abordó por dos vías: ataque nucleofílico de una amina quiral a un isocianocomplejo aquiral o, alternativamente, ataque nucleofílico a un isocianocomplejo quiral con una amina aquiral.

Los carbenos de oro quirales del tipo HBHC **IV-2-6** se sintetizaron por ataque nucleófilo al isocianocomplejo [AuCl(CNPy-2)] (**IV-1**)[26] con las aminas o diaminas primarias quirales del Esquema 12.



Esquema 12. Síntesis de carbenos de oro(I) quirales HBHC

Análogamente a lo descrito para carbenos no quirales HBHC´s, en los espectros de RMN de ^{1}H registrados a temperatura ambiente en $CDCl_3$ sólo se observan las señales correspondientes a un único isómero. Se observan las dos señales correspondientes a los protones N-H claramente diferenciadas. El desplazamiento químico de uno de los protones a campo bajo es característico de la existencia de un enlace de hidrógeno intramolecular en disolución entre el protón de la amina y el nitrógeno del grupo 2-piridilo, lo que da lugar a un ciclo de 6 miembros. Esta interacción intramolecular se mantiene en estado sólido (Figura 11).

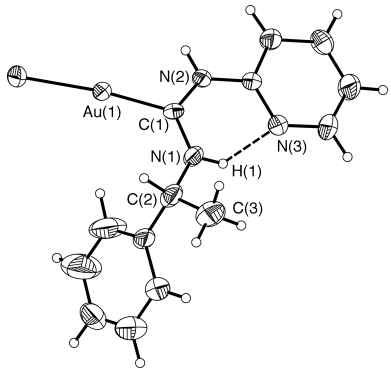


Figura 11. Estructura de rayos X de **IV-**(*R*)**-2**

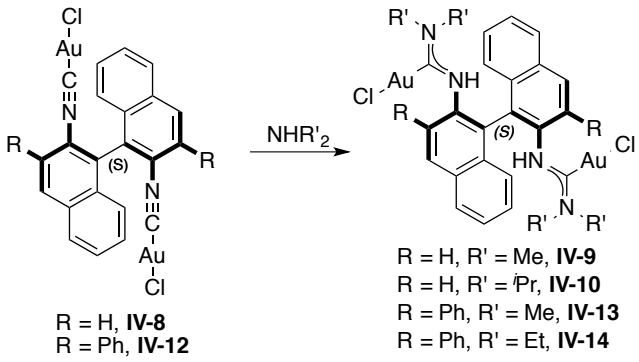
La síntesis de carbenos binucleares acíclicos quirales se llevó a cabo partiendo de un isocianocomplejo de oro(I) donde el isocianuro fuese quiral. El isocianuro que se eligió es el 2,2'-diisociano-1,1'-binaftilo por ser un ligando que, debido a su enorme requerimiento estérico, impide el giro entorno al enlace C-C de los dos grupos naftilo. El resultado de esta restricción en el giro es que posee quiralidad axial, lo que le hace ser un buen candidato si se utiliza como ligando auxiliar de catalizadores en síntesis enantioselectiva. Se sintetizaron los ligandos tanto con Ph como con H en la posición 3 y 3' del diisocianuro (R = H, **IV-7**; R = Ph, **IV-11**).

El método de síntesis de estos ligandos 2,2'-diisociano-1,1'-binaftilo descrito en la bibliografía era el utilizado para otro tipo de isocianuros no quirales, es decir, por tratamiento de la correspondiente amina con ácido fórmico a reflujo en tolueno para obtener la formamida y posterior tratamiento con NaOH y $CHCl_3$ para obtener el isocianuro.[56,57] Sin embargo, esta forma de obtener la formamida conduce al producto poco enriquecido enantioméricamente, ya que en las condiciones de reacción (calentamiento durante un largo periodo de tiempo a la temperatura de reflujo del tolueno puede conducir a que se supere la barrera energética necesaria para que haya giro entorno al enlace de los grupos naftilo, lo que conduce a la racemización. Se decidió entonces obtener los ligandos diisocianuro enantioméricamente puros haciendo reaccionar las correspondientes (*S*)-1,1'-binaftil-2,2'-diaminas sustituidas en posición 3,3' con anhídrido fórmico-acético.[58]

Los carbenos de oro(I) quirales acíclicos **IV-9-10,13-14** se sintetizaron por ataque nucleofílico a los isocianocomplejos binucleares de oro(I) **IV-8** y **IV-12**, que a

[56] Yamamoto, Y.; Hagiwara, T.; Yamazaki, H. *Inorganica Chimica Acta* **1986**, *115*, L35–L37.
[57] Weber, W. P.; Gokel, G. W.; Ugi. I. *Angew. Chem., Int. Ed. Engl*. **1972**, *11*, 530–531.
[58] Todos los detalles sintéticos se recogen en la parte experimental de la publicación original. Ver Bartolomé, C.; García-Cuadrado, D.; Ramiro, Z.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758–9764.

su vez fueron obtenidos a partir del correspondiente precursor con tetrahidrotiofeno [AuCl(tht)] por sustitución del tht con el correspondiente diisocianuro quiral. Únicamente se llevaron a cabo reacciones utilizando aminas secundarias para reducir el número de confórmeros presentes en los carbenos sintetizados (Esquema 13).



Esquema 13. Síntesis de carbenos NAC quirales

Los espectros de ^{1}H NMR de **IV-9** y **IV-10** en $CDCl_3$ muestran las señales de un único isómero; sin embargo, dado que estos complejos son binucleares, los espectros de ^{1}H de RMN de disoluciones de **IV-13** y **IV-14** muestran las señales correspondientes a una mezcla de hasta tres confórmeros uno de ellos mayoritario. Los datos espectroscópicos de los que disponemos no permiten asignar cuál de las posibles conformaciones está favorecida. La Figura 12 muestra la estructura de Rayos X del complejo **IV-9**.

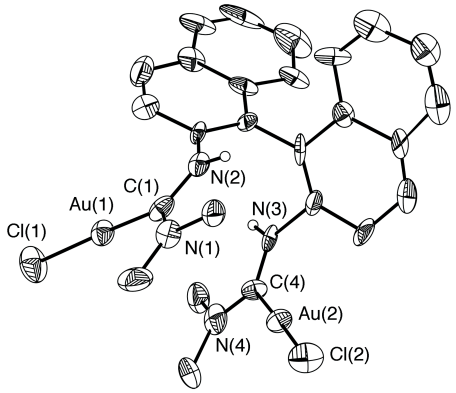


Figura 12. Estructura de Rayos X de **IV-9**

En el isómero aislado, el centro metálico y el grupo naftilo se disponen en *syn*, conformación que previsiblemente reduce la elevada congestión estérea de la molécula.

Como ya se comentó, el ligando 2,2'-diisociano-1,1'-binaftilo posee quiralidad axial, de modo que la configuración absoluta encontrada para el complejo **IV-9** es *S*.

Actividad catalítica de carbenos HBHC y NAC quirales de oro(I)

Se eligieron dos transformaciones enantioselectivas para estudiar la actividad de los carbenos HBHC y NAC quirales: En primer lugar se probaron reacciones de hidrofuncionalización de alenos y, en concreto, se hicieron pruebas de hidroalcoxilación de alenos. El segundo tipo de transformación que se eligió fue la ciclopropanación enantioselectiva de olefinas.[59]

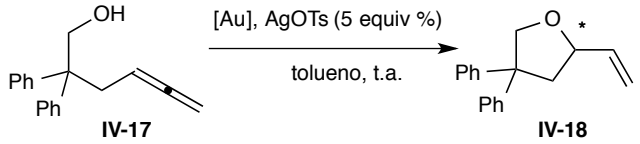
Hidroalcoxilación enantioselectiva de alenos

La adición de un enlace O-H de un alcohol en un enlace C-C doble o triple representa una interesante aproximación a la síntesis de éteres cíclicos. Sin embargo, a pesar de que se han desarrollado un gran número de hidroalcoxilaciones de enlaces múltiples C-C catalizadas por metales de transición, apenas existen ejemplos de hidroalcoxilaciones enantioselectivas.[60,61] Se eligió la reacción de hidroalcoxilación intramolecular catalizada por complejos de oro(I) del tipo μ-(P-P)$[AuCl]_2$ con diferentes difosfinas quirales.[60]

Para el estudio de la actividad catalítica de los carbenos quirales en reacciones de hidroalcoxilación intramolecular enantioselectiva de alcoholes alénicos, se utilizó el aleno **IV-17** (Tabla 9).

[59] Bartolomé, C.; Ramiro, Z.; García-Cuadrado, D.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758–9764.
[60] Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283-285.
[61] Kawamoto, T.; Hirabayashi, S.; Guo, X.-X.; Nishimura, T.; Hayashi, T. *Chem. Commun* **2009**, 3528-3530.

Tabla 9. Hidroalcoxilación enantioselectiva del aleno **IV-17** con carbenos quirales NAC y HBHC

Ensayo	**[Au]**	**Rendimiento**[a] **[%]**	***ee***[b] **[%]**
			
	IV-17	**IV-18**	
1	**IV-2**	67	<1
2	**IV-3**	61	2
3	**IV-4**	95	22
4	**IV-9**	42	20
5	**IV-10**	55	8
6	**μ-(P-P*)[AuCl]$_2$**[c]	73	90

[a]Rendimientos aislados. [b]*ee* determinados por HPLC con columna quiral. [c]P-P* = (*S*)-DTMB-MeOBIPHEP (Ref. 60).

Aunque los rendimientos encontrados en la reacción de ciclación son buenos, los *ee* son bajos. El mejor resultado se consigue con los carbenos **IV-4** (Esquema 12) y **IV-9** (Esquema 13). Este resultado es análogo al encontrado utilizando complejos con difosfinas quirales μ-(P-P)[AuCl]$_2$ con ligandos 2,2-bis(diarilfosfino)-bifenilo como binap o (3,5-xilil)binap, pero muy inferior al publicado para otras fosfinas más voluminosas como (*S*)-DTMB-MeOBIPHEP (Figura 13).[60]

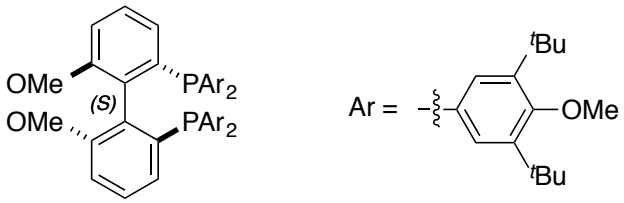


Figura 13. (*S*)-DTMB-MeOBIPHEP

Ciclopropanación enantioselectiva de olefinas

Toste había publicado recientemente un ejemplo de reacción de ciclopropanación enantioselectiva del pivaloato de propargilo con estireno catalizada por oro(I), en concreto por μ-(P-P)[AuCl]$_2$.[62] Los mejores excesos enantioméricos se habían descrito para sistemas en los que la bisfosfina que actuaba como puente en el complejo binuclear era (*R*)-DTBM-SEGPHOS (Figura 14).[63]

[62] Revisión de ciclopropanación de olefinas: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Re*v. **2003**, *103,* 977–1050.
[63] Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003.

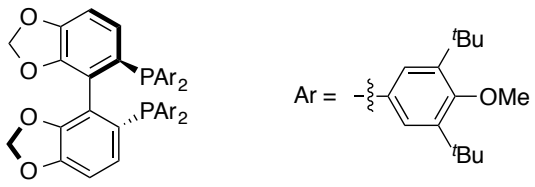
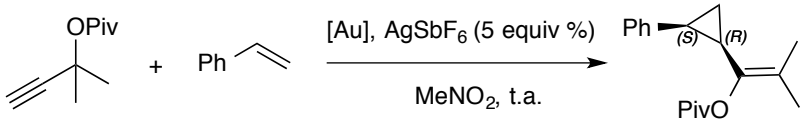


Figura 14. (*R*)-DTBM-SEGPHOS

Los resultados obtenidos se recogen en la Tabla 10. En todos los casos las reacciones de ciclopropanación dan lugar al isómero *cis*, lo que indica una alta diastereoselectividad de la reacción. Los rendimientos obtenidos en muchos de los casos son moderados, si bien el *ee* es bajo. De nuevo, los mejores resultados se consiguen con los carbenos **IV-4** y **IV-9** (ensayos 3 y 6), ambos con un esqueleto basado en el ligando con quiralidad axial 1,1'-binaftilo.

Tabla 10. Ciclopropanación de estireno con pivaloato de propargilo catalizada por NAC y HBHC complejos quirales de oro(I)

Ensayo	**[Au]**	**Rendimiento[a] [%]**	***ee*[b] [%]**
			
	IV-15		**IV-16**
1	**IV-2**	53	<1
2	**IV-3**	54	<1
3	**IV-4**	75	20
4	**IV-5**	78	11
5	**IV-6**	71	5
6	**IV-9**	72	24
7	**IV-10**	70	10
8	**IV-13**	61	8
9	**IV-14**	65	<1
10	**μ-(P-P*)[AuCl]$_2$**[c]	70	81

[a]Rendimientos aislados. [b]*ee* determinados por HPLC con columna quiral. [c] P-P* = (*R*)-DTMB-SEGPHOS (Ref. 63).

Estos resultados inducen a pensar que modificaciones estructurales basadas en este tipo de complejos binucleares podrían mejorar los resultados. Sin embargo, los resultados con **IV-13** y **IV-14**, carbenos con el ligando (3,3'-difenil)-1,1'-binaftilo son sorprendentemente peores. Probablemente, los tres confórmeros presentes en las disoluciones de estos carbenos voluminosos podrían inducir enantioselectividades contrarias, lo que repercutiría en la disminución del exceso enantiomérico observado.

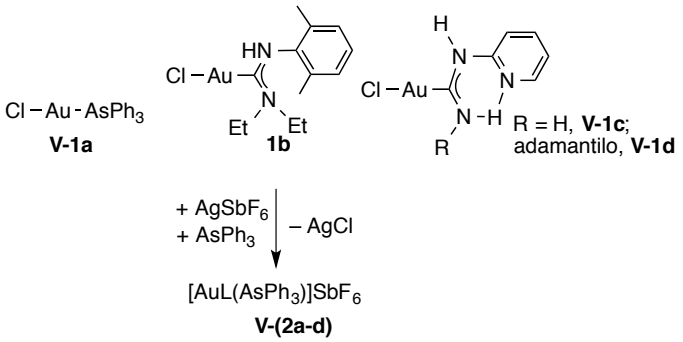
Si bien los excesos enantioméricos obtenidos en las dos transformaciones enantioselectivas elegidas no son muy altos, los sistemas basados en carbenos quirales

NAC y HBHC que hemos desarrollado ofrecen una sólida base para invitar a desarrollos posteriores que mejoren este aspecto. De hecho estos nuevos tipos de carbenos de oro han sido adoptados rápidamente por otros grupos a raíz de nuestra publicación, y son ahora de uso frecuente en catálisis enantioselectiva.[34,35]

$AsPh_3$ como estabilizador de oro(I) en reacciones de ciclación

La activación de enlaces múltiples catalizada por complejos de oro(I) requiere la generación *in situ* de la correspondiente especie catiónica por extracción del haluro con una sal de plata. La presencia de sales de plata en el seno de reacción puede interferir en este tipo de reacciones catalíticas por lo que recientemente se están desarrollando sistemas que eviten su uso. Así, complejos del tipo [AuL(L')]Y (L = fosfinas, fosfitos, carbenos; L' = nitrilo, areno, etc.), o alternativamente complejos neutros [AuYL] con ligandos Y fácilmente desplazables como NTf_2^- están siendo utilizados en este tipo de activaciones. En este trabajo hemos sintetizado carbenos de oro tipo NAC estabilizados con NTf_2^- o, alternativamente, carbenos HBHC catiónicos con trimetoxibenzonitrilo como ligando neutro. Estos carbenos han resultado ser catalizadores activos en diferentes transformaciones orgánicas, tal y como se ha descrito anteriormente. Por otro lado, hemos observado que el complejo catiónico $[Au(AsPh_3)_2](SbF_6)$ es activo en reacciones de transposición de esqueleto de 1,6-eninos. Dado que el ligando $AsPh_3$ apenas ha sido utilizado en sistemas catalíticos, se ha abordado el estudio del intrigante efecto de la presencia de arsina en diferentes transformaciones orgánicas de interés, especialmente ciclaciones, catalizadas por complejos de oro(I). Para ello se llevó a cabo la síntesis de los correspondientes complejos catiónicos obtenidos por extracción del ligando cloruro con una sal de plata en presencia de un equivalente de $AsPh_3$.

Se eligieron para hacer este estudio los complejos NAC y HBHC que aparecen en el Esquema 14 y se incluyó en el estudio de la actividad catalítica el complejo $[AuCl(PPh_3)]$.



Esquema 14. Síntesis de complejos catiónicos con el ligando $AsPh_3$

La estructura de Rayos X de [Au{C(NEt_2)(NHXilil)}($AsPh_3$)](SbF_6) (**V-2b**) confirma la formación del complejo catiónico con el ligando $AsPh_3$. Como se puede observar, el confórmero preferido es el que presenta menor impedimento estérico, análogamente a lo observado en los correspondientes complejos neutros con aminas secundarias como sustituyentes en el carbeno (Figura 15).

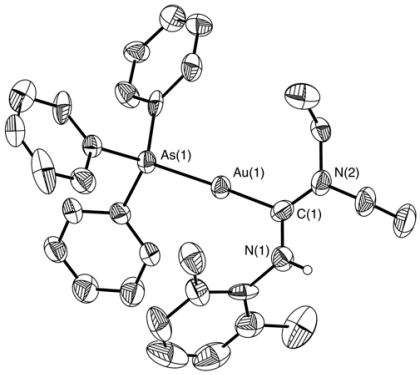


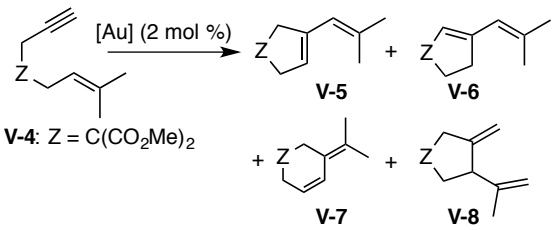
Figura 15. Estructura de rayos X de [Au{C(NEt_2)(NHXilil)}($AsPh_3$)](SbF_6) (**V-2b**)

Se realizó un sondeo preliminar con el fin de comparar la actividad catalítica de [AuClL] (L = NAC, HBHC o $AsPh_3$) como precatalizadores, y con la observada utilizando los correspondientes complejos catiónicos estabilizados con $AsPh_3$. Se eligieron para este estudio ciclaciones y metoxiciclaciones de 1,6-eninos. Se compararon además estos resultados con los obtenidos (o, en algunos casos, los descritos) con el complejo [AuCl(PPh_3)] (**V-3**) sistema muy utilizado en este tipo de catálisis con oro(I).

Se eligió para este estudio la ciclación de 2-(3-metil-2-butenil)-2-(2-propinil)malonato de dimetilo (**V-4**). Los resultados se muestran en la Tabla 11, especificándose en cada caso si durante la reacción se observa descomposición. Como ya habíamos adelantado anteriormente, el complejo [Au($AsPh_3$)$_2$](SbF_6) (**V-2a**) es un

excelente catalizador de esta reacción obteniéndose conversiones y rendimientos cuantitativos en tiempos reducidos (Tabla 11, ensayo 1).

Tabla 11. Ciclación de 2-(3-metil-2-butenil)-2-(2-propinil)malonato de dimetilo (**V-4**)



Ensayo	[Au]	AgX	Tiempo / conversión (reducción de Au)	5/6/7/otros [%]
1	**V-2a**[a]	–	30 min / 100	83/0/17/0
2	**V-2b**[a]	–	4 d / 95	95/0/0/0
3	**V-2b**[b]	–	15 h / 100	88/9/3/0
4	**V-2c**[a]	–	6d / 30	23/0/7/0
5	**V-2c**[b]	–	5 h / 100	83/0/17/0
6	**V-2d**[a]	–	15 h / 32	25/0/7/0
7	**V-2d**[b]	–	5 h /50	19/0/0/31
8	**V-1a**[a]	*	3h / 100 (morado)	8/10/0/82
9	**V-1a**[a]	**	3 h / 100 (violeta tenue)	9/8/0/83
10	**V-3**[a]	*	25 min / 98 (violeta tenue)	34/49/15/0
11	**V-3**[a]	**	3 h /92	28/46/18/0
12	**V-1b**[a]	*	5 min / 100 (morado)	100/0/0/0
13	**V-1b**[a]	**	5 min / 100	61/37/2/0
14	**V-1c**[a]	*	5 min / 100 (morado)	98/0/2/0
15	**V-1c**[a]	**	5 min / 100	83/0/17/0
16	**V-1d**[a]	*	5 min / 100 (morado)	95/0/0/0
17	**V-1d**[a]	**	5 min / 100	88/9/3/0

% determinados por ^{1}H NMR a partir de los sólidos aislados. *2 mol% [Au], 2 mol% $AgSbF_6$. **2 mol% [Au], 2 mol% $AgSbF_6$ y 0.2 mol% $AsPh_3$. [a] CH_2Cl_2, a 25 °C. [b] 1,2-dicloroetano, a 85 °C.

La estabilidad de **V-2a** permite recuperar y reutilizar el catalizador (Tabla 12). Se han realizado también experimentos reduciendo la carga de catalizador hasta veinte veces menos, no observándose repercusión en la actividad (100% de conversión a los 5 minutos de reacción). La reducción de **V-2a** hasta 0.02 mol% mantiene al sistema activo, si bien el tiempo de reacción aumenta considerablemente (72% de conversión en 4 días).

Tabla 12. Experimentos de reciclaje con **V-2a**

Ciclo	conversión / tiempo	5/6/7 [%]
1º	100 / 30 min	76/3/21
2º	100 / 16 h	86/2/12
3º	100 / 36 h	90/0/10
4º	92 / 96 h	64/20/8
5º	40 / 96 h	35/2/3

Sin embargo, la actividad de los correspondientes carbenos catiónicos [AuL($AsPh_3$)](SbF_6) disminuye muy considerablemente con respecto a la observada tanto con **V-2a** como utilizando [AuClL] y una sal de plata como extractor de haluro, obteniéndose muy bajas conversiones en tiempos de reacción muy largos. Resulta prometedor el hecho de que no se observa descomposición en ninguna de estas reacciones, al contrario de lo que sucede utilizando [AuClL] como precatalizadores. Así, cuando la reacción se lleva a cabo a mayor temperatura, en la mayoría de los casos se observa una conversión muy alta y de nuevo rendimientos casi cuantitativos (Tabla 11, ensayos 3, 5 y 7).

Con el fin de profundizar más en el efecto estabilizador de la arsina y su relación con la velocidad de reacción observada se llevaron a cabo una serie de experimentos examinando la actividad de [AuCl($AsPh_3$)] (**V-1a**) y de los carbenos **V-1b-d** en presencia de $AgSbF_6$ y cantidades sub-estequiométricas de arsina (dichos experimentos están marcados en la Tabla 11 con **). La reacción de **V-1a** con un 10 mol% de $AsPh_3$ respecto al oro (ensayo 9) disminuye muy significativamente la descomposición a Au^0; aunque la conversión es muy alta, la reacción no es limpia y el rendimiento de los productos de reacción es muy bajo. Cuando en la catálisis se utiliza [AuCl(PPh_3)] (**V-3**), no se aprecia ningún signo de descomposición. Este excelente resultado con **V-3** se repite con los carbenos de oro **V-1b-d** en presencia de un 10 mol% de $AsPh_3$.

La actividad de **V-1b-d** en presencia de cantidades subestequiométricas de $AsPh_3$ es tal que la carga de catalizador se puede reducir hasta 20 veces (0.1% de **V-1c**, 0.01% de $AsPh_3$) y la reacción de ciclación sigue siendo muy rápida (conversión del 100% en 5 minutos de reacción).

Parece por tanto que el efecto estabilizador de la $AsPh_3$ está relacionado con la capacidad dadora del ligando principal en [AuClL]. Así, cuando L = carbeno, una cantidad sub-estequiométrica de arsina es capaz de estabilizar por completo el sistema catalítico; en cambio, si L = $AsPh_3$, que es mucho menos dador, ese mismo 10 mol% de $AsPh_3$ no es capaz de estabilizar el sistema.

El efecto estabilizador de la arsina se puede extender a otras reacciones de activación de enlaces múltiples como la metoxiciclación de 2-(3-metil-2-butenil)-2-(2-propinil)malonato de dimetilo o la ciclación [4+2] de 2-(3-metil-2-butenil)-2-(3-fenil-2-propinil)malonato de dimetilo.[64]

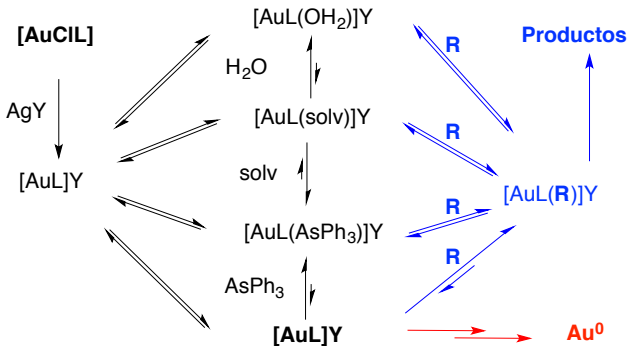
[64] No se incluyen en el resumen estos resultados, que pueden encontrarse con detalle en la publicación original: Bartolomé, C.; Ramiro, Z.; Espinet, P. *Eur. J. Inorg. Chem.* **2014**, 5499–5506.

Por tanto, la adición de cantidades subestequiométricas de $AsPh_3$ reduce y, en muchos casos, evita totalmente la descomposición del catalizador de oro(I). El porcentaje de agente estabilizador es crucial para conseguir esta estabilización de modo que tiene que existir un compromiso entre dicho porcentaje y las condiciones en las que se lleva a cabo la reacción para evitar que el tiempo de reacción aumente. La ausencia de descomposición ha permitido reducir la carga de catalizador sin que la actividad de este se altere considerablemente.

Mecanismo de protección del catalizador con cantidades subestequiométricas de $AsPh_3$

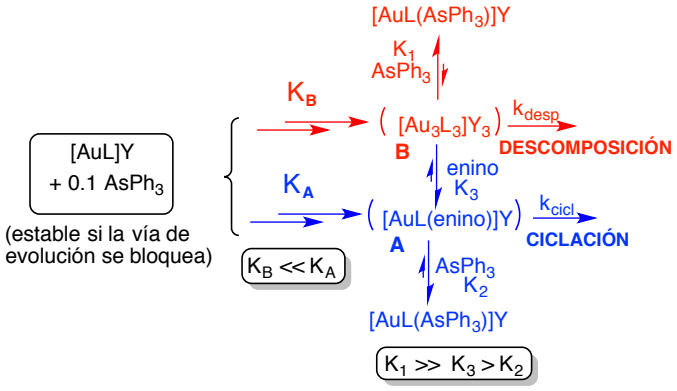
Este es un fenómeno curioso que no se puede entender sobre la base de considerar que la especie catalítica o la que experimenta la descomposición es la que inicialmente proponemos como producto de la extracción de haluro, es decir, [AuL]Y. La adición de un 10% de $AsPh_3$ de ligando protector, formando aproximadamente un 10% de [AuL($AsPh_3$)]Y excepto la cantidad de arsina libre que corresponda a la constante de disociación de este último complejo, dejaría sin proteger aproximadamente el 90 % de [AuL]Y, que debería descomponerse. Puesto que esto no sucede, debemos reconsiderar el planteamiento.

En realidad la situación es más complicada ya que en una catálisis en curso la especie que hemos simplificado como [AuL]Y está implicada en diversos equilibrios con posibles ligandos presentes en disolución como el propio anión Y^-, agua, heteroátomos coordinables presentes en el ligando, etc., como se muestra en el Esquema 15 y hemos comprobado experimentalmente para el caso del agua presente en el disolvente.



Esquema 15. Posibles vías de reacción en condiciones de catálisis (L = carbeno; R = enino)

En un momento dado las reacciones de descomposición y de ciclación deben ocurrir desde los intermedios en equilibrio en las que se originan. Cabe señalar que la reacción de descomposición ocurre también fuera de la catálisis, es decir, cuando el complejo [AuClL] se trata con AgY en ausencia de enino u otro reactivo. Para simplificar (Esquema 16), consideraremos el problema prescindiendo de especificar todas las demás circunstancias que no sean el equilibrio efectivo entre [AuL]Y y las especies que directamente evolucionen a la ciclación (**A**) o a la descomposición (**B**).



Esquema 16. Situación simplificada: Equilibrios entre species implicadas en reacciones de ciclación y de descomposición

Está aceptado que las especies inmediatamente precursoras de la catálisis (en este caso la ciclación de eninos) son del tipo [AuL(enino)]Y. Por otro lado, las evidencias disponibles con respecto a complejos de oro(I) sugieren que la vía de descomposición con formación de oro(0) en ausencia de reductores son, en realidad, reacciones de desproporcionación ($3\ Au^{I} \rightarrow 2\ Au^{0} + Au^{III}$; los complejos de Au^{III} no catalizan estas reacciones).[65] De hecho el comportamiento que intentamos explicar apoya esta vía de descomposición.

La evolución del sistema hacia la reacción de ciclación requiere la formación del intermedio [AuL(enino)]Y (**A**) y es fácil imaginar que la coordinación de enino, disponible en exceso ya que es el reactivo, debe ser termodinámicamente muy favorable frente a la situación [AuL]Y, con un oro monocoordinado y un orbital vacante. Desde [AuL(enino)]Y la ciclación es una reacción intramolecular con una dependencia cinética de orden 1 con respecto a la concentración de **A**. La presencia de cantidades de $AsPh_3$ subestequiométricas con respecto a la concentración de **A** producirán únicamente cierta disminución de la velocidad de reacción dependiendo de las concentraciones concretas.

[65] Kumar, M.; Jasinki, J.; Hammond, G. M.; Xu B. *Chem. Eur. J.* **2014**, *20*, 3113-3119

Muy diferente es el caso de la reacción de descomposición para la que, asumiendo una vía de desproporcionación, proponemos la formación previa de una especie de tres átomos de oro, **B** (la propuesta $[Au_3L_3]Y_3$ es solo tentativa para indicar la necesidad de una cooperación de tres átomos de oro en el estado de transición). Si la propia concentración de [AuL]Y en un escenario como el del Esquema 16 debe ser muy baja, la de una especie trinuclear debe ser muchísimo menor. Por otro lado, la dependencia de la velocidad de desproporcionación respecto a la de oro desnudo debe ser mayor que la dependencia de la concentración de oro en la reacción de ciclación (que, de forma simplificada, podemos considerar que son de orden tres y uno respectivamente). En concentraciones muy bajas de oro la velocidad de reacción de descomposición debe verse enormemente perjudicada por estos dos factores y la disminución de la misma por cantidades subestequiométricas de arsina puede ser varios órdenes de magnitud la observada para la reacción de ciclación.

Podemos dar una visión alternativa de los dos efectos. Para la ciclación la concentración de [AuL(enino)]Y es superior a la de $AsPh_3$ libre subestequiométrica y el efecto de coordinación de la $AsPh_3$ deja todavía en actividad un elevado porcentaje del intermedio [AuL(enino)]Y (Esquema 16, **A**), por lo que la reacción continúa aunque a menor velocidad. Pero para la descomposición la concentración de $AsPh_3$ libre es muy superior a la del intermedio $[Au_3L_3]Y_3$ (**B**): la formación de este precisa de la colisión de tres moléculas del desnudo [AuL]Y en una atmósfera de muchas moléculas de $AsPh_3$ libre que tenderán a capturar el [AuL]Y, $[Au_2L_2]Y_2$, o $[Au_3L_3]Y_3$ en forma de $[AuL(AsPh_3)]Y$ (Esquema 16), por lo que esa colisión de tres partículas se hace estadísticamente muy improbable. En consecuencia, la velocidad de descomposición se ve profundamente disminuida hasta poder hacerse inobservable.

Los comentarios anteriores permiten entender que el efecto de un aditivo sobre dos procesos diferentes puede ser muy distinto y, en concreto, que un aditivo puede proteger el catalizador sin paralizar la catálisis, aunque ésta se vea afectada en alguna medida ($k_{ciclación} >> k_{desproporcionación}$). El efecto discutido requiere que un porcentaje del aditivo quede en forma libre en disolución. Así, $[AuL(AsPh_3)]Y$ disocia parcialmente $AsPh_3$. El uso de un mejor ligando en cantidades subestequiométricas, por ejemplo PPh_3 debería ser menos efectivo como protector al dejar menor concentración de PPh_3 libre en el equilibrio. En efecto, en dos ensayos paralelos utilizando idénticas condiciones con $AsPh_3$ y PPh_3 y sin enino, se observa un progreso de la descomposición en la

reacción protegida con cantidad subestequiométrica de PPh_3 mientras la protegida con la misma cantidad subestequiométrica de $AsPh_3$ permanece inalterada (Figura 16).

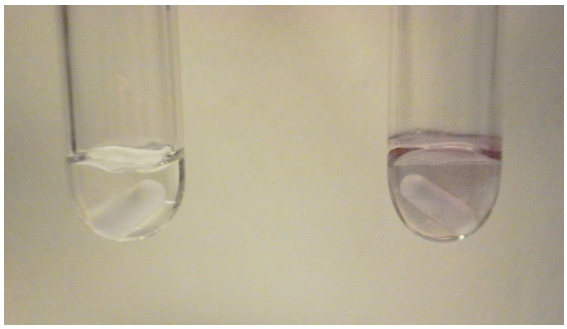


Figura 16. Experimentos llevados a cabo con [AuCl(carbeno)] en presencia de $AgSbF_6$ con 5 mol% de $AsPh_3$ (izquierda) y 5 mol% de PPh_3 (derecha) tras 9 h a temperatura ambiente

Estos experimentos se llevaron a cabo en presencia de 5 mol% de ligando estabilizador. Con cantidades menores tanto de PPh_3 como de $AsPh_3$ se observa descomposición a tiempos de reacción mucho menores (Figura 17), siendo este efecto más acusado con PPh_3, confirmando la previsión de que el mejor ligando es mucho peor protector.

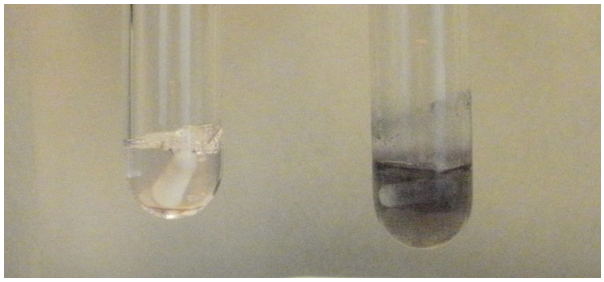


Figura 17. Experimentos llevados a cabo con [AuCl(carbeno)] en presencia de $AgSbF_6$ con 2.5 mol% de $AsPh_3$ (izquierda) y 2.5 mol% de PPh_3 (derecha) tras 50 min a temperatura ambiente

Está bien probado en la bibliografía que la PPh_3 no actúa como reductor en estas condiciones (de hecho se bloquea la descomposición si se aumenta la cantidad de PPh_3, todavía en proporciones subestequiométricas), por lo que este ensayo confirma la hipótesis de que un buen ligando protege peor que uno malo, y en consecuencia es un excelente apoyo a que la descomposición del complejo de Au^I procede por la vía de desproporcionación a Au^0 y Au^{III}.

Conclusiones

Se han sintetizado diferentes carbenos [AuCl{C(NHR)(NHPy-2)}] cuya estructura cíclica soportada por un enlace de hidrógeno intramolecular los hace no sólo estructuralmente similares a los carbenos NHC (Nitrogen Heterocyclic Carbenes) sino también activos en reacciones de reorganización de esqueleto de 1,n-eninos.

La estructura cíclica soportada por esta interacción de hidrógeno se rompe en presencia de algunos disolventes muy polares, como alcoholes. Sorprendentemente la excelente actividad de este sistema en reacciones catalíticas en las que no existe esta interacción intramolecular se mantiene, lo que permite concluir que la presencia de un ligando carbeno heterocíclico en el catalizador, no es crucial. Puede esperarse que otros carbenos no cíclicos presenten actividad semejante a los heterocíclicos en multitud de transformaciones orgánicas.

En efecto, estos resultados preliminares nos empujaron a desarrollar nuevos sistemas de oro(I) basados en carbenos acíclicos, cuya ventaja con respecto a los heterocíclicos convencionales es la facilidad de obtener series de carbenos donde se modifiquen las características electrónicas o estéreas del carbeno de forma sencilla eligiendo como nucleófilos aminas con los sustituyentes adecuados. La actividad de estos carbenos NAC (Nitrogen Acyclic Carbenes) no se ha limitado a reacciones de ciclación de eninos, sino que se ha demostrado que son catalizadores excelentes en diversas reacciones intra e intermoleculares.

A este respecto, se pueden conseguir, de nuevo muy fácilmente, carbenos de oro(I) quirales eligiendo adecuadamente o el isocianocomplejo de oro(I) o la amina, de manera que si uno de los dos es quiral, el carbeno de llegada lo es también. Se pueden conseguir de este modo tanto carbenos cíclicos quirales de oro(I) derivados del [AuCl(CNPy-2)] por adición de aminas quirales, como carbenos acíclicos quirales de oro(I) derivados del clorocomplejo con 2,2'-diisociano-1,1'-binaftilo ó 1,1’-binaftil-(3,3’-difenil)-2,2’-diisocianuro ligandos que poseen quiralidad axial.

Aunque los resultados preliminares sobre la actividad catalítica de los carbenos quirales resultaron prometedores, aunque no espectaculares ya que los *ee* en las reacciones enantioselectivas probadas en ningún caso superaron el 25%. Para nuestra satisfacción nuestro concepto de sistemas NAC y HBHC quirales y los propios sistemas

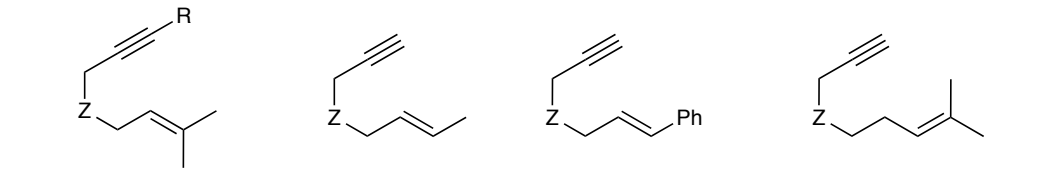
se han utilizado, por grupos más potentes, como plantilla para diseñar nuevos carbenos quirales con nuestro mismo esqueleto pero diferentes sustituyentes, llegando a inducir altísimas enantioselectividades.

La presencia de cantidades subestequiométricas de $AsPh_3$ como aditivo reduce y, en muchos casos, elimina totalmente la indeseada descomposición de los sistemas catalíticos de oro(I), y mantiene, en general, unas velocidades de reacción aceptables. En presencia de arsina se puede reducir la cantidad de catalizador hasta un orden de magnitud sin que se altere la velocidad del proceso. La estabilidad de los sistemas catiónicos [Au(carbeno)($AsPh_3$)](SbF_6) es tal que el catalizador se puede reutilizar sin que la actividad se vea drásticamente afectada durante los tres primeros ciclos.

Metodología Empleada

Metodología sintética

De forma general, todas las reacciones descritas en este trabajo se han realizado bajo atmósfera de nitrógeno, utilizando las técnicas convencionales de Schlenk. Los disolventes fueron purificados de acuerdo con los procedimientos estándar[66] o por un sistema de purificación de disolventes, SPS. Los compuestos [AuCl(tht)],[45] [AuCl(CNPy-2)],[26] [AuCl(CNp-Tolil)],[43] [AuCl(CN-2,6-Xilil)],[44] [AuCl(CN^{t}Bu)],[42] [AuCl($CNC_6H_5CO_2H$)],[41] [AuCl($CNC_6H_4CO_2Et$)],[42] [AuCl($AsPh_3$)] (**V-1a**),[23b,23g] [Au($AsPh_3$)$_2$](SbF_6) (**V-2a**),[67] [AuCl(PPh_3)] (**V-3**),[68] $AgNTf_2$,[69] los eninos (Figura 18),[17,23,70] homopropargilsulfóxido (Figura 19, **III-4**),[25,49] N-alenilcarbamato (Figura 19, **III-6**),[53] 2,2-difenil-4,5-hexadienol (Figura 19, **III-8 = IV-17**),[53] pivaloato de propargilo (Figura 19, **IV-15**)[71] y (*S*)-2,2'-(3,3'-difenil)binaftilamina[72] se sintetizaron de acuerdo con los procedimientos descritos en la bibliografía. El resto de reactivos se adquirieron de fuentes comerciales y se utilizaron sin posterior purificación. La cromatografía en capa fina se hizo usando TLC con lámina de aluminio con 0.2 mm de gel de sílice (Merck GF234). Las purificaciones cromatográficas se realizaron usando sílica gel de grado flash (SDS S-2 Chromatogel 60 ACC, 40-60 μm). Para la separación de los enantiómeros se utilizó un equipo de cromatografía Hewlett-Packard equipado con una columna de HPLC Chiracel OD-H de 25 cm de largo. Los espectros de RMN fueron obtenidos a 25 ºC en un Bruker AC300, ARX 300, Bruker Avance 400 Ultrashield, Varian MR 400 o Varian VNMRS 500.



Z = $C(CO_2Me)$
R = H (**I-16a** = **II-16a** = **V-4**)
Ph (**II-9e** =**V-10**)

Z = $C(CO_2Me)$
(**I-16b** = **II-9b**)

Z = $C(CO_2Me)$ (**I-16c**)
$C(SO_2Ph)$ (**I-16d**)
NTs (**I-16e** = **II-9c**)

Z = $C(CO_2Me)$ (**I-16f** = **II-9d**)

Figura 18. Eninos de partida sintetizados

[66] Perrin, D. D.; Armarego, W. F. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U. K., **1988**.
[67] Tripathi, U. M.; Schier, A.; Schmidbaur, H. *Z. Naturforsch. B* **1998**, *53*, 171–174.
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[70] Muñoz, M. P.; Méndez, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Synthesis* **2003**, 2898–2902.
[71] Chakraborti, A. K.; Sharma, L.; Gulhane, R. *Tetrahedron* **2003**, *59*, 7661–7668.
[72] Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *J. Org. Chem*. **2008**, *73*, 7387–7389.

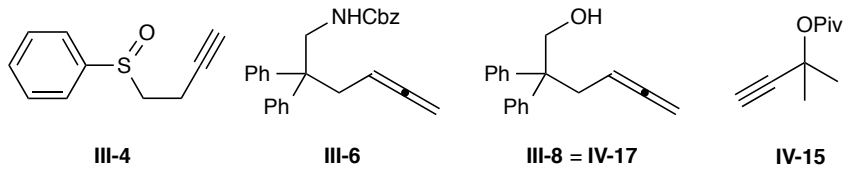
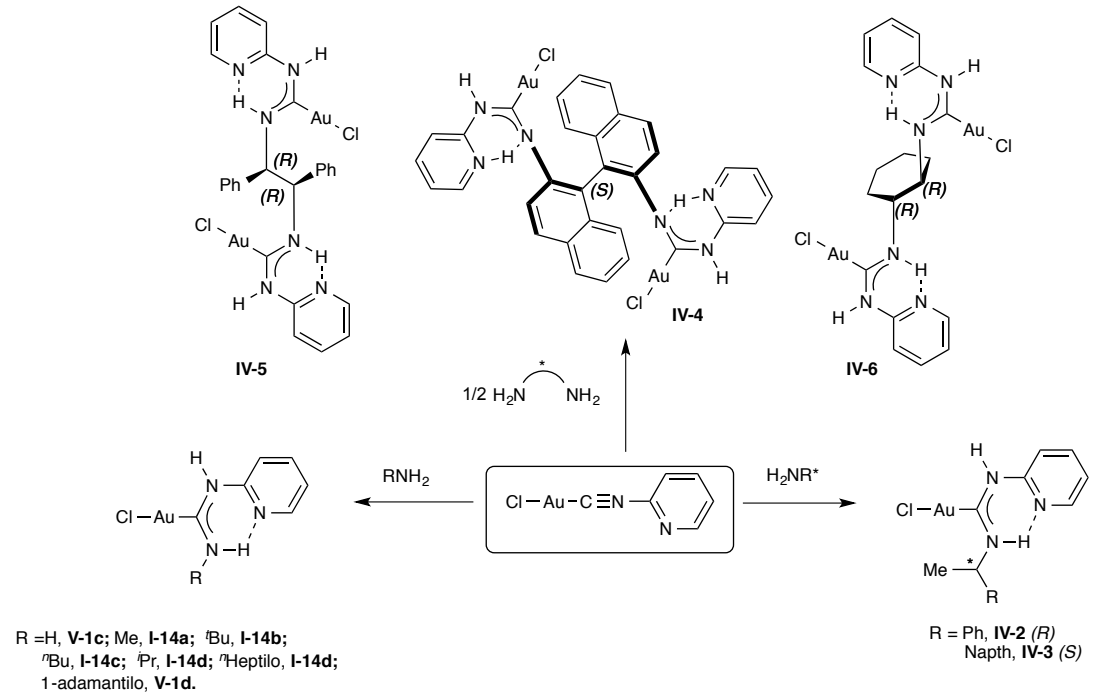


Figura 19. Otros productos de partida sintetizados

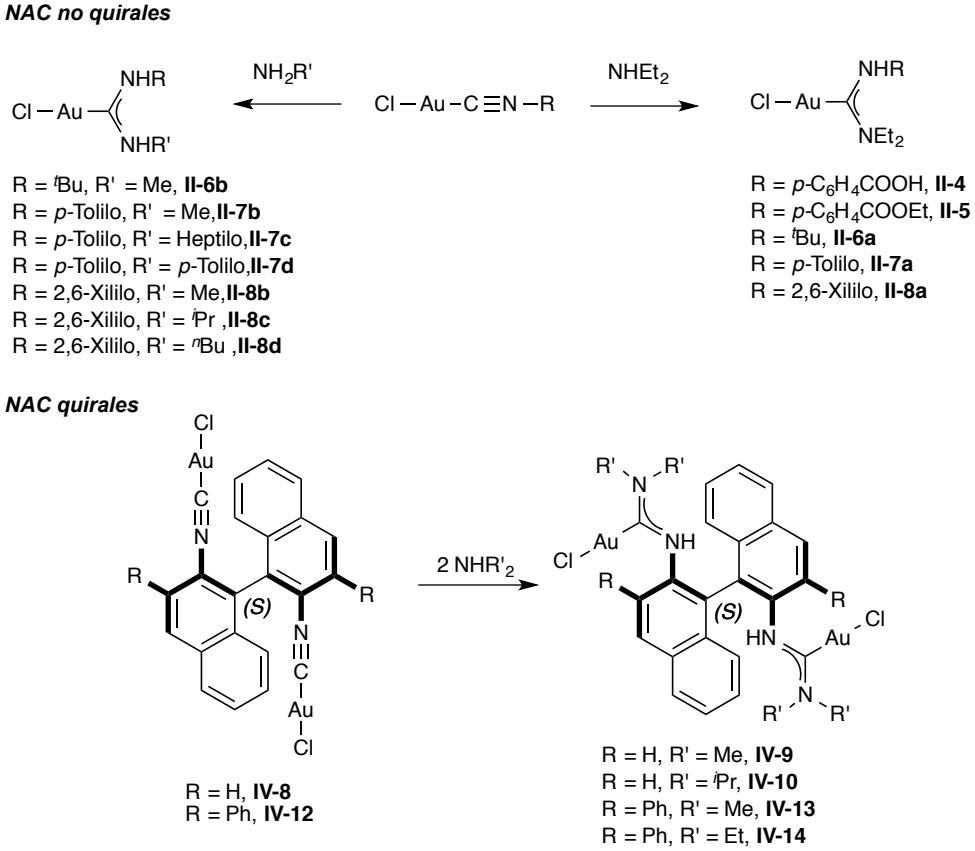
Síntesis de carbenos de oro(I) HBHC neutros (artículos I, IV y V)



Esquema 17. Síntesis de carbenos HBHC de Au^{I} neutros

Sobre una disolución de [AuCl(CN2-Py)] en THF o CH_2Cl_2 (10 mL por 0.1 mmol de complejo) se añade con un exceso del 10% sobre la cantidad equimolar la correspondiente amina primaria H_2RN o la mitad de la cantidad equimolar de la diamina primaria H_2NRNH_2, también con un exceso del 10%. La reacción se mantiene a temperatura ambiente, y se sigue su evolución por IR en disolución. Cuando no se observa absorción ν(CN) la reacción ha terminado. Se lleva a sequedad, y el residuo sólido blanco se lava con *n*-hexano para eliminar el exceso de amina, y se recristaliza en THF/*n*-hexano o CH_2Cl_2/*n*-hexano. El sólido blanco obtenido se lava con *n*-hexano y se seca a vacío.

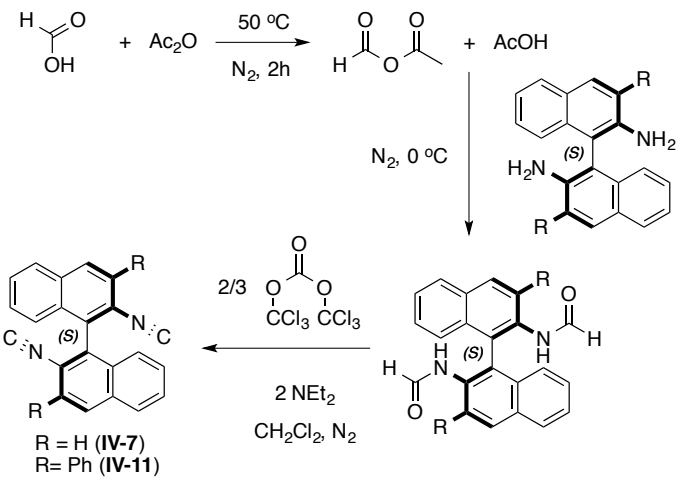
Síntesis de carbenos de oro(I) NAC neutros (artículos II, IV)



Esquema 18. Síntesis de carbenos NAC neutros de Au^I poner un dos en la amina

Sobre una disolución de [AuCl(CNR)] en THF o CH_2Cl_2 (10 mL por 0.1 mmol de complejo) se añade, con un exceso del 10% sobre la cantidad estequiométrica, la correspondiente amina primaria H_2RN o $HNEt_2$. Se sigue el procedimiento utilizado en la síntesis de los carbenos HBHC.

Síntesis de precursores de los carbenos NAC de oro(I) quirales: Artículo IV



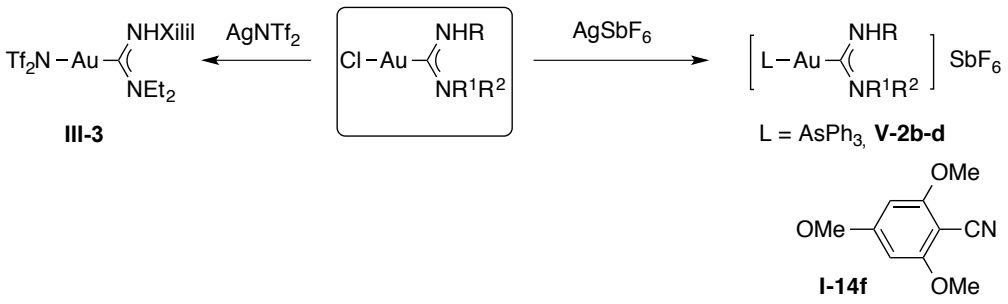
Esquema 19. Síntesis de (*S*)-(+)-1,1'-binaftil-2,2'-diisocianuro y (*S*)-1,1'-bifennil-(3,3'-difenil)-2,2'-diisocianuro

(*S*)-(+)-1,1'-binaftil-2,2'-diisocianuro. Sobre 1.37 mmol de Ac_2O a 0 ^oC se añaden 1.69 mmol de ácido fórmico y se calienta a 50 ^oC durante dos horas manteniendo atmósfera inerte. Se enfría hasta temperatura ambiente y se adicionan 1.5 mL de THF. La mezcla de reacción se enfría a 0 ^oC y se añaden 0.528 mmol de (*S*)-(–)-1,1'-binaftil-2,2'-diamina. Pasados 20 min se mantiene a temperatura ambiente durante 4 h y la reacción se sigue por TLC (hexano/acetato de etilo; 1:1). Una vez finalizada la reacción se extrae con éter sobre Na_2CO_3 saturado. Se seca a vacío hasta sequedad. El residuo se purifica mediante filtración en gel de sílice usando como eluyente hexano/acetato de etilo; 1:1. Se precipita en CH_2Cl_2/pentano, obteniendo (91 % Rto.) de (*S*)-(–)-1,1'-binaftil-2,2'-diformamida, usada en la siguiente transformación sin purificación. Sobre una disolución de (*S*)-(–)-1,1'-binaftil-2,2'-diformamida 0.482 mmol y trietilamina (16.38 mmol) en 10 mL de CH_2Cl_2 a 0 ^oC y en atmósfera inerte se adicionan gota a gota 0.387 mmol de trifosgeno disuelto en 8 mL de CH_2Cl_2. La reacción se mantiene a temperatura ambiente durante 3 horas. Se añade agua, se concentra y se purifica por cromatografía en columna usando alúmina neutra y como eluyente una mezcla de hexano/éter 1:5. Se lleva hasta sequedad total, obteniéndose 2,2'-diisociano-1,1'-binaftilo (74 % Rto.).

(*S*)-1,1'-binaftil-(3,3'-difenil)-2,2'-diisocianuro. Sobre 1.55 mmol de Ac_2O a 0 ^oC se añaden 1.91 mmol de ácido fórmico y se calienta a 50 ^oC durante dos horas manteniendo atmósfera inerte. Se enfría hasta temperatura ambiente y se adicionan

1.5mL de THF. La mezcla de reacción se enfría a 0 ^{o}C y se añaden 0.597 mmol de (*S*)-2,2'-(3,3'-difenil)binaftilamina. Pasados 20 min se mantiene a temperatura ambiente durante 10 h, después se mantiene otras dos horas a 50 ^{o}C y la reacción se sigue por TLC (hexano/acetato de etilo; 1:1). Una vez finalizada la reacción se extrae con éter sobre Na_2CO_3 saturado. Se lleva hasta sequedad y se seca a vacío. El residuo se purifica mediante filtración en sílica gel usando como eluyente hexano/acetato de etilo; 1:1. Se precipita en CH_2Cl_2/pentano, obteniendo (73 % Rto.) de (*S*)-2,2'-(3,3'-difenil)binaftilformamida, usada en la siguiente transformación sin purificación. Sobre una disolución de (*S*)-2,2'-(3,3'-difenil)binaftilformamida (0.386 mmol) y trietilamina (16.38 mmol) en 16 mL de CH_2Cl_2 a 0 ^{o}C, se adicionan gota a gota 0.283 mmol de trifosgeno disuelto en 10 mL de CH_2Cl_2. La reacción se mantiene a temperatura ambiente durante 3 horas. Se añade agua, se concentra y se purifica por cromatografía en columna usando alúmina neutra y como eluyente una mezcla de hexano/éter 1:3 y después hexano/acetato de etilo 7:3. Se lleva hasta sequedad total, obteniéndose (*S*)-1,1'-binaftil-(3,3'-difenil)-2,2'-diisocianuro (81 % Rto.).

Síntesis de carbenos NAC y HBHC de oro(I) con ligandos fácilmente desplazables



Esquema 20. Síntesis complejos catiónicos [Au(carbeno)L]SbF_6 (**V-2b-d** y **I-14f**) y neutro [Au(NTf_2){C(NEt_2)(NHXilil)}](**III-3**)

[Au(carbeno)L]SbF_6 (L = 2,4,6-trimetoxibenzonitrilo, Artículo I; L = $AsPh_3$, V)

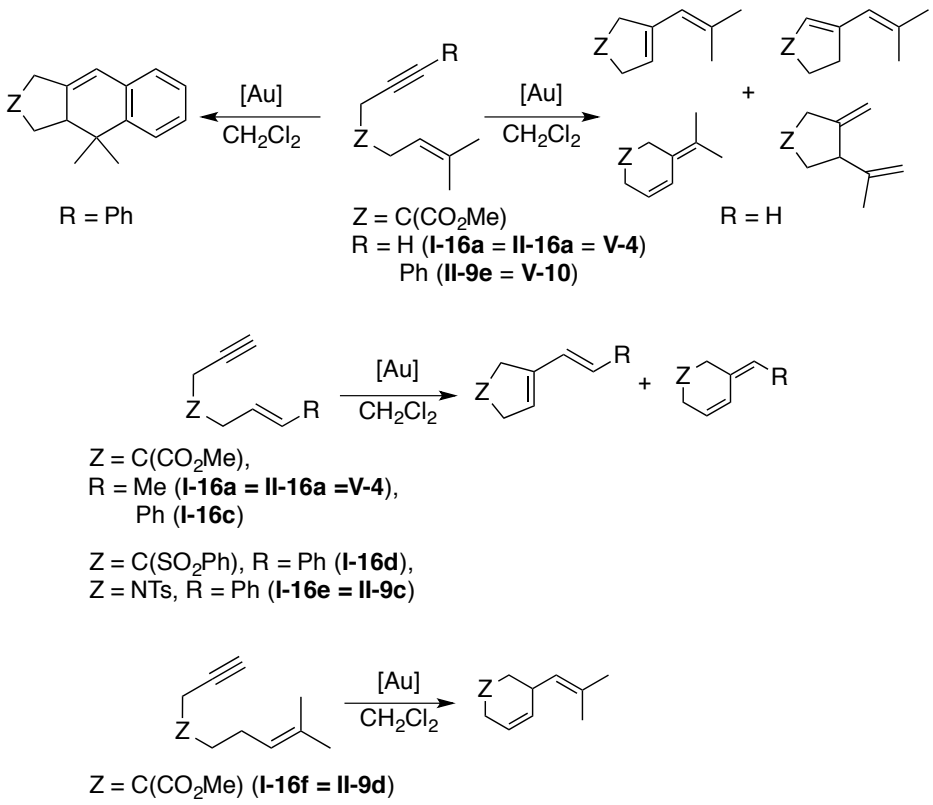
Sobre una disolución de [AuCl(carbeno)] en CH_2Cl_2 se adiciona un equivalente de $AgSbF_6$ en presencia de L (cuando L = $AsPh_3$ se añade un equivalente; cuando L es 2,4,6-trimetoxibenzonitrilo, se añade exceso). Tras la aparición de AgCl, la mezcla se filtra (filtro doble HPLC Teflon), se añade Et_2O o hexano[73] y se cristaliza.

[73] El disolvente adecuado en cada caso está especificado en la Parte Experimental de los Artículos I, III o V.

[Au(NTf$_2$){C(NEt$_2$)(NHXilil)}] ***(III-3)****, Artículo III*

Sobre una disolución de [AuCl{C(NHEt$_2$)(NHXilil)}] (**III-2**) (0.23 mmol) en 15 mL de CH_2Cl_2 se adicionan 0.23 mmol de $AgNTf_2$. Se sigue el procedimiento utilizado en la síntesis de [Au(carbeno)L]SbF_6.

Procedimiento General para las reorganizaciones de esqueleto de 1,n-eninos (n = 6, 7) catalizadas por carbenos de Au^I (Artículos I, II y V)



Esquema 21. Reacciones de ciclación de 1,n-eninos

Reorganización con carbenos neutros de oro(I) en presencia de $AgSbF_6$ (Artículos I, II, V)

Una disolución del correspondiente enino (0.15-0.2 mmol) en CH_2Cl_2 se añade sobre [AuCl(carbeno)] (2-5 %mol)[74] y la cantidad estequiométrica de $AgSbF_6$ en CH_2Cl_2. La reacción se sigue por TLC. Una vez finalizada, se desactiva el catalizador con una disolución de NEt_3 0.1 M en hexano y el bruto de reacción se purifica a través de una

[74] $AsPh_3$ (10 mol% con respecto a la cantidad de catalizador) únicamente se añadió para el artículo V en los experimentos realizados con cantidades subestequiométricas de $AsPh_3$.

columna de gel de sílice (AcOEt/Hexano) obteniéndose los correspondientes compuestos o mezclas dependiendo del enino de partida.

Reorganización con [Au(carbeno)L](SbF$_6$) (L = 2,4,6-trimetoxibenzonitrilo, Artículo I; L = AsPh$_3$, Artículo V)

Una disolución del correspondiente enino (0.15-0.2 mmol) en CH_2Cl_2 se añade sobre otra de [Au(carbeno)L](SbF$_6$) (2-5 %mol) en CH_2Cl_2. La reacción se sigue por TLC. Una vez finalizada, se desactiva el catalizador con una disolución de NEt_3 0.1 M en hexano y el bruto de reacción se purifica a través de una columna de gel de sílice (AcOEt/Hexano) obteniéndose los correspondientes compuestos o mezclas dependiendo del enino de partida.

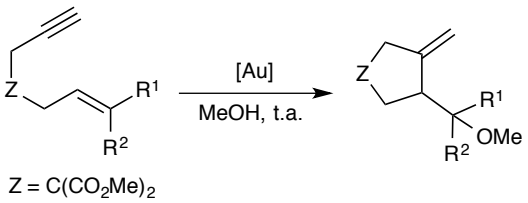
*Procedimiento de reciclaje de [Au(AsPh$_3$)$_2$](SbF$_6$) (**V-2a**) en reacciones de reorganización de **V-4** (Artículo V)*

Una disolución de **V-4** (0.2 mmol) en CH_2Cl_2 se añade sobre otra disolución de [Au(AsPh$_3$)$_2$](SbF$_6$) (2 mol%) en CH_2Cl_2. La reacción se monitoriza por espectroscopia de RMN. Cuando finaliza la reacción, se evapora el disolvente, y el producto de ciclación se extrae con hexano y se filtra a través de gel de sílice, recuperándose el catalizador como un sólido blanco en el fondo del matraz. Su pureza se confirma por espectroscopia de RMN. El catalizador se disuelve en CH_2Cl_2 y se mezcla con otra disolución de **V-4** (0.2 mmol) en CH_2Cl_2 produciéndose de nuevo la reacción de ciclación. Se repite el procedimiento hasta 5 veces.

*Transposición de esqueleto de **V-4** con 0.1 mol% de [AuCl{C(NH$_3$)(NHPy-2)}](**V-2c**)(Artículo V)*

En un Schlenk secado a la llama se añade $AgSbF_6$ (0.1 mol%, 100 µL de una disolución de $AgSbF_6$ 2×10^{-3} M en acetona) y $AsPh_3$ (0.01 mol%, 50 µL de una disolución 4×10^{-4} M en CH_2Cl_2), y se elimina el disolvente a vacío. Se añade [AuCl{C(NH$_3$)(NHPy-2)}] (0.1 mol%, 0.0710 mg, 2×10^{-4} mmol) disuelto en CH_2Cl_2 (1 mL). A continuación se añade **V-4** (48.0 mg, 0.2 mmol) en 1 mL de CH_2Cl_2. La reacción se monitoriza por RMN de ^{1}H. Una vez finalizada, se desactiva el catalizador con una disolución de NEt_3 0.1 M en hexano y el bruto de reacción se purifica a través de una columna de gel de sílice (AcOEt/Hexano) obteniéndose los correspondientes productos de ciclación.

Procedimiento General para las metoxiciclaciones de 1,n-eninos (n = 6, 7) catalizadas por carbenos de Au^I (Artículos I, II y V)



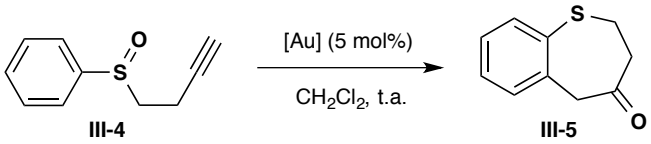
Metoxiciclación con carbenos neutros de oro(I) en presencia de $AgSbF_6$ (Artículos I, II, V)

Una disolución del correspondiente enino (0.15-0.2 mmol) en MeOH se añade sobre [AuCl(carbeno)] (2-5 mol%)[74] y la cantidad estequiométrica de $AgSbF_6$ en MeOH. La reacción se sigue por TLC. Una vez finalizada, se desactiva el catalizador con una disolución de NEt_3 0.1 M en hexano y el bruto de reacción se purifica a través de una columna de gel de sílice (AcOEt/Hexano) obteniéndose el producto de metoxiciclación.

Metoxiciclación con [Au(carbeno)L](SbF$_6$) (L = 2,4,6-trimetoxibenzonitrilo, Artículo I; L = $AsPh_3$, Artículo V)

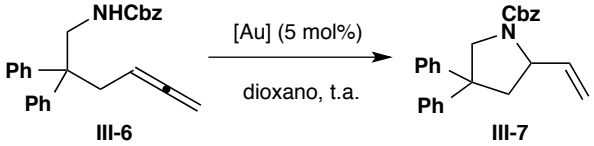
Una disolución del correspondiente enino (0.15-0.2 mmol) en MeOH se añade sobre [Au(carbeno)L](SbF$_6$) (2-5 mol%) en MeOH. La reacción se sigue por TLC. Una vez finalizada, se desactiva el catalizador con una disolución de NEt_3 0.1 M en hexano y el bruto de reacción se purifica a través de una columna de gel de sílice (AcOEt/Hexano) obteniéndose el producto de metoxiciclación.

Procedimiento General para la reorganización de homopropargilsulfóxido catalizada por carbenos de Au^{I} (Artículo III) [25,52]



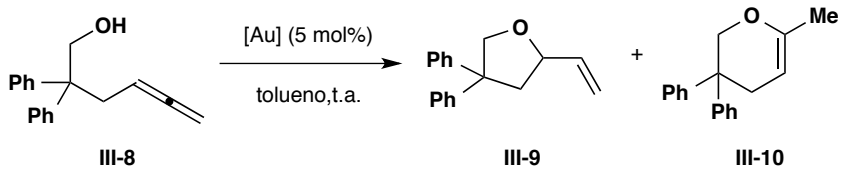
En un schlenk se disuelve [AuCl(carbeno)] (5 mol%) en 1 mL de CH_2Cl_2 y se añade $AgSbF_6$ o $AgNTf_2$ (5 mol%). La mezcla se deja reaccionar 10 min (Nota: cuando se utiliza como catalizador [Au(NTf_2){C(NEt_2)(NHXilil)}](**III-3**), no se añade sal de plata). A continuación se adiciona **III-4** (1 equiv) disuelto en 1 mL de CH_2Cl_2. La reacción se sigue por TLC hasta la consumición total de los productos de partida. A continuación, la mezcla de reacción se carga directamente en una columna de sílica gel, con eluyente acetato de etilo/ hexano (5/95), obteniéndose la benzotiepinona **III-5**.

Procedimiento General para la exo-hidroaminación intramolecular de N-alenilcarbamato [53] ***catalizada por carbenos de Au^{I} (Artículo III)***



En un schlenk se disuelve [AuCl(carbeno)] (5 mol%) en 1 mL de dioxano y se añade AgOTs (5 mol%). La mezcla se deja reaccionar 10 min (Nota: cuando se utiliza como catalizador [Au(NTf_2){C(NEt_2)(NHXilil)}](**III-3**), no se añade sal de plata). A continuación se adiciona *N*-alenil carbamato **(III-6)** (1 equiv) disuelto en 1 mL de dioxano. La reacción se sigue por TLC hasta la consumición total de los productos de partida. La mezcla resultante se concentra y se extrae en una placa filtrante directamente con Kieselguhr; la elución para la columna cromatográfica se realiza con acetato de etilo/hexano (1:4) y se aísla **III-7** puro como un aceite viscoso incoloro.

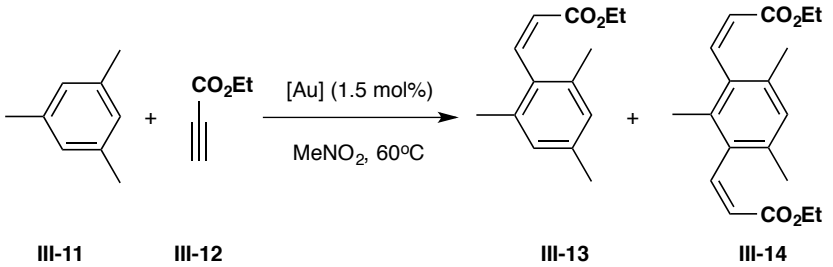
Procedimiento general para la hidroalcoxilación intramolecular del 2,2-difenil-4,5-hexadienol,[53] catalizada por carbenos de Au^{I} (Artículos III y IV)



III-8 **III-9** **III-10**

En un schlenk se disuelve [AuCl(carbeno)] (5 mol%) en 1 mL de tolueno y se añade AgOTs (5 mol%). La mezcla se deja reaccionar 10 min (Nota: cuando se utiliza como catalizador [Au(NTf$_2$){C(NEt$_2$)(NHXilil)}](**III-3**), no se añade sal de plata). A continuación se adiciona 2,2-difenil-4,5-hexadien-1-ol **(III-8)** (1 equiv) disuelto en 1 mL de tolueno. La reacción se sigue por TLC hasta la consumición total de los productos de partida. La mezcla resultante se concentra y se extrae en una placa filtrante directamente con kieselguhr; la elución para la columna cromatográfica se realiza con acetato de etilo/hexano (1:50 → 1:20) y se aísla 4,4-Difenil-2-viniltetrahidrofurano (**III-9**) puro como un aceite incoloro.

Procedimiento General para la hidroarilación del éster de ácido acetilcarboxílico,[54a] ***catalizada por carbenos de Au^{I} (Artículo III)***

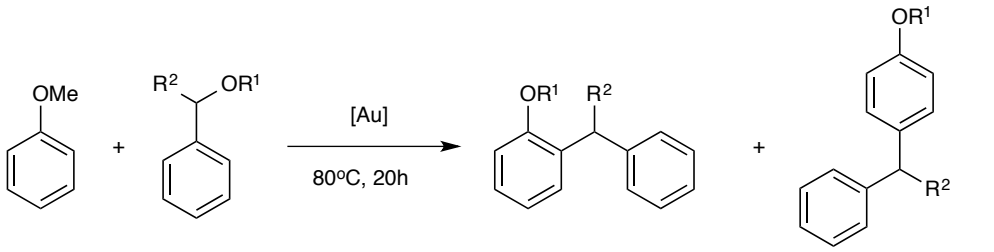


III-11 **III-12** **III-13** **III-14**

En un schlenk se disuelve [AuCl(carbeno)] (1.5 mol%) en 1 mL de nitrometano y se añade AgNTf$_2$ (1.5 mol%). La mezcla se deja reaccionar 10 min (Nota: cuando se utiliza como catalizador [Au(NTf$_2$){C(NEt$_2$)(NHXilil)}](**III-3**), no se añade sal de plata). A continuación se adiciona **III-11** (10 equiv) y **III-12** (1equiv) disueltos en 1 mL de nitrometano. La reacción se mantiene a 60 ºC durante 4h. Después de enfriar, el disolvente y el exceso de areno se eliminan a vacío. El rendimiento y relación de los

compuestos finales (**III-13** y **III-14**) se estiman por espectroscopia de RMN de ^{1}H con 1,2-dicloroetano como referencia interna.

Procedimiento General para la bencilación del anisol[55] catalizada por carbenos de Au^I (Artículo III)



III-15

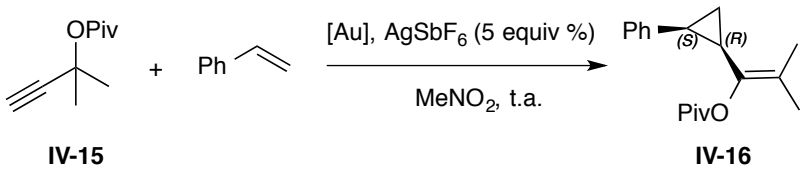
R^1 = Ac, R^2 = Me **(III-16)**
R^1 = R^2 = H **(III-19)**

R^1 = Ac, R^2 = Me **(III-17)**
R^1 = R^2 = H **(III-20)**

R^1 = Ac, R^2 = Me **(III-18)**
R^1 = R^2 = H **(III-21)**

En un schlenk se disuelve [AuCl(carbeno)] (5 ó 10 mol%) en 5 mL de anisol y se añade $AgNTf_2$ (5 ó 10 mol%) (Nota: cuando se utiliza como catalizador [Au(NTf_2){C(NEt_2)(NHXilil)}](**III-3**), no se añade sal de plata). A continuación se adicionan 0.5 mmol de acetato de 1-feniletilo (**III-16**) ó de alcohol bencílico (**III-19**). La reacción se mantiene a 80 ºC durante 20h. A continuación se añade agua y el producto se extrae con CH_2Cl_2. La fase orgánica se seca con $MgSO_4$ y los disolventes se evaporan a vacío. El rendimiento y la relación entre los productos finales (**III-17/III-18** y **III-20/III-21**) se determinaron por espectroscopia de RMN de ^{1}H con 1,2-dicloroetano como referencia interna.

Procedimiento General para la ciclopropanación enantioselectiva de olefinas con éster propargílico catalizada por carbenos de Au^I (Artículo IV)



IV-15 **IV-16**

En un schlenk se disuelve el carbeno quiral de oro neutro (5 equiv%) en 1.5 mL de nitrometano y se añade $AgSbF_6$ (5 equiv%). La mezcla se deja reaccionar 10 min. pivaloato de propargilo (**IV-15**) (1 equiv) en $MeNO_2$ y estireno (4 equiv). La reacción se sigue por TLC hasta la consumición total del producto de partida. La mezcla resultante se concentra y se añade directamente a la columna de gel de sílice; la elución se realiza con una mezcla de hexano/éter (97:3) obteniendo **IV-16** analíticamente puro.

Técnicas de caracterización utilizadas

La metodología empleada para la caracterización tanto de los complejos de oro(I) sintetizados como de las reacciones catalíticas que se describen en esta memoria implica la utilización de una gran diversidad de técnicas instrumentales que se describen a continuación.

Espectroscopia de infrarrojo

El seguimiento de la reacción para aquellos complejos de oro(I) donde desaparece la banda de absorción correspondiente ν(CN) a los ligandos isocianuro se ha llevado a cabo por espectroscopia infrarroja en disolución, mediante la observación de la desaparición de las bandas de tensión CN. Los espectros de IR se han registrado en un aparato Perkin-Elmer RX I FT-IR o 1720X con una resolución de 4 cm^{-1}. Para los espectros en disolución se ha utilizado una celda de CaF_2 de 0.1 mm de espesor.

Espectroscopia de resonancia magnética nuclear

Los espectros de resonancia magnética nuclear (RMN) se han registrado en instrumentos Bruker AC-300, ARX-300, AV-400, Varian MR 400 ó Varian VNMRS 500 empleando en todos los casos la señal del deuterio para el mantenimiento y homogeneidad del campo. Los valores de los desplazamientos químicos (δ) se expresan en partes por millón (ppm) siendo valores positivos los que indican desplazamientos a frecuencias más altas o campos más bajos. Las constantes de acoplamiento (*J*) se expresan en hercios (Hz). Todos los espectros de ^1H RMN están referidos a la señal del TMS.

Análisis elemental de C, H y N

Los análisis elementales de C, H y N se han realizados en un microanalizador Perkin Elmer 2400B del área de Química Inorgánica de la Universidad de Valladolid.

Polarimetría

La rotación óptica de las moléculas quirales se midió en un polarímetro Perkin-Elmer 343. Las disoluciones se prepararon c = 0.5 o 1 (0.05 o 0.1 mg / mL) en el disolvente indicado en cada caso.

Cromatografía de líquidos de alta resolución

Para la separación de los enantiómeros formados en las reacciones estereoselectivas, se ha utilizado la técnica de HPLC, analizando las muestras con un equipo de cromatografía Hewlett-Packard de módulos equipados con una columna de HPLC Chiracel OD-H de 25 cm de largo.

Difracción de rayos X

Para la determinación estructural por difracción de rayos X, los monocristales se han medido en un difractómetro Bruker AXS SMART 1000, o bien Oxford Diffraction Super Nova, provistos de detector CCD, usando radiación Mo-Kα monocromada mediante un cristal de grafito. Los datos se han integrado con el programa SAINT,[75] o CrysAlisPro[76] y para la resolución de las estructuras se ha usado SHELXTL[77] o SIR2002[78] bajo WINGX.[79] En general se ha aplicado una corrección de absorción semi-empírica con el programa SADABS,[80] y en algunos casos se ha usado una corrección analítica mediante indexación de caras, con el programa CrysAlisPro. Los cálculos de parámetros geométricos se han hecho con SHELXTL y PARST [81] y los gráficos se han hecho con SHELXTL y Mercury. [82]

[75] *SAINT+*. SAX area detector integration program. Version 6.02. Bruker AXS, Inc. Madison, WI, **1999**.
[76] CrysAlisPro-Data collection and integration software. Oxford Diffraction Ltd. **2009**.
[77] G. M. Sheldrick *Acta Cryst.* **2008**, *A64,* 112. SHELXTL, An integrated system for solving, refining, and displaying crystal structures from diffraction data. Version 5.1. Bruker AXS, Inc. Madison, WI, **1998**.
[78] M. C.Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidory, R. Spagna, *SIR2002, A program for automatic solution and refinement of crystal structures. J. Appl. Cryst.* **2003**, *36*, 1103.
[79] L. J. Farrugia *J. Appl. Cryst.*, **1999**, *32*, 837–838.
[80] G. M. Sheldrick; *SADABS*, Empirical Absorption Correction Program. University of Göttingen, Germany, **1997**.
[81] (a) M. Nardelli, *Comput. Chem.,* **1983**, 7, 95–158. (b) M. Nardelli, *J. Appl. Crystallogr.*, **1995**, *28*, 659.
[82] MERCURY: (a) I. J. Bruno, J. C. Cole, P. R. Edgington, M. K. Kessler, C. F. Macrae, P. McCabe, J. Pearson, R. Taylor *Acta Crystallogr*. **2002**, *B58*, 389–397. (b) C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. van de Streek *J. Appl. Crystallogr.*, **2006**, *39*, 453–457.

Artículo I

Gold(I) Complexes with Hydrogen-Bond Supported Heterocyclic Carbenes as Active Catalysts in Reactions of 1,6-Enynes

Camino Bartolomé, Zoraida Ramiro, Patricia Pérez-Galán, Christophe Bour, Mihai Raducan, Antonio M. Echavarren, and Pablo Espinet**

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Gold(I) Complexes with Hydrogen-Bond Supported Heterocyclic Carbenes as Active Catalysts in Reactions of 1,6-Enynes

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Complexes [AuCl{C(NHR)(NHPy-2)}] (Py-2 = 2-pyridyl; R = Me, ^{t}Bu, ^{n}Bu, ^{i}Pr, ^{n}heptyl) have been prepared in a modular way from [AuCl(CNPy-2)]. The carbene moiety has a hydrogen-bond supported heterocyclic structure similar to the nitrogen heterocyclic carbenes in the solid state, and in CH_2Cl_2 or acetone solution, which is open in the presence of MeOH. The compounds are good catalysts for the skeletal rearrangement of enynes, and for the methoxycyclization of enynes. In contrast, the complexes [AuCl{C(NHR)(NHPy-4)}] are scarcely active due to the blocking effect of the coordination position required for the catalysis by the nitrogen of the NHPy-4 group.

Introduction

Gold(I) carbene complexes of the type AuCl{C(NRH)-(NHPy-*n*)}] (Py = pyridyl; n = 2,4), obtained by nucleophilic addition of primary amines to pyridylisocyanides coordinated to gold, have been reported recently.[1,2] In the case of gold(I) carbenes derived from 2-pyridyl isocyanide, a strong intramolecular hydrogen bond produces a planar cycle (structure **B**, Figure 1), somewhat reminiscent of that of the nitrogen heterocyclic carbenes (NHCs, structure **A**, Figure 1). We will refer to them as hydrogen bond supported heterocyclic carbenes (HBHCs). In all the HBHC carbenes synthesized, the hydrogen-bond-supported cyclic structure is observed in the solid state and maintained in solution in $CDCl_3$, and acetone-d_6.[1] By contrast, for carbenes derived from 4-pyridyl isocyanide, only intermolecular hydrogen bonds are formed in the solid state, which are broken in solution to give, predominantly, the noncyclic structures **C** and **D** in Figure 1.[2]

Gold NHC complexes, although known for more than 20 years,[3] have only recently become relevant in NHC chemistry because of their catalytic applications in organic synthesis.[4] The straightforward preparative method of their somehow related HBHCs complexes allows for the easy modular design and preparation of series of compounds where the R modifier can be easily varied in order to tune the steric and electronic properties of the complex. This invited us to check the catalytic performance of the HBHC carbenes derived from 2-pyridyl isocyanide and, for comparison, the related noncyclic carbenes derived from 4-pyridyl isocyanide.

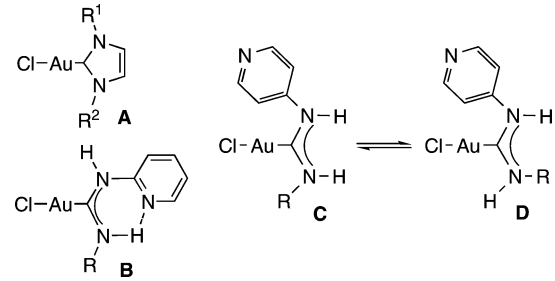

Figure 1. Gold(I) complexes with NHC (**A**), HBHC (**B**), and noncyclic (**C** and **D**) carbene derived from 4-pyridyl isocyanide.

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[§] Universidad de Valladolid.
[†] Institute of Chemical Research of Catalonia (ICIQ).

(1) Bartolomé, C.; Carrasco-Rando, M.; Coco, S.; Cordovilla, C.; Martín-Alvarez, J. M.; Espinet, P. *Inorg. Chem.* **2008**, *47*, 1616–1624.
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(4) (a) Hashmi, A. S. J. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3265. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. **2008**, *108*, 3351–3378. (g) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.

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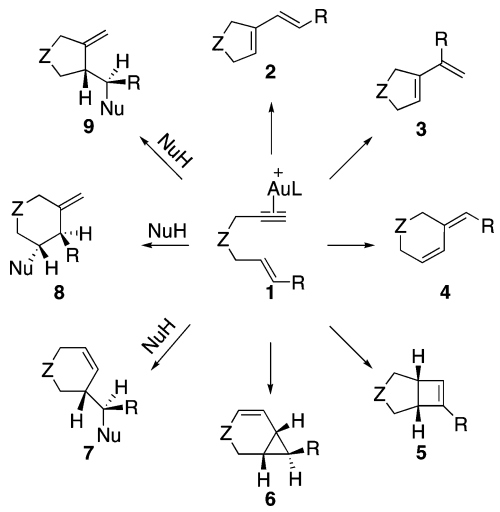
Scheme 1



In this respect, interesting gold catalyzed reactions are the skeletal rearrangements and other cyclization of enynes. The activation of 1,6-enynes via the η^2-alkyne gold complex **1** can afford a variety of compounds (Scheme 1).[5] In the absence of nucleophiles, enynes usually evolve by skeletal rearrangement to form dienes **2** (single cleavage) and/or **3** (double cleavage). Products of endocyclic skeletal rearrangement **4**,[5,6] cyclobutenes **5**,[5] and bicyclic products of intramolecular cyclopropanation **6**, have also been obtained.[7] In the presence of nucleophiles, adducts **7**−**9** have been produced in stereospecific processes.[5,8−11] More complex transformations are also possible starting from more functionalized enynes.[12]

Although most of the reactions in Scheme 1 use phosphines as the gold ligand, complexes with highly donating NHCs such as **10a**−**d** (Figure 2) have been found to be good precatalysts for some reactions of enynes.[12a,13] The actual catalyst is formed in solution by treatment with a silver salt to extract the chloride. Related complexes with NTf_2 as ligand (**11a**−**b**),[14,15] and cationic complexes (e.g., **12**) derived from **10d**,[16,17] or the phosphite complex **13**,[17] have also been reported active.

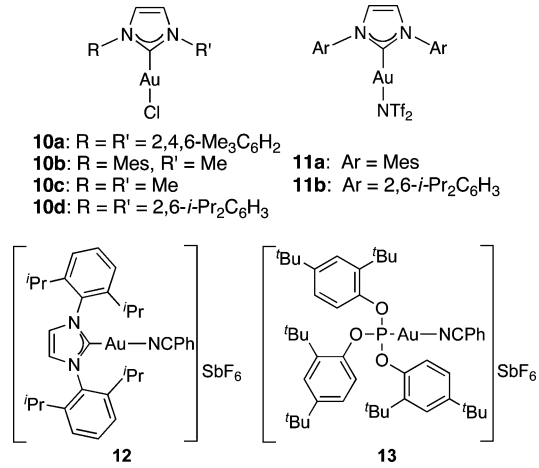


Figure 2. Gold complexes used as catalysts for skeletal rearrangement of enynes.

With these precedents in mind, the aim of this work is to check the catalytic activity of HBHC (**B**), and noncyclic (**C**−**D**) carbene complexes in the cyclization of 1,6-enynes, having the reported work with NHCs carbenes as reference. Thus selected AuCl{C(NRH)-(NHPy-*n*)}] ($n = 2, 4$) complexes prepared for this purpose have been tested in the skeletal rearrangement and in the methoxycyclizations of 1,6-enynes. The HBHC gold carbenes, derived from 2-pyridyl isocyanide, are highly active, whereas 4-pyridyl isocyanide derivatives are almost inactive. The steric and electronic features of the amine chosen for the nucleophilic attack to the coordinated isocyanide induce substantial changes in the catalytic activity of the complexes, and in the products formed.

Results and Discussion

Synthesis and Structural Characterization of the Gold Carbene Complexes. The neutral gold carbene catalysts **14a**−**e** were prepared by nucleophilic attack to the gold coordinated isocyanide with differently hindered primary amines to tune the steric requirement of the alkyl group

(5) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406. (b) 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. (c) 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. (d) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916–5923.
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(14) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159.
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(16) de Frémont, P.; Stevens, E. D.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Nolan, S. P. *Chem. Commun.* **2006**, 2045–2047.
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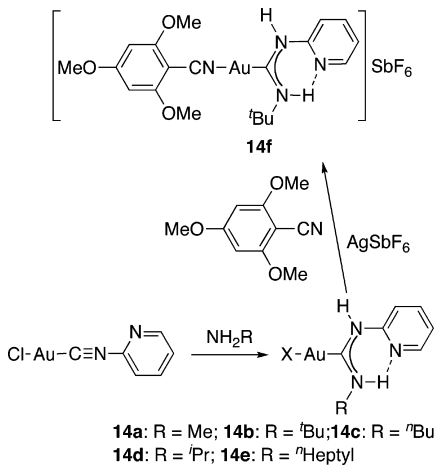
Scheme 2. Synthesis of the Gold Carbene Derivatives **14**



R (Scheme 2). All the complexes are white, air stable solids. The carbene [AuCl{C(NHMe)(NHPy-2)}] (**14a**) has been reported already.[1] Once the carbene has been formed, the R group will be located close to the gold atom, and might have some steric influence on the reaction. As observed in the ^{1}H NMR of **14a** in $CDCl_3$, there are two different signals for the two N−H protons, one at ca. 12.5 ppm and another in the range 9.5−8 ppm. The chemical shift of the low-field signal reveals the existence in solution of an intramolecular hydrogen bond between the amide proton and the nitrogen of the 2-pyridyl group forming a 6-member cycle. This feature is also observed in acetone-d_6 solution.

X-ray quality crystals suitable for single crystal diffraction were obtained for [AuCl{C(NH^{t}Bu)(NHPy-2)}] (**14b**), and the expected intramolecular hydrogen bond was confirmed. There are two very similar independent molecules of **14b** in the asymmetric unit. The molecular structure of one of them is shown in Figure 3, with selected bond lengths and angles.

The complex shows a nearly linear geometry for gold. The gold atom is located in the hinge defined by a CMe_2 fragment

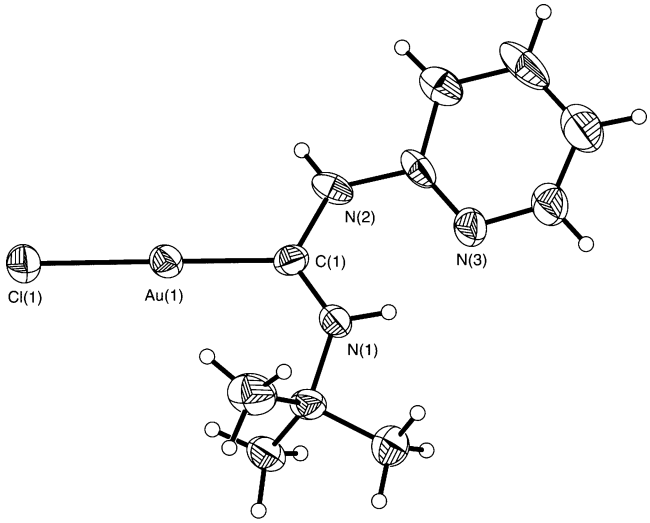


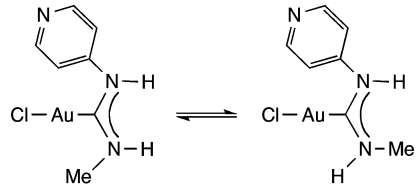
Figure 3. X-ray structure for [AuCl{C(NH^{t}Bu)(NHPy-2)}] (**14b**). Selected bond lengths (Å): Au(1)−Cl(1) = 2.301(3); Au(1)−C(1) = 2.016(12); C(1)−N(2) = 1.365(13); C(1)−N(1) = 1.309(13); N(3)−H(1A) = 1.786(1). Selected bond angles (°): C(1)−Au(1)−Cl(1) = 179.6(3); N(2)−C(1)−N(1) = 118.1(10); N(3)−H(1A)−N(1) = 138.41(5).

of the ^{t}Bu group. The Au−Cl distance in **14b** is longer than that for $[AuCl_2]^-$ (2.257 Å),[18] as a consequence of the high *trans* influence of the carbene ligand.[3,19] The Au−C distance is within the range found for similar gold(I) carbenes.[20] The C(1)−N(2) and C(1)−N(1) distances are within the range found for other Au(I) carbene complexes, and much shorter than the C(sp^2)−N single bond distance of 1.45 Å,[21] indicating a significant π-bonding contribution to the bond. The conformer found in this structure has the N−H of the formerly *tert*-butylamine group oriented toward the nitrogen of the pyridyl group. The H···N distance and the corresponding N−H···N angle are within the range of moderate intramolecular N···H hydrogen bonds.[22] The spectroscopic evidence discussed before supports that the conformation observed in the solid state is retained in solution in chloroform and in acetone, and is the same for all the complexes derived from 2-pyridyl isocyanide.

A cationic gold complex **14f** derivative was prepared from **14b** as a white, air stable solid, by chloride abstraction with $AgSbF_6$ in the presence of excess 2,4,6-trimethoxybenzonitrile. The 2,4,6-trimethoxybenzonitrile is a labile ligand, which is coordinated to gold in the solid state (ν_{CN} = 2261 cm^{-1}), but is displaced by the solvent in acetone (ν_{CN} = 2221 cm^{-1}). The ^{1}H NMR spectra in CD_2Cl_2 are complex and show two species in solution, as broad signals, probably due to competition of water in the solvent as ligand, along with slow exchange. In fact, addition of CD_3CN displaces the spectra to the formation of one single species, which is the same observed for **14f** in CD_3CN as solvent, and shows free 2,4,6-trimethoxybenzonitrile. Thus, it is concluded that acetonitrile has displaced the 2,4,6-trimethoxybenzonitrile from gold. The availability of this cationic precursor, which should allow for easy η^2-coordination of the reagent in the catalysis, avoids the presence of silver salts in the catalytic pot and reduces the possibility of silver promoted side reactions. In our cases, the catalytic behavior of **14f** and **14b** + $AgSbF_6$ are practically identical (see later).

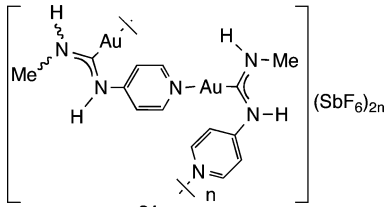
Only one complex derived from 4-pyridyl isocyanide, [AuCl{C(NHMe)(NHPy-4)}] (**15**), was prepared and studied, in view of the poor catalytic behavior observed (see later). It was prepared as reported for analogous carbene complexes.[2] Up to four isomers might be formed, depending on the arrangement of the 4-pyridyl group and the Me group, but the ^{1}H NMR spectra showed only the two isomers depicted in Figure 4, which were assigned by irradiation and

(18) Braunstein, P.; Müller, A.; Bögge, H. *Inorg. Chem.* **1986**, *25*, 2104–2106.
(19) (a) Bovio, B.; Burini, A.; Pietroni, B. R. *J. Organomet. Chem.* **1993**, *452*, 287–291. (b) Wang, H. M. J.; Chen, C. Y. L.; Lin, I. J. B. *Organometallics* **1999**, *18*, 1216–1227.
(20) (a) Balch, A. L.; Olmstead, M. M.; Vickery, J. C. *Inorg. Chem.* **1999**, *38*, 3494–3499. (b) Beck, W.; Weigand, W.; Nagel, U.; Schaal, M. *Angew. Chem., Int. Ed.* **1984**, *23*, 377–378. (c) Banditelli, G.; Bonati, F.; Calogero, S.; Valle, G.; Wagner, F. E.; Wordel, R. *Organometallics* **1987**, *6*, 2019. (d) White-Morris, R. L.; Olmstead, M. M.; Balch, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 1033–1040.
(21) Pauling L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University: Ithaca, NY, 1960; p 282.
(22) Hydrogen bonding distance ranges proposed in the literature: strong, 1.2−1.5 Å; moderate, 1.5−2.2 Å; weak, 2.2−3.2 Å: Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.



15

Figure 4. Conformers observed for **15** in solution.



21

Figure 5. Coordination polymer obtained by coordination of the dangling pyridyl group to the gold center.

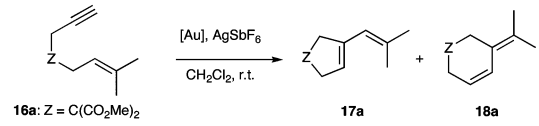
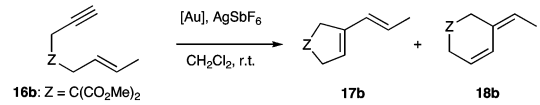
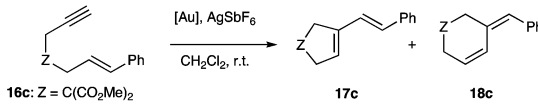
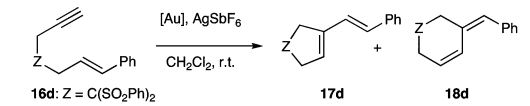
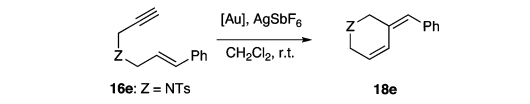
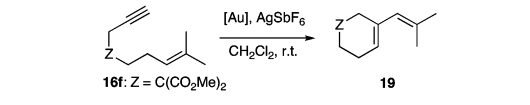
NOE experiments. These have a syn arrangement of the 4-pyridyl and Au moieties. The minor signals correspond to the isomer on the right of the figure, and the major to the less crowded isomer on the left. The isomer ratio changes with the polarity of the solvent (acetone-d_6 or $CDCl_3$), suggesting a slow exchange process in solution.

Catalytic Reactions. The reactions were carried out dissolving the catalyst and the 1,6-enyne in CH_2Cl_2 (skeletal rearrangements) or methanol (methoxycyclizations) and, except when the complex was cationic, adding $AgSbF_6$ to extract the chloride and allow for coordination of the enyne to the Au center. In general the catalysis with carbene gold complexes containing the 2-pyridyl group was very effective (somewhat less effective for the methoxycyclizations as observed also with other catalysts).[5c,12a] The different catalysts provided variations in yield (higher for bulkier R substituents), but also interesting variations in the major product when more than one was formed. The catalytic results for skeletal rearrangement of 1,6-enynes and for methoxycyclizations of 1,6-enynes using the gold catalysts derived from 2-pyridyl isocyanide afford fairly good yields (see later numeric results).

In contrast, the catalytic activity drops dramatically for the gold catalyst containing a 4-pyridyl group (complex **15**). The reaction conditions explain the poor activity of **15**. In the presence of a silver salt, the N atom of the pyridyl group, which in this case is not neutralized by a strong hydrogen bond interaction, can coordinate to the gold center, blocking the active site of the catalyst. Moreover, the resulting polymer is insoluble and the gold catalyst precipitates. In fact, treatment of **15** with $AgSbF_6$ in a separate reaction led to the formation of insoluble polymers **21** (Figure 5), which could not be separated from the insoluble silver chloride formed in the reaction but was easily detected by infrared. The weight of the precipitate accounted for the sum of the expected polymer plus the expected AgCl. The insolubility of the polymer precluded further characterization.

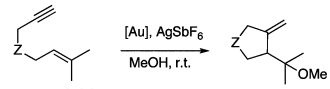
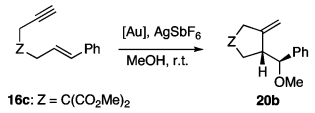
The catalytic results for the skeletal rearrangement of 1,6-enynes are listed in Table 1. The gold carbenes **14a**−**d** catalyze efficiently the skeletal rearrangement of 1,6-enynes

Table 1. Skeletal Rearrangement of 1,6-Enynes with Catalysts **14a**−**f** and **15**[a]

entry	[Au]	Time	Product(s) (Yield, %, ratio)
			
	16a: Z = $C(CO_2Me)_2$		**17a** **18a**
1	**14a**	2 min	**17a** + **18a** (89, 30:1)
2	**14b**	2 min	**17a** + **18a** (93, 31:1)
3	**14c**	5 min	**17a** (88)
4	**14d**	5 min	**17a** (73)
5	**14e**	5 min	**17a** (89)
6[b]	**14f**	5 min	**17a** + **18a** (94, 46:1)
7	**15**	24 h	**17a** + **18a** (5, 1:0)
			
	16b: Z = $C(CO_2Me)_2$		**17b** **18b**
8	**14a**	2 min	**17b** (85)
9	**14b**	2 min	**17b** + **18b** (80, 7:1)
10	**15**	24 h	**17b** (10)
			
	16c: Z = $C(CO_2Me)_2$		**17c** **18c**
11[c]	**14a**	35 min	**17c** + **18c** (100, 1:2.7)
12[c]	**14b**	35 min	**17c** + **18c** (100, 1:2.8)
13[c]	**15**	1 h	-[d]
			
	16d: Z = $C(SO_2Ph)_2$		**17d** **18d**
14	**14a**	30 min	**17d** + **18d** (81, 1.6:1)
15	**14b**	7 min	**17d** + **18d** (91, 1.6:1)
16	**15**	30 h	-[d]
			
	16e: Z = NTs		**18e**
17	**14a**	24 h	**18e** (16)
18	**14b**	1 h	**18e** (60)
19	**15**	24 h	**18e** (12)
			
	16f: Z = $C(CO_2Me)_2$		**19**
20	**14a**	10 min	**19** (90)
21	**14b**	5 min	**19** (96)
22	**15**	24 h	**19** (8)

[a] Reactions carried out in CH_2Cl_2 with 2 mol% catalyst. [b] Reaction run in the absence of $AgSbF_6$. [c] 5 mol% catalyst. [d] Starting material was recovered.

Table 2. Methoxycyclizations of 1,6-Enynes with Catalysts **14a**−**f** and **15**[a]

entry	[Au]	Time	Product(s) (Yield, %)
			
	16a: Z = $C(CO_2Me)_2$		**20a**
1	**14a**	3 h	**20a** (20)
2	**14b**	3 h	**20a** (70)
3	**14c**	2 h	**20a** (44)
4	**14d**	2 h	**20a** (33)
5	**14e**	2 h	**20a** (39)
6[b]	**14f**	2 h	**20a** (80)
7	**15**	3 h	**20a** (17)
			
	16c: Z = $C(CO_2Me)_2$		**20b**
8	**14a**	3 h	**20b** (55)
9	**14b**	3 h	**20b** (59)
10	**15**	3 h	-[b]

[a] Reactions carried out in CH_2Cl_2 with 5 mol% catalyst. [b] Starting material was recovered.

16a−**d** with similar efficiency (Table 1, entries 1−5, 8, 9, 11, 12, 14, 15, 20, and 21), although for the cyclization of **16e** and **16f** the most sterically hindered carbene **14b** affords better results than **14a** (compare Table 1, entries 17/18 and 20/21). The cationic complex **14f** and the mixture **14b** + $AgSbF_6$ catalyze the rearrangement of **14a** with similar efficiency (Table 1, entries 2 and 6). Finally, complex **15** results are very inefficient, for the reasons discussed above (Table 1, entries 7, 10, 13, 16, 19, and 22).

It is interesting to compare the performance of these new catalysts with the highly efficient cationic gold complexes **12** and **13** (Figure 2).[17] For example, whereas enyne **16c** reacts with catalysts **14a** and **14b** to give the product of endo cyclization **18c** as the major compound (ca. 1:3 **17c/18c**, Table 1, entries 11 and 12), complexes **12** and **13** favor the product of exo cyclization **17c** (50:1 for **12**, 73%, and 2.2:1 for **13**, 76%). For comparison, the reaction of **16c** with $[Au(PPh_3)Cl]/AgSbF_6$ gave and an almost equimolar ratio of **17c/18c**.[5c] Thus, the availability of a family of modular catalysts can be interesting to tune the reaction selectively toward different products, even at the expense of some loss of yield or activity.

The catalytic results for methoxycyclizations of 1,6-enynes are listed in Table 2. As for the cyclizations, the derivative with 4-pyridyl shows the poorest results (Table 2, entries 7 and 10), whereas the others display variable yields depending on the R group. The cationic complex **14f** and the combination **14b** + $AgSbF_6$ provide the product of methoxycyclization **20a** in the best yields (Table 2, entries 2 and 6). For comparison, catalysts **12** and **13** (5 mol%) afford similar yields in the methoxycyclization of enyne **16a** (68 and 76%, respectively) compared to those achieved using **14b**/$AgSbF_6$ or **14f** (Table 2, entries 2 and 6). However, although the reactions with **12** and **13** were faster (30 min vs 2−3 h), significant amounts (ca. 10%) of a methyl ketone, a product of a formal Markovnikov addition of water to the alkyne function of **16a**, were also observed. Thus, in this respect, the new catalysts used here are advantageous.

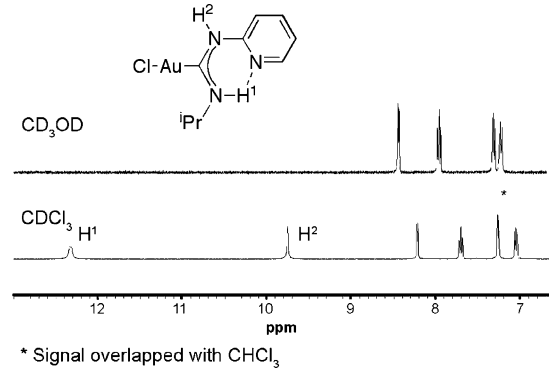


Figure 6. ^1H NMR of the aromatic and NH region for [AuCl{C(NH^{i}Pr)(NHPy-2)}] (**14d**) in $CDCl_3$ and CD_3OD at room temperature, showing that both N−H hydrogen atoms quickly exchange with CD_3OD.

Table 3. Crystal Data and Structure Refinement for [AuCl{C(NH*t*Bu)(NHPy-2)}] (**14b**)

empirical formula	$C_{10}H_{15}AuClN_3$
formula weight	409.67
temperature (K)	298(2)
wavelength (Å)	0.71073
crystal system	triclinic
space group	$P\bar{1}$
a (Å)	10.746(4)
b (Å)	10.834(4)
c (Å)	13.974(5)
α (deg)	109.282(7)
β (deg)	92.789(7)
γ (deg)	119.223(6)
V (Å^3)	1296.0(8)
Z	4
D_{calc} (g cm^{-3})	2.100
absorption coefficient (mm^{-1})	11.531
F(000)	768
crystal size (mm)	0.08 × 0.08 × 0.07
theta range for data collection	1.60 to 26.49°
reflections collected	11309
independent reflections	5293
absorption correction	semiempirical from equivalents
maximum and minimum transmission factor	1 and 0.758239
data/restraints/parameters	5293/0/277
goodness-of-fit on F^2	0.975
R_1 [$I > 2\sigma(I)$]	0.0472
wR_2 (all data)	0.1258

Since the methoxycyclizations require the presence of MeOH, the effect of this solvent on the intramolecular hydrogen bond was studied. It turned out that both N−H bonds exchange quickly with the deuterion of CD_3OD, supporting that the intramolecular hydrogen bond is split in the presence of MeOH (Figure 6).

In other words, the complexes **14** cannot be considered HBHCs when use in this solvent or in the presence of MeOH as reagent. Yet, the open carbene complexes formed in MeOH are very active catalysts, and the fall in yield observed in Table 2 should not necessarily be related to the splitting of the hydrogen bond supported ring, as the alkoxycycliza-

tions usually give lower yields with the carbene-gold complexes.[5c,12a] The splitting of the ring could have been a source of complication for reactions of skeletal rearrangements (Table 1), as any structural change of the catalyst can induce the formation of different products, but the HBHC structure of the ligand is well controlled in these reactions, since opening of the ring does not occur in CH_2Cl_2.

Conclusions

The complexes [AuCl{C(NHR)(NHPy-2)}] can be prepared in a modular way from [AuCl(CNPy-2)]. Depending on the solvent, they behave as hydrogen bond supported heterocyclic carbenes, structurally similar to the nitrogen heterocyclic carbenes (in acetone or CH_2Cl_2), or as noncyclic carbenes where the structural rigidity has been relaxed (in MeOH). The compounds are good catalysts for the skeletal rearrangement of enynes, affording somewhat different outcomes of the cyclizations as compared to other catalysts, and also for the alkoxycyclization of enynes. In contrast, the complexes [AuCl{C(NHR)(NHPy-4)}] are scarcely active due to the blocking effect by the nitrogen of the NHPy-4 group of the coordination position required for the catalysis. The modular construction of the catalysts makes them an attractive alternative to tune the catalysis.

Experimental Section

General Conditions. All reactions were carried out under dry N_2. The solvents were purified according to standard procedures.[23] [AuCl(CNPy-2)],[1] [AuCl(CNPy-4)],[2] and enynes **16a**−**f**,[5,6] were prepared according to literature procedures. The rest of the reactants are commercially available. Infrared spectra were recorded in Perkin-Elmer 883 or 1720X equipment. NMR spectra were recorded with Bruker AC300, ARX 300 and Bruker Avance 400 Ultrashield instruments. ^{1}H NMR spectra are referred to TMS. Elemental analyses were performed with a Perkin-Elmer 2400B microanalyzer. High resolution mass spectra were recorded in a Waters LCT Premier (ESI) spectrometer.

Synthesis of Carbenes 14b−**e. [AuCl{C(NH^{t}Bu)(NHPy-2)}] (14b).** tBuNH$_2$ (0.95 mmol, 100 μL) was added to a solution of [AuCl(CNPy-2)] (0.252 g, 0.75 mmol) in CH_2Cl_2 (30 mL). After 15 min stirring at room temperature, the solution did not show n(CN) IR absorption. The pale yellow solution was filtered through Celite, the volatiles were pumped off, and the pale-violet residue was crystallized from CH_2Cl_2/n-hexane. The colorless crystals obtained were washed with n-hexane (3 × 5 mL) and vaccuum-dried, yielding 0.202 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ 12.96 (br, 1H, NHC(CH$_3$)$_3$), 9.64 (br, 1H, NHC$_5$H$_4$N), 8.20 (d, J = 5.2 Hz, 1H, NHC$_5H_4$N), 7.71 (m, 1H, NHC$_5H_4$N), 7.25 (d, J = 7.7 Hz, 1H, NHC$_5H_4$N), 7.05 (m, 1H, NHC$_5H_4$N), 1.66 (s, 9H, NHC(CH_3)$_3$). Anal. Calcd for $C_{10}H_{15}AuClN_3$: C, 29.32; H, 3.69; N, 10.26. Found: C, 29.65; H, 3.72; N, 10.10.

[AuCl{C(NH^{n}Bu)(NHPy-2)}] (14c). n-Butylamine (0.5 mmol, 50.0 μL) was added to a solution of [AuCl(CNPy-2)] (0.168 g, 0.5 mmol) in CH_2Cl_2 (40 mL). Work up as for **14b** yielded 0.151 g (74%). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ 12.46 (br, 1H, NH^nBu), 9.91 (br, 1H, NHC$_5$H$_4$N), 8.21 (d, J = 5.0 Hz, 1H, NHC$_5H_4$N), 7.68 (tm, J = 8.3 Hz, 1H, NHC$_5H_4$N), 7.29 (m, J = 8.3 Hz, 1H, NHC$_5H_4$N), 7.05 (m, J = 6.4 Hz, 1H, NHC$_5H_4$N), 3.78 (q, J = 6.8 Hz, 2H, NHCH_2C$_3$H$_7$), 1.67 (m, 2H, NHCH$_2$C$_3H_7$), 1.41 (m, 2H, NHCH$_2$C$_3H_7$), 0.92 (t, J = 7.4 Hz, 3H, NHCH$_2$C$_3H_7$). Anal. Calcd for $C_{10}H_{15}AuClN_3$: C, 29.32; H, 3.69; N, 10.26. Found: C, 29.60; H, 3.29; N, 10.36.

[AuCl{C(NH^{i}Pr)(NHPy-2)}] (14d). Isopropylamine (0.5 mmol, 43 μL) was added to a solution of [AuCl(CNPy-2)] (0.168 g, 0.5 mmol) in CH_2Cl_2 (40 mL). Work up as for **14b** yielded 0.171 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ 12.32 (d, br, 1H, J = 6.5 Hz, NH^iPr), 9.76 (br, 1H, NHC$_5$H$_4$N), 8.21 (d, J = 5.3 Hz, 1H, NHC$_5H_4$N), 7.70 (tm, J = 6.7 Hz, 1H, NHC$_5H_4$N), 7.27 (d, J = 8.3 Hz, 1H, NHC$_5H_4$N), 7.05 (tm, J = 6.6 Hz, 1H, NHC$_5H_4$N), 4.38 (dsep, J = 8, 6.5 Hz, 1H, NHCH(CH$_3$)$_2$), 1.36 (d, J = 8.0 Hz. 6H, NHCH(CH_3)$_2$). Anal. Calcd for $C_9H_{13}AuClN_3$: C, 27.32; H, 3.31; N, 10.62. Found: C, 27.62; H, 3.06; N, 10.53.

[AuCl{C(NHC$_7$H$_{15}$)(NHPy-2)}] (14e). n-Heptylamine (0.15 mmol, 22.5 μL) was added to a solution of [AuCl(CNPy-2)] (0.051 g, 0.15 mmol) in CH_2Cl_2 (20 mL). Work up us for **14b** yielded 0.45 g (66%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ 12.46 (br, 1H, NHC$_7$H$_{15}$), 9.77 (br, 1H, NHC$_5$H$_4$N), 8.20 (d, J = 4.1 Hz, 1H, NHC$_5H_4$N), 7.71 (tm, J = 6.8 Hz, 1H, NHC$_5H_4$N), 7.25 (m, 1H, NHC$_5H_4$N), 7.06 (m, 1H, NHC$_5H_4$N), 3.78 (q, J = 6.3 Hz, 2H, NHCH_2C$_6$H$_{13}$), 1.69 (m, 2H, NHCH$_2$C$_6H_{13}$), 1.26 (m, 8H, NHCH$_2$C$_6H_{13}$), 0.84 (t, J = 5.2 Hz, 3H, NHCH$_2$C$_6H_{13}$). Anal. Calcd for $C_{13}H_{21}AuClN_3$: C, 34.56; H, 4.69; N, 9.30. Found: C, 34.75; H, 4.45; N, 9.14.

[{Trimethoxybenzonitrile}Au{C(NH^{t}Bu)(NHPy-2)}]SbF$_6$ (14f). A solution of [AuCl{C(NH^{t}Bu)(NHPy-2)}] (**14b**) (41 mg, 0.10 mmol) and 2,4,6-trimethoxybenzonitrile (59 mg, 0.30 mmol, 3 equiv) in dry CH_2Cl_2 (1 mL) was added over a solution of $AgSbF_6$ (35 mg, 0.10 mmol) in CH_2Cl_2 (0.6 mL). A white precipitate appeared immediately. After stirring for 5 min, the mixture was filtered (double HPLC Teflon filter). Addition of Et_2O (5 mL) led to the formation of the cationic complex as a white air stable precipitate which was filtered, washed with Et_2O (2 × 5 mL) and air-dried (50 mg, 62%). ^{1}H NMR (400 MHz, CD_3CN) δ 13.29 (br s, 1H), 9.27 (br s, 1H), 8.32−8.31 (m, 1H), 7.87−7.83 (m, 1H), 7.20 (dd, J = 6.9, 5.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.23 (s, 2H), 3.88 (s, 6H), 3.86 (s, 3H), 1.63 (s, 9H); HRMS-ESI: 567.1698; Calcd for $C_{20}H_{26}AuN_4O_3$: 567.1671; Anal. Calcd for $C_{20}H_{26}AuF_6N_4O_3Sb$: C, 29.91; H, 3.26; N, 6.98; Found: C, 30.03; H, 3.26; N, 6.98. IR (solid): ν(CN) = 2261 cm^{-1}.

[AuCl{C(NHMe)(NHPy-4)}] (15). $MeNH_2$ (0.95 mmol, 100 μL) was added to a solution of [AuCl(CNPy-4)] (0.252 g, 0.75 mmol) in dichloromethane (30 mL). Work up us for **14b** yielded 0.202 g (66%). ^{1}H NMR (300 MHz, Me_2CO-D_6, 295 K): δ 9.50 (br, 1H, NHC$_5$H$_4$N, minor), 8,93 (br, 1H, NHC$_5$H$_4$N), 8.56 (m, 5H, NHCH$_3$ + NHC$_5H_4$N), 7.78 (m, 2H, NHC$_5H_4$N), 7.71 (m, 2H, NHC$_5H_4$N, minor), 3.38 (s, 3H, NHCH_3), 3.12 (d, J 4.1, 3H, NHCH_3, minor). Anal. Calcd for $C_7H_9AuClN_3$: C, 22.87; H, 2.47; N, 11.43; Found: C, 22.86; H, 2.76; N, 11.29.

Catalytic Procedures. All reactions were carried out under N_2 in solvents dried using a solvent purification system (SPS). Thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234). Chromatography purifications were carried out using flash grade silica gel (SDS S-2 Chromatogel 60 ACC, 40−60 μm). NMR spectra were recorded at 23 °C on a Bruker Avance 400 Ultrashield. Compounds **16a**−**20b** tested in catalysis have been reported before.[5c]

General Procedure for Skeletal Rearrangement of 1,6-Enynes. Procedure with Catalysts 14a−**e and 15.** The enyne (0.15−0.2 mmol) and the gold(I) complex (2−5 mol%) were dissolved with stirring in a solution of $AgSbF_6$ in CH_2Cl_2 (2 mM,

2 mL; 2−5 mol% $AgSbF_6$). After the time indicated in Table 1 (monitored by TLC), the reaction was quenched with a drop of NEt_3 and then directly purified through a short column of silica (AcOEt/hexane) to give the corresponding compounds.

Procedure with the Cationic Complex 14f. The enyne (0.15−0.2 mmol) and the cationic gold(I) complex (2−5 mol%) were dissolved with stirring in CH_2Cl_2 (2 mL). After the time indicated in Table 1 (monitored by TLC), the reaction was quenched with 1 mL of a solution of NEt_3 (0.1 M) and then directly purified through a short column of silica (AcOEt/hexane) to give the corresponding compounds.

General Procedure for Methoxycyclizations of 1,6-Enynes. Procedure with Catalysts 14a-e and 15. The enyne (0.15−0.2 mmol) and the gold(I) complex (2−5 mol%) were dissolved with stirring in a solution of $AgSbF_6$ in MeOH (2 mM, 2 mL; 2−5 mol% $AgSbF_6$). After the time indicated in Table 2 (monitored by TLC), the reaction was quenched with a drop of NEt_3 and then directly purified through a short column of silica (AcOEt/Hexane) to give the corresponding compounds.

Procedure with the Cationic Complex 14f. The enyne (0.15−0.2 mmol) and the cationic gold(I) complex (2−5 mol%) were dissolved with stirring in MeOH (2 mL). After the time indicated in Table 2 (monitored by TLC), the reaction was quenched with 1 mL from a solution of NEt_3 (0,1 M) and then directly purified through a short column of silica (AcOEt/Hexane) to give the corresponding compounds or mixtures.

Experimental Procedure for X-ray Crystallography. Suitable single crystals of **14b** were obtained by layering hexane in a dichloromethane solution of the corresponding compound. Crystals were mounted in glass fibers, and diffraction measurements were made using a Bruker SMART CCD area-detector diffractometer with Mo−K_α radiation (l = 0.71073 Å).[24] Intensities were integrated from several series of exposures, each exposure covering 0.3° in w, the total data set being a hemisphere.[25] Absorption corrections were applied, based on multiple and symmetry-equivalent measurements.[26] The structures were solved by direct methods and refined by least-squares on weighted F^2 values for all reflections (see Table 3).[27] All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All the hydrogen atoms, including those involved in hydrogen bonding, were calculated with a riding model. Complex neutral-atom scattering factors were used.[28] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publications with the deposition number CCDC-696928. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.)+44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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Artículo II

Nitrogen Acyclic Gold(I) Carbenes: Excellent and Easily Accessible Catalysts in Reactions of 1,6-Enynes

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Nitrogen Acyclic Gold(I) Carbenes: Excellent and Easily Accessible Catalysts in Reactions of 1,6-Enynes

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Complexes [AuCl{C(NHR)(NHR′)}] and [AuCl{C(NHR)(NEt$_2$)}] (R = ^{t}Bu, *p*-Tol, Xylyl, *p*-C$_6$H$_4$-COOH, *p*-C$_6$H$_4$COOEt, R′ = Me, ^{n}Bu, ^{i}Pr, ^{n}heptyl, *p*-Tol) have been prepared by reaction of the corresponding isocyanogold complexes [AuCl(CNR)] with either primary amines or diethylamine. All the prepared carbenes are reactive and highly selective catalysts for skeletal rearrangement, methoxycyclization of 1,6-enynes, and other mechanistically related gold-catalyzed transformations. Overall, these easily accessible nitrogen acyclic carbene (NAC) gold complexes were not second to NHC complexes and were advantageous to obtain different products.

Introduction

The importance of gold complexes with nitrogen heterocyclic carbenes (NHCs) as catalysts in organic synthesis has been well demonstrated.[1−5]

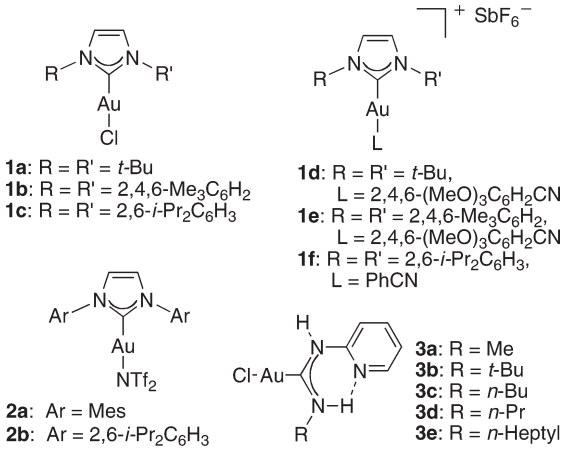

Figure 1. NHCs and HBHCs used as catalysts for skeletal rearrangement of enynes.

Many heterocyclic gold carbenes (Figure 1) have been found to be good precatalysts for reactions of enynes.[2,6−9] In these reactions, the catalyst is formed in solution from complexes such as **1a**−**c** after chloride abstraction with a silver salt. Alternatively, cationic complexes stabilized with benzonitrile ligands **1d**−**f** have also been used as catalysts.[10] Similar complexes with NTf$_2$ (Tf = trifluoromethanesulfonyl) as a labile ligand (**2a**,**b**),[11,12] are also catalytically active.

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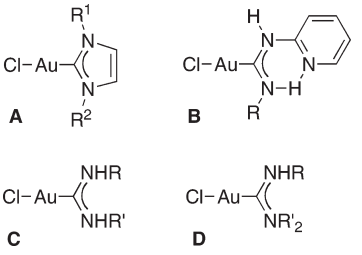


Figure 2. Gold(I) complexes with NHC (**A**), HBHC (**B**), and NAC (**C** and **D**) ligands.

The recently reported gold(I) carbene complexes of the type AuCl{C(NHR)-(NHPy-2)}][13] (**3**) also turned out to be good precatalysts in the skeletal rearrangement of enynes.[14] These carbenes have been called HBHCs (hydrogen bond supported heterocyclic carbenes) because the hydrogen-bonded cyclic structure (Figure 2, **B**) is maintained in solution.[13,14] These HBHCs also happened to catalyze efficiently the alkoxycyclization of enynes in alcohols as solvent.[14] As the intramolecular hydrogen bond is split in the presence of alcohols,[14] under the reaction conditions these catalysts should be acting as nitrogen acyclic carbene (NAC) gold complexes (Figure 2, **C** and **D**). This observation might be interesting for catalytic purposes because it is easier to prepare series of gold carbene complexes with a systematic variation of their steric and electronic properties in NAC than in NHC or HBHC systems. For this purpose, the rather general addition of primary or secondary amines to isocyanide gold complexes will yield the corresponding carbene gold complex combining the substituents provided by the two organic fragments.

Therefore, we decided to focus on the catalytic activity of nitrogen acyclic gold carbenes in the skeletal rearrangement, methoxycyclizations of 1,6-enynes, and mechanistically related processes, to compare the catalytic behavior of these NACs with the results obtained not only with the well-known NHCs but also with the recently reported HBHCs. For this purpose, we have synthesized different series of NAC gold(I) complexes of the type [AuCl{C(NHR)(NHR′)}] (Figure 2, **C**) or [AuCl{C(NHR)(NEt_2)}] (Figure 2, **D**) by nucleophilic addition of primary amines or diethylamine to isocyanogold complexes.

Results and Discussion

Synthesis and Structural Characterization of Gold Carbene Complexes. The neutral gold carbene catalysts **4**−**8** were synthesized by nucleophilic attack to gold alkyl or aryl isocyanide complexes [AuCl(CNR)] (R = *p*-C_6H_4COOH,[15] *p*-C_6H_4COOEt, ^{t}Bu,[16] *p*-Tol,[17] Xylyl[18]) with differently hindered primary amines or with a secondary amine such as diethylamine (Scheme 1). The starting isocyano-gold complexes had been previously reported, except [AuCl(CN*p*-C_6H_4COOEt)],

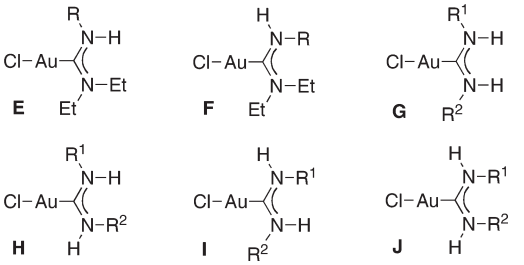
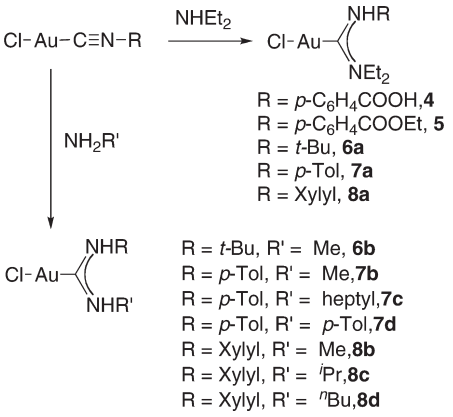


Figure 3. Possible stereoisomers for the NAC complexes.

Scheme 1. Synthesis of the Gold Carbene Derivatives



which was obtained from [AuCl(tht)] (tht = tetrahydrothiophene)[19] by substitution of tht with CN(*p*-C_6H_4-COOEt),[15] as reported for similar gold compounds.[20] The complexes [AuCl{C(NH^{t}Bu)(NEt_2)}][21] (**6a**) and [AuCl{C(NH*p*-Tol)(NH*p*-Tol)}][22] (**7d**) have already been published.

The gold NAC complexes were identified by elemental and spectroscopic analysis. The carbene C−N bond shows a considerable multiple character, which produces an important restriction to rotation and can give rise to stereoisomers (Figure 3).

Two stereoisomers (**E** and **F**) are possible for carbenes from secondary amines, but **F** looks clearly disfavored on the grounds of steric factors. In fact, for the latter, the less hindered **E** stereoisomer has been confirmed in the solid state by X-ray diffraction studies in the complexes [Au(C≡C*p*-R-C_6H_4){C(NH^{t}Bu)(NEt_2)}] (R = NO_2, *p*-NO_2-C_6H_4, (*E*)-CH=CH*p*-NO_2-C_6H_4),[23] [{AuC(NH^{t}Bu)(NEt_2)}$_2$-(μ-C≡CC_6H_4C≡C)],[24] [Au(*C*-acac){C(NH^{t}Bu)(NEt_2)}],[24] and [Au{C(NH^{t}Bu)(NEt_2)}{$CH_2S(O)Me_2$}]ClO_4,[24] whereas **F** has not been observed. The **E** stereoisomer was also confirmed in the solid state by X-ray diffraction studies, and in solution by NOE experiments, for the gold carbene complexes [AuCl{C(NEt_2)-(NHPy-2)}][13] and [AuR{C(NEt_2)(NHPy-4)}] (R = C_6F_5, Fmes).[25] Stereoisomer **E** is also the only one observed in this

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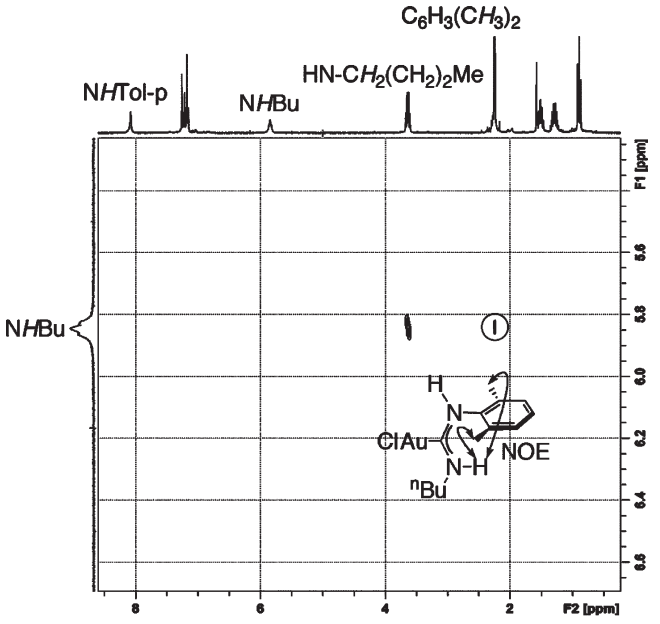


Figure 4. $^1H-^1H$ NOESY spectrum of **8d** (N*H*Bu region) registered at 295 K. The N*H*Bu shows a NOE with the methyl hydrogen atoms of the 2,6-xylyl group at 2.24 ppm (cross-peak in the circle), as well as with the hydrogen atoms of the contiguous methylene of the ^{n}Bu chain.

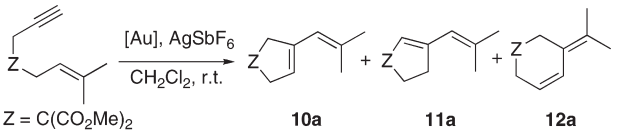
work in the ^1H NMR spectra of all the carbene gold complexes [AuCl{C(NHR)(NEt_2)}] (**4**, **5**, and **6a**−**8a**).

Up to four stereoisomers (**G**−**J**) are possible for complexes formed from primary amines. Often, more than one stereoisomer is observed, and these data are given in the Experimental Section. Although **J** is clearly the most disfavored for steric reasons, it is not easy to predict which of the other three stereoisomers should be preferred. The configuration of the major stereoisomer was assigned for all the complexes on the basis of NOE experiments (slow exchange was observed during the experiments at room temperature in some cases, and some NOE experiments were carried out at 243 K). Figure 4 shows the $^1H-^1H$ NOESY spectrum of **8d**, in which a NOE is observed between the hydrogen of the N*H*Bu group and the singlet of the methyl substituents of the 2,6-xylyl. The major stereoisomer for all the neutral complexes having at least one aryl group (R^1 = aryl; these are all, except **6b**) is stereoisomer **I**, having the aryl *anti* to the gold atom, regardless of R^2; moreover, **I** is the only stereoisomer observed for **8c** and **8d**. For complex **6b** (R^1 = ^{t}Bu; R^2 = Me) the major stereoisomer is **H**, with the bulky ^{t}Bu group *syn* to the gold atom.

Catalytic Reactions. The results obtained for the gold-catalyzed skeletal rearrangement of 1,6-enyne **9a** are summarized in Table 1. All the gold carbenes **4**−**8** catalyze this reaction, but the efficiency and selectivity observed change with the substituents of the carbene. Up to three different products have been isolated in the skeletal rearrangement reaction of **9a**: the product of exo cyclization, **10a**, the product of the endo cyclization, **12a**,[26] and the diene **11a** arising from the isomerization of the endo cyclic double bond of **10a**.[3a,c] Diene **11a** has been observed in reactions of **9a** catalyzed by $FeCl_3$ and as a minor product in reactions catalyzed by different Au(I) complexes.[3c] Then, in this

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

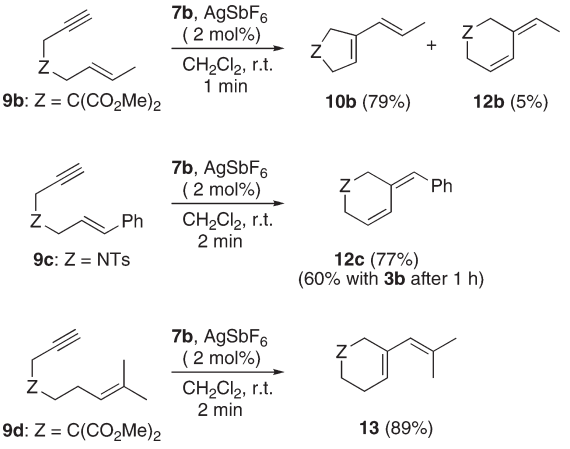
Table 1. Skeletal Rearrangement of Enyne 9a with the Series of Catalysts 4−8.[a]



entry	[Au]	product(s) (yield, %)
1	**4**	**10a** (74) + **11a** (6) + **12a** (2)[b]
2	**5**	**10a** (51) + **11a** (12)
3	**6a**	**10a** (81) + **12a** (2)[b]
4	**6b**	**10a** (35) + **11a** (21) + **12a** (1)[b]
5	**7a**	**10a** (50) + **11a** (15)
6	**7b**	**10a** (85) + **12a** (3)
7	**7b**	**10a** + **12a** (30:1) (88)[c]
8	**7c**	**10a** (98)
9	**7d**	**10a** (61) + **11a** (12)
10	**8a**	**10a** (100)
11	**8b**	**10a** (100)
12	**8c**	**10a** (8) + **11a** (17)
13	**8d**	**10a** (5) + **11a** (8)

[a] Reactions were carried out at room temperature with 2 mol % catalysts for 5 min. Yields were determined by GC. [b] Yield determined by ^1H NMR. [c] Isolated yield.

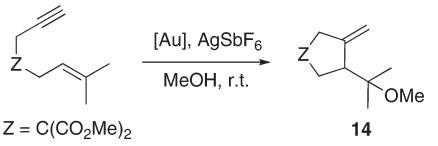
Scheme 2. Skeletal Rearrangements Catalyzed by 7b



respect, the new catalysts used here are more selective and are advantageous to obtain different products. Catalysts **6a**, **7b**, **7c**, **8a**, and **8b** give exclusively or almost exclusively the exo product **10a** (Table 1, entries 3, 6−11). Poor yields were observed using complexes **8c**,**d**, bearing bulkier substituents (Table 1, entries 12 and 13). Previous results using HBHC-Au(I) complexes **3a**−**e** as catalysts led also to **10a** and **12a** (≥30:1 ratio) in 73−89% yield.[14] All these results demonstrate that most NAC-Au(I) complexes are, at least, as reactive and selective as the previously reported more complex carbene-Au(I) complexes.

Additional experiments were performed with complex **7b** as catalyst using 1,6-enynes **9b**,**c** and 1,7-enyne **9d** as substrates (Scheme 2). Thus, the skeletal rearrangement of **9b** provided the exo product **10b** in 79% yield, along with 5% of the product of endo-type cyclization, **12b**, whereas **9c** led exclusively to exo **12c** in higher yield in much shorter reaction time than that using the HBHC-Au(I) catalyst **3b**. Rearrangement of 1,7-enyne **9d** was also fast, with catalyst **7b** leading to diene **13** in excellent yield. This result is comparable to that reported using the cationic catalyst

Table 2. Methoxycyclization of 1,6-Enyne 9a with the Series of Catalysts 4−8 and 1a−c[a]



entry	[Au]	time (h)	yield, %
1	**4**	2	85
2	**5**	2	74
3	**6a**	2	83
4	**6b**	2	65
5	**7a**	2	70
6	**7b**	2	83
7	**7c**	2	44
8	**7d**	2	72
9	**8a**	2	99
10	**8b**	2	92
11	**8c**	2	71
12	**8d**	2	85
13	**1a**	1.5	71
14	**1b**	5	87
15	**1c**	24	34

[a] Reactions were carried out at room temperature with 2 mol % catalyst for 2 h. Yields were determined by ^{1}H NMR.

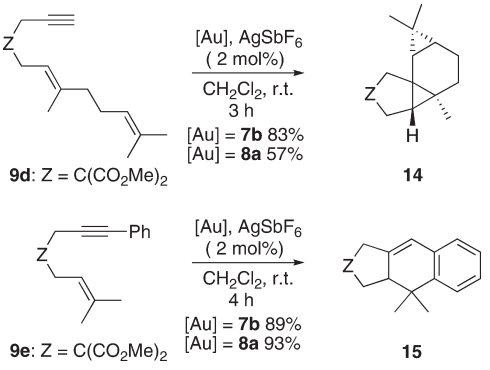
$[Au(PPh_3)(NCMe)]SbF_6$ (2 mol %), which led to **13** in 86% yield after 5 min.[27]

Reactions of 1,6-enynes in alcohols or water as solvent or cosolvent led to the cyclization of the enyne with concomitant addition of a molecule of the alcohol (alkoxy- or hydroxycyclization reaction).[3,28] Interestingly, although these processes are much slower than the skeletal rearrangements, no rearrangement is usually observed in the presence of alcohols, which suggests that the slower cyclization is due to the immediate in situ formation of complexes [AuL(ROH)]X, of lower catalytic activity, in which a molecule of alcohol or water strongly binds to the gold(I) center. These reactions are expected to show a higher dependence on the electronic and steric nature of the L ligands. Therefore, we studied the methoxycyclization of 1,6-enyne **9a** in pure methanol using the new complexes **4**−**8** as catalysts (Table 2). We also compared their performance with that of known catalysts **1a**−**c**.

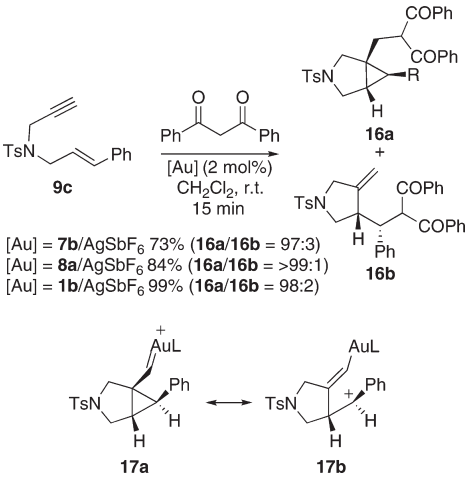
The cleanest reactions and better yields were obtained using catalysts **8a** and **8b** (Table 2, entries 9 and 10). The best NHC complexes **1a**−**c** do not outperform these results,[6a] and the HBHC-Au(I) complexes **3a**−**e** led to poorer yields (20−79%), even using 5 mol % catalyst.[14]

We also carried out the cyclization of dienyne **9d** using **7b** or **8a** and $AgSbF_6$ (Scheme 3). The cyclization led to the expected tetracyclic compound **14**[3a,29] in 83% and 57% yield, respectively. Under these conditions, less that 1% of the skeletal rearrangement product of **9d** was detected in the crude mixture. Skeletal rearrangement of **9d** was formed in significant amounts with some Au(I)- and Pt(II)-phosphine complexes.[29] Similarly, the [4+2] cycloaddition of **9e** proceeded smoothly at room temperature with **7b** or **8a** as precatalysts to give **15** in very good yields, comparable to those obtained under similar conditions using phosphine-Au(I) complexes.[6]

Scheme 3. Cyclization Reactions Catalyzed by 7b and 8a



Scheme 4. Reactions of 1,6-Enyne 9c with Dibenzoylmethane



Finally, we probed the site selectivity of the gold(I) complexes bearing NAC ligands in the reaction of 1,6-enyne **9c** with dibenzoylmethane as the nucleophile to give adducts **16a** and/or **16b** (Scheme 4). We have recently found that the site of nucleophilic attack on intermediate **17** depends on the nature of the L ligand[10] and reflects the dual character, carbene-like or carbocationic, of the intermediates involved in the cyclizations of enynes.[30,31] Thus, a highly electrophilic complex bearing a bulky phosphite ligand gave preferentially **16b** (up to 95:5 ratio) as a result of the attack at the cationic center of **17b**, whereas exclusive attack at the carbene carbon yielding **16a** occurred using the complex **1b** with the IMes ligand.[10] A complex with a bulky dialkylbiarylphosphine ligand, which is of intermediate electrophilicity, gave a 2:1 mixture of **16a** and **16b**.[10] Therefore, we decided to probe the site selectivity of gold(I) catalysts bearing NAC ligands in

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(28) (a) Nevado, C.; Charruault, 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. (b) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J. P. *Chem. Commun.* **2004**, 850–851. (c) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J. P.; Michelet, V. *Synlett* **2007**, 1780–1784. (d) Chao, C.-M.; Toullec, P. Y.; Michelet, V. *Tetrahedron Lett.* **2009**, *50*, 3719–3722. (e) Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538–545.

(29) 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.

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

(31) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.III; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482–486.

this reaction. In the event, using complexes **7b** and **8a**, adduct **16a** was obtained with high regioselectivity. The results obtained with **8a** are better than those with **1b** and as good as those obtained with the cationic complex obtained from **1b**, [Au(IMes)(2,4,6-$(MeO)_3C_6H_2CN$)]SbF_6, which were the best so far.[10] These results reflect the highly electron-donating character of the NAC, which leads to cyclization of enynes through intermediates that show a significant gold-carbene character.

Conclusions

The modern development of fascinating isolable NHC ligands and the catalytic properties of their complexes have somehow obscured so far the existence of the old, known nitrogen acyclic carbene complexes (NACs). The latter can be easily obtained from widespread isocyanide complexes of transition metals and primary or secondary amines. An advantage of this classic methodology over the NHCs is that, at least for late transition metals, it provides an easy way to obtain organized series of catalysts from a single isocyanide complex precursor, by varying the amine. Moreover, these catalysts will contain carbene ligands that are not otherwise accessible because they do not exist as free molecules.

We have shown here that these easily accessible NACs complexes are interesting catalysts that have been disregarded in favor of the more fashionable NHC complexes but, at least for some purposes, perform as efficiently as the latter. Actually, complexes [AuCl{C(NHR)(NHR′)}] and [AuCl{C(NHR)(NEt_2)}] with acyclic carbene ligands (NAC ligands) show a reactivity as catalysts in reactions of 1,6- and 1,7-enynes comparable to or higher than that displayed by gold(I) complexes with N-heterocyclic ligands. In methanol, these new NAC gold complexes are more reactive than those with hydrogen bond supported heterocyclic carbenes (HBHC). The complexes [AuCl{C(NHMe)(NH*p*Tol)}] (**7b**) and [AuCl{C(NEt_2)(NHXylyl)}] (**8a**) have proved particularly efficient.

It looks reasonable that this type of metal complexes of NAC ligands should be incorporated in the armory of metal-catalyzed reactions.

Experimental Section

General Conditions. All reactions were carried out under dry N_2. The solvents were purified according to standard procedures.[32] Enynes **9a**−**d** were prepared according to literature procedures.[3,26] The other reagents are commercially available. Infrared spectra were recorded in Perkin-Elmer 883 or 1720X equipment. NMR spectra were recorded with Bruker AC300, ARX 300, and Avance 400 Ultrashield instruments. ^{1}H NMR spectra are referred to TMS. Elemental analyses were performed with a Perkin-Elmer 2400B microanalyzer.

Synthesis of Carbenes. [AuCl{C(NH(*p*-C_6H_4COOH)-(NEt_2)}] (4). $HNEt_2$ (0.32 mmol, 33 μL) was added to a solution of [AuCl(CN*p*-C_6H_4COOH)] (120 g, 0.32 mmol) in THF (30 mL). After 15 min of stirring at room temperature, the solution did not show *ν*(CN) IR absorption. The volatiles were removed, and the white residue was washed with *n*-hexane to remove the excess of amine and crystallized from CH_2Cl_2/*n*-hexane. The white solid obtained was washed with *n*-hexane (3 × 5 mL) and vacuum-dried, yielding 0.134 g (92%). ^{1}H NMR (300 MHz, acetone-d_6): δ 9.35 (br s, 1H, NH), 8.03 (d, *J* = 8.8 Hz, 2H, ArH), 7.69 (d, *J* = 8.6 Hz, 2H, ArH), 4.09 (q, *J* = 7.1 Hz, 2H, CH_2), 3.75 (q, *J* = 7.2 Hz, 2H, CH_2), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3), 1.33 (t, *J* = 7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{12}H_{16}AuClN_2O_2$: C, 31.84; H, 3.56; N, 6.19. Found: C, 32.01; H, 3.46; N, 6.01.

[AuCl{C(NH(*p*-C_6H_4COOEt)(NEt_2)}] (5). $HNEt_2$ (1.32 mmol, 136 μL) was added to a solution of [AuCl(CN*p*-C_6H_4COOEt)] (0.540 g, 1.32 mmol) in CH_2Cl_2 (30 mL). Workup for **4** yielded 0.472 g (98%). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.00 (AA′ part of a AA′BB′ system, 2H, ArH), 7.85 (br s, 1H, NH), 7.61 (BB′ part of a AA′BB′ system, 2H, ArH), 4.36 (q, *J* = 7.0 Hz, 2H, CH_2), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 3.51 (q, *J* = 7.1 Hz, 2H, CH_2), 1.40 (t, *J* = 7.0 Hz, 3H, CH_3), 1.33−1.30 (m, 6H, CH_3). Anal. Calcd for $C_{14}H_{20}AuClN_2O_2$: C, 34.98; H, 4.19; N, 5.83. Found: C, 35.32; H, 4.25; N, 6.01.

[AuCl{C(NH^{t}Bu)(NHMe)}] (6b). $MeNH_2$ (2.50 mmol, 110 μL, 40% solution in water) was added to a solution of [AuCl(CN^{t}Bu)] (0.200 g, 0.633 mmol) in CH_2Cl_2 (30 mL). Workup for **4** yielded 0.140 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (br s, 1H, NH major), 6.68 (br s, 1H, NH minor), 6.30 (br s, 1H, NH minor), 5.96 (br, 1H, N*H*Me, major), 3.24 (d, *J* = 5.2 Hz, 3H, CH_3 minor), 2.78 (d, *J* = 5.2 Hz, 3H, CH_3), 1.61 (s, 9H, $C(CH_3)_3$), 1.57 (s, 9H, $C(CH_3)_3$ minor). Stereoisomeric ratio: 4:1. Anal. Calcd for $C_6H_{14}AuClN_2$: C, 20.79; H, 4.07; N, 8.08. Found: C, 21.20; H, 3.80; N, 7.92.

[AuCl{C(NEt_2)(NHTol-*p*)}](7a). Et_2NH (0.60 mmol, 62 μL) was added to a solution of [AuCl(CNTol-*p*)] (0.175 g, 0.50 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.189 g (89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (br, 1H, N*H*$C_6H_4CH_3$), 7.34 (d, *J* = 8.3 Hz, 2H, NH$C_6H_4CH_3$), 7.14 (d, *J* = 7.9 Hz, 2H, NH$C_6H_4CH_3$), 4.01 (q, *J* = 7.2 Hz, 2H, N(CH_2CH_3)$_2$), 3.47 (q, *J* = 7.2 Hz, 2H, N(CH_2CH_3)$_2$), 2.32 (t, *J* = 7.2 Hz, 6H, N(CH_2CH_3)$_2$) Anal. Calcd for $C_{12}H_{18}AuClN_2$: C, 34.10; H, 4.29; N, 6.63. Found: C, 33.81; H, 4.03; N, 6.25.

[AuCl{C(NHMe)(NHTol-*p*)}] (7b). $MeNH_2$ (0.75 mmol, 65 μL, 40% solution in water) was added to a solution of [AuCl(CNTol-*p*)] (0.193 g, 0.50 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.068 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (br s, 1H, N*H*, major), 7.69 (br s, 1H, N*H*, minor), 7.44−6.89 (m, 3H, arom, major, 3H, arom, minor, 1H, N*H*, minor), 6.33 (br, 1H, N*H*Me, major), 3.24 (d, *J* = 4.6 Hz, 3H, CH_3, major), 2.97 (d, *J* = 5.2 Hz, 3H, CH_3, minor), 2.37 (s, 3H, Ar-CH_3, major), 2.31 (s, 3H, Ar-CH_3, minor). Stereoisomeric ratio: 2:1. Anal. Calcd for $C_9H_{12}AuClN_2$: C, 28.40; H, 3.18; N, 7.36; Found: C, 28.94; H, 2.80; N, 7.32.

[AuCl{C(NHC$_7$H$_{15}$)(NHTol-*p*)}] (7c). *n*-Heptylamine (0.75 mmol, 112 μL) was added to a solution of [AuCl(CNTol-*p*)] (0.175 g, 0.5 mmol) in CH_2Cl_2 (40 mL). Workup as for **4** yielded 0.168 g (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (br, 1H, N*H*, minor 1), 8.00 (br, 1H, N*H*Tol-*p*), 7.67 (br, 1H, N*H*, minor 2), 7.44 (d, *J* = 5.7 Hz, 2H, NH$C_6H_4CH_3$, minor 1), 7.40 (d, *J* = 6.0 Hz, 2H, NH$C_6H_4CH_3$, minor 2), 7.27 (d, *J* = 6.2 Hz, 2H, NH$C_6H_4CH_3$), 7.15 (d, *J* = 6.0 Hz, 2H, NH$C_6H_4CH_3$, minor 2), 7.11 (d, *J* = 5.7 Hz, 2H, NH$C_6H_4CH_3$, minor 1), 7.08 (d, *J* = 6.2 Hz, 2H, NH$C_6H_4CH_3$), 6.98 (br, 1H, N*H*, minor 1 + minor 2), 6,37 (br, 1H, N*H*C_7H_{15}), 3.73 (br, 2H, NHC$H_2C_6H_{13}$, minor), 3.66 (q, *J* = 6.3 Hz, 2H, NHC$H_2C_6H_{13}$), 3.22 (q, *J* = 6.2 Hz, 2H, NHC$H_2C_6H_{13}$, minor), 2.38 (s, 3H, NH$C_6H_4CH_3$), 2.30 (s, 3H, NH$C_6H_4CH_3$, minor), 2.25 (s, 3H, NH$C_6H_4CH_3$, minor), 1.58 (m, 2H, NHC$H_2C_6H_{13}$), 1.27 (m, 8H, NHC$H_2C_6H_{13}$), 0.87 (t, *J* = 5.2 Hz, 3H, NHC$H_2C_6H_{13}$). Stereoisomeric ratio: 10:1:2. Anal. Calcd for $C_{15}H_{24}AuClN_2$: C, 38.76; H, 5.20; N, 6.03. Found: C, 39.10; H, 4.80; N, 6.19.

[AuCl{C(NHTol-*p*)(NHTol-*p*)}] (7d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (br, 2H, N*H*Tol-*p*, minor), 8.73 (br, 1H, N*H*Tol-*p*, major), 7.99 (8.73 (br, 1H, N*H*Tol-*p*, major), 7.50 (d, *J* = 8.0 Hz 4H, NH$C_6H_4CH_3$, minor), 7.35 (d, *J* = 8.2 Hz, 2H, NH$C_6H_4CH_3$), 7.31 (d, *J* = 8.2 Hz, 2H, NH$C_6H_4CH_3$), 7.20 (d, *J* = 7.9 Hz, 2H, NH$C_6H_4CH_3$), 7.11 (m, 2H, NH$C_6H_4CH_3$, major + 4H, NH$C_6H_4CH_3$, minor), 2.40 (s, 3H, NH$C_6H_4CH_3$,

(32) Perrin, D. D.; Armarego, W. F. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988.

major), 2.30 (s, 3H, $NHC_6H_4CH_3$, major), 2.27 (s, 6H, $NHC_6H_4CH_3$, minor). Stereoisomeric ratio: 10:1.

[**AuCl{C(NHXylyl)(NEt$_2$)}**] (**8a**). $HNEt_2$ (1.098 mmol, 161 μL) was added to a solution of [AuCl(CNXylyl)] (0.200 g, 0.549 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.190 g (79%). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.47 (br s, 1 H, N*H*), 7.21−7.05 (m, 3H ArH),), 4.02 (q, J = 7.2 Hz, 2H, CH_2), 3.50 (q, J = 7.3 Hz, 2H, CH_2), 2.24 (s, 6H, Ar-CH_3), 1.36 (t, J = 7.3 Hz, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{13}H_{20}AuClN_2$: C, 35.75; H, 4.62; N, 6.41. Found: C, 35.74; H, 4.22; N, 6.53.

[**AuCl{C(NHXylyl)(NHMe)}**] (**8b**). $MeNH_2$ (1.098 mmol, 95 μL, 40% solution in water) was added to a solution of [AuCl(CNXylyl)] (0.200 g, 0.549 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.163 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (br s, 1H, N*H*, minor 1), 7.67 (br s, 1H, N*H*, major), 7.28−7.05 (m, 3H, major, 6H, minor 1, 6H, minor 2, 1H, N*H*, minor 2), 5.83 (br, 1H, N*H*Me, major), 5.70 (br, 1H, N*H*Me, minor 1), 5.08 (br, 1H, N*H*Me, minor 2), 3.24 (d, J = 4.7 Hz, 3H, C*H*$_3$, major), 3.13 (d, J = 4.7 Hz, 3H, C*H*$_3$, minor 1), 3.06 (d, J = 4.7 Hz, 3H, C*H*$_3$, minor 2), 2.34 (s, 6H, Ar-C*H*$_3$, minor 1), 2.28 (s, 6H, Ar-C*H*$_3$, minor 2), 2.24 (s, 6H, Ar-C*H*$_3$, major). Stereoisomeric ratio: 5:1:1. Anal. Calcd for $C_{10}H_{14}AuClN_2$: C, 30.43; H, 3.58; N, 7.10. Found: C, 30.93; H, 3.48; N, 6.91.

[**AuCl{C(NHXylyl)(NH^{i}Pr)}**] (**8c**). ^{i}PrNH$_2$ (0.825 mmol, 71 μL) was added to a solution of [AuCl(CNXylyl)] (0.200 g, 0.55 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.197 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (br s, 1H NH), 7.26 (t, J = 6.2 Hz, 1H, ArH), 7.17 (d, J = 6.7 Hz, 2H, ArH), 5.57 (br d, J = 8.9 Hz, 1H, N*H*^{i}Pr), 4.49 (m, 1H, CH), 2.23 (s, 6H, Ar-CH_3), 1.17 (d, J = 6.6 Hz, 6H, CH_3). Anal. Calcd for $C_{12}H_{18}AuClN_2$: C, 34.10; H, 4.29; N, 6.63. Found: C, 34.52; H, 4.05; N, 6.87.

[**AuCl{C(NHXylyl)(NHBu)}**] (**8d**). $BuNH_2$ (0.824 mmol, 82 μL) was added to a solution of [AuCl(CNXylyl)] (0.150 g, 0.412 mmol) in CH_2Cl_2 (30 mL). Workup as for **4** yielded 0.091 g (51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (br s, 1H N*H*Xylyl), 7.27−7.16 (m, 3H, ArH), 5.86 (br, 1H, N*H*Bu), 3.64 (q, J = 7.1 Hz, 2H, CH_2), 2.24 (s, 6H, Ar-CH_3), 1.52 (q, J = 6.8 Hz, 2H, CH_2), 1.33−1.25 (m, 4H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{13}H_{20}AuClN_2$: C, 35.75; H, 4.62; N, 6.41. Found: C, 35.59; H, 4.14; N, 6.16.

Catalytic Procedures. All the reactions were carried out under N_2 in solvents dried using a solvent purification system. Thin-layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234). Chromatography purifications were carried out using flash grade silica gel (SDS S-2 Chromatogel 60 ACC, 40−60 μm). NMR spectra were recorded at 25 °C on a Bruker Avance 400 Ultrashield. Compounds **9a**−**14** tested in catalysis have been reported before.[3c]

General Procedure for Skeletal Rearrangement of 1,6-Enynes. Procedure with Catalysts 4−8. The enyne (0.15−0.2 mmol) and the gold(I) complex (2−5 mol %) were dissolved with stirring in a solution of $AgSbF_6$ in CH_2Cl_2 (2 mM, 2 mL; 2−5 mol % $AgSbF_6$). After the indicated time (monitored by TLC), the reaction was quenched with a solution of Et_3N in hexanes (0.1 M, 2 mL) and filtered through a pad of silica gel that was eluted with Et_2O. Isolated products were purified by flash column chromatography (EtOAc/hexane).

General Procedure for Methoxycyclizations of 1,6-Enynes. Procedure with Catalysts 4−8. The enyne (0.15−0.2 mmol) and the gold(I) complex (2 mol %) were dissolved with stirring in a solution of $AgSbF_6$ (2 mol %) in MeOH (2 mM, 2 mL). After 5 min, the reaction was quenched with a solution of Et_3N in hexanes (0.1 M, 2 mL) and filtered through a pad of silica gel that was eluted with Et_2O. Isolated products were purified by flash column chromatography (EtOAc/hexane).

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Artículo III

Exploring the Scope of Nitrogen Acyclic Carbenes (NACs) in Gold-Catalyzed Reactions

*Camino Bartolomé, Domingo García-Cuadrado, Zoraida Ramiro, and Pablo Espinet**

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Exploring the Scope of Nitrogen Acyclic Carbenes (NACs) in Gold-Catalyzed Reactions

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The catalytic activity of the recently reported nitrogen acyclic carbene (NAC) complexes of gold(I) has been investigated and compared with the reported activity of other gold(I) and gold(III) complexes. The complexes studied, [AuCl{C(NEt_2)(NHTol-*p*)}], [AuCl{C(NEt_2)(NHXylyl)}], and [Au(NTf_2){C(NEt_2)(NHXylyl)}], are very active in processes such as the rearrangement of homopropargylsulfoxides, the intramolecular hydroamination of *N*-allenyl carbamates, the intramolecular hydroalkoxylation of allenes, the hydroarylation of acetylenecarboxylic acid ester, and the benzylation of anisole. Although the NAC ligands have not been optimized for the reactions tested, the yields obtained are usually similar and sometimes better than those reported with other catalysts, showing that the presence of N−H bonds and the wider N−C−N angle in the NAC (as compared to the NHC) complexes are not detrimental for the catalysis. For the hydroarylation reaction (where two competing products can be formed), the NAC complexes allow favoring one over the other. For the benzylation of anisole the selectivity is complementary to that obtained using H[$AuCl_4$] as catalyst, and depending on the substrate, the NAC gold(III) complexes outperform the activity of H[$AuCl_4$]. On average, the reactivity found suggests that the basicity of NACs toward gold(I) is very similar to that of NHCs and higher than that of phosphines.

Introduction

In contrast to the scarce attention paid just twenty years ago to gold complexes as catalysts, they are now recognized as very active compounds in many organic transformations.[1] Much research in the topic has been carried out on classical complexes with phosphine ligands, but in the last years nitrogen heterocyclic carbene ligands (NHCs) have gained attention,[2] because, as an advantage on phosphines, they are not prone to oxidation. Moreover, recently, Bertrand et al. have successfully used very interesting cationic gold(I) complexes with five-membered cyclic (alkyl)(amino)-carbene (CAAC) ligands as catalysts in some organic transformations.[3]

To the widely used NHC catalysts and the much less exploited CAACs, we recently added two other carbene types, the so-called hydrogen-bonded heterocyclic complexes (HBHCs)[4,5] and the nitrogen acyclic complexes (NACs),[6] both shown in Scheme 1. Although gold(I) complexes of the NAC type have been long known,[7−9] they had never been applied in catalysis previous to our works showing their high catalytic activity in the skeletal rearrangement and in the alkoxycyclization of 1,6-enynes.[5,6,10]

As we showed by NMR in our previous works,[5,6] depending on the ability of the solvent to break the intramolecular

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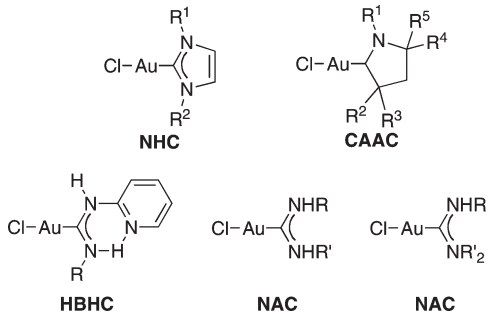
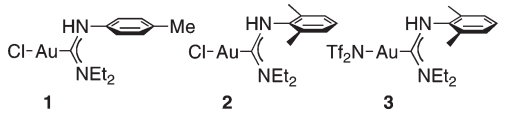
Scheme 1. Types of Gold(I) Carbene Complexes

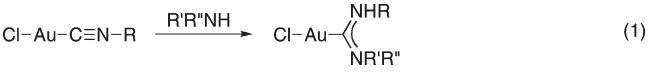


Scheme 2. Types of Carbene Gold(I) Complexes



hydrogen bond in HBHCs, these are structurally similar (cyclic) to the NHC carbenes (in acetone or CH_2Cl_2) or become similar to the NACs in solvents where the intramolecular hydrogen bond has been split (in MeOH). The fact that the HBHC gold complexes were similarly active in methoxycyclization of enynes, where their cyclic structure is broken,[5] and in cyclization reactions in CH_2Cl_2, where its cyclic structure is preserved, suggested that, except for the possible influence in the spatial arrangement of the substituents, the cyclic or acyclic structure of the carbene is not a crucial difference. In fact both types of gold complexes (NACs and HBHCs) showed similar catalytic activity.[5,6]

The HBHC ligands require the cumbersome low-yield synthesis of 2-pyridyl isocyanide, but the easy synthesis of NAC metal complexes by simple nucleophilic attack of amines to gold(I) isocyanide complexes (even from commercial isocyanides and amines) (eq 1)[11] makes NAC advantageous over NHC complexes to produce a series of gold catalysts and easily tune their electronic and steric characteristics.



(1)

However, these NAC complexes (also the HBHCs) have two peculiar features that make them different from the NHCs: (i) In the absence of structural distortions by the substituents, the N−C−N angle at the carbene atom should be about 60°, compared to about 72° for the NHCs, which means that, for similar electronic influences by the substituents, the expected order of carbene basicity should be NACs < NHCs.[12] (ii) Due to the method of synthesis, the coordinated carbenes have at least one (for secondary amines) or two (for primary amines) active N−H hydrogen atoms, which might interfere for some applications. These two features could be detrimental for the activity of NACs catalysts, so we decided to examine their scope of application by examining their performance, compared to the best results found in several reported gold-catalyzed processes.

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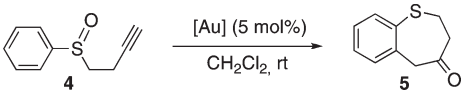
Table 1. NAC Gold-Catalyzed Rearrangement of Homopropargylsulfoxide



entry	[Au]	AgX	yield [%]
1	**1**	$AgSbF_6$	62[a]
2	**1**	$AgNTf_2$	75[a]
3	**2**	$AgNTf_2$	82[a]
4	**2**	$AgSbF_6$	76[a]
5	**3**		60[a]
6	$[AuCl(PPh_3)]$	$AgSbF_6$	30[a] (34[b])
7	$[AuCl(PPh_3)]$	$AgNTf_2$	30[a]
8	$[AuCl(P(p\text{-}CF_3C_6H_4)_3)]$	$AgSbF_6$	25[b]
9	[AuCl(IMes)]	$AgSbF_6$	76[a] (94[b])
10	[AuCl(IMes)]	$AgNTf_2$	77[a]
11	$[AuCl_2(N{-}O)]$[c]		93

[a] Our result, ^1H NMR yield. [b] Literature, isolated yield, see ref 16. [c] See ref 15.

This should give us information about the feasibility of application of the NAC-type carbenes in gold catalysis and about the actual nucleophilicity of this structural type of carbenes compared to other ligands used in gold(I) catalysis.

Results and Discussion

Complexes **1** and **2** have been reported before[6] and were chosen for the tests because they had been found particularly efficient and highly selective in the skeletal rearrangement and methoxycyclization of 1,6-enynes (Scheme 2).[6] Complex **3**, with the weakly coordinated counteranion bis(trifluoromethanesulfonyl)imidate, was synthesized by reaction of the neutral gold(I) carbene **2** with $AgNTf_2$,[13] affording in good yield a white and fairly stable solid.

The catalytic reactions chosen to test the activity of the NAC gold(I) complexes were carried out under the standard conditions used for the reported references (this means that the performance with NACs was not optimized) and, except for $[Au(NTf_2)\{C(NEt_2)(NHXylyl)\}]$ (**3**), adding a silver salt to extract the chloride *in situ* to allow for the coordination of the substrate to the Au center.[14]

1. Rearrangement of Homopropargylsulfoxides. Zhang and Li have demonstrated that dichloro(pyridine-2-carboxylato)gold(III) is active for this reaction in the absence of a silver salt (Table 1, entry 11).[15] With gold(I), Saphiro and Toste have reported that phosphine complexes [AuClL] (L = PPh_3, $P(p\text{-}CF_3C_6H_4)_3$) are active catalysts for the rearrangement of the homopropargylsulfoxide **4** to 1-benzothiepin-4-one **5** in the presence of $AgSbF_6$.[16] However, the yield obtained with PPh_3 was low (34%, Table 1, entry 6[b]), and it was even worse with the poorer donor phosphine $P(p\text{-}CF_3C_6H_4)_3$ (25%, Table 1, entry 8).[16] In our hands (entries 6[a] and 7), similar poor results have been obtained by using $[AuCl(PPh_3)]$ and $AgNTf_2$ instead of $AgSbF_6$ (Table 1, entry 7).

(13) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.

(14) The reactions in the literature have been repeated in our lab, as suggested by one reviewer, for better comparison. When there is a significant difference, both results are given in the tables.

(15) Zhang, L.; Li, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159.

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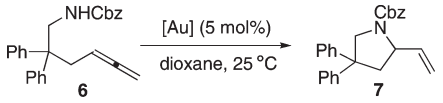
Table 2. NAC Gold-Catalyzed Intramolecular *exo*-Hydroamination of *N*-Allenyl Carbamate



entry	[Au]	AgX	yield [%]
1	**2**	AgOTs	92[a]
2	**3**		78[a]
3	[AuClP(*t*-Bu)$_2$(*o*-biphenyl)]	AgOTf	95[b]

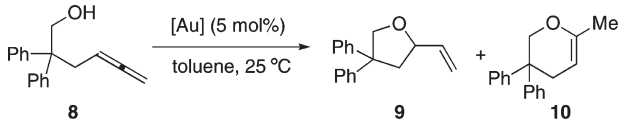
[a] Our result, isolated yield. [b] Literature, ref 18.

The better donor NHC ligand IMes was reported by Toste to afford 94% yield (Table 1, entry 9[b]);[16] in the same reaction conditions, our yield calculated by ^{1}H NMR was not as high, whether with $AgSbF_6$ or with $AgNTf_2$ as chloride scavenger (entries 9[a] and 10). The results obtained with **1**−**3**, shown in Table 1, are in the range of activity of their analogous NHC (somewhat better or worse depending on the experiment reference (our own or the data in the literature), which is consistent with the presumption that NACs should be in the order of basicity of NHCs, maybe a bit less basic than them. Under the same conditions NAC complexes compare favorably with phosphines, as expected.[17] Thus, the yields in this reaction seem to follow the order of basicity of the ligand.

2. Intramolecular Hydroamination of *N*-Allenyl Carbamates. As nitrogen and oxygen heterocycles are a part of the structure of a wide range of biologically active systems, the design of new catalysts for the synthesis of heterocyclic compounds is a very attractive field. The gold(I)-catalyzed intramolecular hydroamination of *N*-allenyl carbamates such as **6** (Table 2) has been reported with an equimolecular mixture of [AuClP(*t*-Bu)$_2$(*o*-biphenyl)] and AgOTf (Table 2, entry 3) and is very selective toward *exo*-hydroamination.[18] We find that the NAC gold(I) complexes **2** and **3** are also very active catalysts for this *exo*-hydroamination. When a mixture of **2** and AgOTs was used, the hydroamination of the allenyl carbamate **6** led to isolation of 2-vinylpyrrolidine **7** in 92% yield (Table 2, entry 1), similar to the yield reported using [AuClP(*t*-Bu)$_2$(*o*-biphenyl)] as precatalyst and AgOTf. The reaction carried out using **3** as catalyst with NTf_2 as ligand was about as effective (Table 2, entry 2).

3. Intramolecular *exo*-Hydroalkoxylation of Allenes. NAC gold(I) complexes are also active catalysts in the intramolecular hydroalkoxylation of 2,2-diphenyl-4,5-hexadienol **8**. Widenhoefer et al. reported that the regioselectivity of this reaction has a very strong dependence on the counterion.[18] For instance, the reaction carried out using a mixture of [AuClP(*t*-Bu)$_2$(*o*-biphenyl)] and AgOTf had a very low regioselectivity (Table 3, entry 3), producing a 1.3:1 mixture of tetrahydrofuran **9** and dihydropyran **10** in 85% yield; however, the same reaction using AgOTs instead of AgOTf to extract the chloride was highly regioselective, again in favor of the *exo*-hydroalkoxylation product **9** (Table 3, entry 4). In the presence of AgOTs, the NAC complex **2** was not only very efficient for the hydroalkoxylation but also highly selective toward **9** (Table 3, entry 1). The reaction using **3**, with the labile ligand NTf_2, afforded lower yields,

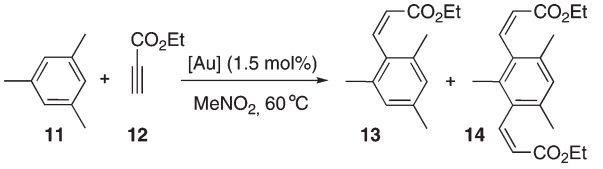
Table 3. NAC Gold-Catalyzed Intramolecular Hydroalkoxylation of 2,2-Diphenyl-4,5-hexadienol



entry	[Au]	AgX	Yield [%]
1	**2**	AgOTs	94/< 1[a]
2	**3**		45/< 1[a]
3	[AuClP(*t*-Bu)$_2$(*o*-biphenyl)]	AgOTf	48/37[b]
4	[AuClP(*t*-Bu)$_2$(*o*-biphenyl)]	AgOTs	91[c]

[a] Isolated yield. [b] Yield determined by GC analysis vs internal standard (see ref 18). [c] Isolated yield in ref 18.

Table 4. NAC Gold-Catalyzed Hydroarylation of Acetylenecarboxylic Acid Ester



entry	[Au]	AgX	Yield [%]
1	**2**	$AgNTf_2$	76/7[a]
2	**3**		78/7[a]
3	[AuCl(PEt$_3$)]	AgOTf	67/20[b]
4	[AuCl(PPh$_3$)$_3$)]	$AgBF_4$	63/6[a] (57/16[c])
5	[AuCl(PPh$_3$)$_3$)]	$AgSbF_6$	77/7[a]

[a] Our results, ^{1}H NMR yield. [b] Reaction run at 25 °C, 5% mol of catalyst. Yield determined by GC analysis vs internal standard (see ref 19.). [c] Reaction run at 60 °C with 5% mol of catalyst. Yield determined by GC analysis vs internal standard (see ref 19).

but with high regioselectivity toward the *exo*-hydroalkoxylation product **9**.

4. Intermolecular Hydroarylation of Alkynes. The formation of C−C bonds as a result of the activation of an aromatic C−H bond is an interesting alternative to the use of halogenated derivatives. Reetz and Sommer have reported that [AuCl(PR$_3$)] (R = Et, Ph) are active precatalysts in the intermolecular hydroarylation of alkynes.[19] The reactions of mesitylene **11** with the electron-poor alkyne **12**, catalyzed with [AuCl(PR$_3$)] and a silver salt (Table 4, entries 3−5), produced the desired product **13** in moderate yields. Although high *Z*-selectivity was obtained in both cases, considerable percentages of the second alkyne addition product **14** were also formed. In this case both the NAC precatalyst **2** (with an equimolecular amount of $AgNTf_2$) and catalyst **3** were apparently more active and more chemoselective than the phosphine complexes used in the original paper, leading to the formation of **13** in better yields and with a much lower percentage of **14** (Table 4, entries 1 and 2). However, repeating the reactions with PPh_3 and analyzing the results by ^{1}H NMR, we found that the results with both types of ligand are very similar in our hands.

5. Benzylation of Arenes. Beller et al. have reported that H[AuCl$_4$] is active in the benzylation of arenes and heteroarenes.[20]

(17) Phosphines have been ranked as less basic than NHCs in ref 12.
(18) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073.
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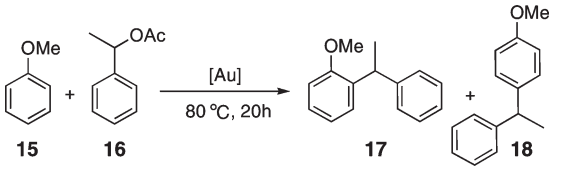
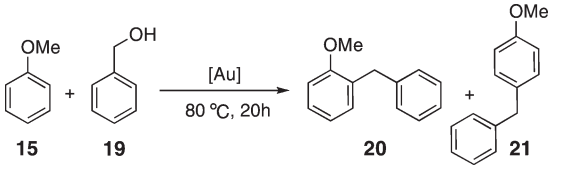
Table 5. NAC Gold-Catalyzed Benzylation of Anisole with 1-Phenylethyl Acetate



entry	[Au]	AgX	yield [%] (ratio)
1	**1**	$AgNTf_2$	95 (22/78)[a,b]
2	**1**	$AgNTf_2$	96 (19/81)[a,c]
3	**3**		94 (18/82)[a,b]
4	**3**		97 (23/77)[a,c]
5	$H[AuCl_4]$		82 (22/78)[a,b]
6	$H[AuCl_4]$		99 (13/87)[d]

[a] Our results, ^{1}H NMR yield. [b] 10 mol %. [c] 5 mol %. [d] Reaction run with 10% mol of catalyst. Yield determined by GC analysis vs internal standard (see ref 20).

Table 6. NAC Gold-Catalyzed Benzylation of Anisole with Benzyl Alcohol



entry	[Au]	AgX	yield[a] [%] (ratio)
1	**1**[b]	$AgNTf_2$	96 (40/60)
2	**1**[c]	$AgNTf_2$	91 (40/60)
3	**3**[b]		94 (40/60)
4	**3**[c]		66 (40/60)
5	$H[AuCl_4]$[b]		15 (33/67)

[a] ^{1}H NMR yield. [b] 10 mol %. [c] 5 mol %.

We have also explored the activity of this process with our gold(I) NACs. The benzylation of anisole **15** with 1-phenylethyl acetate **16** catalyzed with $HAuCl_4$ was reported to give the corresponding *para*-isomer **18** in very good yield. The reaction is not regioselective, and *ortho*-isomer **17** is also observed (Table 5, 99% yield determined by GC (o/p = 13/87), entry 6,[20] and 82% yield determined by ^{1}H NMR (o/p = 22/78), entry 5, our result). Our gold(I) NAC complexes are also active in this reaction, affording also excellent yields (Table 5, entries 1−4). The regioselectivity is nearly the same as with $HAuCl_4$, and the major regioisomer in this case is still **18**. The load of catalyst can be reduced, compared to the use of $HAuCl_4$, from 10 to 5 mol %, affording the same excellent yields.

Additional experiments were performed using a different benzylating agent (**19**, not reported in ref 20). The results obtained for the gold-catalyzed benzylation of anisole with benzyl alcohol are summarized in Table 6. The gold carbenes **1** and **3** catalyze this reaction (Table 6, entries 1−4). It is remarkable that, in contrast with the reported related reaction in Table 5, entry 6), the yields are here much better (about 90% versus 15%) than those obtained using the reported Au(III) system (Table 6, entry 5), even with lower load of catalyst (entry 2).

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Conclusions

The scope of application of NACs as ligands for gold-catalyzed reactions looks very large. The catalyzed reactions are not disturbed by the presence of N−H bonds in the NAC ligand. Considering that the ground properties of a ligand can be tuned by changing substituents, the catalytic system [AuX(NAC)] looks extremely flexible and interesting for gold(I)-catalyzed processes: changes are particularly accessible for NACs, as they are directly made from accessible isocyanides and amines. In different reactions, these ligands behave (as far as yields are concerned) as well as or better than phosphines (even without optimization of the reaction) and are comparable to NHCs. Furthermore, in the benzylation of arenes, reported in the literature with $H[AuCl_4]$, our gold(I) ligands perform much better than the gold(III) catalyst. Taking the yields as a rough indication of reactivity, the trends observed do not contradict the expectations from the calculated order of basicity of ligands PR_3 < NACs < NHCs,[12] although practically there is no difference in behavior between NACs and NHCs.

Experimental Section

General Conditions. All reactions were carried out under dry N_2 atmosphere. The solvents were purified according to standard procedures. Complexes [AuCl{C(NEt_2)(NHTol-*p*)}] (**1**),[6] [AuCl{C(NEt_2)(NHXylyl)}] (**2**),[6] $AgNTf_2$,[21] **4**,[16] **6**,[18] **8**,[18] and **16**[22] were prepared according to literature procedures. The rest of the reactants are commercially available.

Infrared spectra were recorded in Perkin-Elmer 883 or 1720X equipment. NMR spectra were recorded with Bruker AC300 and ARX 300 and Bruker Avance 400 Ultrashield instruments. ^{1}H NMR spectra are referred to TMS.

[Au(NTf_2){C(NEt_2)(NHXylyl)}] (3). $AgNTf_2$ (89 mg, 0.229 mmol) was added to a solution of [AuCl{C(NEt_2)(NHXylyl)}] (**2**) (100 mg, 0.229 mmol) in dry CH_2Cl_2 (15 mL). A white precipitate appeared immediately. After stirring for 5 min, the mixture was filtered (double HPLC Teflon filter). Addition of Et_2O (5 mL) led to the formation of the cationic complex as a white solid, which was filtered, washed with Et_2O (2 × 5 mL), and vacuum-dried (122 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.05 (m, 3 H, Ar*H*), 6.76 (br s, 1 H, N*H*), 3.94 (q, J = 7.1 Hz, 2 H, NCH_2CH$_3$), 3.55 (q, J = 7.5 Hz, 2 H, NCH_2CH$_3$), 2.24 (s, 6 H, Ar-CH_3), 1.41 (t, J = 7.5 Hz, 3 H, NCH_2CH$_3$), 1.40 (t, J = 7.1 Hz, 3 H, NCH_2CH$_3$). ^{19}F NMR (282.5 MHz, $CDCl_3$): δ −75.87 (s, N(SO_2CF_3)$_2$, 6 F). Anal. Calcd for $C_{15}H_{20}N_3AuF_6O_4S_2$: C, 26.44; H, 2.96; N, 6.17. Found: C, 26.82; H, 2.66; N, 6.20.

Catalytic Procedures. The general procedures followed for the rearrangement of homopropargylsulfoxide,[16] intramolecular *exo*-hydroamination of *N*-allenyl carbamate,[18] intramolecular hydroalkoxylation of 2,2-diphenyl-4,5-hexadienol,[18] hydroarylation of acetylenecarboxylic acid ester,[19] and benzylation of anisole with 1-phenylethyl acetate[20] are similar to those reported (the procedure was also analogous when benzyl alcohol was used as benzylating agent). The ^{1}H NMR yields were obtained by using 1,2-dichloroethane as an internal reference.

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Artículo IV

Synthesis and Catalytic Activity of Gold Chiral Nitrogen Acyclic Carbenes and Gold Hydrogen Bonded Heterocyclic Carbenes in Cyclopropanation of Vinyl Arenes and in Intramolecular Hydroalkoxylation of Allenes

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Article

Synthesis and Catalytic Activity of Gold Chiral Nitrogen Acyclic Carbenes and Gold Hydrogen Bonded Heterocyclic Carbenes in Cyclopropanation of Vinyl Arenes and in Intramolecular Hydroalkoxylation of Allenes

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Mononuclear and dinuclear chiral gold(I) carbene complexes with carbene ligands of the type HBHC (hydrogen bonded heterocyclic carbenes) and NAC (nitrogen acyclic carbenes) have been prepared by reaction of isocyanide gold(I) complexes and chiral amines or diamines. The reaction of [AuCl(CNPy-2)] (**1**) (Py = pyridyl) with the corresponding chiral primary amines afforded the chiral HBHC complexes (*R*)-[AuCl{C(NH(CHMePh))(NHPy-2)}] ((*R*)-**2**), and (*S*)-[AuCl{C(NH{CHMe(1-naphthyl)})(NHPy-2)}] ((*S*)-**3**), while the reaction of 2 equiv of **1** with diamines produced (*S*)-2,2′-bis[NH{C(AuCl)(NHPy-2)}]$_2$-binaphthyl ((*S*)-**4**), (1*R*,2*R*)-1,2-bis[NH{C(AuCl)(NHPy-2)}]-diphenylethane ((1*R*,2*R*)-**5**), and (1*R*,2*R*)-1,2-bis[NH{C(AuCl)(NHPy-2)}]-cyclohexane ((1*R*,2*R*)-**6**). On the other hand the addition of alkyl amines to (*S*)-2,2′-[NCAuCl]$_2$-binaphthyl ((*S*)-**8**) gave the chiral NAC complexes (*S*)-2,2′-bis[NH{C(AuCl)(NMe$_2$)}]$_2$-binaphthyl ((*S*)-**9**) and (*S*)-2,2′-bis[NH{C(AuCl)(N^{i}Pr$_2$)}]$_2$-binaphthyl ((*S*)-**10**), while the addition to (*S*)-2,2′-[NC-AuCl]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-**12**) yielded (*S*)-2,2′-bis[NH{C(AuCl)(NMe$_2$)}]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-**13**) and (*S*)-2,2′-bis[NH{C(AuCl)(NEt$_2$)}]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-**14**). All the complexes are active catalysts in the cyclopropanation of vinyl arenes and in the intramolecular hydroalkoxylation of allenes, providing good yields and modest or poor enantioselectivity. The results show that all these ligands are compatible with different functions and reaction conditions and are worth considering as alternative systems to NHCs or phosphines in gold catalyzed reactions.

Introduction

The past 20 years have seen the development of gold(I) complexes as catalysts for organic transformations,[1] but applications of homogeneous gold catalysts in enantioselective processes have been reported only very recently.[2] The majority of the gold(I) catalytic systems used in enantioselective catalysis are dinuclear complexes of the type μ-(P−P)[(AuX)$_2$] (P−P = chiral bis(phosphine), X = anionic ligand or counterion), although chiral phosphoramidite ligands[3] and chiral counterions[4] have recently emerged as interesting alternatives in gold(I) catalysis.

The catalytic activity of NHC gold(I) complexes in many synthetic processes is well demonstrated.[5] We have recently reported that gold(I) complexes with other types of carbene ligands, that we have named HBHCs (hydrogen bonded heterocyclic carbenes, e.g., [AuCl{C(NRH)(NHPy-2)}]), or NAC (nitrogen acyclic carbenes, e.g., [AuCl{C(NHR)(NHR′)}] or [AuCl{C(NHR)(NR′$_2$)}]), are good catalysts in skeletal rearrangement and in methoxycyclization of enynes,[6−8] suggesting that this kind of carbene complexes should be incorporated

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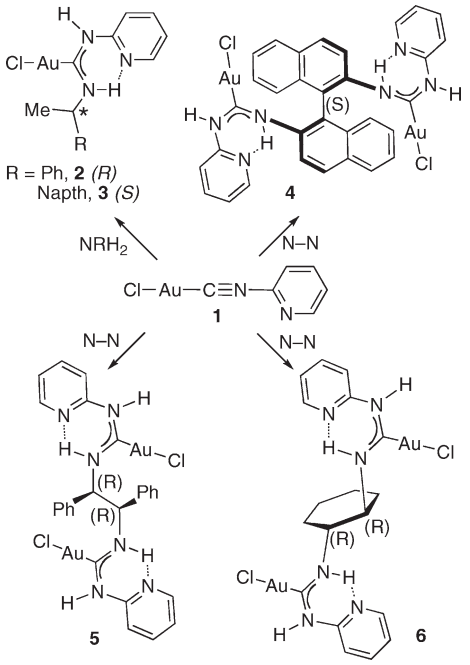
Scheme 1. Synthesis of the Chiral HBHC Gold Complexes **2**−**6**: NRH_2 = (*R*)-NH_2(Me)CH(Ph), **2**; (*S*)-NH_2(Me)CH(naph), **3**; N−N = (*S*)-(-)-1,1′-binapthyl-2,2′-diamine, **4**; (1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamine, **5**; (1*R*,2*R*)-(-)-1,2-diaminecyclohexane, **6**



to the armory of metal-catalyzed reactions and further investigated. We are glad that our kind of NAC complexes have already been adopted by another group working in gold catalysis.[9] An advantage of these two kinds of complexes is that they are prepared by nucleophilic attack of amines to isocyanide gold complexes,[10−12] which provides an easy way to obtain systematic series of chiral carbene gold complexes by simply combining chiral amines or chiral isocyano-gold complexes. The isocyanide ligands are easy to obtain from chiral amines.[13]

Following this methodology we have carried out the synthesis of some chiral mononuclear or binuclear HBHC or NAC gold(I) complexes and studied their catalytic activity and enantioselectivity in two reactions that have been recently reported to be catalyzed by gold catalysts bearing chiral mono or-bidentate phosphane ligands, namely, the cyclopropanation of vinyl arenes[14] and the intramolecular hydroalkoxylation of allenes.[15] Chiral carbene gold(I) complexes have not been explored in gold enantioselective catalysis, except for one report of some monomeric NHC gold(I) complexes that appeared during the preparation of this paper, where the authors report good yields but low or moderate enantioselectivity for the asymmetric cyclization of 1,6-enynes.[16]

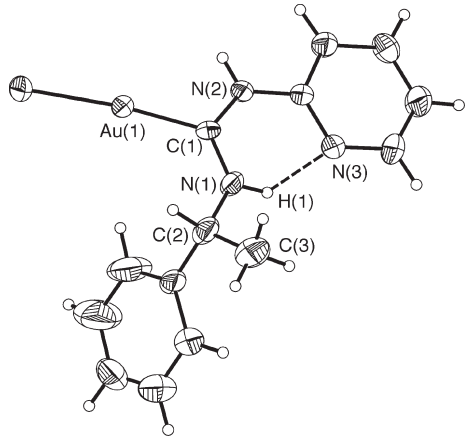


Figure 1. X-ray structure for (*R*)-**2** (only one of the two molecules of the asymmetric unit is shown). Selected bond lengths (Å): Au(1)−Cl(1) = 2.2884(19); Au(1)−C(1) = 1.994(8); C(1)−N(2) = 1.354(10); C(1)−N(1) = 1.297(11); N(3)−H(1A) = 1.898. Selected bond angles (deg): C(1)−Au(1)−Cl(1) = 173.8(2); N(2)−C(1)−N(1) = 118.3(8); N(3)−H(1)−N(1) = 133.70.

Results and Discussion

(a). Synthesis and Structural Characterization of Chiral Gold(I) Carbene Complexes. (a.1). Chiral HBHC Gold Complexes. The neutral chiral gold carbene complexes **2**−**6** (Scheme 1) were prepared by nucleophilic attack to the gold-coordinated isocyanide in [AuCl(CNPy-2)] (**1**)[6] with different chiral primary amines or diamines. All the gold complexes are air stable white solids.

In general, four stereoisomers can be formed for each gold center in gold(I) carbenes derived from primary amines, but only one was observed in the ^{1}H NMR spectra at room temperature in $CDCl_3$ for complexes **2**−**6** (also in Me_2CO-d_6 for **6**). As observed previously for non-chiral HBHCs,[6,7] this confirms the persistence in $CDCl_3$ (and also in Me_2CO-d_6) solution of the intramolecular hydrogen bond between the amide proton and the nitrogen of the 2-pyridyl group, forming a 6-member cycle. The ^{1}H NMR spectra show two N−H signals, one at about 13 ppm and the other at about 9.7 ppm. The chemical shift of the former corresponds to the hydrogen atom involved in the intramolecular hydrogen bonding. This hydrogen interaction is strong enough to stabilize exclusively the otherwise less favored *anti* isomer, as shown in Scheme 1.

X-ray quality crystals suitable for single crystal diffraction were obtained for (*R*)-**2**. There are two independent molecules of complex **2** in the asymmetric unit. The molecular structure of one of them (the other is very similar) is shown in Figure 1, with selected bond lengths and angles. The complex shows, as expected, a roughly linear geometry for gold (angle 173.8°). As observed for other HBHCs,[6,7] the Au−Cl distance in **2** is longer than that in $[AuCl_2]^-$ (2.257 Å),[17] reflecting the high *trans* influence of the carbene ligand.[18] The Au−C distance is within the range found for other HBHC gold(I) carbenes. The C(1)−N(2) and C(1)−N(1) distances are much shorter than the normal

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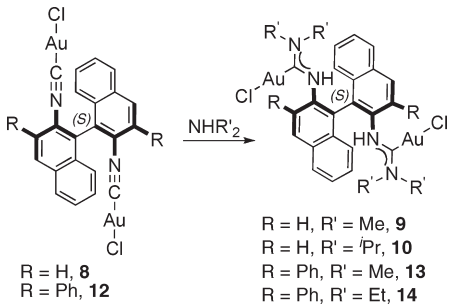
Scheme 2. Synthesis of the Chiral HBHC Gold Derivatives **9**−**10** and **13**−**14**



C(sp^2)−N single bond distance of 1.45 Å,[19] which proves an important N→C π-bonding contribution to the bond. The H···N(3) distance and the corresponding N(1)−H···N(3) angle in the hydrogen bridge are in the range of moderate intramolecular N···H hydrogen bonds.[20]

(a.2). Chiral NAC Gold Complexes. In this case, the chiral binuclear NAC gold(I) complexes (*S*)-**9** and (*S*)-**10** have been prepared by using a chiral isocyanide gold complex (*S*)-2,2′-[NCAuCl]$_2$-binaphthyl ((*S*)-**8**), and non-chiral amines of different steric requirements meant to modify the steric hindrance at the gold(I) reaction site (Scheme 2). We have also used the bulkier isocyanide complex (*S*)-2,2′-[NCAuCl]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-**12**), with a phenyl substituent in the 3,3′-position of the binaphthyl group, to synthesize (*S*)-**13** and (*S*)-**14**. The starting isocyanogold complexes were obtained from [AuCl(tht)] (tht = tetrahydrothiophene),[21] by substitution of tht with (*S*)-(+)-1,1′-Binaphthyl-2,2′-diisocyanide (**7**),[22] or with (*S*)-1,1′-Binaphthyl-(3,3′-diphenyl)-2,2′-diisocyanide (**11**), as reported for related gold compounds.[23] Ligand **11** was synthesized from (*S*)-2,2′-(3,3′-diphenyl)binapthylamine,[24] as reported in the experimental part. The chiral isocyanocomplexes were treated only with secondary amines to reduce the number of possible conformers in the products.

The ^{1}H NMR spectra of complexes **9**−**10** in $CDCl_3$ show the signals of only one isomer. In contrast, compounds **13**−**14** show a mixture of three isomers, and it is not easy to assign the preferred conformations from the spectroscopic data. X-ray quality crystals suitable for single crystal diffraction were obtained for **9**. A perspective view of the molecular structure is given in Figure 2, along with selected bond lengths and angles. The complex shows a nearly linear geometry for gold. The Au−C distance is in the range of distances found for other gold(I) carbenes. As observed for **2**, The C(1)−N(2) and C(1)−N(1) distances are similar to other Au(I) carbene complexes, and shorter than the C(sp^2)−N single bond distance of 1.45 Å, indicating important N→C π-bonding contribution to the bond.

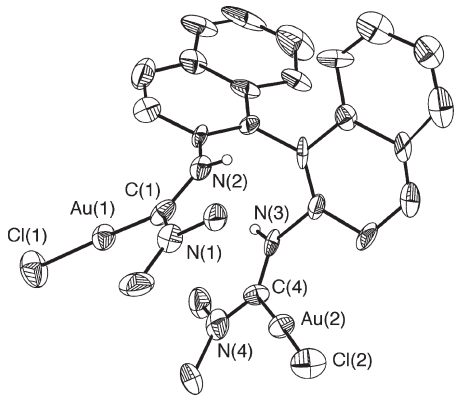


Figure 2. Molecular structure of **9**. Selected bond lengths (Å): Au(1)−Cl(1) = 2.268(7); Au(1)−C(1) 1.98(3); C(1)−N(2) = 1.40(3); C(1)−N(1) = 1.29(2); Au(2)−Cl(2); 2.256(7); Au(2)−C(4) = 2.02(2); C(4)−N(3) = 1.33(2); C(4)−N(4) = 1.36(2). Selected bond angles (deg): C(1)−Au(1)−Cl(1) = 176.8(7); N(2)−C(1)−N(1) = 118(2); C(4)−Au(2)−Cl(2) = 178.7(7); N(3)−C(4)−N(4) = 118.1(19).

Table 1. Gold-Catalyzed Enantioselective Cyclopropanation of Styrene with Propargyl Pivaloate

Entry	[Au]	Yield[a] [%]	*ee*[b] [%]
1	**2**	53	<1
2	**3**	54	<1
3	**4**	75	20
4	**5**	78	11
5	**6**	71	5
6	**9**	72	24
7	**10**	70	10
8	**13**	61	8
9	**14**	65	<1
10	**μ-(P-P*)[AuCl]$_2$**[c]	70	81

[a] Isolated yields. [b] *ee* values determined by HPLC analysis on a chiral stationary phase. [c] P−P* = (*R*)-DTMB-SEGPHOS.[14]

The isomer observed in the X-ray structure displays a *syn* arrangement of the Au center and the N substituent bearing the naphthyl group, which possibly reduces the steric hindrance in the molecule. The same conformation has been observed in the recently reported structures of the gold(I) carbenes [AuCl{C(NEt$_2$)(NHPy-2)}] and [AuFmes{C(NEt$_2$)(NHPy-2)}].[6] In the binaphthyl group, the naphthalene rings make a dihedral angle of 75.68°. The absolute configuration of axially dissymmetric 1,1′-binaphthyl is *S*, the same as the precursor (*S*)-(+)-1,1′-Binaphthyldiisocyanide (**7**), confirming that, as expected, it is not modified during the reaction.

Catalytic Reactions

Two catalytic processes were studied: the cyclopropanation of vinyl arenes and the intramolecular hydroalkoxylation of allenes. The reactions were carried out under standard conditions (not optimized for the ligand), using 5 equiv% of cationic chiral HBHC and NAC catalysts obtained in situ by

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(20) Hydrogen bonding distance ranges proposed in the literature: strong, 1.2−1.5 Å; moderate, 1.5−2.2 Å; weak, 2.2−3.2 Å: Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
(21) Usón, R.; Laguna, A.; Laguna, M. *Inorg. Synth.* **1989**, *26*, 85–91.
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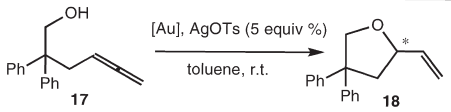
(23) Bayón, R.; Coco, S.; Espinet, P.; Fernández-Mayordomo, C.; Martin-Alvarez, J. M. *Inorg. Chem.* **1997**, *36*, 2329–2334.
(24) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *J. Org. Chem.* **2008**, *73*, 7387–7389.

Table 2. Enantioselective Hydroalkoxylation of Allene **17** with the Chiral Catalysts **2**, **3**, **4**, **9**, and **10**

Entry	[Au]	Yield[a] [%]	*ee*[b] [%]
			
1	**2**	67	<1
2	**3**	61	2
3	**4**	95	22
4	**9**	42	20
5	**10**	55	8
6	**μ-(P-P*)[AuCl]$_2$**[c]	73	90

[a] Isolated yields. [b] *ee* values determined by HPLC analysis on a chiral stationary phase. [c] P−P* = (*S*)-DTMB-MeOBIPHEP.[15]

treating the corresponding neutral carbene complex with an equimolecular amount of silver salt ($AgSbF_6$ or AgOTs).

The reaction of propargyl pivaloate **15** (Table 1) with styrene afforded only the *cis*-cyclopropane **16** in reasonable yields (53−78%), showing that both HBHC and NAC ligands can be applied in this reaction. The highest enantiomeric excesses in the reaction were obtained for **4** and **5** (Table 1, entries *3* and *4*) in the case of HBHC ligands, and for **9** and **10** (Table 1, entries *6* and *7*) in the case of NAC ligands. The enantioselectivity found in all the reactions is very poor compared with the values reported by Toste et al. using as catalyst the binuclear system (*R*)-DTBM-SEGPHOS-gold(I) (Table 1, entry *10*),[14] but it has to be considered that phosphine catalysts (and also NHC systems) are better understood and have been much more elaborated in the past years. In these initial studies of the new HBHC and NAC ligands we see that the best enantioselectivity results, even if modest (11−24% ee), have been obtained with catalysts **4**, **5**, **9**, and **10**, all based on the axially dissymmetric 1,1′-binaphthyl ligand. Obviously further elaboration of these ligands looks more promising than for mononuclear complexes. For this reason, we hoped that catalysts **13** and **14**, based on the bulkier (3,3′-diphenyl)-1,1′-binaphthyl chiral system might be more enantioselective than **9** and **10**, but surprisingly they are clearly worse. Since three conformers are present in solution for **13** and **14**, it might happen that they induced opposite enantioselectivity, in detriment of the overall enantiomeric excess.

Some chiral gold(I) HBHC and NAC complexes were also checked for the enantioselective hydroalkoxylation of the γ-hydroxyallene **17**, and the results are gathered in Table 2. Again, the best enantioselectivity results (22 and 20% ee, Table 2, entries *3* and *4*) are obtained with **4** and **9**. This result is similar to those obtained using binuclear complexes of the type μ-(P−P*)$[AuCl]_2$ with 2,2-bis(diarylphosphino)-biphenyl ligands such as binap or (3,5-xylyl)binap, but much lower that those obtained using the bulkier (*S*)-DTMB-MeOBIPHEP as the chiral ligand (Table 2, entry *6*).[15]

Conclusions

This study confirms the catalytic possibilities of the HBHC and NAC gold systems that we have recently introduced in gold catalysis as alternatives to phosphine and NHC ligands. In effect, the results show that the gold(I) complexes with these ligands are compatible with the conditions and reagents involved in the cyclopropanation of vinyl arenes and the intramolecular hydroalkoxylation of allenes. Moreover, it is demonstrated that enantioselectivity can be induced with these two kinds of ligands.

Certainly the enantiomeric excesses are still poor. This is due to the linear coordination of gold,[25] which places the reactive coordination site far away from the ancillary chiral ligand. However, this is the same problem encountered initially with phosphine and NHC ligands, which have been continuously improved in the past years after successive structural elaborations. Only a few ligand variations have been tested in our initial studies, where the purpose was not still to find optimized conditions for a specific synthesis, but to explore the applicability of these ligand types. The fact that introducing structural and electronic variations in the NAC ligands is easier (particularly for the NAC ligands) than in phosphines or NHCs offers many opportunities for a more flexible tuning of these ligand to the demands of specific reagents, and holds a promise for improved activity and enantioselectivity. Here we find that dinuclear gold complexes offer higher enantioselectivity and are, in principle, the structures of choice for further elaboration.

Experimental Section

General Conditions. In general the reactions were carried out under dry N_2, but the cyclopropanation of styrene was carried out in the air without problem. The solvents were purified according to standard procedures. [AuCl(tht)],[21] [AuCl(CNPy-2)] (**1**),[6] and (*S*)-2,2′-(3,3′-diphenyl)binapthylamine[24] were prepared according to literature procedures. The rest of the reactants are commercially available. Infrared spectra were recorded in Perkin-Elmer 883 or 1720X equipment. NMR spectra were recorded with Bruker AC300, ARX 300 and Bruker Avance 400 Ultrashield instruments. ^{1}H NMR spectra are referred to TMS. Elemental analyses were performed with a Perkin-Elmer 2400B microanalyzer.

(*R*)-[AuCl{C(NH(CHMePh))(NHPy-2)}] ((*R*)-2). (*R*)-(+)-α-Methylbenzylamine (154 μL, 1.19 mmol) was added to a solution of **1** (0.200 g, 0.59 mmol) in CH_2Cl_2 (20 mL) and the resultant solution is stirred at room temperature. After 45 min, the solution did not show ν(C≡N) IR absorption. The volatiles were removed, the white residue was recrystallized in CH_2Cl_2/*n*-hexane. The white solid obtained was washed with *n*-hexane (3 × 10 mL) and vacuum-dried, yielding 0.210 g (78%). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K), δ: 12.87 (d, J = 8.1 Hz, 1H, N*H*(CH$_3$)CH(C_6H_5)), 9.53 (br, 1H, N*H*C_5H_4N), 8.25 (d, 1H, J = 1.2 Hz, NHC_5H_4N), 7.73 (m, 1H, NHC_5H_4N), 7.50−7.20 (m, 5H, NH(CH$_3$)CH(C_6H_5)), 7.17 (m, 1H, NHC_5H_4N), 7.08 (m, 1H, NHC_5H_4N), 5.44 (dq, J = 8.3, 6.8 Hz, 1H, C*H*), 1.71 (d, J = 6.8 Hz, 3H, CH-C*H*$_3$). $[\alpha]_D^{25}$ −94.0 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{14}H_{15}N_3ClAu$: C, 36.74; H, 3.30; N, 9.18. Found: C, 37.09; H, 3.15; N, 9.17.

(*S*)-[AuCl{C(NH(CHMe(1-Naphthyl)))(NHPy-2)}] ((*S*)-3). (*S*)-(-)-1-(1-naphthyl)ethylamine (60 μL, 0.37 mmol) was added to a solution of **1** (0.118 g, 0.35 mmol) in CH_2Cl_2 (20 mL), and the resultant solution was stirred at room temperature. Work up as for **2** yielded 0.153 g of a white solid (86%). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K), δ: 12.98 (d, J = 8.3 Hz, 1H, N*H*(CH$_3$)CH($C_{10}H_7$), 9.86 (br, 1H, N*H*C_5H_4N), 8.24 (m, 1H, NHC_5H_4N), 8.17 (m, 1H, $C_{10}H_7$), 7.75 (m, 1H, NHC_5H_4N), 7.70 (m, 2H, $C_{10}H_7$), 7.35 (m, 3H, $C_{10}H_7$), 7.30 (m, 1H, NHC_5H_4N), 7.17 (m, 1H, NHC_5H_4N), 7.03 (m, 1H, NHC_5H_4N), 6.13 (dq, J = 7.7, 6.8 Hz,

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1H, C*H*), 1.84 (d, J = 6.8 Hz, 3H, CHCH_3). $[\alpha]_D^{25}$ +147.0 (c 0.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}AuClN_3$: C, 42.58; H, 3.37; N, 8.28. Found: C, 42.91; H, 3.46; N, 7.77.

(*S*)-2,2′-bis[NH{C(AuCl)(NHPy-2)}]$_2$-binaphthyl ((*S*)-4). (*S*)-(−)-1,1′-binapthyl-2,2′-diamine (15 mg, 0.053 mmol) was added to a solution of **1** (0.034 g, 0.1 mmol) in THF (10 mL). Work up as for **2** yielded 0.030 g of a white solid (61%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K), δ: 14.22 (s, 2H, N*H*-Binaphthyl), 10.25 (s, 2H, N*H*C_5H_4N), 8.22 (d, J = 8.0 Hz, 2H, binaphthyl), 7.95 (dd, J = 8.8, 8.0 Hz, 2H, binaphthyl), 7.60 (t, J = 9.0 Hz, binaphthyl), 7.58 (m, 2H, NH-C_5H_4N), 7.43 (m, 6H, binaphthyl), 7.01 (m, d, J = 8.0 Hz, NH-C_5H_4N, 2H), 6.70 (m, 2H, NHC$_5H_4$N), 6.56 (m, 2H, binaphthyl). $[\alpha]_D^{25}$ +192.0 (c 1, $CHCl_3$). Anal. Calcd for $C_{32}H_{24}Au_2Cl_2N_6$: C, 40.14; H, 2.53; N, 8.78. Found: C, 40.25; H, 2.80; N, 9.08.

(1*R*,2*R*)-1,2-bis[NH{C(AuCl)(NHPy-2)}]-diphenylethane ((1*R*, 2*R*)-5). (1*R*, 2*R*)-(+)-1,2-diphenylethane-1,2-diamine (0.035 g, 0.165 mmol) was added to a solution of **1** (0.101 g, 0.33 mmol) in CH_2Cl_2 (30 mL). Work up as for **2** yielded 0.115 g of a white solid (85%). ^{1}H NMR (400 MHz, Me_2CO-d_6, 295 K), δ: 13.82 (s, 2H, N*H*), 10.33 (s, 2H, N*H*C_5H_4N), 8.56 (d, J = 4.0 Hz, 2H, C_5H_4N), 7.90 (m, 2H, C_5H_4N), 7.40−7.15 (m, 14H, C_6H_5 and NHC$_5H_4$N), 6.00 (m, 2H, C_6H_5CH,). Anal. Calcd for $C_{26}H_{24}Au_2Cl_2N_6$: C, 35.27; H, 2.73; N, 9.49. Found: C, 36.14; H, 2.85; N, 8.99. $[\alpha]_D^{25}$ +6.0 (c 1, Me_2CO).

(1*R*,2*R*)-1,2-bis[NH{C(AuCl)(NHPy-2)}]-cyclohexane ((1*R*, 2*R*)-6). (1*R*, 2*R*)-(−)-1,2-diaminecyclohexane (0.020 g, 0.165 mmol) was added to a solution of **1** (0.101 g, 0.33 mmol) in CH_2Cl_2 (30 mL). Work up as for **2** yielded 0.071 g of a white solid (58%). ^{1}H NMR (400 MHz, Me_2CO-d_6, 295 K), δ: 12.93 (s, 2H, N*H*), 10.13 (s, 2H, N*H*C_5H_4N), 8.53 (d, J = 4.0 Hz, 2H, C_5H_4N), 7.86 (m, 2H, C_5H_4N), 7.20 (m, 4H, NHC$_5H_4$N), 4.41 (m, 2H, NC*H*$(CH_2)_4$C*H*N), 2.28 (m, 2H, NCH(CH_2)$_4$CHN), 1.80 (m, 2H, NCH(CH_2)$_4$CHN), 1.70 (m, 2H, NCH(CH_2)$_4$CHN), 1.50 (m, 2H, NCH(CH_2)$_4$CHN). Anal. Calcd for $C_{18}H_{22}Au_2Cl_2N_6$: C, 27.46; H, 2.82; N, 10.68. Found: C, 27.52; H, 2.94; N, 10.34. $[\alpha]_D^{25}$ −153.4 (c 1, Me_2CO).

(*S*)-(+)-1,1′-Binaphthyl-2,2′-diisocyanide (7). Formic acid (64 μL, 1,69 mmol) was added to a 0 °C acetic anhidride (129 μL, 1.37 mmol). After the addition, the solution was stirred at 50 °C for 2 h and then cooled to room temperature. THF (1.5 mL) was added, the solution was cooled down to 0 °C, and (*S*)-(−)-1,1′-binapthyl-2,2′-diamine (150 mg, 0.528 mmol) was added and after 20 min the mixture was allowed to warm to ambient temperature and be stirred for 4 h. Then, the volatiles were pumped off, and the crude formamide was purified by dissolving it in *n*-hexane:ethyl acetate (1:1) and passing the solution through silicagel. The volatiles were pumped off, and the solid was crystallized in dichloromethane/pentane. The white solid obtained was washed with pentane (3 × 10 mL) and vacuum-dried, yielding 0.164 g (91%) of 2,2′-binaphthyldiformamide that was used in the subsequent transformation.[26] To a solution of (*S*)-(−)1,1′-binapthyl-2,2′-diformamide (1.394 g, 4.094 mmol) and triethylamine (2.3 mL, 16.38 mmol) in 50 mL of dichloromethane, a solution of trichloromethylcarbonate (triphosgene) (0.850 g, 2.87 mmol) in 10 mL of dichloromethane was added dropwise. The mixture was stirred for 3 h and then the solvent was removed on a rotary evaporator. The resulting residue was chromatographed (silica gel, diethylether/hexane, 5:1 as eluent), and the solvent was evaporated to obtain the product as a white solid. (74% yield). IR: 2118 cm^{-1} ν(C≡N). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K), δ: 8.08 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 7.60 (dd, J = 7.0, 8.5 Hz, 2H), 7.41 (dd, J = 7.0, 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H). Anal. Calcd. for $C_{22}H_{12}N_2$: C, 86.82; H, 3.97; N, 9.20. Found: C, 86.37; H, 4.12; N, 9.46. $[\alpha]_D^{25}$ +66 (c 1, benzene).

(*S*)-2,2′-[NCAuCl]$_2$-binaphthyl ((*S*)-8). A 0.250 g portion of **7** (0.82 mmol) was added to a solution of [AuCl(tht)] (0.527 g, 1.64 mmol) in dichloromethane (20 mL). After 15 min of stirring at room temperature the volatiles were pumped off, and the pale gray residue was washed with *n*-hexane (3 × 5 mL) and crystallized from dichloromethane/*n*-hexane. The white solid obtained was decanted, washed with *n*-hexane (3 × 5 mL) and vacuum-dried, yielding 0.567 g (73%). IR: 2217 cm^{-1} ν(C≡N). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K), δ: 8.24 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.76 (ddd, J = 8.1, 6.8, 1.1 Hz, 2H), 7.53 (ddd, J = 8.1, 6.8, 1.1 Hz, 2H), 7.17 (dd, J = 8.6, 6.8 Hz, 2H). $[\alpha]_D^{25}$ −5.0 (c 1, $CHCl_3$). Anal. Calcd. for $C_{22}H_{12}N_2Au_2Cl_2$: C, 34.35; H, 1.57; N, 3.64. Found: C, 34.51; H, 1.80; N, 3.65.

(*S*)-2,2′-bis[NH{C(AuCl)(NMe$_2$)}]$_2$-binaphthyl ((*S*)-9). Dimethylamine (150 μL, 0.26 mmol) was added to a solution of **8** (0.100 g, 0.13 mmol) in THF (15 mL), and the resultant solution was stirred at 40 °C. After 3 h, the solution did not show ν(C≡N) IR absorption. Work up as for **2** yielded 0.084 g of a white solid (75%). ^{1}H RMN (400 MHz, Me_2CO-d_6, 295 K): δ (ppm) 8.17−8.10 (m, 4H), 8.07 (d, J = 8.1 Hz, 2H), 7.99 (br, 2H, N*H*), 7.54 (ddd, J = 15.1, 7.1, 0.8 Hz, 2H), 7.31 (ddd, J = 15.3, 8.3, 0.8 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 3.64 (s, 6H, N(CH_3)$_2$), 2.69 (s, 6H, N(CH_3)$_2$). $[\alpha]_D^{25}$ −121.0 (c 1, $CHCl_3$). Anal. Calcd for $C_{26}H_{26}Au_2Cl_2N_4$: C, 36.34; H, 3.05; N, 6.52. Found: C, 35.93; H, 2.95; N, 6.28.

(*S*)-2,2′-bis[NH{C(AuCl)(N^{i}Pr$_2$)}]$_2$-binaphthyl ((*S*)-10). Isopropylamine (29 μL, 0.203 mmol) was added to a solution of **8** (0.071 g, 0.092 mmol) in THF (15 mL), and the resultant solution was stirred at 40 °C. After 3 h, the solution did not show ν(C≡N) IR absorption. Work up as for **2** yielded 0.072 g of a white solid (80%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ (ppm) 8.44 (d, J = 12.0 Hz, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 12.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.44 (t, J = 8.0 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.19 (br, 2H, N*H*), 5.21 (m, 2H, N{C*H*-$(CH_3)_2$}), 3.52 (sep, J = 4.0 Hz, 2H, N{C*H*$(CH_3)_2$}), 1.27 (d, J = 4.0 Hz, 6H, N{CH(CH_3)$_2$}), 1.18 (d, J = 8.0 Hz, 6H, N{CH-(CH_3)$_2$}), 0.78 (d, J = 12.0 Hz, 6H, N{CH(CH_3)$_2$}), 0.43 (d, J = 8.0 Hz, 6H, N{CH(CH_3)$_2$}). $[\alpha]_D^{25}$ −171.0 (c 1, $CHCl_3$). Anal. Calcd for $C_{34}H_{42}Au_2Cl_2N_4$: C, 42.03; H, 4.36; N, 5.77. Found: C, 42.65; H, 4.06; N, 5.30.

(*S*)-1,1′-Binaphthyl-(3,3′-diphenyl)-2,2′-diisocyanide (11). Formic acid (72 μL, 1,91 mmol) was added to a 0 °C acetic anhidride (146 μL, 1.55 mmol). After the addition, the solution was stirred at 50 °C for 2 h and then cooled to room temperature. THF (1.5 mL) was added, the solution was cooled down to 0 °C, and (*S*)-2,2′-(3,3′-diphenyl)-binapthylamine[24] (261 mg, 0.597 mmol) was added and after 20 min the mixture was allowed to warm to ambient temperature, stirred for 10 h, and kept stirring at 50 °C for 2 h. Then, the volatiles were pumped off, and the crude formamide was chromatographed (silica gel, *n*-hexane:ethyl acetate 1:1 as eluent) yielding 0.215 g (73%) of 2,2′-(3,3′-diphenyl)binaphthyldiformamide that was used in the subsequent transformation.[26] To a solution of (*S*)-2,2′-(3,3′-diphenyl)-binaphthyldiformamide (0.190 g, 0.386 mmol) and triethylamine (215 μL, 16.38 mmol) in 16 mL of dichloromethane, a solution of trichloromethylcarbonate (triphosgene) (0. 084 g, 0.283 mmol) in 10 mL of dichloromethane was added dropwise. The mixture was stirred for 3 h, and then the solvent was removed on a rotary evaporator. The resulting residue was chromatographed (silica gel, CH_2Cl_2/hexane, 1:3 as eluent), and the solvent was evaporated to obtain the product as a white solid yielding 0.143 g (81%). IR (THF): 2114s cm^{-1} (C≡N). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K), δ: 8.09 (s, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.69 (m, 4H), 7.61 (m, 2H), 7.53 (m, 4H), 7.47 (m, 2H), 7.42 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H). Anal. Calcd. for $C_{34}H_{20}N_2$: C, 89.45; H, 4.42; N, 6.14. Found: C, 89.38; H, 4.54; N, 5.68. $[\alpha]_D^{25}$ +117.0 (c 1, $CHCl_3$).

(*S*)-2,2′-[NCAuCl]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-12). A 0.100 g portion of **11** (0.219 mmol) was added to a solution of [AuCl-(tht)] (0.140 g, 0.438 mmol) in THF (20 mL). After 15 min of stirring at room temperature the volatiles were pumped off, and the pale gray residue was washed with *n*-hexane (3 × 5 mL) and crystallized from dichloromethane/*n*-hexane. The white solid

(26) The procedure described by Ugi et al. for other isocyanides (ref 13) was used, using triphosgene instead of phosgene as a dehydrating agent.

obtained was decanted, washed with *n*-hexane (3 × 5 mL), and vacuum-dried, yielding 0.174 g (86%). IR: 2211s ν(C≡N). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K), δ: 8.23 (s, 2H), 8.14 (d, J = 8.0 Hz, 2H), 7.78 (t, J = 8.0 Hz, 2H), 7.57 (m, 10H), 7.52 (t, J = 8.0 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H). Anal. Calcd. for $C_{34}H_{20}N_2Au_2Cl_2$: C, 44.32; H, 2.19; N, 3.04. Found: C, 43.95; H, 2.15; N, 2.96.

(*S*)-2,2′-bis[NH{C(AuCl)(NMe$_2$)}]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-13). Dimethylamine (6.33 μL of a 2 M solution in THF, 0.120 mmol) was added to a solution of **12** (50 mg, 0.054 mmol) in THF (15 mL), and the resultant solution was stirred at room temperature until the solution did not show ν(C≡N) IR absorption. Work up as for **2** yielded 0.027 g of a white solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K), δ: 8.11 (s, 2H, major), 8.08 (s, 2H, minor), 8.07 (s, 2H, minor), 8.03 (d, J = 3.0 Hz, 2H), 7.86 (d, J = 3.0 Hz, 2H), 7. 96 (d, J = 3.0 Hz, 2H), 7.70−7.20 (m, 16H), 7.00 (s, 2H, N*H*, minor), 6.45 (s, 2H, N*H*, major), 6.41 (s, 2H, N*H*, minor), 3.29 (s, 6H, N(CH_3)$_2$, major), 3.16 (s, 6H, N(CH_3)$_2$, minor), 3.0 (s, 12H, N(CH_3)$_2$, minor), 2.40 (s, 12H, N(CH_3)$_2$, major), 2.35 (s, 12H, N(CH_3)$_2$, minor), 1.94 (s, 12H, N(CH_3)$_2$, minor). Stereoisomeric ratio: 2:1:1. $[\alpha]_D^{25}$ −96.0 (*c* 0.5, $CHCl_3$). Anal. Calcd. for $C_{38}H_{34}N_4Au_2Cl_2$: C, 45.12; H, 3.39; N, 5.54. Found: C, 45.34; H, 3.01; N, 5.46.

(*S*)-2,2′-bis[NH{C(AuCl)(NEt$_2$)}]$_2$-3,3′-Ph$_2$-binaphthyl ((*S*)-14). Diethylamine (7.4 μL, 0.072 mmol) was added to a solution of **12** (30 mg, 0.032 mmol) in THF (10 mL), and the resultant solution was stirred at room temperature until the solution did not show ν(CN) IR absorption. Work up as for **2** yielded 0.020 g (58%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 295 K), δ: 8.14 (s, 2H), 8.10 (s, 2H), 8.05 (s, 2H), 8.04 (d, J = 4.0 Hz, 2H), 7.99 (d, J = 4.0 Hz, 2H), 7. 96 (d, J = 4.0 Hz, 2H), 7.70−7.10 (m, 16H), 6.94 (s, 2H, N*H*), 6.50 (s, 2H, N*H*), 6.39 (s, 2H, N*H*), 3.93 (m, 2H, N(CH_2CH$_3$)$_2$), 3.63 (m, 4H, N(CH_2CH$_3$)$_2$), 3.47 (m, 2H, N(CH_2CH$_3$)$_2$), 3.35 (m, 2H, N(CH_2CH$_3$)$_2$), 3.55 (m, 2H, N(CH_2CH$_3$)$_2$), 3.10 (m, 2H, N(CH_2CH$_3$)$_2$), 2.70 (m, 4H, N(CH_2CH$_3$)$_2$), 2.65 (m, 2H, N(CH_2CH$_3$)$_2$), 2.57 (m, 2H, N(CH_2CH$_3$)$_2$), 2.10 (m, 2H, N(CH_2CH$_3$)$_2$), 0.70 (m, 12H, N(CH$_2$CH_3)$_2$), 0.58 (t, J = 7.0 Hz, 6H, N(CH$_2$CH_3)$_2$), 0.23 (t, J = 7.0 Hz, 6H, N(CH$_2$CH_3)$_2$), 0.12 (t, J = 7.0 Hz, 6H, N(CH$_2$CH_3)$_2$), −0.01 (t, J = 7.0 Hz, 6H, N(CH$_2$CH_3)$_2$). Stereoisomeric ratio: 1:1:1. $[\alpha]_D^{25}$ −125.0 (*c* 0.5, $CHCl_3$). Anal. Calcd. for $C_{42}H_{42}N_4Au_2Cl_2$: C, 47.25; H, 3.97; N, 5.25. Found: C, 47.17; H, 4.27; N, 5.17.

Experimental Procedure for X-ray Crystallography. Suitable single crystals of **2** and **9** were obtained by layering hexane in a THF solution of the corresponding compound. Crystals were mounted in glass fibers, and diffraction measurements were made using a Bruker SMART CCD and Varian Supernova area-detector diffractometers with Mo−K$_a$ radiation (λ = 0.71073 Å).[27] Intensities were integrated from several series of exposures, each exposure covering 0.3° in ω, the total data set being a hemisphere.[28] Absorption corrections were applied, based on multiple and symmetry-equivalent measurements.[29] The structures were solved by direct methods and refined by least-squares on weighted F^2 values for all reflections (see Table 3).[30] All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All the hydrogen atoms, including those involved in hydrogen bonding, were calculated with a riding model.[31] Complex neutral-atom scattering factors were used.[32] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publications with the deposition numbers CCDC-777502 for **2** and CCDC-777503 for **9**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Table 3

	2	**9**
empirical formula	$C_{14}H_{15}AuClN_3$	$C_{26}H_{26}Au_2Cl_2N_4$
formula weight	457.71	859.34
temperature	293(2) K	298(2)
wavelength (Å)	0.71073	0.71073
crystal system	orthorhombic	orthorhombic
space group	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)
a (Å)	9.6832(2)	7.372(5)
b (Å)	16.2667(3)	16.075(12)
c (Å)	19.8061(4)	23.682(18)
β (deg)	90.00	90.00
V (Å^3)	3119.73(11)	2807(4)
Z	8	4
D_{calc} (g cm^{-3})	1.949	2.034
absorption coefficient (mm^{-1})	9.592	10.654
F(000)	1727	1608
crystal size (mm)	0.3345 × 0.3196 × 0.0834	0.20 × 0.04 × 0.04
θ range for data collection	2.94 to 26.37°	1.53 to 26.60°
reflections collected	31001	24822
independent reflections	6368 [*R*(int) = 0.0620]	5813 [*R*(int) = 0.1343]
absorption correction	analytical	multiscan
data/restraints/parameters	6368/0/345	5813/0/312
Flack parameter	−0.013(11)	0.00(3)
goodness-of-fit on F^2	1.040	1.013
R_1 [$I > 2\sigma(I)$]	0.0430	0.0495
wR_2 (all data)	0.0838	0.1670

General Procedures for the Catalytic Reactions. All the reactions were carried out under N_2 in solvents dried using a Solvent Purification System (SPS). Thin layer chromatography (TLC) was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck 60 F254). Chromatography purifications were carried out using flash grade silica gel (SDS S-2 Chromatogel 60 ACC, 40−60 μm). NMR spectra were recorded at 25 °C on a Bruker Avance 400 Ultrashield. 2,2-Diphenyl-4,5-hexadien-1-ol,[33] and propargyl pivaloate,[34] were synthesized employing published procedures. Chiral HPLC was performed on a Hewlett-Parkard chromatograph equipped with a 25 cm Chiracel OD-H column.

Intramolecular Hydroalkoxylation of 2,2-Diphenyl-4,5-hexadien-1-ol. A mixture of the neutral gold carbene (0.05 equiv) and AgOTs (0.05 equiv) in toluene (1 mL) was stirred at room temperature for 10 min, and treated with 2,2-diphenyl-4,5-hexadien-1-ol (1 equiv) in toluene. The resulting suspension was stirred at room temperature and followed by TLC. Column chromatography of the reaction mixture (hexane/EtOAc 20:1) gave 2-vinyltetrahydrofurane as a colorless oil.

(27) (a) *SMART V5.051 diffractometer control software*; Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1998. (b) *CrysAlisPro*, Version 1.171.33.48; Oxford Diffraction Ltd.: Abingdon, U.K.

(28) (a) *SAINT V6.02 integration software*; Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1999. (b) *CrysAlisPro*, Version 1.171.33.48; Oxford Diffraction Ltd.: Abingdon, U.K.

(29) (a) Sheldrick, G. M. *SADABS: A program for absorption correction with the Siemens SMART system*; University of Göttingen: Göttingen, Germany, 1996. (b) *CrysAlisPro*, Version 1.171.33.48; Oxford Diffraction Ltd.: Abingdon, U.K.

(30) *SHELXTL program system version 5.1*; Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1998.

(31) To correct the systematic shortening of N−H bonds measured by X-ray diffraction, normalized H atom positions were used. An N−H distance of 1.009 Å was imposed. This value has been observed in amines by neutron diffraction: Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

(32) *International Tables for Crystallography*; Kluwer: Dordrecht, The Netherlands, 1992; Vol. *C*.

(33) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Hua Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073.

(34) Chakraborti, A. K.; Sharma, L.; Gulhane, R. *Tetrahedron* **2003**, *59*, 7661–7668.

Cyclopropanation of Styrene with Propargyl Pivaloate. The gold catalyst was generated by mixing the corresponding neutral gold carbene (0.05 equiv), $AgSbF_6$ (0.05 equiv), and NO_2Me (3 mL) and stirring at room temperature for 10 min. Then, propargyl pivaloate (1 equiv) in NO_2Me (3 mL) and styrene (4 equiv) were added. The resulting suspension was stirred at room temperature and followed by TLC. The resulting mixture was concentrated and column chromatography purified (hexane/Et_2O 97:3) to yield the analytically pure cyclopropane.

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Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

Artículo V

Protection of the Gold(I) Catalyst by $AsPh_3$ in Reactions of Enynes

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Protection of the Gold(I) Catalyst by $AsPh_3$ in Reactions of Enynes

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Keywords: Carbene ligands / Enynes / Cyclization / Gold / Arsenic

Neutral gold complexes with hydrogen-bond-supported heterocyclic carbene (HBHC) and nitrogen acyclic carbene (NAC) ligands have been synthesized by the reactions of isocyanogold derivatives [AuCl(CNR)] with amines. Cationic [Au(carbene)($AsPh_3$)][SbF_6] complexes have also been prepared. The catalytic activity of both types of complex (for the former, $AgSbF_6$ is used to extract the halide ligand) in the skeletal rearrangement and methoxycyclization of enynes has been studied. The cationic complexes with $AsPh_3$ are active but slower; advantageously, they do not decompose during the catalysis. In contrast, the catalysts formed in situ from the neutral halide complexes are very fast but undergo decomposition. An interesting trade-off was found by adding substoichiometric amounts of $AsPh_3$ (e.g., 10 mol-%) relative to the gold catalyst {[Au(carbene)Cl] + $AgSbF_6$}, which prevents or dramatically reduces the decomposition. This protecting ligand promises to prevent or minimize the undesired decomposition of gold catalysts.

Introduction

The last two decades have seen major developments in Au^I-catalyzed processes, which usually employ cationic complexes.[1] These complexes, which activate unsaturated molecules towards nucleophilic attack by coordination of the double or triple bond to the Au^I cation, are often generated in situ by extraction of the halide ligand (X) from [AuXL] with a silver salt AgY.[2] Solutions of the compounds as contact or separated $[AuL]^+Y^-$ ion pairs can be formed.

It has been suggested that silver salts can interfere with or play a role in the catalysis;[3] hence, there is some interest in systems that avoid the in situ generation of the catalyst.[4] Ligand-stabilized cationic complexes [AuL(L′)]Y (L = phosphine, phosphite, carbene; L′ = nitrile, arene, etc.),[5] neutral systems [AuYL] in which Y^- is an effective leaving group [e.g., NTf_2^- (Tf = trifluoromethylsulfonyl)[6] or other weakly coordinating anions], and the versatile [Au(OH)(IPr)] [IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)][7] have been used as excellent catalysts for different processes. For instance, neutral gold(I) complexes with phosphine [Au(NTf_2)(PPh_3)], N-heterocyclic carbene (NHC) [Au(NTf_2)(NHC)],[8] and nitrogen acyclic carbene (NAC) ligands [Au(NTf_2)(NAC)][9] have been reported as catalysts that undergo easy NTf_2^- displacement by the incoming reagent. Cationic Au^I complexes [AuL(L′)]Y can often be isolated and handled under ordinary conditions.[10] Thus far, the ancillary stabilizing L′ ligands most commonly used in these cationic catalysts are nitriles with different substituents.[4] Simple molecules such as MeCN and PhCN can be used, but trimethoxybenzonitrile increases the stability of the cationic catalyst,[11] and complexes with hydrogen-bond-supported heterocyclic carbene (HBHC)[12] or NAC ligands have been used as catalysts.[13]

A frequent but hardly mentioned problem of gold catalysis is the formation of metallic gold during the catalysis or at the end of the process; in principle, this should be detrimental to the turnover number (TON) of the process and to the reusability of the catalyst.[14] As the residual activity of the catalyst is often not checked once the experiment has finished, it is difficult to estimate from the reported results whether the catalysts could be reused at all. The stabilization of catalysts that show obvious signs of decomposition should be welcome.

Recently, we observed a positive stabilizing effect upon the addition of $AsPh_3$ to a Au/Pd bimetallic catalytic system.[15] This has prompted us to examine the potential of $AsPh_3$ to stabilize gold catalysts as a stoichiometric (L/$AsPh_3$ 1:1) or substoichiometric additive. The total suppression of the decomposition was found in most cases. The effect of $AsPh_3$ on the recyclability of the catalyst was also investigated.

Results and Discussion

Synthesis and Structural Characterization of the Neutral and Cationic Gold Complexes

The complexes used for this study are shown in Scheme 1. The neutral carbene complexes **1b**–**1d** were prepared by the nucleophilic attack of an amine (the simplest

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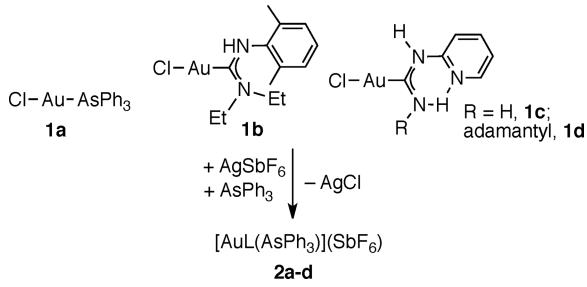
NH_3, the bulky 1-adamantylamine, and the commercially available Et_2NH) on gold isocyanide complexes.[9,12,13] The $AsPh_3$ cationic carbene complexes **2a**–**2d** were obtained by abstraction of the chloride ion with $AgSbF_6$ in the presence of 1 equiv. of $AsPh_3$. All of the complexes are colorless air-stable solids and were fully characterized.



Scheme 1. Synthesis of neutral and cationic gold complexes.

For the carbene complexes **1c** and **1d**, the ^1H NMR resonance at $\delta \approx 12$ ppm confirms the existence in solution of an intramolecular N–H–N hydrogen bond between the amide proton and the nitrogen atom of the 2-pyridyl (Py-2) group to form a six-membered cycle.[12a,16] Although four stereoisomers are possible for each gold center in the gold HBHC complexes derived from primary amines, only one was observed.

The ORTEP representation of the molecular structure of $[AuCl\{C(NH_2)(NHPy\text{-}2)\}]_3{\cdot}OC_4H_8$ (**[1c]**·OC_4H_8) is shown in Figure 1 along with selected bond lengths and angles. The structure is a polymeric chain, in which the asymmetric unit is a trimer with Au···Au distances in the range of other previously proposed attractive aurophilic interactions [Au(1)···Au(2) 3.3457(9) Å, Au(2)···Au(3) 3.3426(9) Å].[17] These trimeric units self-associate to form extended chains connected by somewhat longer (3.493 Å) intertrimer Au···Au interactions. In addition to the aurophilic interactions, intermolecular N–H···Cl hydrogen bonds within the usual range for H···Cl distances[18] reinforce the formation of the trimers and the chains in the crystal network (Table 1). Similar intermolecular contacts have been previously reported for analogous HBHC gold systems in the solid state.[12a,13,16] The polynuclear structure is not expected to survive in solution under catalytic conditions, and a monomeric linear structure is assumed.

The X–Au–L geometry around the gold atom is always linear. The Au–Cl and Au–C distances are similar to those of other carbene gold(I) complexes.[12,13,16,19] The conformer found in the structure is determined by the formation of a hydrogen bond between the N–H group formerly of the ammonia molecule and the pyridyl group. The H···N distance and the corresponding N–H···N angle are within the range of moderate intramolecular N···H hydrogen bonds.[20] Selected hydrogen bond lengths and angles are presented in Table 1.[21] The ^1H NMR spectrum confirms that this intramolecular H bond is retained in chloroform and acetone solution, as observed for all of the related complexes that our group reported previously.[12a,13,16]

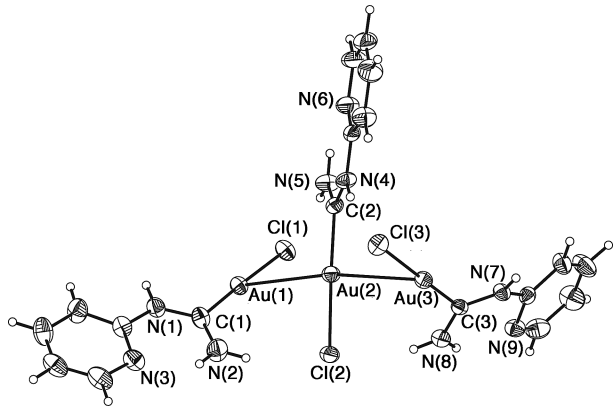


Figure 1. X-ray structure of **[1c]**·OC_4H_8; the tetrahydrofuran molecule is omitted for clarity. Selected bond lengths [Å] and angles [°]: Au(1)–Cl(1) 2.311(2), Au(1)–C(1) 1.992(9), C(1)–N(1) 1.337(10), C(1)–N(2) 1.301(11), Au(2)–Cl(2) 2.312(2), Au(1)–C(1) 1.987(8), C(2)–N(5) 1.291(10), C(2)–N(4) 1.372(10), Au(3)–Cl(3) 2.309(2), Au(3)–C(3), 1.970(8), C(3)–N(7) 1.330(9), C(3)–N(8) 1.342(9), Au(1)–Au(2) 3.3457(9), Au(2)–Au(3) 3.3426(9); C(1)–Au(1)–Cl(1) 178.0(3), N(2)–C(1)–N(1) 116.8(8), C(2)–Au(2)–Cl(2) 177.7(2), N(5)–C(2)–N(4) 117.7(8), C(3)–Au(3)–Cl(3) 175.7(2), N(7)–C(3)–N(8) 116.4(7).

Table 1. Selected bond lengths [Å] and angles [°] for the hydrogen bonds observed in **[1c]**·OC_4H_8.

Intramolecular N–H···N hydrogen bonds			
N(3)···H(2A)	1.842(2)	N(2)–H(2A)···N(3)	132.18(3)
N(6)···H(5A)	1.908(2)	N(6)–H(5A)···N(5)	130.3(3)
N(9)···H(8A)	1.880(2)	N(8)–H(8A)···N(9)	130.1(3)
Intermolecular N–H···Cl hydrogen bonds			
Cl(1)···H(5B)	2.321(2)	Cl(1)···H(5B)–N(5)	164.31(3)
Cl(2)···H(2B)	2.261(2)	Cl(2)···H(2B)–N(2)	160.72(3)
Cl(2)···H(8B)	2.286(2)	Cl(2)···H(8B)–N(2)	160.16(3)
Cl(3)···H(4B)	2.298(2)	Cl(3)···H(4B)–N(4)	167.95(3)

The complex $[Au\{C(NEt_2)(NHxylyl)\}(AsPh_3)][SbF_6]$ (**2b**) was also studied by X-ray diffraction as an example of a cationic complex with $AsPh_3$.

The molecular structure of **2b** is shown in Figure 2 with selected bond lengths and angles. As observed for **1c**, **2b** shows a nearly linear geometry and has a C(1)–Au(1)–As(1) angle of 177.4(4)° and typical Au–C and C–N bond lengths. The conformer found for **2b** has the xylyl group oriented away from the ethyl groups of the amine moiety; this orientation reduces the intramolecular hindrance in the carbene moiety. This kind of stereoisomer has been systematically found in other solid-state structures of related neutral complexes such as $[Au(C{\equiv}C\textit{p}\text{-}R\text{-}C_6H_4)\{C(NH\textit{t}Bu)(NEt_2)\}]$ (R = NO_2, $\textit{p}\text{-}NO_2\text{–}C_6H_4$, (*E*)-CH=CH$\textit{p}$-$NO_2$–$C_6H_4$),[22] $[Au(\textit{C}\text{-acac})\{C(NEt_2)(NH\textit{t}Bu)\}]$ (acac = acetylacetonate), $[\{AuC(NEt_2)(NH\textit{t}Bu)\}_2(\mu\text{-}C{\equiv}CC_6H_4C{\equiv}C)]$, $[Au\{C(NEt_2)(NH\textit{t}Bu)\}\{CH_2S(O)Me_2\}]ClO_4$,[23] and $[AuR\{C(NEt_2)(NHPy\text{-}4)\}]$ [Py-4 = 4-pyridyl, R = C_6F_5, 2,4,6-tris(trifluoromethyl)phenyl (Fmes)].[19a]

The catalytic activities of the synthesized gold complexes with carbene and arsine ligands were tested in the cyclization and methoxycyclization of 1,6-enynes under different

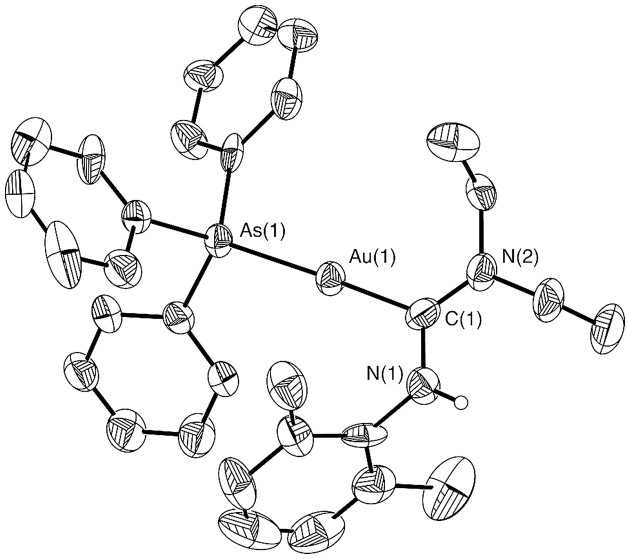


Figure 2. X-ray structure of **2b**. Selected bond lengths [Å] and angles [°]: Au(1)–C(7) 2.022(13), Au(1)–As(1) 2.3769(13), C(1)–N(2) 1.312(14), C(1)–N(1) 1.318(15); C(1)–Au(1)–As(1) 177.4(4), N(2)–C(1)–N(1) 118.2(13).

conditions. The very popular complex [AuCl(PPh_3)] (**3**) was also used as a reference in some reactions.

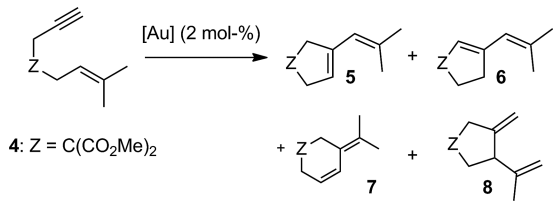
Catalytic Reactions

Skeletal Rearrangement of 1,6-Enyne 4

The catalytic results obtained for the gold-catalyzed cyclization of dimethyl 2-(3-methyl-2-butenyl)-2-(2-propynyl)-malonate (**4**) are summarized in Table 2.

When catalyst decomposition was clear (the appearance of purple nanoparticles or a dark precipitate), this is indicated in the table. Up to three different products were observed in these reactions: the product of the *exo* cyclization, **5**; the product of the *endo* cyclization, **7**; and the diene **6**, formed from **5** by isomerization of the endocyclic double bond. In one case, a fourth product, **8**, was also observed (see below). Both **3** and [AuCl($AsPh_3$)] (**1a**) are perfectly stable under silver-free catalytic conditions but do not catalyze any of the reactions discussed here. However, in contrast to [Au(PPh_3)$_2$][SbF_6], which is very stable but totally inactive, the cationic [Au($AsPh_3$)$_2$][SbF_6] (**2a**) does catalyze the cyclization of **4** at a reasonable rate and provides quantitative conversion in 30 min (Table 2, Entry 1). Interestingly, the reaction mixture did not show any sign of catalyst decomposition. The stability of this catalyst allowed us to perform recycling tests. This activity proved that the catalyst was active, but its practicality was severely affected by the difficulty to efficiently recover the small proportion of catalyst between experiments (Table 3, for details of the procedure, see Exp. Sect.). Moreover, when the amount of **2a** was reduced to 0.02 mol-%, the cyclization still occurred efficiently, although at a slower rate (72% conversion in 4 d), and no decomposition to gold was observed.

Table 2. Skeletal rearrangement of enyne **4**.



Entry	[Au]	AgX	Time/conversion [%][a] (Au reduction)	Yield **5/6/7**/ other [%][a]
1	**2a**[b]	–	30 min/100	83:0:17:0
2	**2b**[b]	–	4 d/95	95:0:0:0
3	**2b**[c]	–	15 h/100	88:9:3:0
4	**2c**[b]	–	6 d/30	23:0:7:0
5	**2c**[c]	–	5 h/100	83:0:17:0
6	**2d**[b]	–	15 h/32	25:0:7:0
7	**2d**[c]	–	5 h/50	19:0:0:31
8	**1a**[b]	[d]	3 h/100 (deep purple)	8:10:0:82
9	**1a**[b]	[e]	3 h/100 (very pale purple)	9:8:0:83
10	**3**[b]	[d]	25 min/98 (very pale purple)	34:49:15:0
11	**3**[b]	[e]	3 h/92	28:46:18:0
12	**1b**[b]	[d]	5 min/100 (deep purple)	100:0:0:0
13	**1b**[b]	[e]	5 min/100	61:37:2:0
14	**1c**[b]	[d]	5 min:100 (deep purple)	98:0:2:0
15	**1c**[b]	[e]	5 min/100	83:0:17:0
16	**1d**[b]	[d]	5 min/100 (deep purple)	95:0:0:0
17	**1d**[b]	[e]	5 min/100	88:9:3:0

[a] Determined by ^{1}H NMR spectroscopy of the isolated solids. [b] Solvent CH_2Cl_2, 25 °C. [c] Solvent 1,2-dichloroethane, 85 °C. [d] Reactions with 2 mol-% [Au] and 2 mol-% $AgSbF_6$. [e] Reactions with 2 mol-% [Au], 2 mol-% $AgSbF_6$, and 0.2 mol-% $AsPh_3$.

Table 3. Recycling of **2a**.

Cycle	Conversion/time	**5/6/7** [%]
First	100/30 min	76:3:21
Second	100/16 h	86:2:12
Third	100/36 h	90:0:10
Fourth	92/96 h	64:20:8
Fifth	40/96 h	35:2:3

These exciting results suggested a possible simple solution to the problem of the instability of some gold catalysts. Thus, other catalysts and conditions were investigated to explore the generality of the $AsPh_3$ effect.

In reactions with other [AuClL] complexes with $AgSbF_6$ as the halide extractor and no stabilizing additive, we found a high yield of the products (**5–7**) and a fast reaction rate for **3** (25 min, 98%, Table 2, Entry 10), in agreement with previously reported results.[24] In contrast, extensive catalyst decomposition and a poor yield were obtained for **1a** with $AgSbF_6$ (Table 2, Entry 8). The conversion was high, but the reaction was not clean, and a mixture containing high percentages of other unidentified products was obtained. For the three carbene-containing catalysts **1b**–**1d** (Table 2, Entries 12, 14, and 16), the reactions proceeded well or very well and were usually very fast, but decomposition of the catalyst was observed in all cases.

The carbene complexes [AuL($AsPh_3$)][SbF_6] (**2b**–**2d**) can be prepared in situ or isolated (Scheme 1) and used as catalysts to avoid the in situ use of silver. In our tests, they were

used as isolated complexes. They were active cyclization catalysts, although the rearrangement reactions were noticeably slower than they were with **2a**. However, it was promising that no decomposition was observed for any of the catalysts, even after long reaction times. For instance, **2b** produced a 95% conversion and no traces of Au^0 after 4 d at room temperature (Table 2, Entry 2). In the other cases (Table 2, Entries 4 and 6), the much lower yields for similar or longer reaction times suggest that the reaction rates were slower; again, no traces of decomposition were observed. Fortunately, the stability of these catalysts allowed us to increase the temperature of the reaction to 85 °C (in 1,2-dichloroethane), which dramatically increased the reaction rate. Under these new reaction conditions, **2b** and **2c** led to the nearly quantitative cyclization of **4** in a few hours rather than days (Table 2, Entries 3 vs. 2 and 5 vs. 4). For **2d**, containing the bulkiest carbene ligand, the nonconjugated diene **8**, which was not observed in the reactions at room temperature, was the major product (50% conversion, 19% yield of **5** and 31% yield of **8**; Table 2, Entry 7). This reaction was still slow at 85 °C. Diene **8** has been previously observed in cyclizations with [Au(*o*-biphenP*t*Bu$_2$)(NCMe)][SbF_6] [*o*-biphenP*t*Bu$_2$ = di-*tert*-butyl(2-phenylphenyl)phosphane][24] or with gold nanoparticles supported on TiO_2.[25]

To find a good compromise between catalyst stability and reaction rate, the activity of **1a**–**1d** was examined for the in situ reaction with $AgSbF_6$ in the presence of a substoichiometric amount of $AsPh_3$ (Table 2, Entries 9, 13, 15, and 17). Thus, the addition of 10 mol-% of $AsPh_3$ relative to [AuCl($AsPh_3$)] (i.e., 2 mol-% of Au catalyst and 0.2 mol-% of added $AsPh_3$) and the silver salt noticeably decreased the formation of Au^0; however, the reaction was not clean, and the yield of the cyclization products did not improve (Table 2, Entry 9 vs. 8). For comparison, the presence of 0.2 mol-% of $AsPh_3$ in the reaction with **3** totally inhibited the small amount of decomposition to metallic gold. The reaction became slower, and the yield of cyclization products was nearly the same as that obtained in the absence of $AsPh_3$ (3 h, 92%; Table 2, Entry 11).[26] An excellent result was obtained for the reactions of **1b**–**1d** with $AgSbF_6$ in the presence of 0.2 mol-% of $AsPh_3$. The yields were as good as those obtained in the absence of arsine,[12,13] but, interestingly, the reduction of the catalyst to Au^0 was totally suppressed (Table 2, Entries 13, 15, and 17).

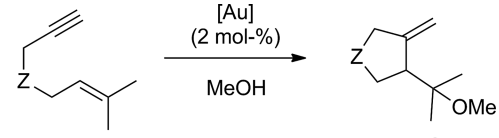
As observed for the experiments with **2a**–**2c**, the catalysts stabilized by the addition of $AsPh_3$ remain active once the reaction has finished; this provides a method to achieve higher turnover numbers with lower catalyst loadings or recyclable catalysts and allows higher reaction temperatures that compensate for the otherwise lower reaction rates. As a further example, the loading of catalyst [AuCl{C(NH_2)(NHPy-2)}] (**1c**) in the presence of a substoichiometric amount of $AsPh_3$ could be reduced twenty times (0.1 mol-% **1c**, 0.01 mol-% of added $AsPh_3$), and the reaction was still very fast. No decomposition of the Au^I carbene complex was observed, and 100% conversion was obtained in 5 min.

Overall, the results in Table 2 provide some interesting hints for the understanding of the observed effects: (1) complex **2a** is very active and stable under catalytic conditions, (2) complexes [Au(carbene)($AsPh_3$)][SbF_6] are also stable but much less active (slower rates), (3) the addition of substoichiometric amounts of $AsPh_3$ to in situ reactions with $AgSbF_6$ efficiently stabilizes the catalysts produced from the halide precursors, and only the arsine complex **1a** still produces some traces of Au^0 during its use as catalyst, and (4) the stabilization by added $AsPh_3$ takes place at the cost of an important reduction of the reaction rate. The requirement of added arsine for stabilization seems to be related to the donor ability of the main ligand L: no added $AsPh_3$ is needed for L = PPh_3 and substoichiometric $AsPh_3$ is needed for L = carbene, but the same amount of $AsPh_3$ is not sufficient for total stabilization when L is the weaker donor $AsPh_3$.

Methoxycyclization of 1,6-Enyne

The effects of $AsPh_3$ observed for the cyclization of **4** were further investigated in the methoxycyclization of **4**.[2,27] The protecting effect of $AsPh_3$ was very similar to that observed previously. The results are collected in Table 4. The potential competitive formation of rearrangement products was not observed, and only the methoxycyclization product **9** was isolated.

Table 4. Methoxycyclization of enyne **4**.



4: Z = C(CO_2Me)$_2$ **9**

Entry	[Au]	AgX	Time/conversion [%][a] (Au reduction)	Yield [%][a]
1	**1a**[b]	[c]	15 h/95	88
2	**1a**[b]	[d]	15 h/95	91
3	**2a**[b]	–	15 h/89	78
4	**1b**[b]	[c]	2 h/100 (deep purple)	99
5	**1b**[b]	[d]	2 h/100 (very pale purple)	99
6	**2b**[b]	–	96 h/37	32
7	**2b**[e]	–	48 h/88	84
8	**1c**[b]	[c]	24 h/9 (purple)	6
9	**1c**[b]	[d]	15 h/59	57
10	**2c**[b]	–	96 h/–	–
11	**2c**[e]	–	48 h/8	4
12	**1d**[b]	[c]	15 h/95 (deep purple)	76
13	**1d**[b]	[d]	15 h/95	93
14	**2d**[b]	–	96 h/24	20
15	**2d**[e]	–	48 h/77	75

[a] Determined by ^{1}H NMR spectroscopy of the isolated solids. [b] Solvent MeOH, 25 °C. [c] Reactions with 2 mol-% [Au] and 2 mol-% $AgSbF_6$. [d] Reactions with 2 mol-% [Au], 2 mol-% $AgSbF_6$, and 0.2 mol-% $AsPh_3$. [e] Solvent MeOH, 70 °C.

As previously reported,[24] **1a** is an excellent precatalyst for the methoxycyclization of **4**, and **9** was obtained in very good yields (Table 4, Entry 1).[28] The same reaction with **1b** or **1d** and $AgSbF_6$ afforded **9** (Table 4, Entries 4 and 12);[13] however, the reduction of the Au^I complex to Au^0

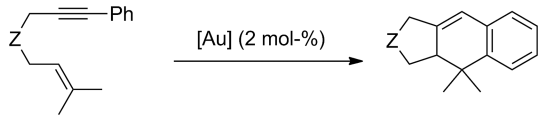
was observed. The reactions of **1a**–**1d** with 0.2 mol-% of $AsPh_3$ in the presence of $AgSbF_6$ led to the formation of **9** in very good yields (Table 4, Entries 2, 5, 9, and 13). Again, no decomposition of the catalyst was observed for **1a**–**1d** in the presence of substoichiometric amounts of $AsPh_3$.

As observed in the skeletal rearrangement described above, the cationic **2a** afforded **9** in 78% isolated yield after 15 h at room temperature (Table 4, Entry 3), and the reaction did not show any sign of decomposition. The conversions with carbene complexes **2b** and **2d** were very low even after long reaction times (Table 4, Entries 6 and 14). No conversion was observed with the ammonia derivative **2c** as catalyst (Table 4, Entry 10). The reaction was accelerated at higher temperature, and higher conversion was obtained without decomposition of the catalyst at 70 °C in methanol (Table 4, Entries 7 and 15). Complex **2c** was again less active, and only an 8% conversion was observed at the same time and temperature (Table 4, Entry 11).

Cyclization of 1,6-Enyne 10

We also examined the cyclization of the internal enyne dimethyl 2-(3-methyl-2-butenyl)-2-(3-phenyl-2-propynyl)-malonate (**10**). The results are summarized in Table 5.

Table 5. Cyclization of enyne **10**.



10: Z = $C(CO_2Me)_2$ **11**

Entry	[Au]	AgX	Time/conversion [%][a] (Au reduction)	Yield [%][a]
1	**1a**	[b]	4 h/100 (deep purple)	79
2	**1a**	[c]	4 h/100 (very pale purple)	82
3	**3**	[b]	12 h/100	83[29]
			2 h/100 (purple)	58
4	**3**	[c]	3 h/92 (very pale purple)	87
5	**1b**	[b]	4 h/100 (deep purple)	93
6	**1b**	[c]	4 h/100 (very pale purple)	98
7	**1d**	[b]	4 h/100 (deep purple)	96
8	**1d**	[c]	20 h/100	97

[a] Determined by ^1H NMR spectroscopy of the isolated solids. [b] Reactions with 2 mol-% [Au] and 2 mol-% $AgSbF_6$. [c] Reactions with 2 mol-% [Au], 2 mol-% $AgSbF_6$, and 0.2 mol-% $AsPh_3$. Solvent CH_2Cl_2 at 25 °C.

The [4+2] cycloaddition reaction of **10** proceeded at room temperature with **1a**, **1b**, or **1d** as precatalyst to afford **11** in very good yields (Table 5, Entries 1, 5, and 7), comparable to those obtained under similar conditions with other NAC or HBHC precatalysts[12,13] or with Au^I phosphine complexes (Table 5, Entry 3).[29]

Again, the addition of 0.2 mol-% of $AsPh_3$ in the presence of $AgSbF_6$ dramatically reduced the deposition of Au^0 that had been clearly observed in the absence of arsine (Table 5, Entries 2, 4, 6, and 8). By contrast, the cationic catalysts **2a**–**2d** failed in this cyclization, although no decomposition was observed even after long reaction times in dichloromethane. Different solvents and temperatures (1,2-dichloroethane at 85 °C) produced some conversion to **11**, but the reaction was still very slow.

Conclusions

The use of substoichiometric $AsPh_3$ as an additive prevents or minimizes the undesired decomposition of gold catalysts, and the reaction rates remain acceptable. Moreover, by tuning the amount of $AsPh_3$, the catalyst load can be reduced, although longer reaction times are required. The lower reaction rate in the presence of $AsPh_3$ can be compensated by using somewhat higher reaction temperatures, taking advantage of the stabilization of the catalyst. It is most interesting that, in the presence of arsine, concentrations of the gold catalyst one or two orders of magnitude below their routine use are still sufficient for a fast catalysis in one run. Catalyst recycling is less efficient owing to mechanical loss during the recovery of the very small amounts of catalyst used.

Experimental Section

General: All reactions were performed under dry N_2. Solvents were purified according to standard procedures.[30] Complexes [AuCl($AsPh_3$)] (**1a**),[29] [Au($AsPh_3$)$_2$][SbF_6] (**2a**),[31] [AuCl{C(NEt$_2$)(NHxylyl)}] (**1b**),[13] and [AuCl(PPh_3)] (**3**)[32] and enynes dimethyl 2-(3-methyl-2-butenyl)-2-(2-propynyl)malonate (**4**)[33] and dimethyl 2-(3-methyl-2-butenyl)-2-(3-phenyl-2-propynyl)malonate (**10**)[29] were prepared according to literature procedures. The rest of the reactants are commercially available. The infrared spectra were recorded with Perkin–Elmer 883 or 1720X instruments. The NMR spectra were recorded with Bruker Avance 400 Ultrashield, Varian 400-MR, and Varian 500/54 Premium Shielded instruments. The ^1H NMR spectra were referenced to tetramethylsilane (TMS). The elemental analyses were performed with a Perkin–Elmer 2400B microanalyzer.

[AuCl{C(NH$_2$)(NHPy-2)}] (1c): An aqueous solution of ammonia (76 μL, 1 mmol, 25% w/w) was added to a solution of [AuCl(CNPy-2)][16] (336.5 mg, 1 mmol) in CH_2Cl_2 (20 mL), and the resultant solution was stirred at room temperature. After 5 min, the IR spectrum of the solution did not show any ν(C≡N) bands. The volatiles were removed in vacuo, and the white residue was recrystallized from tetrahydrofuran/hexane (THF/hexane). The colorless solid obtained was washed with hexane (3 × 10 mL) and vacuum-dried to yield **1c** (342.0 mg, 97%). ^1H NMR (300 MHz, [D_6]acetone, 295 K): δ = 11.79 (br., 1 H, NH), 11.22 (br., 1 H, NH), 8.95 (br., 1 H, N*H*C$_5$H$_4$N), 8.37 (d, J = 3.2 Hz, 1 H, NHC$_5$*H*$_4$N), 7.91 (m, 1 H, NHC$_5$*H*$_4$N), 7.26 (m, 2 H, NHC$_5$*H*$_4$N) ppm. $C_6H_7AuClN_3$ (353.56): calcd. C 20.38, H 2.00, N 11.88; found C 20.44, H 2.10, N 11.58.

[AuCl{C(NHadamantan-1-yl)(NHPy-2)}] (1d): Complex **1d** was obtained similarly from 1-adamantylamine (74.0 mg, 0.49 mmol) and [AuCl(CNPy-2)] (150.0 mg, 0.46 mmol) in THF (20 mL), yield 144.0 mg (98%). ^1H NMR (400 MHz, $CDCl_3$, 295 K): δ = 12.84 (br., 1 H, NH) 8.89 (br., 1 H, N*H*C$_5$H$_4$N), 8.20 (d, J = 4 Hz, 1 H, NHC$_5$*H*$_4$N), 7.71 (m, 1 H, NHC$_5$*H*$_4$N), 7.06 (m, 2 H, NHC$_5$H$_4$N), 2.34 (m, 6 H, CH_2), 2.12 (m, 3 H, CH), 1.66 (m, 6 H, CH_2) ppm. $C_{16}H_{21}AuClN_3$ (487.78): calcd. C 39.40, H 4.34, N 8.61; found C 39.63, H 4.31, N 8.70.

[Au(AsPh$_3$){C(NEt$_2$)(NHxylyl)}][SbF$_6$] (2b): AgSbF$_6$ (102.0 mg, 0.280 mmol) and AsPh$_3$ (87.0 mg, 0.280 mmol) were added to a solution of **1b** (122.0 mg, 0.280 mmol) in CH_2Cl_2 (15 mL). A colorless precipitate appeared immediately. The mixture was stirred for 5 h and then filtered (double HPLC Teflon® filter). The addition of pentane (5 mL) precipitated the cationic complex **2b** as a colorless solid, which was collected by filtration, washed with pentane (3× 5 mL), and vacuum-dried (218.0 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ = 7.91 (br. s, 1 H, NH), 7.54–7.43 [m, 9 H, As(C_6H_5)$_3$], 7.18–7.16 [m, 6 H, As(C_6H_5)$_3$], 7.12–7.02 (m, 3 H, ArH), 3.91 (q, J = 8.0 Hz, 2 H, NCH_2CH$_3$), 3.66 (q, J = 8.0 Hz, 2 H, NCH_2CH$_3$), 2.28 (s, 6 H, Ar–CH$_3$), 1.41 (t, J = 7.2 Hz, 3 H, NCH$_2$CH_3), 1.40 (t, J = 7.2 Hz, 3 H, NCH$_2$CH_3) ppm. $C_{31}H_{35}AsAuF_6N_2Sb$ (943.26): calcd. C 39.47, H 3.74, N 2.97; found C 39.61, H 3.88, N 3.06.

[Au(AsPh$_3$){C(NH$_2$)(NHPy-2)}][SbF$_6$] (2c): AgSbF$_6$ (39.0 mg, 0.11 mmol) and AsPh$_3$ (34.0 mg, 0.11 mmol) were added to a solution of **1c** (40.0 mg, 0.11 mmol) in CH_2Cl_2 (15 mL). A colorless precipitate appeared immediately. The mixture was stirred for 2 h and then filtered (double HPLC Teflon® filter). The addition of Et_2O (5 mL) led to the formation of the cationic complex as a colorless air-stable precipitate, which was collected by filtration, washed with Et_2O (3× 5 mL), and air-dried (67.2 mg, 71%). ^{1}H NMR (400 MHz, [D$_6$]acetone, 295 K): δ = 11.87 (br. s, 1 H, NH), 10.36 (br. s, 1 H, NH), 9.04 (br. s, 1 H, NH), 8.42 (m, 1 H, NHC$_5H_4$N), 7.96 (m, 1 H, NHC$_5H_4$N), 7.55–7.44 [m, 15 H, As(C_6H_5)$_3$], 7.29 (m, 1 H, NHC$_5H_4$N) ppm. $C_{24}H_{22}AsAuF_6N_3Sb$ (860.08): calcd. C 33.51, H 2.78, N 4.89; found C 33.76, H 3.03, N 4.95.

[Au(AsPh$_3$){C(NHadamantan-1-yl)(NHPy-2)}][SbF$_6$] (2d): AgSbF$_6$ (46.0 mg, 0.13 mmol) and AsPh$_3$ (41.0 mg, 0.13 mmol) were added to a solution of **1d** (65.0 mg, 0.13 mmol) in CH_2Cl_2 (15 mL). A colorless precipitate appeared immediately. The mixture was stirred for 5 h and then filtered (double HPLC Teflon® filter). The addition of hexane (5 mL) led to the formation of the cationic complex as a colorless air-stable precipitate, which was collected by filtration, washed with hexane (3× 5 mL), and air-dried (112.0 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$, 295 K): δ = 13.43 (br. s, 1 H, NH, conformer A), 13.24 (br. s, 1 H, NH, conformer B), 9.26 (br. s, 1 H, NH, conformer C), 9.23 (br. s, 1 H, NHC$_5$H$_4$N, conformer A), 8.87 (br. s, 1 H, NHC$_5$H$_4$N, conformer B), 8.18 (m, 1 H, NHC$_5H_4$N), 8.01 (br. s, 1 H, NH, conformer C), 7.86–7.61 (m, 1 H, NHC$_5H_4$N), 7.59–7.43 [m, 15 H, As(C_6H_5)$_3$], 7.43–6.97 (m, 2 H, NHC$_5H_4$N), 2.36–1.18 (m, 15 H, CH$_2$ and CH) ppm; conformers A/B/C ratio, 1:0.6:0.4. $C_{34}H_{36}AsAuF_6N_3Sb$ (994.30): calcd. C 41.07, H 3.65, N 4.23; found C 41.23, H 3.91, N 4.41.

Catalytic Procedures: All reactions were performed under N_2 in dry CH_2Cl_2 [dried with a solvent purification system (SPS)]. Thin layer chromatography was performed with aluminum TLC sheets with 0.2 mm of silica gel (Merck GF234). Chromatography purifications were performed with flash grade silica gel (SDS S-2 Chromatogel 60 ACC, 40–60 μm).

Procedure for the Skeletal Rearrangement of 1,6-Enynes with 1a–1d and 3: A solution of the enyne (0.2 mmol) in CH_2Cl_2 (1 mL) was added to a mixture of the Au^I chloro complex (4×10^{-3} mmol), $AgSbF_6$ (1.40 mg, 4×10^{-3} mmol), and $AsPh_3$ (4×10^{-4} mmol, 816 μL, 4.9×10^{-4} M in CH_2Cl_2) in CH_2Cl_2 (1 mL).[34] The reaction was monitored by NMR spectroscopy or TLC, quenched with a drop of a 0.1 M solution of NEt_3 in hexane, and then directly purified through a short column of silica (AcOEt/hexane) to give the organic products.

Procedure for the Skeletal Rearrangement of 1,6-Enynes with 2a–2d: A solution of the enyne (0.2 mmol in 1 mL of CH_2Cl_2) was added to a solution of the corresponding cationic Au^I complex (4×10^{-3} mmol) in CH_2Cl_2 (1 mL). The reaction was monitored by NMR spectroscopy or TLC, quenched with a drop of a 0.1 M solution of NEt_3 in hexane, and then directly purified through a short column of silica (AcOEt/hexane) to give the organic products.

Skeletal Rearrangement of 4 with 1c: $AgSbF_6$ (0.1 mol-%, 100 μL of a 2×10^{-3} M solution of $AgSbF_6$ in acetone) and $AsPh_3$ (0.01 mol-%, 50 μL of a 4×10^{-4} M solution of $AsPh_3$ in CH_2Cl_2) were placed in a flame-dried Schlenk flask, and the volatiles were removed in vacuo. Complex **1c** (0.0710 mg, 2×10^{-4} mmol) was added, and the solids were dissolved in CH_2Cl_2 (1 mL). A solution of **4** (48.0 mg, 0.2 mmol in 1 mL of CH_2Cl_2) was added, and the reaction was monitored by NMR spectroscopy. After 5 min, the conversion was 100% as calculated by NMR spectroscopy. To record the NMR spectra, an aliquot of 20 μL was quenched with a drop of a 0.1 M solution of NEt_3 in dichloromethane. Then, the volatiles were removed in vacuo, and CH_2Cl_2 was added. The solution was filtered through silica, the volatiles were evaporated under vacuum, and the residue was dissolved in $CDCl_3$.

Procedure for the Recycling of 2a: A solution of **4** (48.0 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **2a** (4.20 mg, 4×10^{-3} mmol) in CH_2Cl_2 (1 mL). The reaction was monitored by NMR spectroscopy. Upon completion, the volatiles were removed, and the cyclization product was extracted with hexane and filtered through silica gel. Catalyst **2a** was recovered as a colorless solid. Its purity was confirmed by NMR spectroscopy. The residue was dissolved in CH_2Cl_2 (1 mL) and mixed with another solution of **4** (48.0 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) to perform a new cyclization reaction. It should be noted that the physical loss of the catalyst is probably important in the decrease in activity after each cycle.

Methoxycyclization of 4 with 1a–1d: A solution of **4** (48.0 mg, 0.2 mmol) in MeOH (1 mL) was added to a mixture of the Au^I complex (4×10^{-3} mmol), $AgSbF_6$ (1.40 mg, 4×10^{-3} mmol), and $AsPh_3$ (4×10^{-4} mmol, 816 μL, 4.9×10^{-4} M in CH_2Cl_2) in MeOH (1 mL).[35] The reaction was monitored by NMR spectroscopy or TLC and then directly purified by filtration through a short column of silica (AcOEt/Hexane) to give the corresponding compounds.

Methoxycyclization of 4 with 2a–2d: A solution of **4** (48.0 mg, 0.2 mmol in 1 mL of MeOH) was added to a solution of the corresponding cationic Au^I complex (4×10^{-3} mmol) in MeOH (1 mL). The reaction was monitored by NMR spectroscopy or TLC and then directly purified through a short column of silica (AcOEt/hexane) to give the corresponding compound.

X-ray Crystallography: Suitable single crystals of **1c** and **2b** were obtained by layering hexane over dichloromethane solutions of the corresponding compounds. The crystals were mounted on glass fibers, and the diffraction measurements were performed with a Bruker SMART CCD area-detector diffractometer with Mo-K_α radiation (λ = 0.71073 Å).[36] The intensities were integrated from several series of exposures; each exposure covered 0.3° in ω, and the total data set was a hemisphere.[37] Absorption corrections were applied on the basis of multiple and symmetry-equivalent measurements.[38] The structures were solved by direct methods and refined by least-squares techniques on weighted F^2 values for all reflections (see Table 6).[39] All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. All hydrogen atoms, including those involved in hydrogen bonding, were calculated with a riding model. Complex neutral-atom scattering factors were used.[40]

Table 6. Crystal data and structure refinement for **1c** and **2b**.

	1c	**2b**
Empirical formula	$C_{7.33}H_{9.67}AuClN_3O_{0.33}$	$C_{31}H_{35}AsAuF_6N_2Sb$
Formula weight	1032.8	943.25
Temperature [K]	293(2)	293(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	triclinic	orthorhombic
Space group	$P\bar{1}$	*Pbca*
a [Å]	10.144(2)	16.4233(6)
b [Å]	11.572(3)	17.8431(7)
c [Å]	15.700(4)	22.9145(8)
α [°]	109.64(4)	90
β [°]	93.42(4)	90
γ [°]	113.64(4)	90
V [Å^3]	1548.9(6)	6714.9(4)
Z	6	8
$D_{calcd.}$ [g cm^{-3}]	2.429	1.866
Absorption coefficient [mm^{-1}]	14.463	6.203
F(000)	1040	3616
Crystal size [mm]	0.35 × 0.15 × 0.12	0.25 × 0.23 × 0.02
θ range for data collection [°]	2.01 to 25.42	2.28 to 27.88
Reflections collected	12322	14801
Independent reflections	5617	6933
Absorption correction	SADABS	analytical
Maximum and minimum transmission factor	1 and 0.190394	0.934 and 0.645
Data/restraints/parameters	5617/20/344	6933/0/383
Goodness-of-fit on F^2	1.020	0.928
R_1 [$I > 2\sigma(I)$]	0.0399	0.0621
wR_2 (all data)	0.1055	0.1024

CCDC-970372 (for **1c**) and -970373 for (for **2b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Anexo:

Resumen de Resultados en Estancia Breve

Resumen resultados de estancia breve

Como anexo a las publicaciones anteriores, se presenta a continuación un breve resumen del trabajo realizado en una estancia breve llevada a cabo en el periodo de beca de esta tesis doctoral durante los meses de enero y febrero de 2012 en el grupo de investigación del Profesor T. Brent Gunnoe, de la Universidad de Virginia, E.E.U.U.

Los resultados más relevantes se publicaron en el artículo:

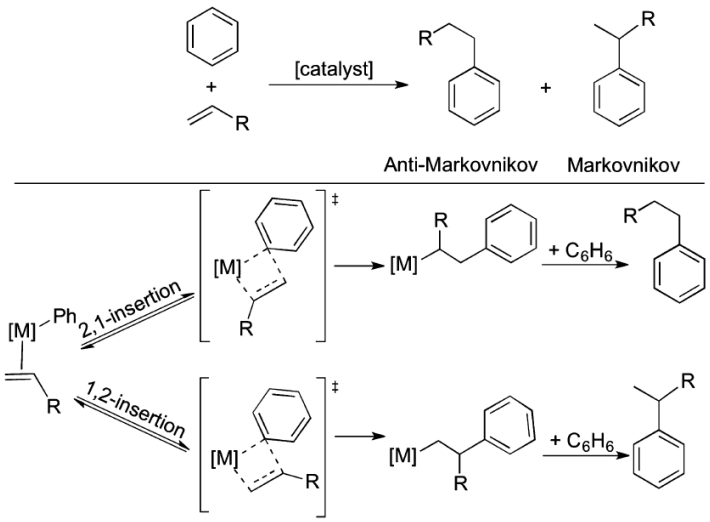
"Pt^{II}-Catalyzed Hydrophenylation of α-Olefins: Variation of Linear/Branched Products as a Function of Ligand Donor Ability"

McKeown, B. A.; Prince, B. M.; Ramiro, Z.; Gunnoe, T. B.; Cundari, T. R.

ACS Catal. **2014**, *4,* 1607−1615

El principal objetivo de este trabajo consistió en utilizar catalizadores de Pt^{II} para llevar a cabo reacciones de hidroarilación de olefinas sustituidas, con el fin de entender los factores que influyen en su regioselectividad, lo que permitiría controlar y mejorar esta reacción.

Cuando se utilizan como sustratos olefinas sustituidas, existe la posibilidad de obtener los productos anti-Markovnikov o Markovnikov (Esquema A1).



Esquema A1. Hidrofenilación de α-olefinas catalizada por metales de transición

El producto anti-Markovnikov, lineal, resulta de una inserción 2,1 y se ha descrito que se obtiene mayoritariamente cuando el catalizador es un complejo de Ir o Ru, con una selectividad moderada.[83]

Por el contrario, con los catalizadores de Pt catiónicos empleados en este trabajo se obtiene mayoritariamente el producto Markovnikov, ramificado. La reacción más sencilla de este tipo es la que tiene lugar entre benceno y propileno donde los productos posibles son *n*-propilbenceno y cumeno en distintas proporciones. El grupo de Gunnoe ya había descrito la obtención de una relación aproximadamente 3:1 a favor de la formación de cumeno (producto Markovnikov) empleando como catalizador [(^{t}bpy)Pt(Ph)(THF)](BAr´$_4$), análogo a los utilizados en este trabajo.[84]

La reacción se extendió al uso de otras olefinas como 1-penteno, ciclohexeno o aceptores de Michael como metacrilato con resultados prometedores.

Adicionalmente, se pretendía comprender la influencia de la habilidad dadora del ligando 2,2´-bipiridina en la reacción de hidroarilación de α-olefinas y en la relación entre los productos isómeros obtenidos (lineal/ramificado). Para ello se llevaron a cabo distintas funcionalizaciones en las posiciones 4,4´ de dicho ligando, lo que permitió establecer una clara tendencia. Se establece una relación lineal entre el logaritmo del ratio cumeno/*n*-propilbenceno y el parámetro de Hammett del sustituyente de las posiciones 4 y 4´ del ligando bipiridina (Figura A1).

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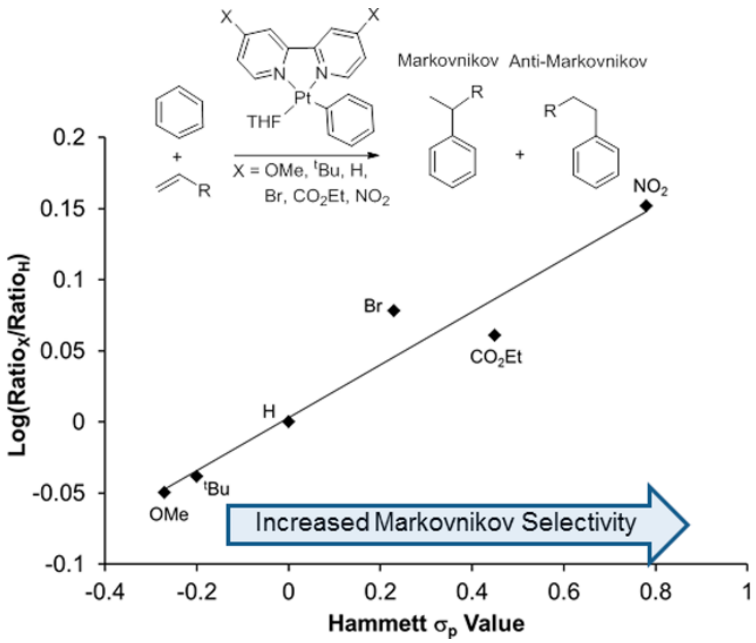

Figura A1. Gráfica de Hammett

De esta representación se deduce que la presencia de sustituyentes electroatractores en el ligando, que hacen a este menos dador, aumenta el cociente entre los productos ramificado y lineal. Se concluye que la capacidad dadora del ligando tiene una influencia cuantificable, aunque no muy grande, en la inserción del propileno en el enlace Pt–Ph y en la selectividad de la reacción.

Lamentablemente, no se puede establecer una relación similar al funcionalizar el areno con sustituyentes que tengan diferentes características electrónicas, de manera que no existe correlación entre el parámetro σ de Hammett del benceno funcionalizado y la selectividad entre los productos Markovnikov o anti-Markovnikov de los alquilarenos obtenidos.

Por último, como complemento al trabajo experimental se realizaron estudios computacionales (DFT) sobre el mismo sistema. Estos estudios predicen que la 1,2-inserción que conduce al producto ramificado (Markovnikov) es cinéticamente más favorable que la 2,1-inserción. La Figura A2 recoge los resultados computacionales en la etapa de inserción para distintos sustituyentes en el ligando bipiridilo del catalizador. Estos cálculos permiten además comprobar que la etapa limitante en este tipo de reacciones es la activación del enlace C–H del benceno.

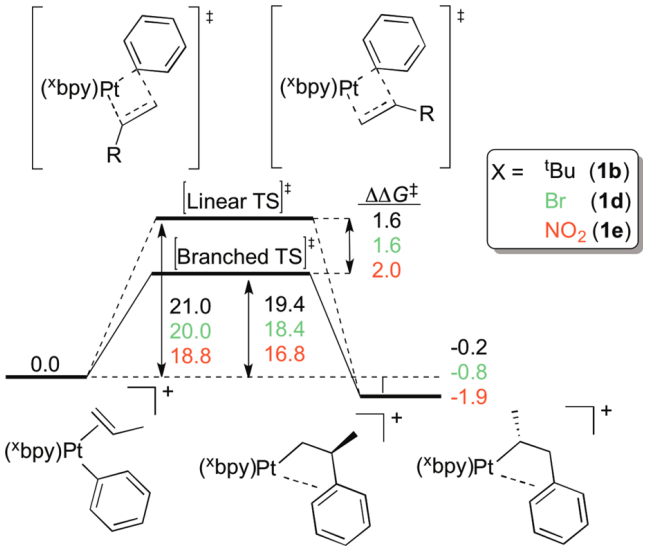

Figura A2. Energía libre de Gibbs en Kcal/mol de las distintas especies y de los estados de transición en la inserción de propileno en el enlace Pt–Ph en el complejo $[(^{x}\text{bpy})\text{Pt}(\text{Ph})(\eta^2\text{-}C_3H_6)]^+$

En conclusión, el diseño del catalizador es clave en la selectividad de la reacción, ya que, a pesar de que los cambios llevados a cabo en este trabajo son mínimos, se observan considerables efectos en el ratio obtenido entre los productos lineal y ramificado. Esto sugiere que modificaciones más drásticas en el catalizador y en la capacidad dadora de los ligandos, pueden conducir a cambios más pronunciados en la selectividad de la reacción, incluso alterar cuál es el producto mayoritario si se disminuye la barrera de activación de la 2,1-inserción frente a la 1,2.

Artículo VI

Pt^{II}-Catalyzed Hydrophenylation of α‑Olefins: Variation of Linear/Branched Products as a Function of Ligand Donor Ability

Bradley A. McKeown, Bruce M. Prince, Zoraida Ramiro, T. Brent Gunnoe*, and Thomas R. Cundari*

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Pt^{II}-Catalyzed Hydrophenylation of α-Olefins: Variation of Linear/Branched Products as a Function of Ligand Donor Ability

Bradley A. McKeown,[†] Bruce M. Prince,[‡] Zoraida Ramiro,[†] T. Brent Gunnoe,*[,†] and Thomas R. Cundari*[,‡]

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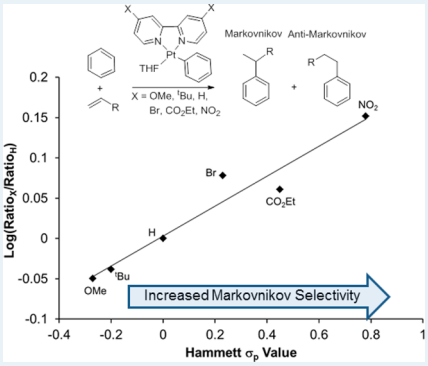
Supporting Information

ABSTRACT: The Pt^{II} complexes $[(^{x}bpy)Pt(Ph)(THF)]^{+}$ (^{x}bpy = 4,4′-X_2-2,2′-bipyridyl; x = OMe (**1a**), ^{t}Bu (**1b**), H (**1c**), Br (**1d**), CO_2Et (**1e**) and NO_2 (**1f**)] catalyze the formation of *n*-propylbenzene and cumene from benzene and propene. The catalysts are selective for branched products, and the cumene/*n*-propylbenzene ratio decreases with increasing donor ability of the ^{x}bpy ligand. DFT(D) calculations predict more favorable activation barriers for 1,2-insertion into the Pt−Ph bond to give branched products. The calculations indicate that 1,2-insertion of propene should be faster than 2,1-insertion for all Pt(II) catalysts studied, but they also indicate that cumene/*n*-propylbenzene selectivity is under Curtin−Hammett control.

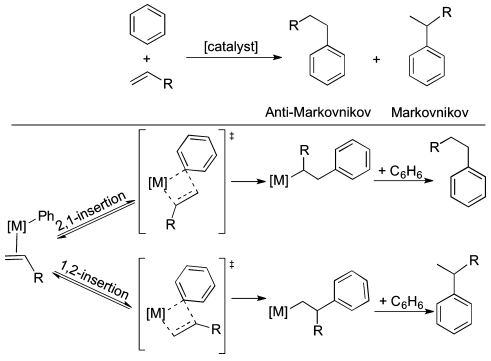


KEYWORDS: *platinum, hydroarylation, α-olefins, C−H activation, Curtin−Hammett principle*

INTRODUCTION

Transition-metal-catalyzed hydroarylation of substituted olefins by a nonacidic pathway (i.e., non-Friedel−Crafts catalysis) offers the opportunity to control the regioselectivity of olefin insertion into the M−aryl bond to obtain either Markovnikov or anti-Markovnikov products.[1] For example, catalysts that can bias 2,1- over 1,2-insertion with α-olefins could selectively produce linear alkyl arenes that are not accessible with acid-based methodologies (Scheme 1).[2] The hydrophenylation of α-olefins using Ru or Ir catalyst precursors has been reported to favor the formation of the anti-Markovnikov over Markovnikov addition products with moderate selectivity (∼1.5:1 linear-to-branched ratio for both catalysts).[1a,3]

Scheme 1. Product Selectivity from Transition Metal Mediated Hydrophenylation of α-Olefins Can Be Dictated by the Selectivity of Insertion into the M−Ph Bond



Unlike the Ir and Ru catalysts, product selectivity for Pt^{II}-catalyzed hydrophenylation of propylene favors Markovnikov addition products. Goldberg and co-workers reported that a (pyridyl)pyrrolide ligated Pt^{II} catalyst precursor catalyzes the formation of cumene and *n*-propylbenzene from benzene and propylene in an ∼6:1 ratio.[4] In addition, we have reported that $[(^{t}bpy)Pt(Ph)(THF)][BAr'_4]$ (**1b**; ^{t}bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine; Ar′ = 3, 5-$(CF_3)_2$−C_6H_3) catalyzes the formation of cumene and *n*-propylbenzene in an ∼3:1 ratio (Chart 1).[5] Vitagliano and Tesauro studied the stoichiometric C−C bond formation from cationic Pt^{II}(aryl)(olefin) (aryl = C_6H_5, 4-C_6H_4R, or 3-C_6H_4R; R = OMe or Me) complexes containing *N*,*N* bidentate ligands.[6] These complexes effectively mediate migratory insertion of $H_2C{=}CHR$ (R = H, Me, or Ph) into the Pt−C_{aryl} bond. Consistent with the results from Pt^{II}-catalyzed propene hydrophenylation, 1,2-insertion and subsequent protonolysis yields the branched product.

The proposed mechanism for transition-metal-catalyzed olefin hydrophenylation involves two principal steps: olefin insertion into the M−Ph bond and benzene C−H activation (Scheme 2).[1,3,4,7] The Pt^{II} complex **1b** has been demonstrated

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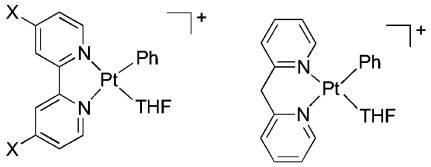
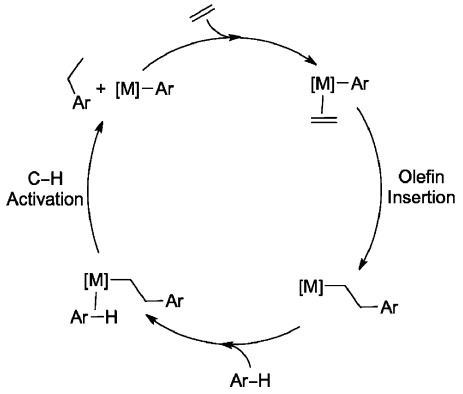
Chart 1. Catalysts Studied for Hydroarylation of Substituted Olefins



X = OMe (**1a**), ^{t}Bu (**1b**), H (**1c**), Br (**1d**), CO_2Et (**1e**), NO_2 (**1f**)

(**2**)

Scheme 2. Generic Catalytic Cycle for Transition-Metal-Catalyzed Olefin Hydroarylation Proposed for Ru-, Ir- and Pt-based Catalyst Precursors



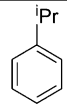
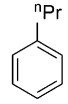
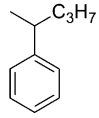
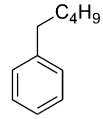
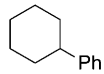
to insert ethylene into the Pt–Ph bond in the presence of excess olefin to yield $[(^t\text{bpy})Pt(CH_2CH_2Ph)(\eta^2\text{-}C_2H_4)]^+$, which is the proposed resting state of catalytic ethylene hydrophenylation.[7h,8] We recently reported that expansion of the chelate ring size using $[(\text{dpm})Pt(Ph)(THF)][BAr'_4]$ (**2**; dpm = di(2-pyridyl)methane) results in an increase in the catalytic efficiency for ethylene hydrophenylation.[8a]

As previously reported,[8b] the donor ability of bipyridyl ligands for Pt^{II} catalyzed ethylene hydrophenylation influences the selectivity for ethylbenzene vs styrene, and we sought to determine the extent to which ancillary ligand donor ability could be used to alter selectivity for hydrophenylation of α-olefins. In this report, catalytic activity is evaluated using longer-chain and internal olefins as well as Michael acceptors for complexes **1b** and **2.** The impact of 2,2′-bipyridyl ligand donor ability on Pt^{II}-catalyzed hydroarylation of α-olefins is examined using various 2,2′-bipyridyl ligands with different 4,4′ substituents (Chart 1). A clear trend for the influence of bpy donor ability has been established.

RESULTS AND DISCUSSION

The hydroarylation of substituted olefins was studied using complexes **1b** and **2** as catalyst precursors. Under conditions of 0.01 mol % catalyst relative to benzene (1 mM Pt and 11 M benzene) and 0.1 MPa of propylene at 100 °C, catalysis with complex **1b** results in 33.5 (4 h) and 39.8 (16 h) turnovers (TO) of cumene and *n*-propylbenzene in an approximate 3:1 ratio (Table 1). Traces of isomers of di- and tripropylbenzenes were also detected. Although the formation of the Markovnikov addition product cumene is favored, the observation of significant quantities of the anti-Markovnikov addition product *n*-propylbenzene (~10 TO after 16 h) provides further support

Table 1. Hydrophenylation of Olefins with $[(^t\text{bpy})Pt(Ph)(THF)][BAr'_4]$ (1b).[a]

Olefin	Alkyl benzene				B:L[b]
		25.0[e] (29.7)[f]		8.5 (10.1)	2.9
		30.2 (31.6)		9.8 (10.3)	3.1
		18.9 (20.9)			–

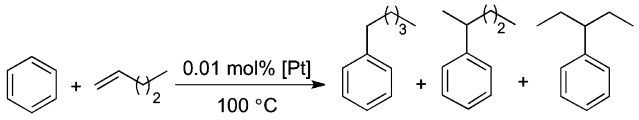
[a]0.01 mol % catalyst (1 mM) dissolved in C_6H_6 with hexamethylbenzene as an internal standard at 100 °C. [b]Ratio of branched to linear isomer after 4 h. [c]0.1 MPa C_3H_6; see ref 10. [d]150 equiv relative to Pt. [e]Turnovers after 4 h as determined by GC/MS. [f]Numbers in parentheses are turnovers after 16 h.

for a nonacid-catalyzed mechanism because acid-based catalysts are highly selective for Markovnikov addition.[2]

Increasing the length of the carbon chain upon substitution of 1-pentene for propylene has a minimal influence on catalyst efficiency and selectivity. Using 150 equiv of 1-pentene (relative to **1b**), 40 TO of 2-phenylpentane and *n*-pentylbenzene were observed after 4 h at 100 °C in a ~3:1 ratio with no further activity observed after this time point. The formation of approximately 1 equiv (relative to catalyst) of 3-phenylpentane during the hydrophenylation of 1-pentene using complex **1b** indicates that olefin isomerization occurs but is not significantly competitive on the time scale of catalysis. The catalyst is also compatible with disubstituted olefins, as the reaction with cyclohexene results in ~20 TO of phenylcyclohexane after 16 h at 100 °C.

The efficiency of catalytic hydrophenylation of substituted olefins using complex **2** is reduced compared to complex **1b**.[9] Using **2**, propylene hydrophenylation results in 11.8 TO of cumene and *n*-propylbenzene after 4 h in a 4.4:1.0 ratio. Catalysis with 1-pentene and cyclohexene using **2** also results in a reduction in TO compared to the 2,2′-bipyridyl complex **1b** (Schemes 3 and 4). Although **2** is a more effective catalyst for ethylene hydrophenylation,[8a] its efficacy for hydrophenylation of α-olefins is reduced relative to **1b**. We believe that the reduced activity of **2** relative to **1b** is a result of the increased steric bulk of the dpm ligand compared to ^{t}bpy.

Scheme 3. Comparison of Catalytic Hydrophenylation of 1-Pentene (150 equiv relative to Pt) Using Complexes 1b and 2 (0.01 mol % relative to benzene)



Complex	Time	1-phenyl	2-phenyl	3-phenyl
$[(^t\text{bpy})Pt(Ph)(THF)]^+$ (**1b**)	4 hr	9.8	30.2	~1
	16 hr	(10.3)	(31.6)	
$[(\text{dpm})Pt(Ph)(THF)]^+$ (**2**)	4 hr	4.3	12.1	Not Detected
	16 hr	(4.8)	(13.3)	

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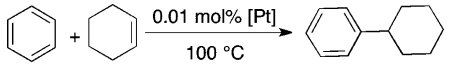
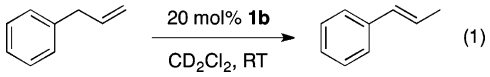
Scheme 4. Comparison of Catalytic Hydrophenylation of Cyclohexene (150 equiv relative to Pt) Using Complexes 1b and 2 (0.01 mol %, 1 mM, relative to benzene)



Complex	Time	TO
[(tbpy)Pt(Ph)(THF)]$^+$ (**1b**)	4 hr	18.9
	16 hr	(20.9)
[(dpm)Pt(Ph)(THF)]$^+$ (**2**)	4 hr	0.8
	16 hr	(1.1)

Intramolecular olefin hydroarylation was attempted with allylbenzene to form indane (eq 1). Heating complex **1b** or **2** in



(1)

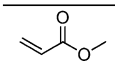
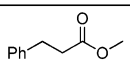
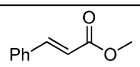
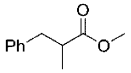
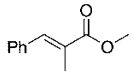
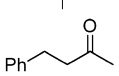
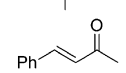
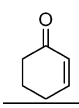
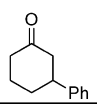
neat allylbenzene at 100 °C resulted in trace amounts of indane (observed by GC/MS). The small amount of cyclized product is not surprising because successful catalysis requires activation of an ortho C−H bond of allylbenzene, and product distributions from ethylene hydroarylation using substituted benzenes demonstrate that ortho C−H activation is not favored relative to meta or para activation.[7h] In addition, cationic Pt^{II} complexes containing phenyl ligands have been reported to be active for the isomerization of allylbenzene to the internal olefin *trans*-β-methyl-styrene.[10] Analysis of the mixture from reaction of both the ^{t}bpy complex **1b** and the dpm complex **2** with allylbenzene reveals that both of these Pt complexes catalyze olefin isomerization. Monitoring the reaction of **1b** (20 mol % relative to substrate) and allylbenzene in CD_2Cl_2 by ^{1}H NMR spectroscopy shows complete conversion of allylbenzene to *trans*-β-methyl-styrene in ∼1 h at room temperature (eq 1).

Functionalized Olefins. Hydrophenylation of α,β-unsaturated carbonyl compounds by complex **1b** was performed to probe catalyst tolerance toward heteroatomic functionality (Table 2). In all cases, catalysis was selective for the anticipated Michael addition product. Catalysis in benzene for 4 h with 0.01 mol % **1b** and 150 equiv of methacrylate (relative to **1b**) at 100 °C results in the formation of 6.8 TO of methyl 3-phenylpropanoate and 4.9 TO of methyl cinnamate (11.7 total TO). This corresponds to a 1.4:1 ratio of saturated to unsaturated products. No further catalytic activity was observed with continued reaction.

The same reaction was performed using methyl methacrylate to determine if the presence of an α-methyl group would inhibit β-hydride elimination after insertion into the Pt−Ph bond and increase selectivity for the saturated addition product. Indeed, the dominant product from catalysis was 2-methyl-3-phenylpropanoate, which was identified by GC/MS and comparison after catalysis of the ^{1}H NMR spectrum of the reaction mixture to reported NMR data.[11] Only trace amounts of 2-methyl-3-phenyl-2-propenoate were observed. Because of a lack of analytically pure material, linear regressions for quantification were not performed, but using the ratio of product to internal standard peak areas, ∼7 TO of 2-methyl-3-phenylpropanoate is estimated from catalysis with **1b** and methyl methacrylate in benzene. Catalysis with methyl vinyl ketone (MVK) or cyclohexenone is less efficient than the analogous reactions with the ester derivatives. For MVK, increased temperature (120 °C) was required to observe the addition product 4-phenylbutan-2-one, but only in near stoichiometric amounts. Approximately 2 TO of 3-phenylcyclohexanone is observed after 16 h at 100 °C for the hydrophenylation of cyclohexenone.

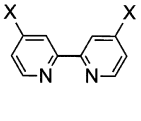
Use of 4,4′-Substituted Bipyridyl Ligands. The series of complexes [(^{x}bpy)Pt(Ph)(THF)][BAr′$_4$] [^{x}bpy = 4,4′-X$_2$-2,2′-bipyridyl; X = OMe (**1a**), ^{t}Bu (**1b**), H (**1c**), Br (**1d**), CO_2Et (**1e**), and NO_2 (**1f**)] was screened for propylene hydrophenylation to evaluate the influence of ligand donor ability on product selectivity (Table 3). Catalysis with complexes **1a**−**1c** demonstrates a slight enhancement in catalytic efficiency compared with catalysis with **1d**−**1f**, which is the same trend in catalyst efficiency that has been observed for ethylene hydrophenylation.[8b] Catalyst precursors **1d**−**1f** exhibit a greater predilection for the formation of unsaturated products (i.e.,

Table 2. Hydrophenylation of Michael Acceptors Using [(^{t}bpy)Pt(Ph)(THF)][BAr′$_4$] (1b)[a]

Olefin	Addition Product			
		6.8[b] (6.9)[c]		4.9 (5.2)
		∼7[d] (∼7)[d]		Trace
		0.7 (1.3)		Trace
		1.6 (1.9)		

[a]0.01 mol % catalyst (1 mM) dissolved in C_6H_6 with 150 equiv of olefin (relative to Pt loading) and hexamethylbenzene as an internal standard at 100 °C. [b]Turnovers after 4 h as determined by GC/MS. [c]Numbers in parentheses are turnovers after 16 h. [d]Turnovers estimated from GC peak area ratios between product and internal standard. [e]Catalysis performed at 120 °C.

Table 3. Comparison of Catalytic Propylene Hydrophenylation Using Complexes 1a−1f.[a]



X	σ_p			B:L[b]
OMe (**1a**)	-0.27	10.6[c] (26.9)[d]	3.7 (9.7)	2.9
^{t}Bu (**1b**)	-0.2	25.0 (29.7)	8.5 (10.1)	2.9
H (**1c**)	0.0	25.8 (31.6)	8.0 (10.3)	3.2
Br (**1d**)	0.23	2.5 (4.2)	0.7 (1.4)	3.8
CO_2Et (**1e**)	0.45	12.1 (18.3)	3.3 (5.1)	3.7
NO_2 (**1f**)	0.78	4.1 (6.5)	0.9 (1.6)	4.6

[a]0.01 mol % catalyst dissolved in C_6H_6 with hexamethylbenzene as an internal standard at 100 °C with 0.1 MPa C_3H_6. [b]Ratio of cumene to *n*-propylbenzene after 4 h. [c]Turnovers after 4 h as determined by GC/MS. [d]Numbers in parentheses are turnovers after 16 h.

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isomers of (propenyl)benzene), as observed by GC/MS, relative to **1a**–**1c**. After 16 h at 100 °C, the nitro-substituted complex **1f** gives 8.1 TO of propylbenzenes with a 4.6:1.0 branched/linear ratio. In contrast, ethylene hydrophenylation using **1f** gives an approximately stoichiometric yield of ethylbenzene and styrene.[8b] The 1,2-insertion of propylene into the Pt–Ph bond forms the intermediate $[(^{NO_2}bpy)Pt(CH_2CH(Me)Ph)]^+$, and the presence of the β-methyl group may result in a difference in activation barrier for β-hydride elimination relative to elimination of styrene from $[(^{NO_2}bpy)Pt(CH_2CH_2Ph)]^+$.[12]

The ratio of cumene/*n*-propylbenzene is influenced by the donor ability of the bipyridyl ligand. For example, catalysis using complex **1a** (OMe, σ_p = −0.27) and 0.1 MPa of propylene (100 °C) results in a cumene/*n*-propylbenzene ratio of 2.9 (after 4 h) compared with 4.6 for complex **1f** (NO_2, σ_p = 0.78). A Hammett plot was constructed using product ratios (*n*-propylbenzene vs cumene), and the Hammett parameter, σ_p (Figure 1). Although the effects of substituted pyridyl ligands

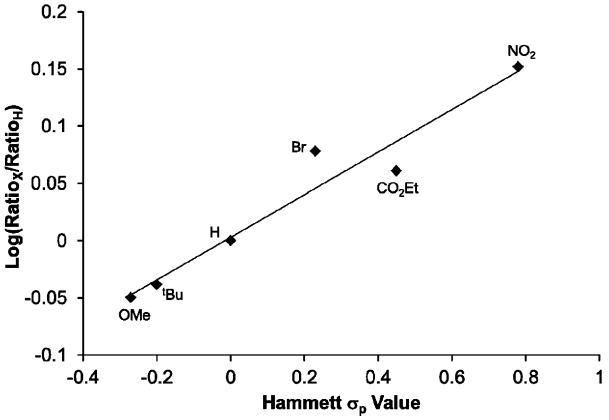
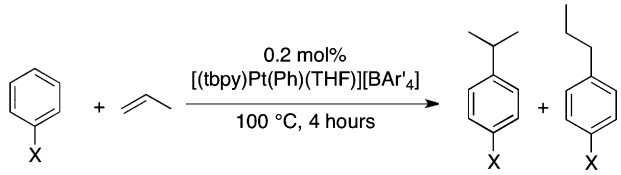


Figure 1. Hammett plot using the ratios of cumene to *n*-propylbenzene from $[(^x bpy)Pt(Ph)(THF)]^+$-catalyzed propylene hydrophenylation after 4 h at 100 °C with 0.1 MPa of ethylene (slope = 0.2, R^2 = 0.94).

are rarely amenable to Hammett correlations,[13] a good linear correlation is observed (R^2 = 0.94). The plot demonstrates that less-donating 4,4′ substituents result in an increase in the ratio of cumene/*n*-propylbenzene, but the magnitude of the slope (ρ = 0.2) suggests that the ligand donor ability has a small, but clear and quantifiable, influence on the selectivity for propylene insertion into the Pt–Ph bond and overall product selectivity.

Functionalized Arenes. Next, we sought to determine the electronic effect of arene functionality on linear/branched selectivity. The isomers of propylene hydroarylation using anisole, benzene, and chlorobenzene were resolved using GC/MS. Only para-substituted isomers were used for comparison, but meta- and ortho-substituted benzenes were also observed. Comparing the peak area ratios of 4-^{i}Pr-1-X-C_6H_4 and 4-^{n}Pr-1-X-C_6H_4 (X = OMe, H and Cl) after 4 h of heating at 100 °C under 0.1 MPa of propylene with 0.2 mol % **1b** demonstrates no correlation between the Hammett σ parameter of the benzene functionality and Markovnikov/anti-Markovnikov product selectivity for the resulting alkyl arenes (Scheme 5). Catalysis with both anisole (OMe, σ_p = −0.27) and chlorobenzene (Cl, σ_p = 0.23) provides a greater predilection for formation of the isopropyl functionalized arene compared with that of benzene.

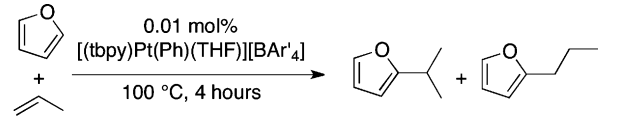
Scheme 5. Comparison of Branched to Linear Ratios of Propylene (0.1 MPa) Hydroarylation Using Substituted Benzenes



X	σ_p	Branched : Linear Ratio
OMe	-0.27	3.30(5)
H	0.0	2.9(3)
Cl	0.23	4.1(5)

Functional groups on benzene exert little influence on selectivity for catalytic propylene hydroarylation; however, the substitution of benzene for furan biases the reaction to favor the Markovnikov addition product by a substantial amount (Scheme 6). After 4 h at 100 °C, complex **1b** catalyzes the

Scheme 6. Ratio of 2-Isopropylfuran and 2-*n*-Propylfuran from Propylene (0.1 MPa) Hydroarylation with Furan and $[(^t bpy)Pt(Ph)(THF)]^+$ at 100 °C after 4 h, as Determined from Peak Area Ratios from Analysis by GC/MS



formation of 2-isopropylfuran and 2-*n*-propylfuran in an approximate 44:1 ratio, as determined by comparison of peak areas from GC/MS analysis.

Computational Studies. Density functional theory (DFT-(D)) was employed to probe hydroarylation of α-olefins catalyzed by $[(^x bpy)Pt(Ph)]^+$ complexes (x = ^{t}Bu, NO_2 or Br). The Gaussian 09[14] package was used to perform all simulations. All stationary points were obtained using the B3LYP[15] functional with a pseudopotential scheme that is valence double-ζ-plus-polarization (CEP-31G(d)) on the main group elements and triple-ζ on the transition metals. Reported Gibbs free energies were determined at 298.15 K and 1 atm and utilize unscaled B3LYP/CEP-31G(d)[16] vibrational frequencies. The D3(BJ) dispersion correction[17] with Becke–Johnson damping[18] was utilized. The modeled system is cationic; thus, the CPCM[19] formalism was used with THF (ε = 7.43) as the solvent. Stationary points were differentiated as minima or transition states (TSs) via computation of the energy Hessian and observation of the correct number of imaginary frequencies, zero (0) and one (1), respectively. Intrinsic reaction coordinates [20] from the TS geometries were computed. All geometry optimizations were performed without symmetry or coordinate restraint, and all complexes were singlets for which restricted Kohn–Sham theory[21] was employed.

Product selectivity for the hydrophenylation of propylene (i.e., linear/branched ratios) could be determined by the regioselectivity of olefin insertion or by the relative rates of subsequent reactions (i.e., Curtin–Hammett conditions). Provided that olefin insertion into the Pt–Ph bond is reversible,

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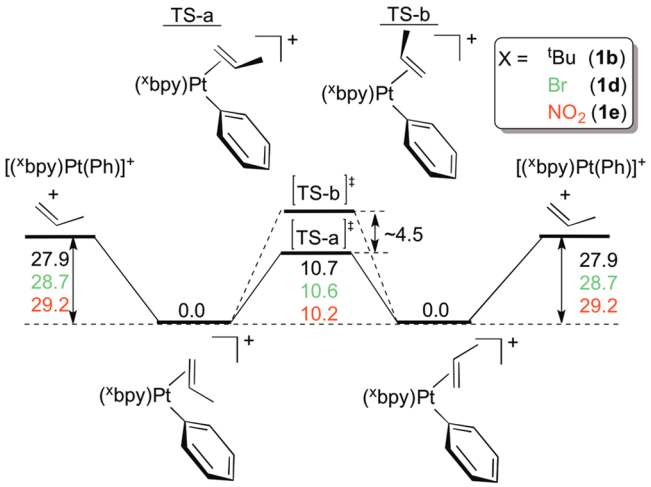
as depicted in Scheme 1, the formation of cumene could be preferential because of more favorable barriers for benzene coordination or C−H activation. Thus, we calculated the energetics of all steps, starting from propylene coordination to the Pt^{II} complexes. For the computational modeling, we focused on three Pt complexes: $[(^{t}bpy)Pt(Ph)]^{+}$ (**1b**), $[(^{Br}bpy)Pt(Ph)]^{+}$ (**1d**), and $[(^{NO_2}bpy)Pt(Ph)]^{+}$ (**1f**).

The energetics of the coordinated propylene complexes $[(^{x}bpy)Pt(Ph)(\eta^3\text{-}C_3H_6)]^{+}$ were studied to assess the preferred olefin binding mode. Calculated stationary points relevant to propylene binding are depicted in Scheme 7 for x = ^{t}Bu (black),

Scheme 7. B3LYP-D3(BJ)/CEP-31G(d)/THF-Calculated Propylene Binding and Rotational Transition States for $[(^{x}bpy)Pt(Ph)(\eta^2\text{-}C_3H_6)]^{+}$[a]



[a]The Gibbs free energy values are given in kcal/mol. The 2,2′-bipyridyl ligand with 4,4′-substituents are color coded: x = ^{t}Bu (black), Br (green), NO_2 (red). Propylene adduct isomers are differentiated by whether the propylene methyl group is proximal or distal to the phenyl ligand, but are nearly degenerate. Model propylene rotational transition states feature the propylene methyl group proximal (TS-a, left) or distal (TS-b, right) to the phenyl ligand.

Br (green), and NO_2 (red) supporting ligand models. In the ground state of $[(^{x}bpy)Pt(Ph)(\eta^3\text{-}C_3H_6)]^{+}$, the C=C bond of propylene is perpendicular to the platinum square plane, which is common for square planar d^8 transition metals.[7h,8a,22] Isomers of propylene coordination are thus differentiated by whether the propylene methyl group is proximal or distal to the phenyl ligand. There is, however, negligible calculated free energy difference (<0.1 kcal/mol) between these isomers for $[(^{x}bpy)Pt(Ph)(\eta^2\text{-}C_3H_6)]^{+}$, implying minimal steric contact between the propylene methyl moiety and the remainder of the complex. Computations revealed subtle distinctions in the propylene rotational barriers and more so in the propylene binding free energies, which are linked to the electronic properties of the bipyridyl substituents (Scheme 7).

Rotation of propylene about the metal/C=C centroid axis leads to two isomeric rotational transition states (Scheme 7 and Figure 2) in which the methyl group of the propylene is either proximal (TS-a) or distal (TS-b) to the phenyl ring, respectively. In the rotational transition states, the C=C bond is in the square plane of the Pt complex. For all complexes modeled, TS-a in Scheme 7 was computed to be lower by ∼4 kcal/mol than TS-b, presumably because of steric hindrance between the methyl group on propylene and a 6-H on the bipyridyl ligand. For all three catalyst models, the calculated $\Delta G^{\ddagger}_{rot}$ is ∼10−11 kcal/mol. There is good agreement between experiment and theory for olefin rotation. For $[(^{t}bpy)Pt(CH_2CH_2Ph)(\eta^2\text{-}C_2H_4)]^{+}$, the experimentally determined and $\Delta G^{\ddagger}_{rot}$ for ethylene rotation is 11.7 kcal/mol at −33.4 °C, and the calculated $\Delta G^{\ddagger}_{rot}$ is 12.4 kcal/mol.[7h] For all three modeled complexes, the dissociation of propylene from $[(^{x}bpy)Pt(Ph)(\eta^2\text{-}C_3H_6)]^{+}$ is calculated to be endergonic by >27 kcal/mol, which is higher by at least 17 kcal/mol in comparison to the propylene rotational transition states (Scheme 7). This suggests that interconversion of the two propylene adduct conformers will involve rotation of the olefin rather than dissociation and recoordination of propylene. When x = NO_2 or Br, propylene binding to the Pt complex is calculated to be more exergonic by 1.3 or 0.8 kcal/mol, respectively, as compared with $[(^{t}bpy)Pt(Ph)]^{+}$ (Scheme 7), which can likely be attributed to the electron-withdrawing nitro or bromo groups on the bpy, which enhances olefin coordination by providing a more electrophilic Pt center.

Selectivity for Branched vs Linear Insertion. Two isomeric pathways for propylene insertion into the Pt−phenyl bond were investigated from $[(^{x}bpy)Pt(Ph)(\eta^2\text{-}C_3H_6)]^{+}$. The two products of propylene insertion yield cumene or *n*-propylbenzene after benzene C−H activation (Scheme 8). For the ^{t}bpy complex, computations reveal a $\Delta\Delta G^{\ddagger}_{ins}$ = 1.6 kcal/mol between transition states for propylene insertion with the lower energy transition state leading to the branched product (Scheme 8). At the same level of theory, relative free energy barriers ($\Delta\Delta G^{\ddagger}_{ins}$) for propylene insertion into the $(^{NO_2}bpy)Pt$−Ph and $(^{Br}bpy)Pt$−Ph bonds were 2.0 and 1.6 kcal/mol. Similar to the ^{t}bpy complex, the $\Delta G^{\ddagger}_{ins}$ leading to the branched product is lower than for the linear product in ^{NO_2}bpy and ^{Br}bpy cases. DFT(D) predicts a slightly enhanced kinetic selectivity for the branched product for the ^{NO_2}bpy complex relative to the ^{t}bpy complex, which is consistent with experimental branched/linear ratios from catalytic hydrophenylation of propylene (see Table 3 and Figure 1). However, as discussed below, the relative rates of 1,2- vs 2,1-propene insertion may not dictate the ultimate selectivity for formation of cumene vs *n*-propylbenzene.

Analysis of atomic charges for the olefin insertion TSs did not reveal any obvious trends to explain product selectivity for 1,2- vs 2,1-insertion as a function of the ^{x}bpy ligand, as expected, given the similar inductive impact of H and methyl substituents. Analysis of the geometries of the propylene insertion TSs showed very modest changes (typically ≪0.05 Å) in bond lengths as a function of the X group or the insertion regiochemistry. In addition, differences in computed electronic energies and enthalpies and free energies were nearly identical, suggesting that preference for insertion mode is due to the looseness or tightness of the TS is not at the root of the observed and computed selectivity differences. The calculations reveal that the 1,2-insertion products are more stable than the 2,1-insertion products by 1.6 (^{t}bpy), 1.5 (^{Br}bpy), and 1.5 kcal/mol (^{NO_2}bpy).

Catalytic Cycle. The catalytic cycle for hydrophenylation was investigated using DFT(D). For the ^{t}bpy catalyst, the potential energy surface (PES) depicts the energy pathway leading to branched and linear alkyl arene (Scheme 9). The reaction coordinates for other catalyst models are similar to Scheme 9 (see Supporting Information). The pertinent free energies for all modeled catalysts are collected in Table 4.

There are two plausible mechanisms for arene C−H bond activation: oxidative hydrogen migration (OHM) and oxidative

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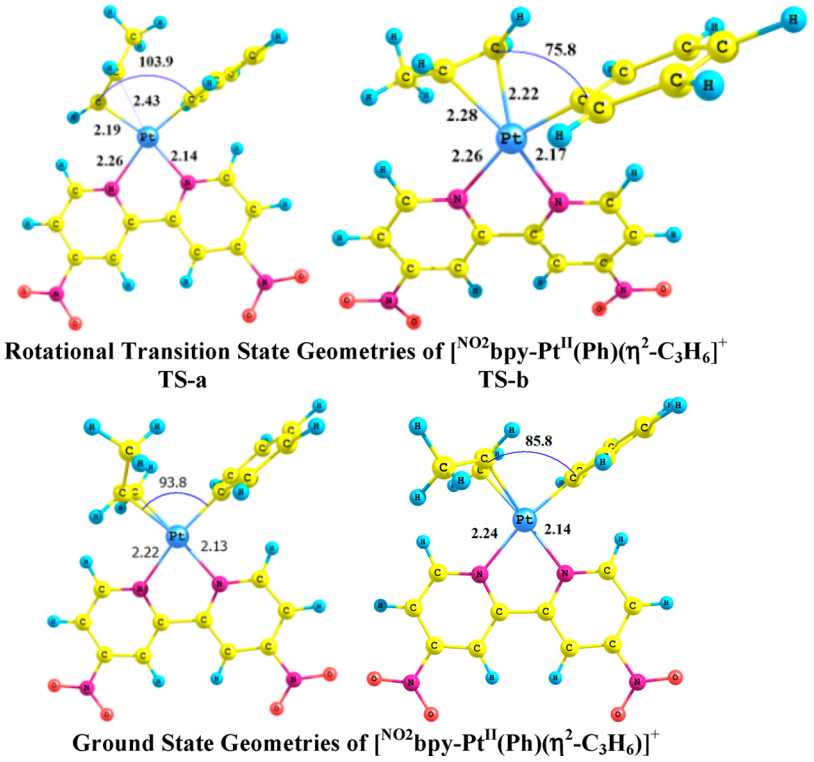
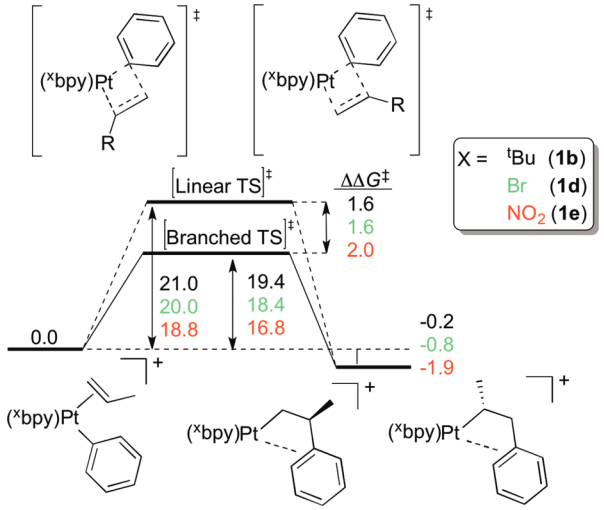


Figure 2. B3LYP/CEP-31G(d)/THF-calculated transition state geometries (top) for propylene rotation and ground state geometries (bottom) for the complex $[(^{NO_2}\text{bpy})\text{Pt}(\text{Ph})(\eta^2\text{-}C_3H_6)]^+$. Bond lengths are in angstroms, and angles are in degrees. Related ^{t}bpy and ^{Br}bpy geometries are in the Supporting Information. Note that geometries differ in the orientation of the methyl substituent on propylene relative to the remainder of the catalyst.

Scheme 8. Calculated Free Energies (kcal/mol) for Propylene Insertion into the Pt−Ph Bond Starting from $[(^{x}\text{bpy})\text{Pt}(\text{Ph})(\eta^2\text{-}C_3H_6)]^+$



addition/reductive elimination (OA/RE), with the latter calculated to be the preferred pathway. A typical benzene oxidative addition TS, which defines the highest computed point on the PES, leading to a branched product, is shown in Figure 3; all other Cartesian coordinates are collected in the Supporting Information.

The benzene C−H activation barrier has been previously reported to be the rate-determining step for catalytic ethylene hydrophenylation catalyzed by **1b**.[7h] Relative to the most stable propylene adduct, $[(^{t}\text{bpy})\text{Pt}(\text{Ph})(\eta^2\text{-propylene})]^+$, the calculated transition state leading to cumene is 22.5 kcal/mol. This is lower in free energy by 1.6 kcal/mol in comparison to the TS for pathway leading to *n*-propylbenzene (Scheme 9 and Table 4). For the ^{NO_2}bpy model, the lowest energy benzene C−H oxidative addition TS is 21.3 kcal/mol (Table 4), lower by 1.2 kcal/mol than for the ^{t}bpy derivative, but nearly identical to the ^{Br}bpy catalyst model. Hence, simulations suggest commensurate activity for the electron-withdrawing substituents, and each marginally lower than the ^{t}bpy congener. In all cases, cumene is predicted to be the preferred product of hydrophenylation of propylene, as is observed experimentally.

Above, we used DFT(D) calculations to assess the kinetic selectivity for 1,2- vs 2,1-insertion, but the calculated energetics suggest that Curtin−Hammett conditions would apply to the Pt^{II} catalyzed propylene hydrophenylation. Thus, the rate of propylene deinsertion and reinsertion into the Pt−Ph bond is predicted to be faster than the rate of benzene C−H activation by either the 1,2- or 2,1-insertion product. Previously, we have reported that the resting state for catalytic hydrophenylation of ethylene using several Ru(II) or Pt(II) catalysts is the insertion product with coordinated ethylene, $\text{M}(CH_2CH_2\text{Ph})(\eta^2\text{-ethylene})$.[1,21,23] Although the spectra are complicated, monitoring the hydrophenylation of propene by **1b** using ^{1}H NMR spectroscopy reveals resonances consistent with the analogous resting state. Table 4 shows calculated energetics for the production of cumene and *n*-propylbenzene for all three Pt complexes. Under Curtin−Hammet conditions, the predicted branched/linear ratio for each catalyst can be estimated using the relative activation barriers for rate-limiting benzene C−H activation. For the ^{t}bpy complex, a $\Delta\Delta G^{‡}$ of 1.6 kcal/mol (favoring cumene production) would give a branched/linear

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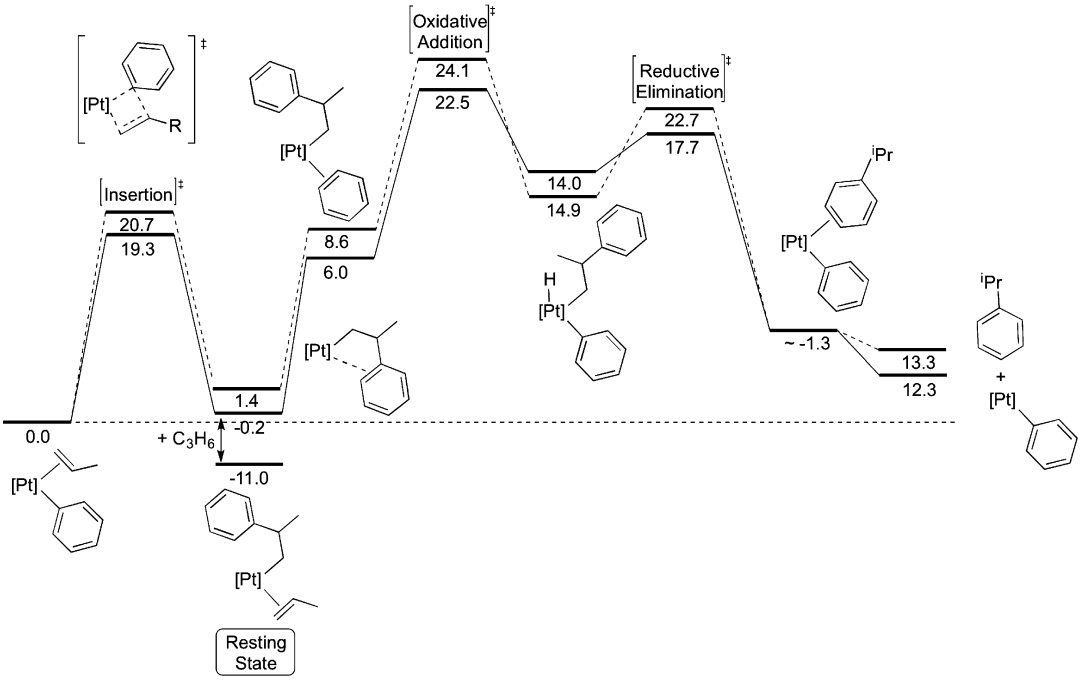
Scheme 9. Calculated Ground and Transition States for Propylene Hydrophenylation To Yield Cumene (solid line) or *n*-Propylbenzene (dashed line) Catalyzed by [(^{t}bpy)Pt(Ph)(THF)][BAr′$_4$] (1b)[a]



[a]Similar pathways are calculated for the ^{Br}bpy (**1d**) and ^{NO_2}bpy (**1f**) derivatives; see Table 4. The Gibbs free energy barriers are in kcal/mol. Ground and transition state structures relevant to the formation of the preferred product, cumene, are shown.

Table 4. Relative Free Energies[a] for Olefin Hydroarylation with ^{x}bpyPt^{II} Complex[b]

	^{t}bpy cumene	^{t}bpy *n*PB	^{NO_2}bpy cumene	^{NO_2}bpy *n*PB	^{Br}bpy cumene	^{Br}bpy *n*PB
[^{x}bpyPt^{II}(Ph)(η^2-C_3H_6)]$^+$	0	0	0	0	0	0
insertion TS	19.3	20.7	16.5	18.4	18.3	19.7
benzene adduct	6.0	8.6	4.5	8.0	5.4	9.1
benzene OA TS	22.5	24.1	21.3	23.0	21.5	23.5
products	12.3	13.3	13.7	14.7	13.1	14.1

[a](B3LYP/CEP-31G(d), STP, kcal/mol, in THF) . [b]The superscript $^{+}$ denotes cationic complexes. All species are d^8 reactants and products with formally d^6-hydride intermediates. OA = oxidative addition.

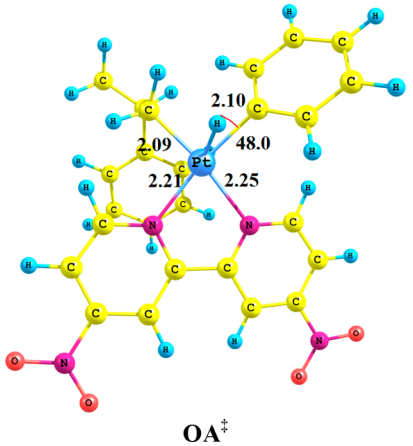


Figure 3. B3LYP/CEP-31G(d)/THF-calculated transition state geometry for C−H bond activation via oxidative addition by complex [^{NO_2}bpyPt(CH$_2$CH(Ph)CH$_3$)]$^+$. Bond lengths are in angstroms, and angles are in degrees.

ratio of ∼4:1 (at room temperature), which is similar to the experimental value of 2.9:1 at 100 °C. The same calculations for the ^{NO_2}bpy ($\Delta\Delta G^{‡}$ = 1.7 kcal/mol) and the ^{Br}bpy ($\Delta\Delta G^{‡}$ = 2.0 kcal/mol) predicts branched/linear ratios of 4.4:1 and 5.8:1, respectively. Although the calculations correctly predict that cumene is favored over *n*-propylbenzene for all ligands ^{x}bpy, the observed experimental trend for variation of branched/linear ratio is not reproduced. These results are not surprising, given the energy differences to accurately model the selectivity trend are much smaller than expected standard errors in the calculations. The most salient result from the calculations, which is well within expected errors, is that the branched/linear ratio is likely a function of Curtin−Hammett conditions and not controlled by the kinetic selectivity for 1,2- vs 2,1-insertion of propene into Pt−Ph bonds.

CONCLUSIONS

In summary, cationic Pt^{II} complexes supported by bipyridyl ligands are effective catalysts for the hydroarylation of substituted olefins. The systematic variation of bipyridyl ligand electronic properties through 4,4′-substitution revealed a correlation between ligand donor ability and product selectivity for propylene hydrophenylation. Increasing the electron-withdrawing properties of the 4,4′ substituent results in an increase in the cumene/*n*-propylbenzene ratio. Computational studies predict that 1,2-insertion (leading to branched product) is kinetically more favorable than 2,1-insertion of propene and that reducing the donor ability of the bpy ligands should further bias the insertion selectivity toward branched products. The results from the calculations also indicate that benzene C−H activation is rate-limiting for pathways leading to either alkyl arene. Thus, Curtin−Hammett conditions are likely responsible

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for product selectivity, and future catalyst design to target linear products should seek to optimize the thermodynamic bias toward 2,1-insertion and lower the activation barrier for benzene C−H activation from the 2,1-insertion product relative to the 1,2-insertion product. Although the magnitude of the changes in branched/linear selectivity is modest for the current set of catalysts, the results suggest that more dramatic changes in ligand donor ability might have more pronounced changes in selectivity.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all synthetic procedures were performed under anaerobic conditions in a nitrogen filled glovebox or by using standard Schlenk techniques. Glovebox purity was maintained by periodic nitrogen purges and was monitored by an oxygen analyzer (O_2 < 15 ppm for all reactions). Diethyl ether was dried by distillation over CaH_2. Tetrahydrofuran and *n*-pentane were distilled over sodium/benzophenone and P_2O_5, respectively. Methylene chloride and benzene were purified by passage through a column of activated alumina. Acetone-d_6 and CD_2Cl_2 were used as received and stored under a N_2 atmosphere over 4 Å molecular sieves. ^{1}H NMR spectra were recorded on a Varian Mercury 300 or Unity Innova 500 MHz or on a Bruker 800 MHz spectrometer. ^{13}C NMR spectra were recorded using a Varian Mercury 300, Unity Innova 500 MHz (operating frequency 75 or 125 MHz, respectively) or using a Bruker 800 MHz spectrometer (operating frequency 201 MHz). All ^{1}H and ^{13}C NMR spectra are referenced against residual proton signals (^{1}H NMR) or the ^{13}C resonances (^{13}C NMR) of the deuterated solvents. ^{19}F NMR (282 MHz operating frequency) spectra were obtained on a Varian 300 MHz spectrometer and referenced against an external standard of hexafluorobenzene (δ = −164.9 ppm). GC/MS was performed using a Shimadzu GCMS-QP2010 Plus system with a 30 m × 0.25 mm SHRXI-5MS column with 0.25 mm film thickness using electron impact (EI) ionization or negative chemical ionization (NCI), which also allows for simulated electron impact (SEI) ionization. Ethylene (99.5%) and propylene (99.5%) were purchased in a gas cylinder from GTS-Welco and used as received. All other reagents were used as purchased from commercial sources. The preparation, isolation, and characterization of 3-phenylcyclohexanone[23] and [(N ∼ N)Pt(Ph)(THF)][BAr′$_4$][7h,8] (**1a**−**1f** and **2**) have been previously reported.

Catalytic Olefin Hydrophenylation with Propylene. A representative catalytic reaction is described. [(^{t}bpy)Pt(Ph)(THF)][BAr′$_4$] (**1b**) (0.019 g, 0.013 mmol) was dissolved in 12.0 mL of benzene containing 0.01 mol % hexamethylbenzene (HMB) relative to benzene as an internal standard. The reaction mixture was placed in a stainless steel pressure reactor, charged with propylene (0.1 MPa), pressurized to a total of 0.8 MPa with N_2, and heated to 100 °C. After a given time period, the reaction mixture was allowed to cool to room temperature and was analyzed by GC/MS. Peak areas of the products and the internal standard were used to calculate product yields. Cumene production was quantified using linear regression analysis of gas chromatograms of standard samples. A set of five known standards consisting of 2:1, 4:1, 6:1, 8:1, and 10:1 molar ratios of cumene to HMB in benzene were prepared. A plot of the peak area ratios vs molar ratios gave a regression line. For the GC/MS system, the slope and correlation coefficients (R^2) for cumene were 0.89 and 0.99, respectively. Identical procedures were used to quantify the production of *n*-propylbenzene (1.19; 0.99).

Catalytic Olefin Hydrophenylation with Non-Gaseous Olefinic Substrates. A representative catalytic reaction is described. [(^{t}bpy)Pt(Ph)(THF)][BAr′$_4$] (**1b**) (0.005 g, 0.003 mmol) was dissolved in 3.0 mL of benzene containing 1-pentene (55 μL, 150 equiv relative to Pt,) and 0.01 mol % hexamethylbenzene relative to benzene as an internal standard. The reaction mixture was placed in a glass pressure tube and heated to 100 °C. After a given time period, the reaction mixture was allowed to cool to room temperature and analyzed by GC/MS. Peak areas of the products and the internal standard were used to calculate product yields from linear regression analysis of standard samples. A set of five known standards consisting of 2:1, 4:1, 6:1, 8:1, and 10:1 molar ratios of alkylbenzene to HMB in CH_2Cl_2 were prepared. A plot of the peak area ratios vs molar ratios gave a regression line. For the GC/MS system, the slope and correlation coefficient (R^2) for each alkylbenzene is as follows: *n*-pentylbenzene (1.10; 0.99), 2-phenylpentane (1.33; 0.99), phenylcyclohexane (0.33; 0.99), 3-phenylcyclohexanone (0.33; 0.99), 4-phenylbutan-2-one (0.31; 0.99), methyl cinnamate (0.50; 0.99), and methyl 3-phenylpropanoate (0.53; 0.99).

ASSOCIATED CONTENT

Supporting Information

Full computational study, including reaction coordinates for all catalyst models. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Abreviaturas

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2,6-*i*-Pr_2-C_6H_3: 2,6-*iso*-propil-fenilo

2,6-Xililo: 2,6-dimetil-fenilo

Ac: Acetato

Anti:antiperiplana

Ar: arilo

Binap: 2,2'-bis(difenilfosfanil)-1,1'-binaftilo.

Biphep: bis(fosfanil)bifenilo.

CAAC: Cyclic Alkyl-Amino Carbenes

Cbz: Carbamato

e.e: exceso enantiomérico

Endo: endocíclico

Et: etilo

Exo: exocíclico

HBHC: hydrogen bond supported heterocyclic carbenes

HPLC: Cromatografía líquida de alta eficacia o High performance liquid chromatography

IMes: *N*,*N*-bis(2,4,6-trimetilfenil)imidazol-2-ilideno)

IPr: *N*,*N*-bis(2,6-diisopropilfenil)imidazol-2-ilideno)

^{i}Pr: *iso*-propilo

IR: Infrarrojo

Me: Metilo

Mes: Mesitilo o 2,4,6-trimetil-fenilo

^{n}Bu: *n*-butilo

NHC: N-heterocilcic carbenes

^{n}Heptyl: *n*-heptilo

Napth: Napthyl o naftil

NHCbz: Carbamato de bencilo

NOE: Efecto Nuclear Overhauser

NOESY: Espectroscopia de Efecto Nuclear Overhauser

NTf_2: bis(trifluorometilsulfonil)imidato

OPiv: Pivaloato o dimetilpropanoato

OTf: triflato o trifluorometilsulfonato

Ph: Fenilo

P-P: difosfina

ppm: partes por millón

p-Tol: *para*-tolil o 4-metil-fenil

Py: piridilo

RMN: Resonancia Mangnética Nuclear

Rto: rendimiento

(*R*)-DTBM-SEGPHOS: (*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butil-4-metoxifenil)fosfino]-4,4′-bi-1,3-benzodioxol

(*S*)-DTMB-MeOBIPHEP: (*S*)-(6,6′-Dimetoxibifenil-2,2′-diil)bis[bis(3,5-di-*tert*-butil-4-metoxifenil)fosfina]

Syn: synperiplana

t.a : temperatura ambiente

TBS: *terc*-butildimetilsililo

^{t}Bu: *terc*-butilo

TES: trietilsililo

Tf: triflato o trifluorometilsulfonato

THF: tetrahidrofurano

tht: tetrahidrotiofeno

Ts: tosilato o *para*-toluensulfonato

TON: turnover number

SPS: sistema de purificación de disolventes.