Cyclization

DOI: 10.1002/anie.200503484

Gold-Catalyzed Intramolecular Reaction of Indoles with Alkynes: Facile Formation of Eight-Membered Rings and an Unexpected Allenylation**

*Catalina Ferrer and Antonio M. Echavarren**

The hydroarylation of alkynes (or alkenylation of arenes) catalyzed by electrophilic transition-metal complexes has emerged as a valuable method for the synthesis of alkenyl arenes and heteroarenes.[1] Reetz and Sommer[2] as well as Shi and He[3] found independently that gold complexes catalyze the intermolecular hydroarylation of alkynes. An intramolecular version was disclosed by Murai, Chatani, and co-workers, who used as catalysts Ru^{II} and Pt^{II} ions[4] as well as $GaCl_3$.[5,6] Fürstner et al. reported a similar reaction for the synthesis of phenanthrenes that is catalyzed by $PtCl_2$ and other metal halides.[7] Sames and co-workers developed an intramolecular hydroarylation catalyzed by $PtCl_4$ that proceeds under mild conditions.[8] Cycloisomerization of ω-aryl-

---

[*] C. Ferrer, Prof. Dr. A. M. Echavarren[+]
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
Fax: (+34) 97-792-0225
E-mail: aechavarren@iciq.es

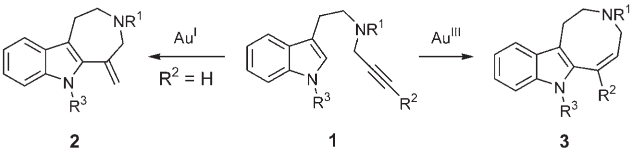
[+] Additional affiliation:
Departamento de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco, 28049 Madrid (Spain)

[**] This work was supported by the MEC (Project CTQ2004-02869), the AGAUR (predoctoral fellowship to C.F.), and the ICIQ Foundation.

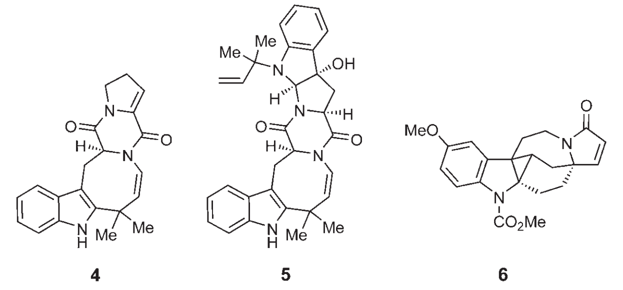
1-alkynes has also been performed with Hg^{II} ions[9] or Tf_2NH.[10]

We have recently reported the cyclization of aryl alkynes with Pt^{II} or Au^{I} catalysts.[11,12] Computational studies[11] indicate that two pathways compete: a Friedel–Crafts alkenylation and a reaction proceeding through metal cyclopropyl carbenes which show very similar activation energies.

We have now found that, whereas substrates **1** cyclize readily with a cationic gold(I) complex to give azepino[4,5-*b*]indole derivatives **2**,[13,14] the more electrophilic $AuCl_3$[15] leads to indoloazocines **3** by an 8-*endo*-dig process (Scheme 1), a cyclization that has not been observed in other hydroarylations of alkynes.[16] This type of regiochemical control by the oxidation state of the metal catalyst appears to be unprecedented.[17] Indoloazocine subunit **3** is present in indole alkaloids such as deoxyisoaustamide (**4**),[18,19] okaramine N,[20] and the lundurines (namely, lundurine A (**5**), Scheme 2).[21–23] We also report an unexpected fragmentation reaction that results in the allenylation of the indole nucleus at C2. As predicted by our previous theoretical study,[11] indoles tethered to alkynes by two or three atoms undergo 6-*endo*-dig and 6-*exo*-dig cyclizations, respectively.

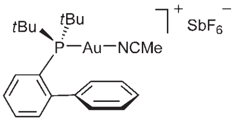


Scheme 1. 7-*exo*-dig versus 8-*endo*-dig cyclization of alkynyl indoles **1**.



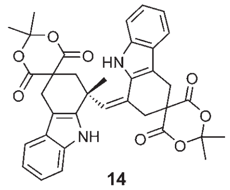
Scheme 2. Representative indoloazocine alkaloids.

Several gold complexes and salts, including new Au^{I} complexes bearing bulky phosphanes or N-heterocyclic ligands,[24,25] were tested in the intramolecular reaction of indoles with alkynes. In general, the best catalyst for the formation of seven-membered rings **2** is cationic gold(I) complex **7**,[25,26] which allows the cyclizations to be performed in the absence of Ag^{I} salts (Table 1). This complex is readily prepared as an air-stable white solid from the corresponding gold chloride complex. Among the solvents screened ($MeNO_2$, acetone, DMF, CH_2Cl_2), the best results were obtained in CH_2Cl_2. Thus, reaction of tryptophan derivative **8a** with complex **7** as catalyst at room temperature for 30 minutes gave azepino[4,5-*b*]indole **9a** cleanly (Table 1, entry 1). In contrast, the reaction of **8a** with $AuCl_3$ gave indoloazocine **10a** cleanly (Table 1, entry 2). Reaction with AuCl also provided **10a**, although significant amounts of depropargylated starting material were also obtained (Table 1, entry 3). Reaction of **8a** with a catalyst made in situ by chloride abstraction from $[AuCl(PPh_3)]$ with $AgSbF_6$ was less selective, and a 1.3:1 mixture of **9a** and **10a** was obtained (Table 1, entry 4). Similar results were obtained with **8b** and **8c** (Table 1, entries 5–9), although in these cases reaction with $AuCl_3$ gave indoloazocines **10b** and **10c** along with seven-membered-ring derivatives **11b** and **11c**, respectively (Table 1, entries 6 and 9). As expected, treatment of **9b** with 5 mol% $AuCl_3$ (CH_2Cl_2, room temperature, 16 h) led quantitatively to **11b**. *N*-Allylindole **8d** provided seven-membered-ring derivative **9d** when **7** was used as the catalyst (Table 1, entry 10). Protic acids do not promote the cyclization of these substrates. Thus, treatment of **8b** with *para*-toluenesulfonic acid (10 mol%) in CH_2Cl_2 at room temperature for 16 h led only to unchanged starting material.



7

Substrate **12**, with a tether of only three atoms, reacted satisfactorily with catalyst **7** in CH_2Cl_2 by a 6-*exo*-dig pathway to give **13** (Table 2, entry 1), whereas $[AuCl(PPh_3)]/AgSbF_6$ gave **13** in lower yield along with dimer **14** (Table 2, entry 2). The configuration of **14** at the exocyclic double bond was determined by a NOESY experiment. Decomposition was observed when $AuCl_3$ was used as the catalyst (Table 2, entry 3). Formation of **14** may involve a proton-catalyzed reaction via a tertiary, benzylic-type carbocation derived from **12**. Reaction of **15** with an unprotected propargyl alcohol moiety proceeded uneventfully with Au^{I} catalysts to give **16** (Table 2, entries 4 and 5). In contrast, reaction of **15** in the presence of $AuCl_3$ gave ketone **17**, as a result of isomerization of the exocyclic double bond (Table 2, entry 6).

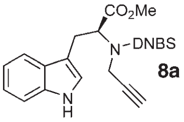
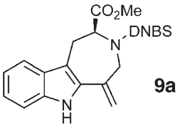
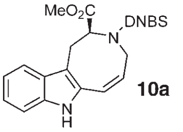
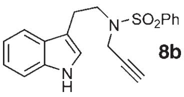
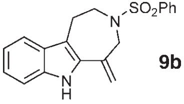
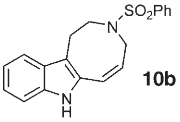
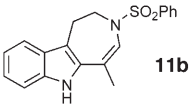
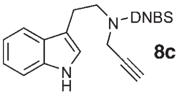
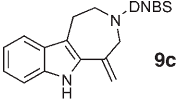
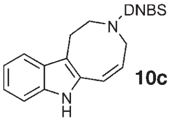
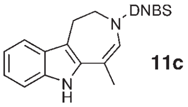
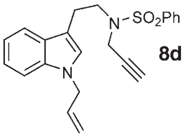
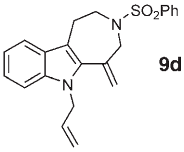


14

Amide **18** afforded 5-methylene-4,5-dihydrooxazole **19** under all the conditions examined (Table 2, entries 7–9), although the best results were obtained with catalyst **7**. This type of reactivity has been described recently by Hashmi et al.[27] using $AuCl_3$ as the catalyst. Dihydrooxazole **19** is remarkably stable and does not isomerize to the oxazole under the different reaction conditions. Derivative **20**, a substrate with a tether of only two atoms, reacted with Au^{I} catalysts through a 6-*endo*-dig pathway to give **21** (Table 2, entries 10 and 11). In this case, no cyclization was observed with $AuCl_3$ (Table 2, entry 12).

Surprisingly, when indole **8d** was treated with $AuCl_3$ (2 mol%) in CH_2Cl_2 at room temperature for 16 h, allene **22** was obtained as a result of an overall intramolecular allenylation at C-2 of the indole by the *N*-propargyl chain (Scheme 3). Tryptophan derivative **23a** provided indoloazocine **24** and allene **25a** (ca. 1:1 mixture) after being heated at

Table 1: Formation of seven- or eight-membered-ring compounds by cyclization of indoles with alkynes catalyzed by gold complexes.

Entry	Indole	Catalyst[a]	*t* [h]	Product(s)	Yield [%]
1	 **8a**	**7**	0.5	 **9a**	82
2	**8a**	$AuCl_3$	0.5	 **10a**	75
3	**8a**	AuCl	1	**10a**	70[b]
4	**8a**	$[AuCl(PPh_3)]/AgSbF_6$	0.5	**9a** + **10a** (1.3:1)	80
5	 **8b**	**7**	16	 **9b**	65
6	**8b**	$AuCl_3$	24	 **10b** +  **11b** **10b** + **11b** (5.4:1)	71
7	**8b**	$[AuCl(PPh_3)]/AgSbF_6$	16	**9b** + **10b** (4:1)	65
8	 **8c**	**7**	16	 **9c**	77
9	**8c**	$AuCl_3$	16	**10c** + **11b** (2.8:1)  **10c** +  **11c**	87
10	 **8d**	**7**	0.5	 **9d**	68

[a] Reactions carried out with 5 mol% of the catalyst in CH_2Cl_2. [b] *N*-Depropargylated starting material was also obtained in 23% yield. DNBS = 2,4-dinitrobenzenesulfonyl.

90 °C in toluene with catalyst **7**. Allene **25b** was also obtained as the major compound from **23b**.

A rationale for the formation of the allene derivatives is provided in Scheme 4. Eight-membered-ring compound **24** may arise from a 1,2-shift of the initially formed iminium cation **I** to give **II** (Scheme 4),[28] which would lose a proton to form **III**, and then form **24** by protodemetalation. An alternative elimination, facilitated by the electron-withdrawing sulfonyl group R^2, would yield allenes **25**. A similar mechanism is probably followed in the formation of allene **22** from **8d** by fragmentation of an Au^{III} intermediate similar to **III**. Fragmentation does not occur with the final indoloazocines. Thus, no reaction was observed on treatment of **24** with **7** (5 mol%) in CH_2Cl_2 at room temperature for 16 h or in toluene at 90 °C for 5 h.

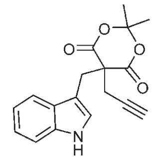
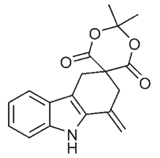
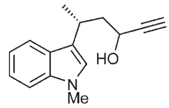
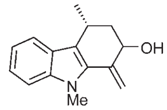
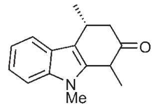
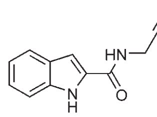
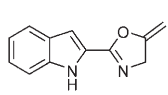
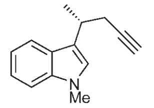
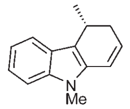
Intermediates **I** and **II** might also be involved in the formation of indoloazocines **10a–c** (Table 1). A related 1,2-shift could also be involved in the formation of six- and seven-membered-ring compounds by exocyclic pathways, although this seems rather unlikely in the 6-*endo*-dig cyclization of **20** to form **21** (Table 1, entries 20–21) which would require a 5-*endo*-dig reaction to form the first spiro intermediate. The different regiochemical outcomes observed in reactions catalyzed by Au^I complex **7** and $AuCl_3$ suggests that different mechanisms are involved in these reactions. It is noteworthy that the most electrophilic Au^{III} catalyst leads to indoloazocines, which according to PM3 calculations are about 2–5 kcal mol^{-1} less stable than their seven-membered-ring isomers **9**.

In summary, we have found a facile annulation of six–eight-membered rings on indoles by cyclization with alkynes catalyzed by Au^I or Au^{III} species. Cationic Au^I complex **7** is the best catalyst for the formation of six- and seven-membered rings through 6-*endo*-dig, 6-*exo*-dig, and 7-*exo*-dig cyclizations. Indoloazocines are obtained with $AuCl_3$ as catalyst through a rare 8-*endo*-dig process. Surprisingly, allenes are formed by a fragmentation reaction. This allenylation provides a simple entry into functionalized indole derivatives such as **22** and **25a–b**, which could be used as scaffolds for additional annulation processes.[29]

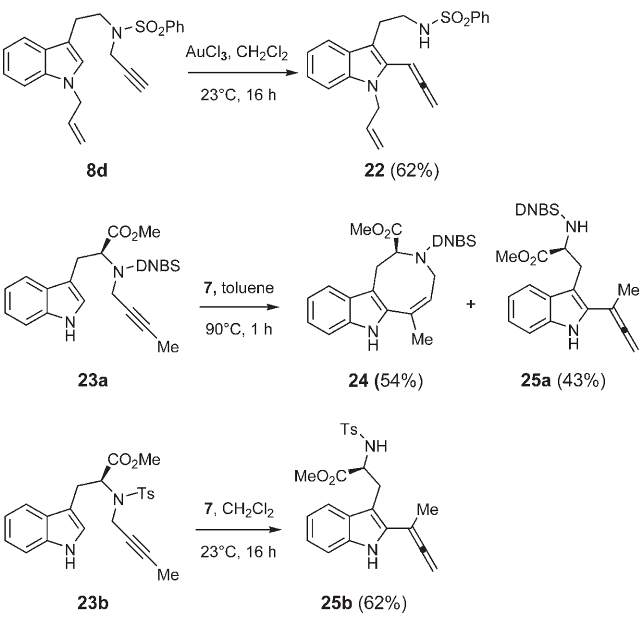
Received: October 2, 2005

Keywords: alkynes · allenes · cyclization · gold · indoles

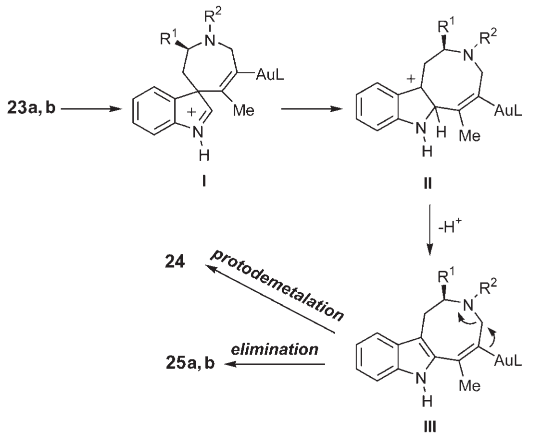
Table 2: Formation of six-membered-ring compounds by cyclization of indoles with alkynes catalyzed by gold complexes.

Entry	Indole	Catalyst[a]	*t* [h]	Product(s)	Yield [%]
1	 **12**	**7**	0.2	 **13**	68
2	**12**	[AuCl(PPh$_3$)]/AgSbF$_6$	0.5	**13**	54[a]
3	**12**	AuCl$_3$	2	–[b]	–
4	 **15**	**7**	0.2	 **16**	72
5	**15**	[AuCl(PPh$_3$)]/AgSbF$_6$	0.2	**16**	60
6	**15**	AuCl$_3$	0.2	 **17**	100
7	 **18**	**7**	16	 **19**	77
8[c]	**18**	[AuCl(PPh$_3$)]/AgSbF$_6$	16	**19**	56
9	**18**	AuCl$_3$	16	**19**	57
10	 **20**	**7**	1	 **21**	92
11	**20**	[AuCl(PPh$_3$)]/AgSbF$_6$	16	**21**	63
12	**20**	AuCl$_3$	24	–[d]	–

[a] Dimer **14** (25%) was also obtained. [b] Decomposition was observed. [c] Starting material was recovered. [d] Reaction carried out in DMF.



Scheme 3. Formation of allenyl indoles.



Scheme 4. Proposed mechanism for the formation of eight-membered-ring compounds **24** and allenes **25**.

---

[1] Review: C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167–182.

[2] M. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485–3496.

[3] Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669–3671.

[4] N. Chatani, H. Inoue, T. Ikeda, S. Murai, *J. Org. Chem.* **2000**, *65*, 4913–4918.

[5] H. Inoue, N. Chatani, S. Murai, *J. Org. Chem.* **2002**, *67*, 1414–1417.

[6] The intermolecular reaction of indoles catalyzed by GaCl$_3$ only takes place with phenylacetylene to give 1,1-bis(1*H*-3-indolyl)-1-phenylethanes: J. S. Yadav, B. V. S. Reddy, B. Padmavani, M. K. Gupta, *Tetrahedron Lett.* **2004**, *45*, 7577–7579.

[7] a) A. Fürstner, V. Mamame, *J. Org. Chem.* **2002**, *67*, 6264–6267; b) A. Fürstner, V. Mamame, *Chem. Commun.* **2003**, 2112–2113;

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

[8] a) S. J. Pastine, S. W. Youn, D. Sames, *Org. Lett.* **2003**, *5*, 1055–1058; b) S. J. Pastine, S. W. Youn, D. Sames, *Tetrahedron* **2003**, *59*, 8859–8868.

[9] M. Nishizawa, H. Takao, V. K. Yadav, H. Imagawa, T. Sugihara, *Org. Lett.* **2003**, *5*, 4563–4565.

[10] L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 10204–10205.

[11] C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155–3164.

[12] C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456–2460; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406.

[13] For recent transition-metal-catalyzed annulations of indoles, see: a) E. M. Beccalli, C. Broggini, *Tetrahedron Lett.* **2003**, *44*, 1919–1921; b) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579; c) C. Liu, X. Han, X. Wang, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 3700–3701; d) C. Liu, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10250–10251; e) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149; f) B. A. Bhanu Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469; g) for a review on palladium-catalyzed synthesis and functionalization of indoles, see: S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920.

[14] For a recent review on indolic natural products, see: M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73–103.

[15] For lead references on the formation of C–C bonds by activation of alkynes with $AuCl_3$, see: a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; b) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769–3771; c) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627–2635; d) A. S. K. Hashmi, L. Ding, J. W. Bats, P. Fischer, W. Frey, *Chem. Eur. J.* **2003**, *9*, 4339–4345; e) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.* **2004**, *116*, 6707–6709; *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547; f) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey, J. W. Bats, *Angew. Chem.* **2005**, *117*, 2858–2861; *Angew. Chem. Int. Ed.* **2005**, *44*, 2798–2801.

[16] For a rare cycloisomerization of 1,7-enynes with a stoichiometric amount of $[Co_2(CO)_8]$ to give 1,3-cyclooctadienes, see: H. Kagoshima, M. Hayashi, Y. Hashimoto, K. Saigo, *Organometallics* **1996**, *15*, 5439–5441.

[17] We have observed a different stereochemical outcome depending on the oxidation state of the palladium catalyst in the cyclization of allylstannanes with alkynes: B. Martín-Matute, E. Buñuel, D. J. Cárdenas, M. Méndez, C. Nieto-Oberhuber, A. M. Echavarren, *J. Organomet. Chem.* **2003**, *687*, 410–419.

[18] a) P. S. Steyn, *Tetrahedron Lett.* **1971**, 3331–3334; b) P. S. Steyn, *Tetrahedron* **1973**, 107–120; c) P. G. Sames, *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51–117.

[19] Synthesis of **4** and related alkaloids: P. S. Baran, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905.

[20] Synthesis of **5**: P. S. Baran, C. A. Guerrero, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 5628–5629.

[21] T.-S. Kam, K.-H. Lim, K. Yoganathan, M. Hayashi, K. Komiyama, *Tetrahedron* **2004**, *60*, 10739–10745.

[22] For indoloazocines as intermediates in the synthesis of other indole alkaloids, see: M. E. Kuehne, S. D. Cowen, F. Xu, L. S. Borman, *J. Org. Chem.* **2001**, *66*, 5303–5316.

[23] Synthesis of indoloazocines: L. G. Voskressensky, T. N. Borisova, L. N. Kulikova, A. V. Varlamov, M. Catto, C. Altomare, A. Carotti, *Eur. J. Org. Chem.* **2004**, 3128–3135, and references therein.

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

[25] C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302–6304; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.

[26] The structure of **7** has been confirmed by X-ray diffraction studies. Details of this structure and those of related Au^I complexes will be reported separately.

[27] S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394.

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

[29] For a recent review on synthetic applications of allenes, see: S.-M. Ma, *Chem. Rev.* **2005**, *105*, 2829–2872.