ORGANIC
LETTERS

2010
Vol. 12, No. 1
116−119

Gold(I)-Catalyzed Tandem C−H and C−C Activation (Cleavage)

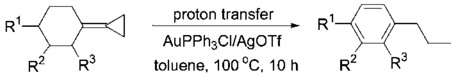
Min Jiang, Le-Ping Liu, Min Shi,* and Yuxue Li*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 China

mshi@mail.sioc.ac.cn; liyuxue@mail.sioc.ac.cn

Received November 9, 2009

ABSTRACT



(R^1 = aromatic group or alkyl group)
(R^2 = aromatic group)
(R^3 = H or alkyl group)

(Cyclopropylidenecyclohexyl)benzene derivatives, a kind of methylenecyclopropane (MCP) containing a cyclohexyl group, can undergo an interesting tandem intramolecular C−H and C−C bond activation through dehydrogenated rearrangement in the presence of AuPPh$_3$Cl/AgOTf by transferring three hydrogen atoms from cyclohexane to cyclopropane, affording the corresponding biaryl derivatives in moderate to good yields. The reaction mechanism has also been carefully investigated by deuterium labeling experiments and DFT calculations.

Metal-catalyzed activation of the C−H bond followed by C−C bond activation is much less frequently observed than the C−H bond or C−C bond activation.[1] A metal-catalyzed tandem C−H bond and C−C bond activation should be the most attractive aspect for many organometallic chemists, due not only to its fundamental scientific interest but also to its potential utility in organic synthesis. Methylenecyclopropanes as highly strained but readily accessible molecules can undergo a variety of ring-opening reactions in the presence of transition metals or Lewis acids because the relief of ring strain provides a potent thermodynamic driving force.[2,3] Moreover, it should also be noted that release of such strain energy (27 kcal/mol)[4] is not sufficient for high reactivity. The π character of the ring bonds of a cyclopropane provides the kinetic opportunity to initiate the unleashing of the strain.[5] Thus far, it has been known that the cyclopropane can undergo the C−C bond cleavage in the presence of various transition metal catalysts, giving the ring-opening products in good yields.[6] During the past few years, gold(I) has emerged as the most powerful soft Lewis acid for activation of alkynes, allenes, and alkenes due to its exceptional alkenophilicity and alkynophilicity.[7] Several C−H bond activations in alkanes have also been achieved with supported or homogeneous gold catalysts.[8] Therefore, we envisaged

---

(1) (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245–269. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (c) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870–883. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610–618. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770, and references therein. (f) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759–1792, and references therein. (g) Steenwinkel, P.; Gossage, R. A.; van Koten, G. *Chem.—Eur. J.* **1998**, *4*, 759–762, and references therein. (h) Murakami, M.; Ito, Y. *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; pp 97−129 and references therein.

(2) Selected reviews. (a) Henry, N. C.; Wong, M. Y.; Chun, W. T.; Yu, C. Y. *Chem. Rev.* **1989**, *89*, 165–198. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1270. (e) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877.

(3) Selected recent contributions from our group. (a) Shi, M.; Liu, L. P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430–7431. (b) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem.—Eur. J.* **2006**, *12*, 510–517. (c) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. (d) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917–4920. (e) Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem.—Eur. J.* **2007**, *13*, 862–869. Recent examples on the C−C and C−H activation of MCPs: (f) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307. (g) Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, *129*, 14836–14837.

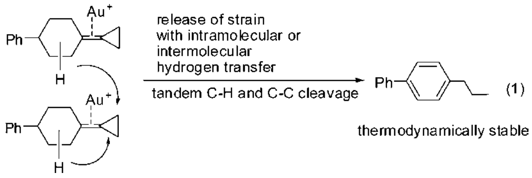
(4) Lukina, M. Y. *Russ. Chem. Rev.* **1963**, *32*, 635–651.

(5) (a) de Meijere, A. *Top. Curr. Chem.* **1988**, *V144*. (b) de Meijere, A., Blechert, S., Eds. *Strain and Its Implications in Organic Chemistry*; NATO ASI series; Kluwer Academic Publishers, 1989.

(6) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721. (b) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154–9155. (c) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164–4165. (d) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123–8124.

10.1021/ol902593f

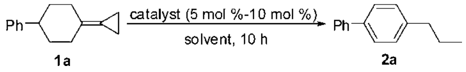
that using (cyclopropylidenecyclohexyl)benzene **1a**, a kind of methylenecyclopropane (MCP) containing cyclohexane, as the substrate an interesting tandem C−H and C−C activation might be able to take place by intramolecular or intermolecular hydrogen transfer from cyclohexane to cyclopropane, affording thermodynamically stable biaryl aromatic compounds in the presence of a Au(I) catalyst (eq 1). In this paper, we wish to report such interesting tandem intramolecular C−H and C−C activation through dehydrogenated rearrangement of **1** in the presence of $AuPPh_3Cl$/AgOTf at high temperature in toluene or xylene to give the corresponding biaryl derivatives in moderate to good yields.



(1)

Initial studies using (cyclopropylidenecyclohexyl)benzene **1a** as the substrate were aimed at determining the optimal reaction conditions for the Lewis acid-catalyzed reactions, and the results of these experiments are summarized in Table 1 (for the detailed description, please see the Supporting Information). We found that the reaction proceeded smoothly in toluene to give 4-propylbiphenyl **2a** in 85% yield within 10 h at 100 °C in the presence of $AuPPh_3Cl$/AgOTf (Table 1, entry 1), and other Lewis acids such as $Sc(OTf)_3$, $Sn(OTf)_2$, $Nd(OTf)_3$, and $BF_3{\cdot}Et_2O$ are not as effective as Au(I) under identical conditions. The combination of $AuPPh_3Cl$/$AgBF_4$ or $AuPPh_3Cl$/$AgSbF_6$ did not have catalytic activity in this reaction, but using $AuCl_3$/AgOTf as the combined catalysts afforded **2a** in 72% yield. Brønsted acid CF_3CO_2H and CH_3CO_2H (HOAc) did not catalyze the reaction, and CF_3SO_3H (HOTf) afforded complex product mixtures under the standard conditions (Table 1, entries 12, 13, and 15). The examination of solvent effects revealed that toluene is the solvent of choice in this reaction (Table 1, entries 16−20).

Table 1. Optimization of the Reaction Conditions for the Rearrangement of MCP **1a**

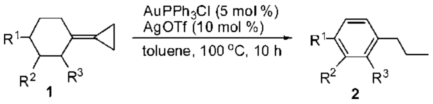


entry^a	solvent	catalyst	temp (°C)	yield (%)^b **2a**
1	**toluene**	**$AuPPh_3Cl$/AgOTf**	**100**	**85**
2	toluene	$AuPPh_3Cl$/$AgSbF_6$	100	NR
3	toluene	$AuPPh_3Cl$/$AgBF_4$	100	NR
4	toluene	$AuPPh_3Cl^c$	100	NR
5	toluene	AgOTf^c	100	NR
6	toluene	$Sc(OTf)_3{}^c$	100	53
7	toluene	$Sn(OTf)_2{}^c$	100	45
8	toluene	$Nd(OTf)_3{}^c$	100	60
9	toluene	$BF_3{\cdot}Et_2O^c$	100	55
10	toluene	$Yb(OTf)_3{}^c$	100	NR
11	toluene	$La(OTf)_3{}^c$	100	NR
12	toluene	$CF_3CO_2H^c$	100	NR
13	toluene	AcOH^c	100	NR
4	toluene	$AuCl_3$/AgOTf	100	72
15	toluene	HOTf^c	100	complex mixtures
16	CH_3CN	$AuPPh_3Cl$/AgOTf	reflux	NR
17	DCE	$AuPPh_3Cl$/AgOTf	reflux	68
18	THF	$AuPPh_3Cl$/AgOTf	reflux	NR
19	CH_2Cl_2	$AuPPh_3Cl$/AgOTf	reflux	NR
20	Et_2O	$AuPPh_3Cl$/AgOTf	reflux	NR

[a] Reaction conditions: **1a** (0.2 mmol), Au catalyst (5 mol %), Ag salt (10 mol %), solvent (2.0 mL), and the reactions were carried out at 100 °C or under reflux. [b] Isolated yields. [c] 10 mol % is used.

With the optimized reaction conditions being identified, we next carried out $AuPPh_3Cl$/AgOTf cocatalyzed rearrangement reactions of a variety of MCPs **1** to evaluate the scope of this reaction. The results are summarized in Table 2. As can be seen from Table 2, as for substrates in which R^1 = aryl and $R^2 = R^3$ = H, the corresponding rearrangement products, 4-propylbiaryls, can be obtained in moderate to good yields within 10 h as the sole products (Table 2, entries 1−10). Adding electron-poor substituents on the benzene rings afforded the products in slightly lower yields (Table 2, entries 2−8 and 9−10). As for MCP **1k** in which R^1 = phenyl, R^2 = H, and R^3 = methyl, the reaction also proceeded smoothly to give the corresponding

Table 2. Gold(I)-Catalyzed Rearrangement of **1** under the Optimal Conditions



entry^a	**1** ($R^1/R^2/R^3$)	yield (%)^b **2**
1	**1a** (C_6H_5/H /H)	**2a**, 85
2	**1b** (*p*-MeC_6H_4/H /H)	**2b**, 77
3	**1c** (*m*-MeC_6H_4/H/H)	**2c**, 79
4	**1d** (*o*-MeC_6H_4/H /H)	**2d**, 76
5	**1e** (*o*,*p*-$Me_2C_6H_3$/H/H)	**2e**, 82
6	**1f** (*m*,*m*-$Me_2C_6H_3$/H/H)	**2f**, 79
7	**1g** (*m*-$MeOC_6H_4$/H /H)	**2g**, 74
8	**1h** (*p*-$MeOC_6H_4$/H/H)	**2h**, 82
9	**1i** (*p*-$C_6H_5C_6H_4$/H/H)	**2i**, 57
10	**1j** (*p*-ClC_6H_4/H/H)	**2j**, 63
11	**1k** (C_6H_5/H/Me)	**2k**, 71
12	**1l** (C_4H_9/H/H)	**2l**, 55

[a] Reaction conditions: **1** (0.2 mmol), $AuPPh_3Cl$ (0.01 mmol), AgOTf (0.02 mmol), toluene (2.0 mL), and the reactions were carried out at 100 °C. [b] Isolated yield.

---

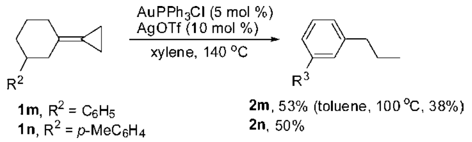
(7) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3183–3211. (b) Jimémez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (e) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752. (f) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203. (g) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391. (h) Arcadio, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795–812. (i) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431–436.

(8) (a) Hill, C. L.; Weinstock, I. A. *Nature* **1997**, *388*, 332–333. (b) Zhao, R.; Ji, D.; Lv, G.; Qian, G.; Yan, L.; Wang, X.; Suo, J. *Chem. Commun.* **2004**, 904–905. (c) Shul'pin, G. B.; Shilov, A. E.; Süss-Fink, G. *Tetrahedron Lett.* **2001**, *42*, 7253–7256.

diaryl derivative **2k** in 71% yield (Table 2, entry 11). Using MCP **1l** in which $R^1 = C_4H_9$ and $R^2 = R^3 = H$, the expected rearrangement product was obtained in 55% yield, indicating the wide substrate generality in this Au-catalyzed reaction (Table 2, entry 12).

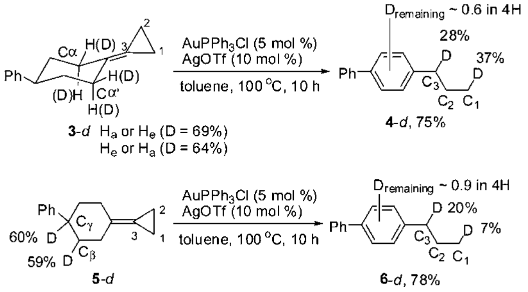
As for MCP **1m** in which $R^1 = H$, $R^2 = C_6H_5$, and $R^3 = H$, using gold(I) as a catalyst at 100 °C in toluene afforded the corresponding product **2m** in 38% yield (Scheme 1). Optimization of the reaction conditions revealed that **2m** could be obtained in 53% yield in xylene at 140 °C (Scheme 1). These reaction conditions also tolerated MCP **1n** (R^2 = *p*-MeC_6H_4), providing the corresponding product **2n** in 50% yield (Scheme 1).

Scheme 1. Au(I)-Catalyzed Rearrangement of MCPs **1m** and **1n**



Deuterium labeling experiments with MCPs **3-*d*** (H_a and H_e or H_e and H_a at C_α and $C_{\alpha'}$ position, D content = 64% and 69%, respectively, on the basis of ^{1}H NMR and EI-Mass spectra) and **5-*d*** (C_β and C_γ, D content = 59% and 60%, respectively) were carried out under the standard conditions to clarify the reaction mechanism (Scheme 2).

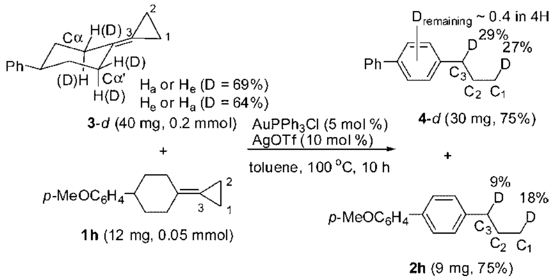
Scheme 2. Deuterium Labeling Experiments for the Rearrangement of MCPs **3-*d*** and **5-*d***



The product **4-*d*** with 37% D content at C_1 and 28% D content at C_3 as well as product **6-*d*** with 7% D content at C_1 and 20% D content at C_3 were obtained in 75% and 78% yield within 10 h, respectively, based on the corresponding ^{1}H NMR spectroscopic data (Supporting Information), suggesting that (1) the hydrogen atoms at C_α or $C_{\alpha'}$ transfer to C_1 and C_3 and (2) the hydrogen atoms at C_β or C_γ also transfer to C_1 and C_3 in the presence of Au(I). In addition, no influence was observed in the presence or absence of molecular oxygen under otherwise identical conditions.

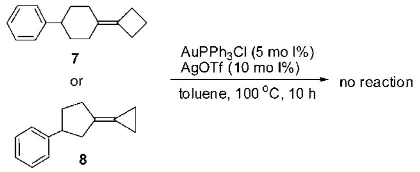
The crossover experiments of **3-*d*** and **1h** under the standard conditions afforded product **4-*d*** with 27% D content and 29% D content at C_1 and C_3 as well as product **2h-*d*** with 18% D content and 9% D content at C_1 and C_3 in 75% and 75% yield, respectively, suggesting that intermolecular hydrogen transferring also takes place under the standard conditions (Scheme 3).

Scheme 3. Crossover Experiments



The control experiments shown in Scheme 4 indicate that a cyclopropane ring and a cyclohexane ring in MCPs **1** are both crucial in this Au(I)-catalyzed transformation since no reaction occurred using **7** and **8** as the substrates under the standard conditions (Scheme 4).

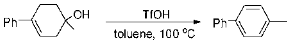
Scheme 4. Control Experiments



To reveal the mechanism of this novel Au(I)-catalyzed tandem C−C and C−H bond cleavage reaction, density functional theory (DFT) studies have been performed with the substrate **1a**.[9] In the calculation, PMe_3 is used instead of PPh_3. Previous theoretical works revealed that this simplification is reasonable.[10] On the basis of a series of systematical investigations, the proposed reaction pathway is shown in Scheme 5. Under the standard reaction conditions, OTf-Au-PPh_3 species is generated in situ. The complex of **1a** with Au^+-PMe_3 (**A-comp**) is 2.0 kcal/mol higher in energy than species **A**, in which Au(I) is coordinated with the OTf^- anion. Therefore, the species **A** is used as the zero reference point of this reaction. In **A-comp**, the complexation of Au(I) with the double bond increases the acidity of the α-H atom in substrate **1a**. In the first step, the OTf^- anion abstracts an α-H atom over a barrier of 19.6 kcal/mol, leading to formation of intermediate **B**. In intermediate **B**, Au forms a covalent bond with C_3 (2.096 Å) stabilizing the carbanion. Then the C_1−C_3 bond is attacked by

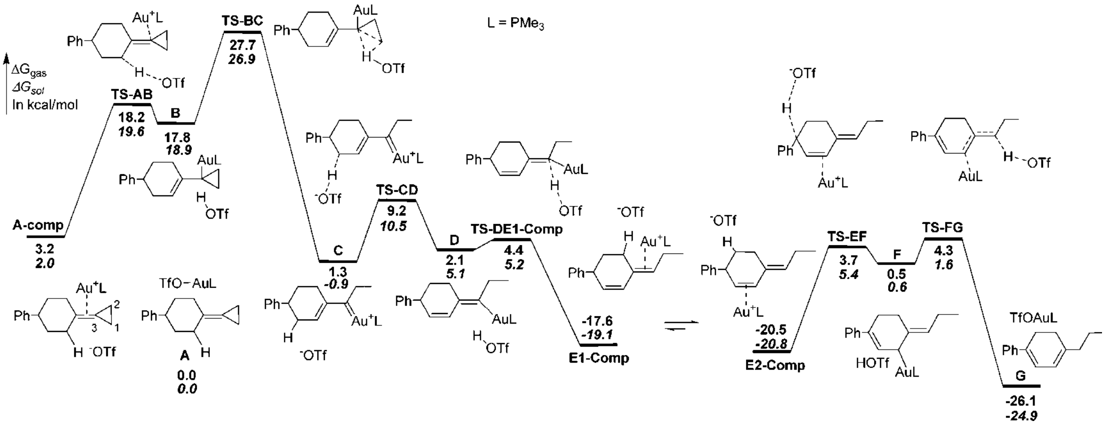
---

(9) See Supporting Information for the details. As for the dehydration and dehydrogenation to give aromatic compound, see: (a) Arumugam, N.; Kumaraswamy, A. *Synthesis* **1981**, 367–368. (b) Woods, G. F.; Oppelt, J. C.; Isaacson, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 5232–5235.



(10) Shi, F.-Q.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503–15512.

Scheme 5. Proposed Mechanism of the Au(I)-Catalyzed Tandem Reaction[a]



[a] The geometries have been fully optimized at the B3LYP/6-31+G**/Lanl2DZ level. The relative free energies in gas phase ΔG_{gas}(298 K) and the relative free energies including solvent effect ΔG_{sol}(298 K) are in kcal/mol.

the proton of the HOTf molecule. The cyclopropane is opened, and the α-H is transferred to C_1, leading to the gold carbenoid intermediate **C**. This is the rate-determining step. Therefore, the whole reaction should be facilitated by the release of the strain energy in the cyclopropane ring. Considering the experimental conditions, the barrier (26.9 kcal/mol) is reasonable. In the next step, the OTf^- anion abstracts a β-H atom over a small barrier of **TS-CD** yielding the alkenylgold intermediate **D**. The protonation of intermediate **D** by HOTf leads to formation of intermediate **E1-Comp** and regenerates the [Au^+] catalyst. **E1-Comp** may transform to its more stable conformational isomer **E2-Comp** via the dissociation/association process of the Au(I) catalyst and the C═C double bonds. The OTf^- anion abstracts the γ-H atom in **E2-Comp**, affording intermediate **F**, which is converted to the cyclohexa-1,2-diene intermediate **G** by protonation on C_3. Our calculation results indicate that Au(I) cannot facilitate the deprotonation of **G** any longer.[9,10] Further control experiments also confirmed that **G** can be easily transformed to the phenyl derivative by deprotonation under the reaction conditions without the assistance of the Au(I) catalyst (Supporting Information).[9]

On the basis of this mechanism, the OTf^-/HOTf pair can act as a proton carrier to finish up the hydrogen transfer intra/intermolecularly, which is consistent with the deuterium-labeling experimental results. Previous DFT studies on the $Au(PR_3)^+$-catalyzed reactions also showed that the counterion OTf^- can assist the 1,2-H shift effectively.[11] In the optimized structures, the OTf^- anion is relatively free and often resides far away from the gold site. This result is also in line with the recent studies.[12]

In conclusion, we have developed an effective $AuPPh_3Cl$/AgOTf-cocatalyzed tandem intramolecular C−H and C−C activation through dehydrogenated rearrangement of methylenecyclopropanes **1** to produce biaryl derivatives in good yields at high temperature. The reaction proceeds through transferring three hydrogen atoms from the cyclohexyl ring to the cyclopropane ring intra/intermolecularly in the presence of Au(I). It should be also noted that intermolecular hydrogen transfer with OTf^- is a very minor process on the basis of the deuterium labeling experiment. Since biaryls constitute core structural units for a wide range of functional molecules[13] and are synthesized primarily using transition-metal-catalyzed aryl−aryl cross-coupling reactions,[14] this new Au(I)-catalyzed process provides an alternative way to attain such compounds. The mechanistic study by DFT calculation shows that OTf^-/HOTf can act as proton carrier to finish up the hydrogen transfer intra/intermolecularly. If using BF_3 as the catalyst, the active species HBF_3OH derived from the reaction of BF_3 with trace amounts of water might be able to trigger a similar hydrogen transfer with BF_3OH^- to afford the corresponding biaryl product.[15] Efforts are in progress to further understand the scope and limitations of this reaction.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (06XD14005, 08dj1400100-2), National Basic Research Program of China (973)-2009CB825300, and the National Natural Science Foundation of China for financial support (20472096, 20872162, 20672127, 20821002, and 20732008).

Supporting Information Available: Detailed description of experimental procedures, full characterization of new compounds shown in Tables 1 and 2 and Schemes 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902593F

---

(11) Xia, Y. Z.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. H. *J. Am. Chem. Soc.* **2008**, *130*, 6940–6941.

(12) Zuccaccia, D.; Belpassi, L.; Tarantelli, F.; Macchioni, A. *J. Am. Chem. Soc.* **2009**, *131*, 3170–3171.

(13) (a) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (b) Baudoin, O.; Gueritte, F. *Stud. Nat. Prod. Chem., Part J* **2003**, *29*, 1109–1121. (c) Ivica, C., Ed. *Synthesis of Biaryls*; Elsevier Ltd.: Oxford, 2004.

(14) (a) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-coupling Reactions*, 2nd ed.; Wiley-VCH: New York, 2004. (b) Miyaura, N., Ed. *Cross-Coupling Reactions: A Practical Guide*; Springer: Berlin, 2002.

(15) (a) Evans, A. G.; Holden, D.; Plesch, P.; Polanyi, M.; Skinner, H. A.; Weinberger, M. A. *Nature* **1946**, *157*, 102–102. (b) Evans, A. G.; Meadows, G. W.; Polanyi, M.; Skinner, H. A.; Weinberger, M. A. *Nature* **1946**, *158*, 94–95.