Organic Letters
Letter
pubs.acs.org/OrgLett

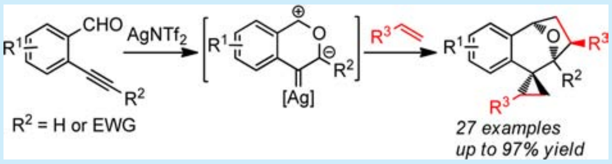
Silver-Catalyzed Reaction of Enynals with Alkenes: A Tandem 1,3-Dipolar Cycloaddition/Cyclopropanation

Renxiao Liang, Tongmei Ma, and Shifa Zhu*

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

Ⓢ *Supporting Information*

ABSTRACT: A silver-catalyzed reaction of enynals with alkenes to synthesize a series of polycyclic compounds has been developed. The reaction occurred smoothly using enynals with electron-deficient alkynes or terminal alkynes as substrates. The reaction was proposed to proceed through a tandem 1,3-dipolar cycloaddition/cyclopropanation process. The preliminary investigations of the asymmetric catalytic version revealed that the biphosphine ligand could be used as the potential efficient chiral ligand.



Since silver salts were applied as homogeneous catalysts in organic synthesis in the late 1990s, a variety of silver-catalyzed transformations have been reported.[1] In previous years, silver salts and complexes were commonly applied as Lewis acids to activate heteroatoms (Figure 1, **I**).[2] Later studies proved that silver salts could also be powerful *π*-activators for carbon−carbon multiple bonds (**II**−**IV**).[3−5]

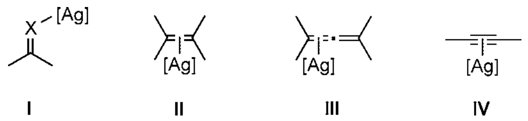
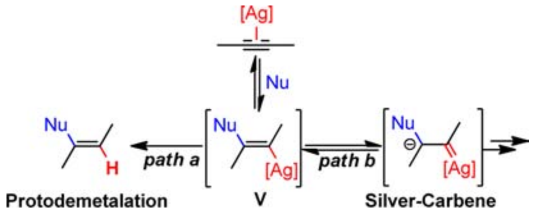


Figure 1. Activation types of silver.

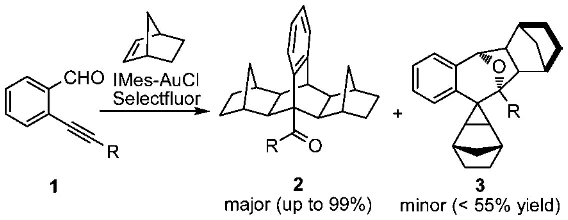
As *π*-activators of the carbon−carbon triple bond, silver-catalyzed transformations of alkynes mainly fall into two important types: (a) the protodemetalation pathway (b) and the silver−carbene pathway (Scheme 1). Generally speaking, the former processes are both dynamically and thermodynamically preferred directions because of the weakness of the Ag−C bond.[6] Therefore, the silver−carbene process (path b), which has commonly existed in diazo chemistry,[7] has rarely been seen in silver-catalyzed transformations of carbon−carbon triple bonds.[8]

Scheme 1. Silver-Catalyzed Reaction of C≡C Bond



Recently, our group has reported a gold-catalyzed reaction of enynals/enynones with norbornenes to synthesize a variety of structurally unique fanlike products **2**. During the reaction course, another product **3**, formed via a tandem 1,3-dipolar cycloaddition/cyclopropanation process, was also observed (Scheme 2),[5a] but the formation of **3** was highly limited to the substrates of norbornene derivatives and low yields (less than 55%). Furthermore, 5 mol % of the gold catalyst loading also made such a system impractical due to the high cost of gold. Therefore, we want revisit this interesting reaction, aiming for achieving better yields, broader substrate scopes, and cheaper catalysts.

Scheme 2. Gold-Catalyzed Enynals with Norborenes

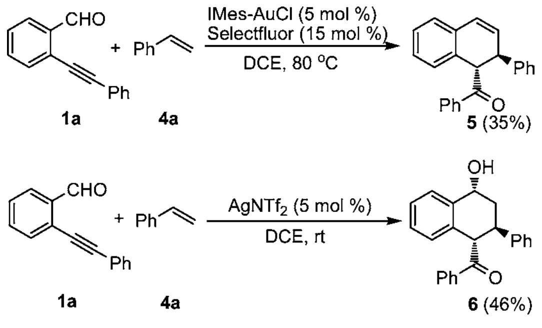


Initially, enynal (**1a**) and styrene (**4a**) were chosen as model substrates for this investigation. As shown in Scheme 3, under the best reaction conditions reported in our previous work,[5a] with IMes-AuCl as catalyst and Selectfluor as additive, the expected 1,3-dipolar cycloaddition/cyclopropanation product could not be detected; the *β*-H elimination product 1,2-dihydronaphthalene **5** was obtained in 35% yield instead.[5k] When silver salts such as $AgNTf_2$, AgOTf, or $AgSbF_6$ were used as catalysts, however, tetrahydronaphthol **6** could be obtained in moderate yields.[2a]

The results were consistent with the conclusion that the protodemetalation process was dynamically and thermodynamically preferred. Furthermore, the aromaticity of the benzopyrilium ion **A** would endow the protodemetalation process with an

Received: June 26, 2014
Published: August 8, 2014

Scheme 3. Reaction of 1a with Styrene



extra stabilizing effect (Scheme 4, path a). In order to realize the metal−carbene pathway b (the 1,3-dipolar cycloaddition/cyclopropanation process), we hypothesized that the intermediate **B** might be efficiently stabilized by introducing an electron-withdrawing group (R = EWG); thus, the negative charge on the dipole would be stabilized (Scheme 4, path b).

Scheme 4. Two Pathways

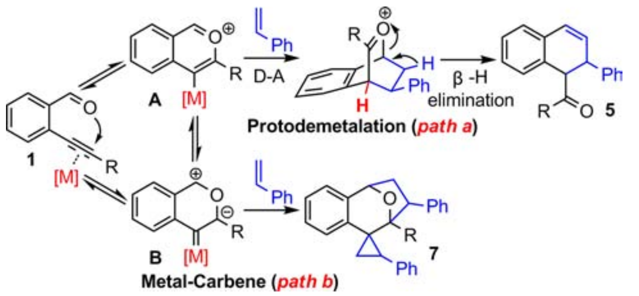
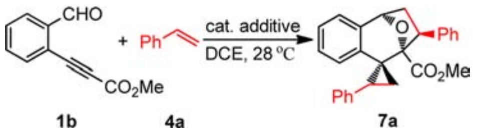


Table 1. Optimization of Reaction Conditions[a]



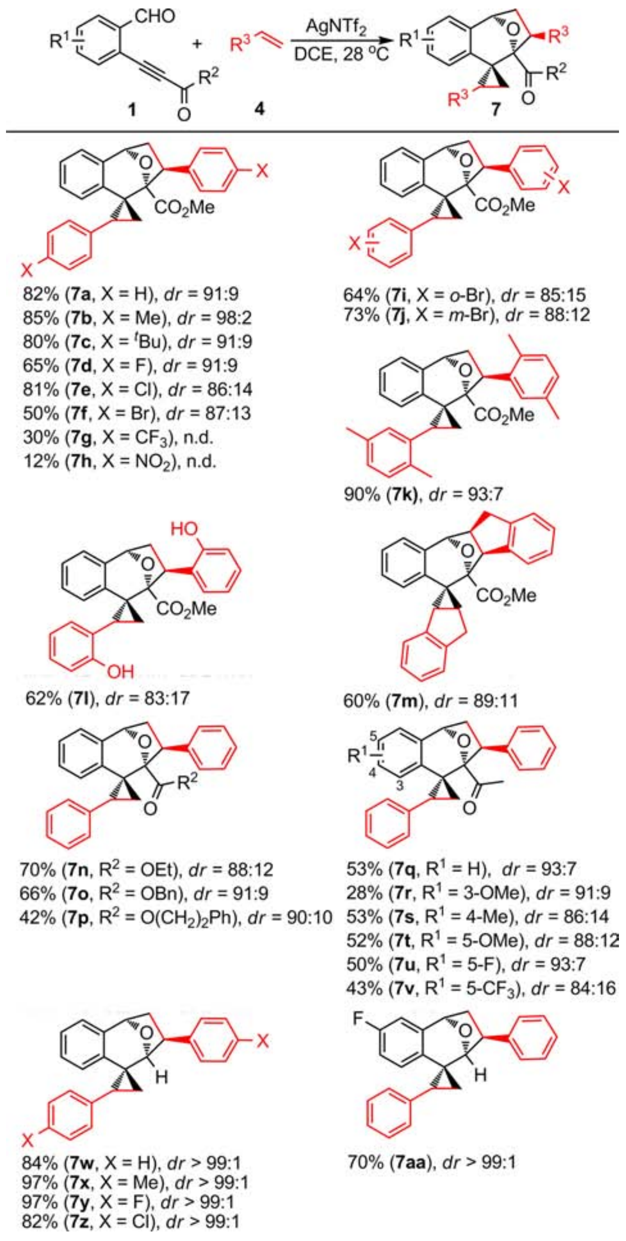
entry	R	cat.	additive	yield[d] (%)	dr[f]
1[b]	CO_2Me	IMes-AuCl	Selectfluor		
2[c]	CO_2Me	SIMes-AuCl	$AgNTf_2$		
3	CO_2Me	$FeCl_3$			
4	CO_2Me	$Cu(OTf)_2$			
5	CO_2Me	$ZnCl_2$			
6	CO_2Me	$PtCl_2$			
7	CO_2Me	$InCl_3$			
8	CO_2Me	$Hg(OTf)_3$			
9	CO_2Me	AgOTf		44	84:16
10	CO_2Me	$AgSbF_6$		51	88:12
11	CO_2Me	$AgNTf_2$		82[e]	89:11
12	CO_2Me	$AgNO_3$			
13	CO_2Me	AgCl			
14[g]	CO_2Me	$AgNTf_2$		trace	
15[h]	CO_2Me	$AgNTf_2$			
16[i]	CO_2Me	$AgNTf_2$		67	87:13
17[j]	CO_2Me	$AgNTf_2$		50	88:12

[a] Unless otherwise noted, the reaction was performed in DCE at 28 °C for 12 h using 5 mol % of catalyst under N_2. The molar ratio of **1b**:**4a** = 1:5. [**1b**] = 0.25 M. DCE = 1,2-dichloroethane, THF = tetrahydrofuran. [b] 5 mol % of IMesAuCl and 15 mol % of Selectfluor, set at 80 °C. [c] 5 mol % of SIMesAuCl and 5 mol % of $AgNTf_2$, set at 28 or 80 °C. [d] The yields were determined by ^1H NMR. [e] Isolated yield. [f] dr values were determined by ^1H NMR. [g] THF as solvent. [h] CH_3CN as solvent. [i] Toluene as solvent. [j] $MeNO_2$ as solvent.

To this end, enynal (**1b**, R = CO_2Me) was then used as the model substrate to reinvestigate the carbene process. Intriguingly, a variety of metal salts or complexes, such as gold, iron, copper, zinc, platinum, mercury, and indium, were proven ineffective for this transformation (Table 1, entries 1−8). Nevertheless, we were encouraged by the observation that the desired product **7a** could be formed when AgOTf was applied as catalyst, albeit in only 44% yield (entry 9). $AgSbF_6$ could catalyze the reaction as well, leading to the product **7a** in 51% (entry 10). To our delight, the reaction could be substantially improved by using $AgNTf_2$ as catalyst, and the product could be obtained in 82% isolated yield (entry 11). The reactions did not occur under the catalysis of $AgNO_3$ and AgCl (entries 12 and 13). When coordinating solvents, THF and CH_3CN, were employed, the reaction was depressed completely (entries 14 and 15). The solvents of toluene and $MeNO_2$ were inferior to DCE, giving the products with lower yields (entries 16 and 17). Furthermore, higher temperature and lower equivalents of olefin also gave lower yields (see Table S1 in the Supporting Information for more details). In all cases, the product **7a** was obtained with the dr ratios being close to 9:1.

With the optimized reaction conditions (Table 1, entry 11) in hand, the substrate scope was then examined. As summarized in Scheme 5, the catalytic process could be successfully applied to a variety of enynals **1** and styrene derivatives **4**. For example, in addition to styrene **4a**, various styrene derivatives could effectively react with enynal **1b** as well (Scheme 5, **7a**−**m**). Both the electron-rich and -poor styrene derivatives could give satisfactory yields (electron rich, **7a**−**c**; electron poor, **7d**−**f**). However, in the case of styrenes substituted with strong electron-withdrawing groups, $-CF_3$ and $-NO_2$, the yields dropped dramatically (**7g**, 30%; **7h**, 12%). The reactions were not sensitive to the steric hindrance (**7i**−**k**). For example, the bulky 2,5-dimethylstyrene gave the product **7k** in 90% yield. The structure and stereochemistry of the major isomer of the products were confirmed by the X-ray diffraction analysis of **7e** (see the Supporting Information). As anticipated, the major isomer was an endo-1,3-dipolar cycloaddition product. The reaction has good functional group tolerance. It occurred smoothly even for 2-hydroxystyrene, giving the product **7l** in 62% yield. Indene, a cyclic substrate, could also be applicable for the transformation and lead to the polycyclic product **7m** in 60% yield. Compared with the alkenes **4**, the reaction was less sensitive to the properties of enynals **1** (**7n**−**v**; 28%−70%). Among four enynals substituted with different esters groups, the bulkier one gave lower yield of product (**7a** > **7n** > **7o** > **7p**). The enynals with acetyl alkyne were less efficient substrates for this process, which gave the products **7q**−**v** in 28%−53% yields, with the dr values being 84:16 to 93:7. The enynal with a substituent at the 3-position gave lower yield (**7r**, 28%) than those with substituents at the 4- or 5-position (**7s**−**v**, 43−53%). These results could be attributed to the greater steric-hindrance of the substituent at 3-position of the enynal, thus remarkably slow down the [2 + 1] cycloaddition process. Interestingly, when the enynals with terminal alkynes were used as substrates, the reactions functioned even better than those with internal alkynes (**7w**−**aa**). The product yields were typically higher than 70%. It is interesting to note that only single isomers were obtained for products **7w**−**aa**.

Scheme 5. Silver-Catalyzed the Reaction of 1 with 4[a]



82% (**7a**, X = H), *dr* = 91:9
85% (**7b**, X = Me), *dr* = 98:2
80% (**7c**, X = ^{t}Bu), *dr* = 91:9
65% (**7d**, X = F), *dr* = 91:9
81% (**7e**, X = Cl), *dr* = 86:14
50% (**7f**, X = Br), *dr* = 87:13
30% (**7g**, X = CF_3), n.d.
12% (**7h**, X = NO_2), n.d.

64% (**7i**, X = *o*-Br), *dr* = 85:15
73% (**7j**, X = *m*-Br), *dr* = 88:12

90% (**7k**), *dr* = 93:7

62% (**7l**), *dr* = 83:17

60% (**7m**), *dr* = 89:11

70% (**7n**, R^2 = OEt), *dr* = 88:12
66% (**7o**, R^2 = OBn), *dr* = 91:9
42% (**7p**, R^2 = $O(CH_2)_2Ph$), *dr* = 90:10

53% (**7q**, R^1 = H), *dr* = 93:7
28% (**7r**, R^1 = 3-OMe), *dr* = 91:9
53% (**7s**, R^1 = 4-Me), *dr* = 86:14
52% (**7t**, R^1 = 5-OMe), *dr* = 88:12
50% (**7u**, R^1 = 5-F), *dr* = 93:7
43% (**7v**, R^1 = 5-CF_3), *dr* = 84:16

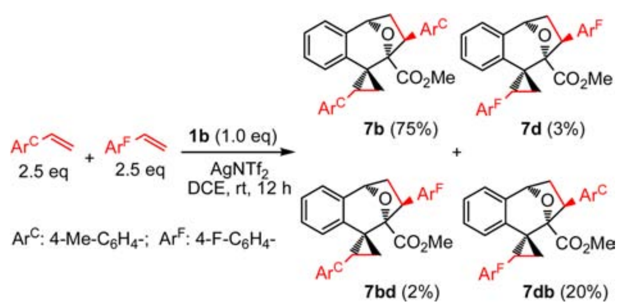
84% (**7w**, X = H), *dr* > 99:1
97% (**7x**, X = Me), *dr* > 99:1
97% (**7y**, X = F), *dr* > 99:1
82% (**7z**, X = Cl), *dr* > 99:1

70% (**7aa**), *dr* > 99:1

[a]The reaction was conducted in DCE at 28 °C for 12 h using 5 mol % of $AgNTf_2$ catalyst under N_2, **1** (0.25 mmol), **4** (1.25 mmol), the yields refer to be isolated, dr values were determined by ^{1}H NMR.

To further elucidate the reactivities of different olefins, a competitive experiment was then conducted (Scheme 6). Under the same reaction conditions, enynal **1b** reacted with the mixture of 4-methylstyrene (2.5 equiv) and 4-fluorostyrene (2.5 equiv). Four anticipated products, **7b**, **7d**, **7bd**, and **7db**, were obtained. Among them, **7bd** and **7db** are the products of the cross-reaction. The product **7b**, which came from the reaction with two electron-rich olefins, dominated in the products distribution (75%). Product **7d**, from two electron-poor olefins, was formed only in 3%. These results clearly indicated that electron-rich olefin has higher reactivity than the electron-poor olefin.

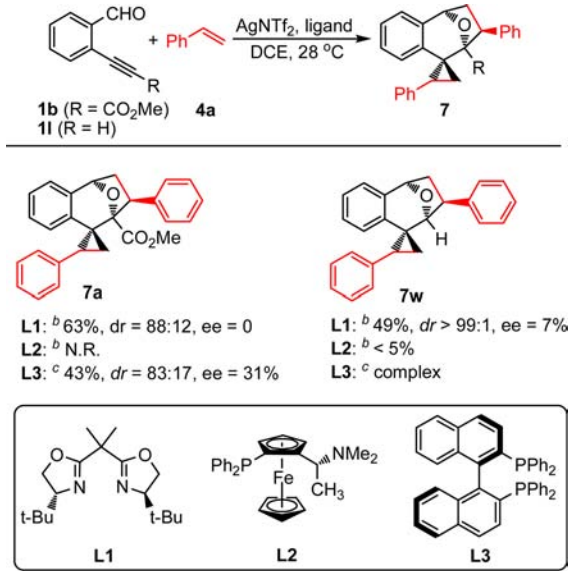
Scheme 6. Competitive Experiment



7b (75%) **7d** (3%)
7bd (2%) **7db** (20%)
Ar^C: 4-Me-C_6H_4-; Ar^F: 4-F-C_6H_4-

Having established a silver-catalyzed reaction of enynals **1** with alkenes **4** as a reliable one-step synthetic process to construct the complex molecule **7**, with 5−6 chiral centers and 1−2 quaternary carbons, we then conducted a study to realize the more challenging asymmetric version of this transformation. As shown in Scheme 7, under the standard reaction conditions, three representative chiral ligands, **L1**−**L3**, were tested for this purpose. The preliminary results revealed that bis-oxazoline ligand **L1** could catalyze the reaction smoothly, affording **7a** and **7w** in 63% and 49% yields, respectively. Nevertheless, the ee values of both products were less than 10%. Monophosphine ligand **L2** was inefficient for this transformation. Surprisingly, the biphosphine ligand **L3** (R-BINAP) could furnish the product **7a** with 31% ee and 43% yield.

Scheme 7. Asymmetric Version Reaction[a]



L1: [b]63%, dr = 88:12, ee = 0
L2: [b]N.R.
L3: [c]43%, *dr* = 83:17, ee = 31%

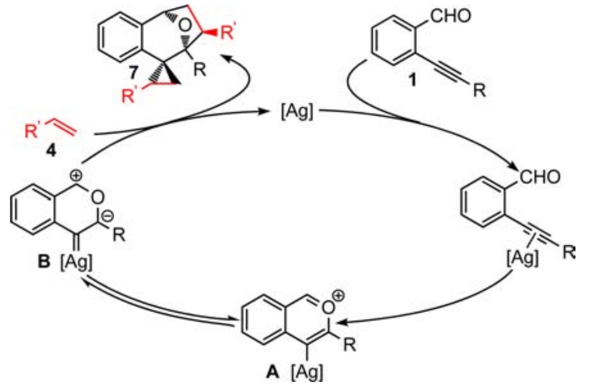
L1: [b]49%, *dr* > 99:1, ee = 7%
L2: [b]< 5%
L3: [c]complex

[a]The reaction was conducted in DCE at 60 °C for 12 h using 10 mol % of $AgNTf_2$ under N_2, enynals **1** (0.25 mmol), styrene **4a** (1.25 mmol); the yields refer to be isolated; dr values were determined by ^{1}H NMR; ee values were determined by HPLC analysis, see the Supporting Information. [b]Ten mol %. [c]Five mol %.

A tentative mechanism for the silver-catalyzed cascade reaction of 1,3-dipolar cycloaddition/cyclopropanation is proposed in Scheme 8. The carbon−carbon triple bond of enynal **1** was initially activated by the silver salt to form pyrylium salt **A**, which then tautomerized to 1,3-dipolar/silver−carbene intermediate **B**. A tandem 1,3-dipolar cycloaddition/cyclopropanation process was then followed to generate the product **7** by trapping the intermediate **B** with alkenes **4**.

In conclusion, a silver-catalyzed reaction of enynals with alkenes to synthesize a series of polycyclic compounds has been developed. The reaction proceeded through a tandem 1,3-

Scheme 8. Proposed Reaction Mechanism



dipolar cycloaddition/cyclopropanation process. To the best of our knowledge, it is the first example of silver-catalyzed 1,3-dipolar cycloaddition/cyclopropanation of enynals with alkenes. The preliminary results revealed that the biphosphine ligand could be used as the potential efficient chiral ligand for the asymmetric reaction. Fundamentally, this catalytic system enriched the knowledge of rapid construction of complex compounds bearing different types of cyclic skeletons. Practically, the ether unit, stained cyclopropane unit, and the ester unit in the molecule would lead to several different complexes through further transformation. Further asymmetric catalytic investigation of this reaction and additional applications of the products are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhusf@scut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for funding from the NNSFC (21172077, 21372086), the Program for New Century Excellent Talents in University (NCET-10-0403), Guangdong NSF (10351064101000000), and The National Basic Research Program of China (973) (2011CB808600), SRF for ROCS, State Education Ministry, and "The Fundamental Research Funds for the Central Universities, SCUT".

■ REFERENCES

(1) For reviews: (a) Munoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164. (b) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (c) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174. (d) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199. (e) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759. (f) Díaz-Requejo, M. M.; Pérez, P. J. *J. Organomet. Chem.* **2005**, *690*, 5441. (g) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993.

(2) (a) Zhu, S.; Liang, R.; Jiang, H.; Wu, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10861. (b) Wile, B. M.; Stradiotto, M. *Chem. Commun.* **2006**, 4104. (c) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (d) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (e) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701.

(3) (a) Ito, Y.; Kato, R.; Hamashima, K.; Kataoka, Y.; Oe, Y.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2007**, *692*, 691. (b) Youn, S. W.; Eom, J. I. *J. Org. Chem.* **2006**, *71*, 6705. (c) Yang, C.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553. (d) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Seiji. *J. Org. Chem.* **1997**, *62*, 776. (e) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329. (f) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

(4) (a) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096. (b) Sromek, A. W.; Kel'In, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (c) VanBrunt, M. P.; Standaert, R. F. *Org. Lett.* **2000**, *2*, 705. (d) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. (e) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169. (f) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450.

(5) (a) Zhu, S.; Zhang, Z.; Huang, X.; Jiang, H.; Guo, Z. *Chem.—Eur. J.* **2013**, *19*, 4695. (b) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677. (c) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (d) Liu, Y.; Zhen, W.; Dai, W.; Wang, F.; Li, X. *Org. Lett.* **2013**, *15*, 874. (e) Vachhani, D. D.; Mehta, V. P.; Modha, S. G.; Van Hecke, K.; VanMeervelt, L.; Van der Eycken, E. V. *Adv. Synth. Catal.* **2012**, *354*, 1593. (f) Prajapati, R. K.; Kumar, J.; Verma, S. *Chem. Commun.* **2010**, *46*, 3312. (g) Su, S.; Porco, J. A. *Org. Lett.* **2007**, *9*, 4983. (h) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (i) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096. (j) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023. (k) Zhu, S.; Huang, H.; Zhang, Z.; Ma, T.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 6113.

(6) (a) Harmata, M., Ed. *Silver in Organic Chemistry*; Wiley: Stanford, 2010; Chapter 1. (b) Brummer, O.; Hoffman, T. Z.; Chen, D.; Janda, K. D. *Chem. Commun.* **2001**, 19. (c) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379. (d) Whitesides, G. M.; Casey, C. P. *J. Am. Chem. Soc.* **1966**, *88*, 4541. (e) Ueeda, R.; Kawasaki, Y.; Tanaka, T.; Okawara, R. *J. Organomet. Chem.* **1966**, *5*, 194. (f) Gilman, H.; Woods, L. A. *J. Am. Chem. Soc.* **1943**, *65*, 435.

(7) (a) Iglesias, M. J.; Nicasio, M. C.; Caballero, A.; Perez, P. J. *Dalton Trans.* **2013**, *42*, 1191. (b) Li, Z.; He, C. *Eur. J. Org. Chem.* **2006**, 4313. (c) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270. (d) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

(8) (a) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (b) Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2672.