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Cobalt(II)-Catalyzed Cross-Coupling between Polyfunctional Arylcopper Reagents and Aryl Fluorides or Tosylates

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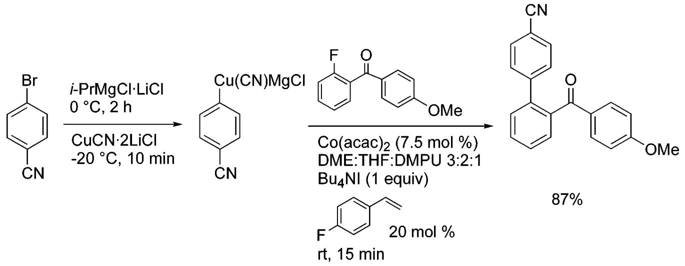
ABSTRACT



Organocopper compounds prepared by the transmetalation of functionalized arylmagnesium halides with CuCN·2LiCl undergo smooth cross-coupling reactions with aryl fluorides and tosylates bearing a carbonyl function in the ortho position in the presence of Co(acac)$_2$ (7.5 mol %), Bu$_4$NI (1 equiv), and 4-fluorostyrene (20 mol %) as promoters in DME/THF/DMPU leading to polyfunctional aromatics or heterocycles.

Transition-metal catalyzed cross-coupling reactions between arylmetals and aryl halides is an actively investigated field in organometallic chemistry. Commonly, palladium and nickel complexes are very active catalysts, and efficient experimental procedures are now available.[1] Although aryl iodides, bromides, and, nowadays, even chlorides[2] have found widespread applications, aryl fluorides[3] and tosylates[4] are by far less used electrophiles. By following the pioneering work of Kochi and others,[5] we recently found that Fe(acac)$_3$ catalyzes cross-coupling reactions between arylcoppers and aryl iodides.[6] In contrast to the elegant work of Fürstner,[7] aryl iodides are the only electrophiles reacting with arylcoppers. However, the cross-coupling between functionalized

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[1] (a) *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (c) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

[2] For a review on Pd-catalyzed cross-coupling reactions with aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

[3] Selected examples: (a) Dankwardt, J. W. *J. Organomet. Chem.* **2005**, *690*, 932, and references therein. (b) Bahmanyar, S.; Borer, B. C.; Kim, Y. M.; Kurtz, D. M.; Yu, S. *Org. Lett.* **2005**, *7*, 1011. (c) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771. (d) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216.

[4] Selected examples: (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (d) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058, and references therein. (e) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364, and references therein.

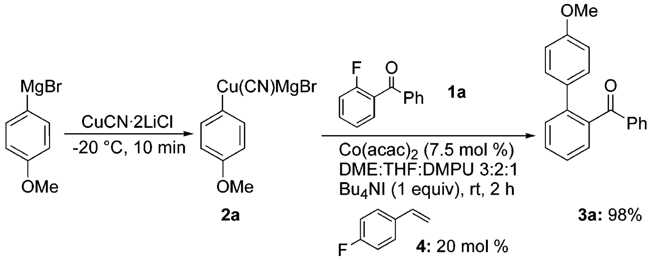
[5] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (c) See also: Molander, G.; Rahn, B.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (d) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (e) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. (f) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621. (g) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (h) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. (i) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081.

[6] Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654.

10.1021/ol0529142 CCC: $33.50

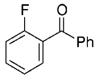
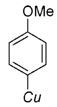
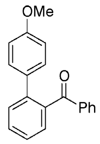
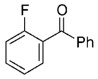
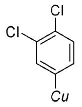
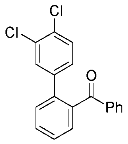
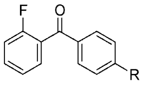
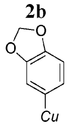
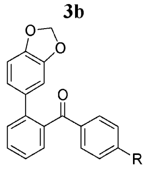
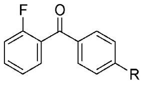
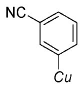
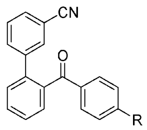
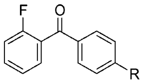
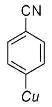
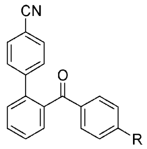
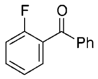
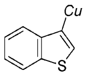
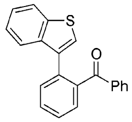
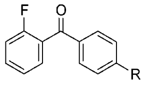
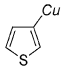
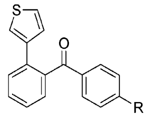
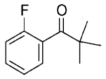
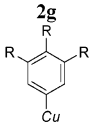
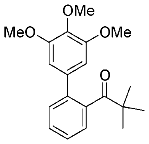
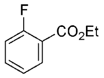
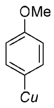
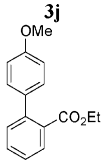
arylcopper reagents and aryl bromides or chlorides could be efficiently performed by using Co(acac)$_2$.[8] The high reactivity of cobalt catalysts for various C−C bond-forming reactions has been recently reported by Cahiez,[9] Oshima,[10] Gosmini,[11] and us.[12] Interestingly, Fürstner has shown that aryl triflates and tosylates can be successfully used in iron-catalyzed cross-coupling reactions with alkylmagnesium reagents.[7b,c] We wish now to report that cobalt-catalyzed aryl−aryl cross-coupling between aryl fluorides or tosylates and arylcopper reagents occurs readily. In preliminary experiments, we have examined the coupling of 2-fluorobenzophenone (**1a**; 1 equiv) with 4-methoxyphenylcopper (**2a**; 3 equiv),[13] which was prepared by the reaction of 4-methoxyphenylmagnesium bromide with CuCN•2LiCl[14] in a 3:2:1 DME/THF/DMPU mixture at room temperature (2 h) with Co(acac)$_2$ (7.5 mol %), 4-fluorostyrene (**4**; 20 mol %),[15] and Bu$_4$NI (1 equiv),[16] as a catalytic system leading to the desired product **3a** in 98% yield (Scheme 1).[17]

Scheme 1. Co(II)-Catalyzed Cross-Coupling between 4-Methoxyphenylcopper (**2a**) and 2-Fluorobenzophenone (**1a**)



To explore the scope of this cross-coupling, we have examined the reactions of various arylcopper reagents of type **2** with aryl fluorides bearing electron-withdrawing substit-

Table 1. Cobalt-Catalyzed Cross-Coupling of Aryl Fluorides

entry	aryl fluoride of type **1**	aryl-copper of type **2**^{a}	product of type **3**	yield^b; conditions
1	 **1a**	 **2a**	 **3a**	98%; 25 °C; 2 h
2	 **1a**	 **2b**	 **3b**	87%; 25 °C; 0.5 h
3	 **1b**: R = OPiv	 **2c**	 **3c**: R = OPiv	72%; 25 °C; 16 h
4	**1c**: R = OMe	**2c**	**3d**: R = OMe	98%; 25 °C; 3 h
5	**1d**: R = NMe$_2$	**2c**	**3e**: R = NMe$_2$	95%; 25 °C; 3 h
6	 **1b**: R = OPiv	 **2d**	 **3f**: R = OPiv	52%; 25 °C; 0.25 h
7	 **1c**: R = OMe	 **2e**	 **3g**: R = OMe	87%; 25 °C; 0.25 h
8	 **1a**	 **2f**	 **3h**	94%; 80 °C; 1 h
9	 **1d**: R = NMe$_2$	 **2g**	 **3i**: R = NMe$_2$	42%; 80 °C; 1 h
10	 **1e**	 R = OMe **2h**	 **3j**	71%; 80 °C; 1 h
11	 **1f**	 **2a**	 **3k**	51%; 80 °C; 0.25 h

[a] The copper reagent is better represented by ArCu(CN)MgX (X = Br, Cl). [b] Yield of analytically pure product.

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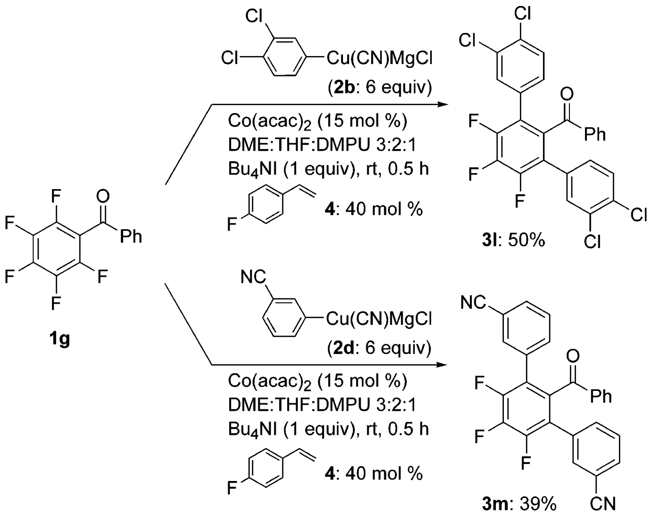
(7) (a) For a review on iron-catalyzed reactions, see: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (d) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (e) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (g) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (h) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (i) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822. (j) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (k) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943. (l) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (m) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161.

(8) Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2947.

(9) (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163.

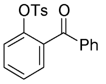
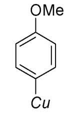
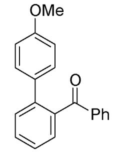
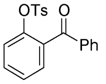
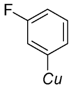
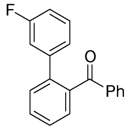
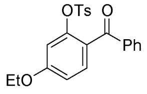
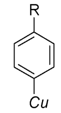
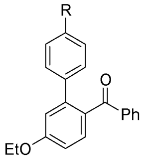
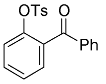
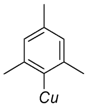
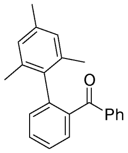
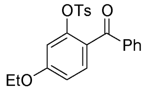
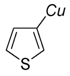
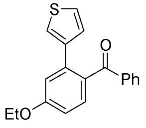
(10) (a) For a review, see: Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (b) Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257. (c) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137. (d) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (e) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem.−Eur. J.* **2004**, *10*, 5640. (f) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514. (g) Mizutani, K.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 3959. (h) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240. (i) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 2368. (j) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3488.

Scheme 2 Co-Catalyzed Diarylation between **1g** and the Arylcopper Compounds **2b** and **2d**



uents. 2-Fluorobenzophenone (**1a**) reacts even faster with 3,4-dichlorophenylcopper (**2b**) (room temperature, 0.5 h), and the corresponding ketone **3b** is obtained in 87% yield (entry 2 of Table 1). Interestingly, functionalized fluorobenzophenones undergo the cobalt-catalyzed cross-coupling reaction as well. Thus, the fluorobenzophenone derivative **1b** bearing a pivalate substituent reacts with arylcopper **2c** at room temperature within 16 h to give the polyfunctional ketone **3c** in 72% yield (entry 3). The reaction between copper reagent **2c** and more electron-rich fluoroketones, which are substituted with an OMe group (**1c**) or a NMe$_2$ group (**1d**) in the para position, proceeds much faster (3 h instead of 16 h), and the coupling products **3d** and **3e** are isolated in 95−98% yield (entries 4 and 5). Remarkably, arylcoppers bearing an electron-withdrawing cyano substituent in the meta (**2d**) or para position (**2e**) give the fastest reactions and react within 15 min at room temperature with the fluorobenzophenones **1b** and **1c** to give the ketones **3f** and **3g**[18] in 52 and 87% yield, respectively (entries 6 and 7).

Table 2. Cobalt-Catalyzed Cross-Coupling of Aryl Tosylates

entry	aryl tosylate of type **5**	arylcopper of type **2**[a]	product of type **3**	yield[b]; conditions
1	 **5a**	 **2a**	 **3a**	82%; 25 °C; 3 h
2	 **5a**	 **2i**	 **3n**	78%; 25 °C; 3 h
3	 **5b**	 **2e:** R = CN	 **3o:** R = CN	78%; 25 °C; 0.25 h
4	**5b**	**2j:** R = Cl	**3p:** R = Cl	96%; 25 °C; 0.25 h
5	 **5a**	 **2k**	 **3q**	54%; 80 °C; 48 h
6	 **5b**	 **2g**	 **3r**	74%; 80 °C; 0.25 h

[a] The copper reagent is better represented by ArCu(CN)MgX (X = Br, Cl). [b] Yield of analytically pure product.

Elevated temperatures are required for the coupling of heterocyclic copper reagents with fluoroketones. 3-Benzo[*b*]thienylcopper (**2f**) smoothly undergoes the cross-coupling with 2-fluorobenzophenone (**1a**) at 80 °C yielding the desired product **3h** in 94% yield (entry 8). Similarly, 3-thienylcopper

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(17) No full conversion is observed if only 1.7 or 2 equiv of copper reagent is used. In the absence of the cobalt catalyst, no product was detected even after 2 days.

(18) Typical procedure for the synthesis of **3g**: A 25 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with *i*-PrMgCl·LiCl (2.63 mL, 3.15 mmol, 1.2 M in THF) and cooled to −20 °C, and 4-bromobenzonitrile (544 mg, 2.99 mmol) was added. The reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h. Subsequently, a solution of CuCN·2LiCl (3.2 mL, 3.2 mmol, 1.0 M in THF) was added. After stirring for an additional 10 min, DME (6 mL), DMPU (2 mL), Bu$_4$NI (370 mg, 1.00 mmol), 4-fluorostyrene (25 mg, 0.20 mmol), Co(acac)$_2$ (19.3 mg, 0.075 mmol), and (2-fluorophenyl)(4-methoxyphenyl)-methanone (230 mg, 1.00 mmol) were added. The reaction mixture was stirred for 15 min at room temperature and quenched with saturated NH$_4$Cl$_{(aq)}$/NH$_3$ (9:1) (50 mL). The organic phase was washed a second time with saturated NH$_4$Cl$_{(aq)}$/NH$_3$ (9:1) (50 mL), and the combined aq phases were extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO$_4$, and filtered, and the solvent was evaporated in vacuo. Flash chromatographical purification on silica gel (pentane/diethyl ether = 4:1) furnished **3g** as a colorless solid (271 mg, 0.87 mmol, 87%, mp: 120.8−122.9 °C).

(**2g**) reacts with **1d**, providing ketone **3i** in 42% yield (entry 9). Finally, even an alkyl-substituted ketone such as **1e** and ethyl 2-fluorobenzoate (**1f**) react with the electron-rich arylcopper reagents **2h** and **2a** at 80 °C yielding ketones **3j** and **3k** in 71 and 51% yield, respectively (entries 10 and 11).

Remarkably, a 2-fold cobalt-catalyzed cross-coupling is possible with the pentafluorinated benzophenone **1g**. Thus, the reactions between **1g** and arylcoppers **2b** and **2d** proceed smoothly at room temperature within 30 min and furnish the expected ketones **3l** and **3m** in acceptable yields (39−50%, Scheme 2).[19]

Aryl tosylates are easily available from phenols. They are more stable and less expensive than the corresponding triflates and are therefore very attractive reagents for cross-couplings. We have found that Co-catalyzed aryl−aryl cross-coupling reactions between aryl tosylates and arylcopper reagents proceed readily. Thus, various copper reagents such as **2a** or **2i** undergo a cross-coupling efficiently with tosylate **5a** furnishing the corresponding ketones **3a** and **3n** after 3 h at room temperature in 82 and 78% yield, respectively (entries 1 and 2 of Table 2). Interestingly, an alkoxy substituent accelerates the Co-catalyzed reaction and the ketones **3o** and **3p** are obtained in 78−96% yield after only 15 min at room temperature (entries 3 and 4).

The presence of ortho substituents in the copper reagent, such as two methyl groups as in mesitylcopper (**2k**), requires an elevated reaction temperature and a longer reaction time. Thus, the reaction between **2k** and tosylate **5a** proceeds at 80 °C (48 h), furnishing the ketone **3q** in 54% yield (entry 5).

Finally, 3-thienylcopper (**2g**) smoothly undergoes the cross-coupling with **5b** at 80 °C within 15 min yielding the desired product **3r** in 74% yield (entry 6).

In summary, we have shown that Co(acac)$_2$ catalyzes the cross-coupling between functionalized arylcopper compounds and various aryl fluorides and tosylates in a DME/THF/DMPU mixture leading to polyfunctional biphenyls. The presence of the promoters 4-fluorostyrene and Bu$_4$NI is crucial for the success of the reaction. Extension of the reaction scope and further mechanistic studies are currently being investigated in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] A mixture of mono- and 2-fold cross-coupling products is obtained, if only 3 equiv of the arylcopper reagents **2b** or **2d** are used.