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CuI/DABCO-Catalyzed Cross-Coupling Reactions of Aryl Halides with Arylboronic Acids

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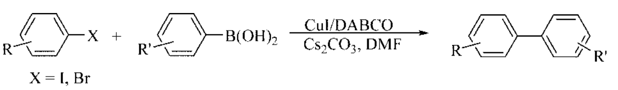
Keywords: CuI / DABCO / Suzuki–Miyaura cross-coupling reaction / Aryl halides / Arylboronic acids

CuI combined with DABCO (1,4-diaza-bicyclo[2.2.2]octane) was developed as an inexpensive and efficient catalytic system for the Suzuki–Miyaura cross-coupling of aryl halides with arylboronic acids. The couplings between aryl iodides and arylboronic acids catalyzed by catalytic amounts of CuI and DABCO proceeded smoothly in moderate to excellent yields. However, the CuI/DABCO system was less efficient in the reactions of aryl bromides, and a higher reaction temperature was required to improve the yield. For the less activated aryl bromides, a stoichiometric amount of CuI together with TBAB was necessary to obtain satisfactory yields.

Introduction

The Suzuki–Miyaura cross-coupling reaction is well-known as an extremely powerful tool for the formation of carbon–carbon bonds in organic synthesis.[1–5] A palladium complex combined with a ligand (usually a phosphane) is the most commonly used catalytic system for the reaction.[1–3] In view of the economy, however, the recovery as well as the recycling of the Pd catalyst is mandatory because of the prices of these catalysts.[3] In addition, the use of a cheaper metal instead of Pd as catalyst provides another attractive route.[1,3–5] Among these, copper has been used in the Suzuki–Miyaura cross-coupling reaction.[1,4] Rothenberg and coworkers have reported that the reactions of a number of aryl halides with phenylboronic acid catalyzed by copper or copper-based nanocolloids were conducted efficiently in moderate to excellent yields. Nevertheless, the couplings of only aryl iodides were investigated when the catalyst was copper alone.[4] Thus, the development of more active copper catalytic systems for the Suzuki–Miyaura cross-coupling reaction to access a wide range of aryl halides including aryl bromides and aryl chlorides is still a challenging area. Very recently, we have described that CuI/DABCO was an effective and inexpensive catalytic system for the Heck reaction.[5] Herein we wish to report a CuI/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl iodides and bromides with arylboronic acids [Equation (1)].[6]



(1)

Results and Discussion

As shown in Table 1, the reaction of 1-iodo-4-methoxybenzene (**1a**) with phenylboronic acid (**2a**) was chosen as a model to test the catalytic activity of CuI/DABCO. A series of ligands were first evaluated (entries 1–8). Without the aid of ligands, the desired product **3** was isolated in a moderate yield after 20 h in the presence of 10 mol-% CuI, 1 mmol Cs_2CO_3, and 3 mL DMF (entry 1). However, the yield increased to nearly quantitative when 20 mol-% DABCO was added (entry 2). Other ligands, such as Et_3N, TMEDA (N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine), DMEDA (N^1,N^2-dimethylethane-1,2-diamine), EDA (ethane-1,2-diamine), PPh_3, and PCy_3 showed suppressed effects (entries 3–8). For example, the yield of **3** was reduced to 31% when DMEDA was used as the ligand (entry 5). Different copper catalysts were then examined, and CuI provided the best results (entries 2 and 9–12). It is noteworthy that no reaction was observed in the absence of copper catalysts (entry 9). Finally, we checked the effects of both the solvents and the bases on the reaction (entries 2 and 13–18). The results demonstrated that the highest yield of **3** was obtained when DMF was employed as the medium together with Cs_2CO_3 as the base.

Subsequently, the CuI/DABCO catalytic system was extended to various aryl iodides and bromides, and the results are summarized in Table 2. Treatment of aryl iodides **1b**–**e** with arylboronic acids **2a**–**d**, CuI (10 mol-%), DABCO (20 mol-%), and Cs_2CO_3 (1 mmol) afforded the desired coupled products **3**–**9** in moderate to excellent yields (entries

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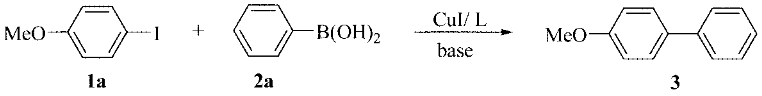
Table 1. Copper-catalyzed cross-coupling reaction of 1-iodo-4-methoxybenzene (**1a**) and phenylboronic acid (**2a**).[a]



Entry	Catalyst	Ligand	Solvent	Base	Yield [%][b]
1	CuI	–	DMF	Cs_2CO_3	78
2	CuI	DABCO	DMF	Cs_2CO_3	98
3	CuI	Et_3N	DMF	Cs_2CO_3	66
4	CuI	TMEDA	DMF	Cs_2CO_3	6
5	CuI	DMEDA	DMF	Cs_2CO_3	31
6	CuI	EDA	DMF	Cs_2CO_3	trace
7	CuI	PPh_3	DMF	Cs_2CO_3	20
8	CuI	PCy_3	DMF	Cs_2CO_3	6
9	–	DABCO	DMF	Cs_2CO_3	NR
10	CuBr	DABCO	DMF	Cs_2CO_3	58
11	Cu_2O	DABCO	DMF	Cs_2CO_3	26
12	$Cu(OAc)_2$	DABCO	DMF	Cs_2CO_3	65
13	CuI	DABCO	*t*-BuOH	Cs_2CO_3	35
14	CuI	DABCO	THF	Cs_2CO_3	trace
15	CuI	DABCO	MeCN	Cs_2CO_3	35
16	CuI	DABCO	DMF	K_2CO_3	35
17	CuI	DABCO	DMF	KOAc	26
18	CuI	DABCO	DMF	*t*-BuOK	7

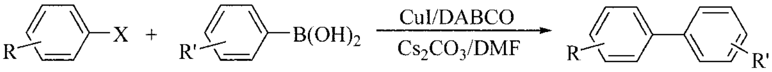
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (10 mol-%), ligand (20 mol-%), and base (1 mmol) in solvent (3 mL) at 125–130 °C for 20 h. [b] Isolated yield.

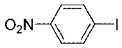
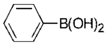
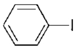
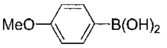
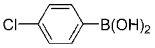
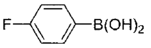
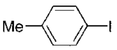
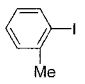
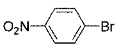
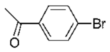
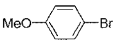
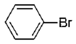
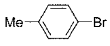
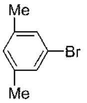
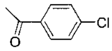
1–7). However, the activity of the CuI/DABCO catalytic system was reduced in the couplings of aryl bromides. Low yields were obtained even from the reaction of the activated bromides **1f** and **1g** with **2a**, performed at 125–130 °C (entries 8 and 10). We were pleased to find that good yields were achieved when the reaction temperature was increased to 150 °C (entries 9 and 11). However, the coupling of the deactivated aryl bromide **1h** was not successful under the same reaction conditions. In many of the earlier reports on Cu-mediated transformations,[7] the addition of a stoichiometric amount of CuI often results in satisfactory yields of the expected products. Accordingly, we decided to increase the amount of CuI to improve the reaction yields. To our delight, the corresponding product **3** was isolated in a moderate yield when the loading of Cu was increased to 100 mol-% (entries 12–14). It is interesting to find that TBAB (Bu_4NBr) has a beneficial effect on the reaction (entries 14–16). In the presence of CuI (100 mol-%) and DABCO (200 mol-%), the coupling of 4-bromo-1-methoxybenezene (**1h**) with **2a** gave the corresponding product **3** in 45% yield (entry 14), whereas the yield of **3** was enhanced to 68% when 0.5 mmol TBAB was added (entry 15). Increasing the amount of TBAB to 1 mmol resulted in 77% yield of **3** (entry 16). Other bromides **1i**–**k** worked well under these conditions (entries 17–20). An attempt to couple the activated chloride **1l** was unsuccessful (entry 21).

Conclusion

In summary, we have developed an inexpensive and efficient protocol for the Suzuki–Miyaura cross-coupling reaction catalyzed by the CuI/DABCO system. A variety of aryl halides including iodides and bromides, whether electron-rich or electron-deficient, all coupled with arylboronic acids to give moderate to excellent yields. Further investigations to extend the application of the system in other coupling transformations and overcome the drawbacks of the less activated aryl bromides are in progress.

Table 2. CuI/DABCO-catalyzed cross-coupling reactions of aryl halides (**1**) with arylboronic acids (**2**).[a]



Entry	ArX	Arylboronic acid	Time [h]	Yield [%][b]
1	 (**1b**)	 (**2a**)	24	55 (**4**)
2	 (**1c**)	(**2a**)	21	84 (**5**)
3	(**1c**)	 (**2b**)	19	99 (**3**)
4	(**1c**)	 (**2c**)	20	68 (**6**)
5	(**1c**)	 (**2d**)	21	30 (**7**)
6	 (**1d**)	(**2a**)	15	95 (**8**)
7	 (**1e**)	(**2b**)	18	74 (**9**)
8	 (**1f**)	(**2a**)	24	28 (**4**)
9[c]	(**1f**)	(**2a**)	24	58 (**4**)
10	 (**1g**)	(**2a**)	72	37 (**10**)
11[c]	(**1g**)	(**2a**)	72	85 (**10**)
12[c]	 (**1h**)	(**2a**)	24	trace (**3**)
13[c,d]	(**1h**)	(**2a**)	48	35 (**3**)
14[c,e]	(**1h**)	(**2a**)	24	45 (**3**)
15[c,e,f]	(**1h**)	(**2a**)	22	68 (**3**)
16[c,e,g]	(**1h**)	(**2a**)	22	77 (**3**)
17[c,e,g]	(**1h**)	(**2b**)	24	81 (**11**)
18[c,e,g]	 (**1i**)	(**2a**)	21	89 (**5**)
19[c,e,g]	 (**1j**)	(**2a**)	40	56 (**8**)
20[c,e,g]	 (**1k**)	(**2a**)	48	44 (**12**)
21[c,e,g]	 (**1l**)	(**2a**)	24	trace (**10**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CuI (10 mol-%), DABCO (20 mol-%), and Cs_2CO_3 (1 mmol) in DMF (3 mL) at 125–130 °C. [b] Isolated yield. [c] At 150 °C. [d] CuI (50 mol-%) and DABCO (100 mol-%). [e] CuI (100 mol-%) and DABCO (200 mol-%). [f] TBAB (0.5 mmol). [g] TBAB (1 mmol).

Experimental Section

General Remarks: ^{1}H- and ^{13}C NMR spectra were recorded with an INOVA-400 (Varian) spectrometer and a Bruker AMX-300 spectrometer with the use of $CDCl_3$ as solvent. All reagents were directly used as obtained commercially. All products **3**–**12** are known, and their analytical data and spectra (^{1}H- and ^{13}C NMR) are available in the Supporting Information.[2–5]

Typical Experimental Procedure for the CuI/DABCO-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions: A mixture of **1** (0.50 mmol), **2** (0.60 mmol), CuI (the indicated amount in Table 1 and Table 2), DABCO (the indicated amount in Table 1 and Table 2), Cs_2CO_3 (2 equiv.), and DMF (3 mL) was stirred under nitrogen at 125–150 °C until the starting material was consumed completely, as determined by TLC. The mixture was then filtered, washed with H_2O, extracted with diethyl ether, and the solvent was evaporated. The residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled products.

Supporting Information (see footnote on the first page of this article): Analytical data and spectra (^{1}H- and ^{13}C NMR) of compounds **3**–**12**.

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[1] For reviews, see: a) F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**; b) N. Miyaura, *Cross-Coupling Reactions*, Springer, Berlin, **2002**; c) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**; d) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–991; e) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; f) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**.

[2] For selected papers on the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction, see: a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.* **2003**, *42*, 3690–3693; b) M. Eckhardt, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643; c) M. C. Willis, L. H. Powell, C. K. Claverie, *Angew. Chem. Int. Ed.* **2004**, *43*, 1249–1251; d) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876; e) S. U. Son, Y. Jang, J. Park, H. B. Na, H. M. Park, H. J. Yun, J. Lee, T. Hyeon, *J. Am. Chem. Soc.* **2004**, *126*, 5026–5027; f) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201; g) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; h) M. Dai, B. Liang, C. Wang, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 221–224; i) J.-H. Li, W.-J. Liu, *Org. Lett.* **2004**, *6*, 2809–2811; j) J.-H. Li, X.-D. Zhang, Y.-X. Xie, *Synlett* **2005**, 1897–1900; k) K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2005**, *44*, 6173–6177; l) D. Liu, W. Gao, Q. Dai, X. Zhang, *Org. Lett.* **2005**, *7*, 4907–4910; m) H. Lebel, M. K. Janes, A. B. Charette, S. P. Nolan, *J. Am. Chem. Soc.* **2004**, *126*, 5046–5047 and references cited therein.

[3] For representative papers on the nickel-catalyzed Suzuki–Miyaura cross-coupling reaction, see: a) S. Saito, S. Ohtani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024–8030; b) D. Zim, V. R. Lando, J. Dupond, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049–3051; c) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447–3452.

[4] For the papers on the copper-catalyzed Suzuki–Miyaura cross-coupling reaction, see; a) M. B. Thathagar, J. Beckers, G. Rothenberg, *J. Am. Chem. Soc.* **2002**, *124*, 11858–11859; b) M. B. Thathagar, J. Beckers, G. Rothenberg, *Adv. Synth. Catal.* **2003**, *345*, 979.

[5] J.-H. Li, D.-P. Wang, Y.-X. Xie, *Tetrahedron Lett.* **2005**, *46*, 4941–4944.

[6] For papers on DABCO as the ligand for other cross-coupling reactions, see: a) J.-H. Li, X.-D. Zhang, Y.-X. Xie, *Synthesis* **2005**, 804–808; b) J.-H. Li, Y. Liang, D.-P. Wang, W.-J. Liu, Y.-X. Xie, D.-L. Yin, *J. Org. Chem.* **2005**, *70*, 2832–2834; c) J.-H. Li, D.-P. Wang, Y.-X. Xie, *Synthesis* **2005**, 2193–2197; d) J.-H. Li, C.-L. Deng, W.-J. Liu, Y.-X. Xie, *Synthesis* **2005**, 3039–3044; e) J.-H. Li, W.-J. Liu, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 5409–5412.

[7] For reviews, see: a) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657; b) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; d) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

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