JOC *Note*

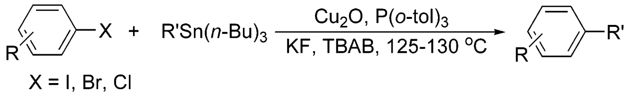
Reusable Copper-Catalyzed Cross-Coupling Reactions of Aryl Halides with Organotins in Inexpensive Ionic Liquids

Jin-Heng Li,* Bo-Xiao Tang, Li-Ming Tao, Ye-Xiang Xie, Yun Liang, and Man-Bo Zhang*

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, China

jhli@hunnu.edu.cn; manbozhang@163.com

Received June 14, 2006



A combination of Cu_2O nanoparticles with P(*o*-tol)$_3$ shows highly catalytic activity for the Stille cross-coupling reaction. A series of copper catalysts and ligands were evaluated, and Cu_2O nanoparticles combined with P(*o*-tol)$_3$ provided the best results. In the presence of Cu_2O nanoparticles and P(*o*-tol)$_3$, a variety of aryl halides including aryl chlorides underwent the Stille reaction with organotins smoothly in moderate to excellent yields using inexpensive TBAB (*n*-Bu_4NBr) as the medium. It is noteworthy that the Cu_2O/P(*o*-tol)$_3$/TBAB system can be recovered and reused at least three times without any loss of catalytic activity among the reactions of aryl iodides and activated aryl bromides.

The Stille cross-coupling reaction is an important transformation in organic synthesis because its products, in particular biarys,[1] play an important role as structural elements of many natural products and biologically active compounds as well as useful intermediates in synthetic organic chemisty.[2] Among these efficient Stille protocols, palladium combined with a ligand (usually a phosphine ligand) is generally employed as the catalytic system.[2−4] However, the cost of these palladium catalysts is considerably expensive. In terms of economy, the use of cheaper metals, such as copper[6−8] and nickel,[9] as the catalysts is an alternative strategy besides the recovery as well as reuse of the expensive palladium catalysts.[2] Although copper as the cocatalyst for the palladium-catalyzed Stille cross-couplings has been reported in many papers,[4] little attention has been attracted on the use of copper as catalyst alone for the reaction.[5−8] Moreover, many copper-mediated protocols required stoichiometric amounts of copper.[5,6] Kang and co-workers first demonstrated that the Stille couplings catalyzed by 10 mol % of CuI alone were conducted smoothly in moderate to high yields with the aid of sodium chlorides.[7] However, the scope was limited to aryl iodides and vinyl iodides, and organostannanes must be added slowly by a syringe pump to improve the yields. The other copper-catalyzed Stille methods were also focused on the activated organohalides, such as acyl chlorides,[8a] ally bromides, proparyl bromides,[8b] and hypervalent iodine compounds.[8c] Thus, the development of an effective copper catalytic system extended the scope to aryl bromides, and aryl chlorides is still a challenging area. Here, we report an effective Cu_2O nanoparticles/P(*o*-tol)$_3$ catalytic system for cross-couplings of aryl halides including aryl chlorides with organotins in TBAB. Importantly, the Cu_2O/P(*o*-tol)$_3$/TBAB system can be recovered

---

(1) Bringmann, G.; Gunther, C.; Ochse, M.; Schupp O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: New York, 2001; Vol. 82, pp 1−293.

(2) For reviews, see the following: (a) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Ed.; J. Wiley & Sons: Chichester, U.K., 2002; p 1123. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (c). Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (d) Miyaura, N. *Cross-Coupling Reaction*; Springer: Berlin, 2002. (e) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (f) Wang D.-P.; Zhang, X.-D.; Liang, Y.; Li, J.-H. *Chin. J. Org. Chem.* **2006**, *26*, 19. (g) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (h) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (i) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(3) For very recent papers on the palladium-catalyzed Stille cross-couplings, see (a) Calo, V.; Nacci, A.; Monopoli, A.; Montingelli, F. *J. Org. Chem.* **2005**, *70*, 6040. (b) Garcia-Martinez, J. C.; Lezutekong, R.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 5097. (c) Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832. (d) Herve, A.; Rodriguez, A. L.; Fouquet, E. *J. Org. Chem.* **2005**, *70*, 1953. (e) Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2005**, *70*, 841. (f) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433. (g) Chiappe, C.; Pieraccini, D.; Zhao, D.; Fei, Z.; Dyson, P. J. *Adv. Synth. Catal.* **2006**, *348*, 68. (h) Li, J.-H.; Liang, Y.; Xie, Y.-X. *Tetrahedron* **2005**, *61*, 7289. (i) Gajare, A. S.; Jensen, R. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Synlett* **2005**, 144.

(4) For representative papers on the use of copper as the cocatalyst for the palladium-catalyzed Stille cross-couplings, see (a) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem.—Eur. J.* **2005**, *11*, 3294. (b) Mazzola, R. D., Jr.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220. (c) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305. (d) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (e) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288. (f) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194. (g) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600. (h) Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19. (i) Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341. (j) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (k) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.

(5) For reviews on copper-catalyzed coupling reactions, see (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(6) For representative papers on the Stille reaction mediated by stoichiometric amounts of copper catalysts, see (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748 and references therein. (b) Wipf, P. *Synthesis* **1993**, 537. (c) Falck, J. R.; Bhatt, R. K.; Ye J. *J. Am. Chem. Soc.* **1995**, *117*, 5973.

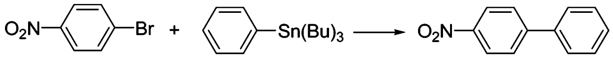
(7) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208.

(8) For papers on the copper-catalyzed Stille reactions of the activated organohalides, such as acyl chlorides, ally bromides, proparyl bromides, and hypervalent iodine compounds, see (a) Wang, Y.; Burton, D. *J. Org. Lett.* **2006**, *8*, 1109. (b) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759. (c) Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 9082.

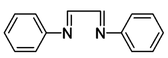
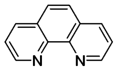
(9) For a representative paper on the nickel-catalyzed Stille reactions, see Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510.

10.1021/jo061220j CCC: $33.50

TABLE 1. Screening the Optimized Reaction Conditions for Copper-Catalyzed Stille Cross-Coupling Reaction of 1-Bromo-4-nitrobenzene (1a) with Tributyl(phenyl)stannane (2a)[a]

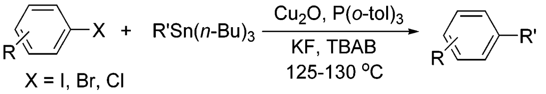


1a **2a** **3**

Entry	[Cu]	Ligand	Ionic liquid	Yield (%)[b]
1	CuI	—	TBAB	8
2	CuI	 (**L**$_1$)	TBAB	68
3	CuI	 (**L**$_2$)	TBAB	trace
4	CuI	DABCO (**L**$_3$)	TBAB	20
5	CuI	Ph_3PO (**L**$_4$)	TBAB	72
6	CuI	PPh_3 (**L**$_5$)	TBAB	18
7	CuI	PCy_3 (**L**$_6$)	TBAB	15
8	CuI	P(*o*-tol)$_3$ (**L7**)	TBAB	85
9[c]	CuI	P(*o*-tol)$_3$ (**L7**)	TBAB	20
10[d]	CuI	P(*o*-tol)$_3$ (**L**$_7$)	TBAB	30
11	CuBr	P(*o*-tol)$_3$ (**L**$_7$)	TBAB	30
12[e]	Cu_2O	P(*o*-tol)$_3$ (**L7**)	TBAB	90
13[f]	*Cu_2O*	P(*o*-tol)$_3$ (**L7**)	*TBAB*	*98*
14[f]	Cu_2O	P(*o*-tol)$_3$ (**L**$_7$)	TBAI	76
15[f]	Cu_2O	P(*o*-tol)$_3$ (**L**$_7$)	TBAC	39
16[f]	Cu_2O	P(*o*-tol)$_3$ (**L**$_7$)	$TBABF_4$	56
17[g]	Cu_2O	P(*o*-tol)$_3$ (**L**$_7$)	$TBABF_4$	96
18[h]	Cu_2O	—	—	10

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.4 mmol), copper (10 mol %), ligand (20 mol %), and $KF \cdot 2H_2O$ (2 equiv) in ionic liquid (1.5 g) at 125−130 °C for 24 h. [b] Isolated yield. [c] TBAF (2 equiv) instead of KF. [d] K_2CO_3 (2 equiv) instead of KF. [e] Common Cu_2O (10 mol %). [f] Cu_2O nanoparticles (10 mol %) as the catalyst. [g] **1a** (3 mmol), **2a** (4 mmol), and Cu_2O nanoparticles (10 mol %) in ionic liquid (5 g). [h] Cu_2O nanoparticles (10 mol %) and NaCl (1 equiv) in NMP (1 mL).

and reused at least three times without a loss of activity in the couplings of aryl iodides and activated aryl bromides (eq 1).



(1)

The Stille cross-coupling reaction of 1-bromo-4-nitrobenzene (**1a**) with tributyl(phenyl)stannane (**2a**) performed in ionic liquids was conducted as a model to screen the optimized reaction conditions, and the results are summarized in Table 1. Initially, a set of ligands, including *N*-(2-(phenylimino)ethylidene)benzenamine (**L**$_1$), 1,10-phenanthroline (**L**$_2$), DABCO (1,4-diaza-bicyclo[2.2.2]octane; **L**$_3$), Ph_3PO (**L**$_4$), PPh_3 (**L**$_5$), PCy_3 (**L**$_6$), and P(*o*-tol)$_3$ (**L**$_7$), were tested using CuI as the catalyst and KF as the base (entries 1−8). The results showed that P(*o*-tol)$_3$ (**L**$_7$) was the most effective ligand in terms of yield (entry 8). Without any ligands, treatment of 1-bromo-4-nitrobenzene (**1a**) with tributyl(phenyl)stannane (**2a**), CuI, $KF \cdot 2H_2O$, and TBAB at 125−130 °C for 24 h afforded the target product **3** in rather low yields (entry 1), whereas the yield of **3** was enhanced to 68% sharply when 20 mol % of **L**$_1$ was added (entry 2). A trace amount of **3** was observed using 1,10-phenanthroline (**L**$_2$) as the ligand (entry 3). DABCO (**L**$_3$), the reported effective ligand in the other copper-catalyzed cross-couplings,[10] gave only 20% yield (entry 4). We were happy to find that among the phosphine ligands, employing P(*o*-tol)$_3$ (**L**$_7$) as the ligand gave the highest yield of the desired product **3** (85% yield; entries 5−8). The effect of the base was then examined, and KF provided better results than TBAF (*n*-Bu_4NF) and K_2CO_3 (entries 8−10). A number of other copper catalysts were also evaluated (entries 11−13). It was a welcome discovery that Cu_2O, in particular Cu_2O nanoparticles,[11] showed higher activity than either CuI or CuBr. In the presence of 10 mol % of Cu_2O, 20 mol % of P(*o*-tol)$_3$ (**L**$_7$), and 2 equiv of KF, a 90% yield of **3** was obtained (entry 12). It is noteworthy that nearly a quantitative yield of the target product **3** was observed using Cu_2O nanoparticles as the catalyst (entry 13). The other inexpensive ionic liquids including TBAI (*n*-Bu_4NI), TBAC (*n*-Bu_4NCl), and $TBABF_4$ (*n*-Bu_4NBF_4) as the media were investigated under the optimized conditions, and they were less effective than TBAB (entries 14−16). Noteworthy is that the process is suitable for the reaction of 3 mmol of substrate **1a** with 4 mmol of **2a** (entry 17). A control reaction was also performed in the presence of 10 mol % of Cu_2O nanoparticles, 1 equiv of NaCl, and 1 mL of NMP at 125−130 °C for 24 h on the basis of the earlier report;[7] however, a low yield was isolated (entry 18)

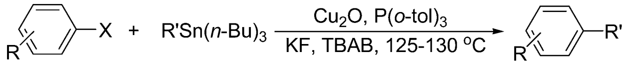
Under the optimized reaction conditions, a variety of aryl halides **1a**−**k** were coupled with organotins smoothly to afford the corresponding products in good yields (Table 2). Moreover, the Cu_2O nanoparticles/P(*o*-tol)$_3$ (**L**$_7$)/TBAB system could be recovered and reused. As demonstrated in Table 2, the coupling of substrate **1a** with **2b** or **2c** was carried out efficiently at 125−130 °C for 20−24 h to offer the corresponding products **4** and **5** in 89% and 94% yields, respectively, in the presence of 10 mol % of Cu_2O nanoparticles, 20 mol % of P(*o*-tol)$_3$ (**L**$_7$), 2 equiv of KF, and 1.5 g of TBAB (entries 1 and 2). To our delight, the Cu_2O nanoparticles/**L**$_7$/TBAB system could be recovered and reused at least three times without a loss of activity in the coupling of **1a** with **2c** (entry 2). After initial experimentation, the reaction mixture was extracted with cylcohexane, and the Cu_2O nanoparticles/**L**$_7$/TBAB system were then solidified (evaporated and cooled) and subjected to a second run of the coupling by charging with the same substrates and base (**1a**, **2c**, and KF). The results of three runs showed that they were almost consistent in yields and rates (run 1, 93%; run 2, 94%; run 3, 96%). Aryl iodides **1b**,**c** and another activated aryl bromide **1d** could also undergo the recoverable and reusable process successfully (entries 3, 4, and 6). However, the catalytic activity of the reusable system was reduced in the second run of the coupling of the deactivated aryl bromide **1g** with **2a** (entry 11). In the first run, a 96% yield of the desired product **7** was isolated after 30 h from the reaction between **1g** and **2a**, whereas the yield of **7** was decreased to 55% in the second run. The activity was further contrasted to the Cu_2O nanoparticles with the common Cu_2O (entries 11 and 12). A 96% yield of **7** was isolated from the coupling between **1g** and **2a** using the Cu_2O nanoparticles as the catalyst, while the yield of **7** was reduced to 80% employing the common Cu_2O as the catalyst. Although the catalytic activity of the Cu_2O nanoparticles and P(*o*-tol)$_3$

---

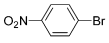
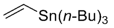
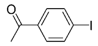
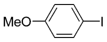
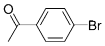
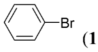
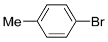
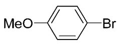
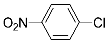
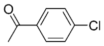
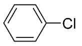
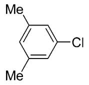
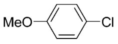
[10] For papers on the use of DABCO as the ligand for the other copper-catalyzed cross-couplings, see (a) Li, J.-H.; Wang, D.-P. *Eur. J. Org. Chem.* **2006**, 2063. (b) Li, J.-H.; Wang, D.-P.; Xie, Y.-X. *Tetrahedron Lett.* **2005**, *46*, 4941.

[11] Cu_2O nanoparticles were synthesized by the known procedure, see Wang, W.; Wang, G.; Wang, X.; Zhan, Y.; Liu, Y.; Zheng, C. *Adv. Mater.* **2002**, *14*, 67.

TABLE 2. Cu_2O Nanoparticles-Catalyzed Stille Cross-Couplings of Aryl Halides (1) with Organotins (2) in TBAB[a]



1 **2** **3-13**

Entry	Aryl halide	R′Sn(n-Bu)$_3$	Recycle no.	Time (h)	yield (%)[b]
1	 (**1a**)	 (**2b**)		24	89 (**4**)
2	(**1a**)	Ph—≡—Sn(n-Bu)$_3$ (**2c**)	1	20	93 (**5**)
			2	20	94 (**5**)
			3	20	96 (**5**)
3	 (**1b**)	PhSn(n-Bu)$_3$ (**2a**)	1	11	90(**6**)
			2	11	93 (**6**)
			3	11	95 (**6**)
4	 (**1c**)	(**2a**)	1	12	87 (**7**)
			2	12	94 (**7**)
			3	12	94 (**7**)
			4	12	95 (**7**)
			5	12	98 (**7**)
5	(**1c**)	(**2c**)		12	90 (**8**)
6	 (**1d**)	(**2a**)	1	27	88 (**6**)
			2	27	89 (**6**)
			3	27	96 (**6**)
7	(**1d**)	(**2c**)		27	91 (**9**)
8	 (**1e**)	(**2a**)		28	107 (**10**)
9	(**1e**)	(**2c**)		28	58 (**11**)
10	 (**1f**)	(**2a**)		29	94 (**12**)
11	 (**1g**)	(**2a**)	1	30	96 (**7**)
			2	30	55 (**7**)
12[c]	(**1g**)	(**2a**)		30	80 (**7**)
13	(**1g**)	(**2c**)		30	8 (**8**)
14	 (**1h**)	(**2a**)		48	92 (**3**)
15	 (**1i**)	(**2a**)		60	90 (**6**)
16	 (**1j**)	(**2a**)		60	91 (**10**)
17	 (**1k**)	(**2a**)		72	92 (**13**)
18	 (**1l**)	(**2a**)		72	10 (**7**)

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.4 mmol), Cu_2O nanoparticles (10 mol %), P(o-tol)$_3$ (**L$_7$**, 20 mol %), and $KF \cdot 2H_2O$ (2 equiv) in TBAB (1.5 g) at 125−130 °C. [b]Isolated yield. [c]Common Cu_2O (10 mol %) instead of Cu_2O nanoparticles.

(**L$_7$**) system was decreased to some extent for the couplings of aryl chlorides, high yields were still achieved after prolonged reaction times (entries 14−17). For example, the bulky chloride **1k** bearing two methyl groups reacted with **2a** for 72 h to give the target product **13** in a 92% yield under the optimized reaction conditions (entry 17). Unfortunately, a low yield of the desired coupled product **7** was observed in the coupling of the deactivated chloride **1l** with **2a** after 72 h under the same conditions (entry 18).

In summary, an efficient and reusable copper-catalyzed Stille coupling protocol has been developed. The reaction showed excellent substituents on the aromatic rings tolerance. Noteworthy is that the Cu_2O nanoparticles/P(o-tol)$_3$/TBAB system displays exceptionally activity and extended the scope to a variety of aryl halides including less active aryl chlorides. Moreover, the Cu_2O/P(o-tol)$_3$/TBAB system can be recovered and reused at least three times without a loss of activity in the couplings of aryl iodides and activated aryl bromides. In addition, the present copper system is considerably inexpensive and readily available, which emerged as an attractive alternative to palladium catalysts for the Stille cross-coupling reaction. Given these advantages, efforts to extend the application of these catalytic system in organic synthesis are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Copper-Catalyzed Stille Cross-Coupling Reaction in TBAB. A mixture of aryl halide **1** (0.3 mmol), organotin **2** (0.4 mmol), Cu_2O (nanoparticles; 10 mol %), P(o-tol)$_3$ (**L$_7$**; 6 mol %), $KF \cdot 2H_2O$ (2 equiv), and TBAB (1.5 g) was stirred at 125−130 °C for the desired time until the complete consumption of the starting material as monitored by TLC. After the reaction was finished, diethyl ether was poured into the mixture. The mixture was then washed with water, extracted with diethyl ether, dried by anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled product.

Typical Experimental Procedure for the Reused Copper-Catalyzed Stille Cross-Coupling Reaction in TBAB. A mixture of aryl halide **1** (0.3 mmol), organotin **2** (0.4 mmol), Cu_2O (nanoparticles; 10 mol %), P(o-tol)$_3$ (**L$_7$**; 6 mol %), $KF \cdot 2H_2O$ (2 equiv), and TBAB (1.5 g) was stirred at 125−130 °C for the desired time until the complete consumption of the starting material as monitored by TLC. After the reaction was finished, the mixture was extracted with cyclohexane (5 mL × 6) and evaporated under vacuum. The residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled product. After initial experimentation, the residue Cu_2O nanoparticles/P(o-tol)$_3$/TBAB system was then solidified (evaporated in vacuo and cooled) and subjected to a second run of the Stille reaction by charging with the same substrates (aryl halide, organotin, and $KF \cdot 2H_2O$).

Acknowledgment. The authors thank Scientific Research Fund of Hunan Provincial Education Department (Grant No. 05B038), the National Natural Science Foundation of China (Grant No. 20572020), Fok Ying Dong Education Foundation (Grant No. 101012), the Key Project of Chinese Ministry of Education (Grant No. 206102), and Hunan Provincial Natural Science Foundation of China (Grant No. 05JJ1002) for financial support.

Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **3**−**13**; typical procedure for the copper-catalyzed Stille reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061220J