

Cross-Coupling Reactions

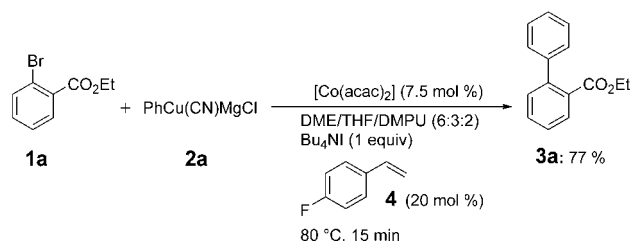
Cobalt(II)-Catalyzed Cross-Coupling of Polyfunctional Aryl Copper Reagents with Aryl Bromides and Chlorides**

Tobias J. Korn and Paul Knochel*

There are now a number of efficient experimental procedures available for palladium- and nickel-catalyzed cross-coupling reactions of aromatic organometallic reagents with aryl halides.^[1,2] However, the high cost of palladium and the required phosphine ligands, as well as the high toxicity of nickel catalysts, led us to explore the use of alternative metals for such coupling reactions. Following the pioneering work of Kochi and co-workers and others,^[3] we found recently that functionalized aryl copper reagents smoothly undergo cross-coupling with aryl iodides in the presence of $[\text{Fe}(\text{acac})_3]$ as the catalyst.^[4] In contrast to the elegant method of Fürstner and co-workers,^[5] in our case only aryl iodides could be used; aryl bromides and chlorides did not react.

To extend the scope of this cross-coupling reaction, we examined other metal salts as catalysts. We reported recently the cobalt(II)-catalyzed cross-coupling of allylic chlorides with dialkyl zinc reagents^[6] and of heteroaromatic chlorides with aromatic and heteroaromatic Grignard reagents.^[7] Other cobalt-catalyzed reactions have also been discovered recently by the research groups of Cahiez,^[8] Oshima,^[9] and Gosmini.^[10] Preliminary experiments showed that $[\text{Co}(\text{acac})_2]$ catalyzes efficiently the cross-coupling of aryl copper derivatives with aryl bromides and chlorides; the reaction is therefore complementary to the recently reported iron-catalyzed process.^[4] As a test reaction, we examined the coupling of ethyl 2-bromobenzoate (**1a**; 1 equiv) with the phenylcopper reagent **2a** (3 equiv),^[11] which was prepared by the reaction of PhMgCl with $\text{CuCN}\cdot 2\text{LiCl}$ ^[12] in a 2:1 mixture of DME/THF at 80 °C. In the absence of the catalyst, no reaction was observed after 4 h; the desired product **3a** was only detected after 24 h.^[13] When $[\text{Co}(\text{acac})_2]$ (10 mol %) was added, a conversion of 46 % was observed after 15 min; however, the conversion increased to just 49 % within the next 4 h of reaction time. A significant improvement was observed upon the addition of Bu_4NI (3 equiv),^[14] which led to a conversion of 81 % after 21 h. The addition of 4-fluorostyrene (**4**; 20 mol %), which was known to promote cross-coupling

reactions,^[15] was not effective alone,^[16] but in combination with Bu_4NI a conversion of 100 % was reached within 21 h. The use of DMPU^[17] as a cosolvent also led to a considerable rate improvement. A conversion of 100 % was now observed after 15 min at 80 °C, with the desired product **3a** formed as the sole product. Under optimized reaction conditions (**1a** (1 equiv), **2a** (1.7 equiv), $[\text{Co}(\text{acac})_2]$ (7.5 mol %), Bu_4NI (1 equiv), **4** (20 mol %)), the ester **3a** was isolated in 77 % yield (Scheme 1).



Scheme 1. The Co^{II} -catalyzed cross-coupling reaction of **2a** with ethyl 2-bromobenzoate (**1a**) under optimized conditions. acac = acetylacetonate, DME = 1,2-dimethoxyethane, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

The additives Bu_4NI and styrene **4** were still required in the polar solvent mixture containing DMPU, as only partial conversion was observed in their absence. We studied the scope of the reaction and found that a broad range of aryl copper reagents of type **2** reacted with a variety of aryl bromides with electron-withdrawing substituents. Thus, the 4-methoxyphenylcopper reagent **2b** underwent a smooth cross-coupling reaction with **1a** at 80 °C to afford the desired biphenyl derivative **3b** in 79 % yield (Table 1, entry 2). Aryl copper species with electron-withdrawing substituents displayed lower reactivity. However, **2c** underwent the coupling with the reactive compound **1b** at 80 °C to give ketone **3c** in 62 % yield (Table 1, entry 3). Similarly, the bromo diester **1c** reacted with various aryl copper derivatives of low reactivity, such as **2d** or **2e**; in these cases the cross-coupling products **3d** and **3e** were isolated in 65 and 54 % yield, respectively (Table 1, entries 4 and 5). The heterocyclic copper reagent **2f** reacted rapidly with **1b** at 80 °C to give the substituted pyridine **3f** in 62 % yield (Table 1, entry 6). As mentioned above, aryl copper compounds with an electron-donating substituent displayed high reactivity in these cross-coupling reactions. Thus, **2b** reacted with **1b** within 1 h at room temperature (89 % yield; Table 1, entry 7). 4-Bromobenzophenone (**1d**) also underwent complete conversion at 25 °C within 7.5 h (73 % yield; Table 1, entry 8). However, 3-bromobenzophenone (**1e**) reacted only slowly in the desired cross-coupling; the expected product **3i** was obtained in 25 % yield after 24 h at room temperature (Table 1, entry 9). Interestingly, the corresponding cyano-substituted aryl copper derivatives **2g–i** reacted smoothly with **1b** to provide ketones **3j–l** in 74–90 % yield (Table 1, entries 10–12). A methyl ketone is an especially sensitive functionality, which can be readily deprotonated by numerous organometallic species. Remarkably, we found that 2-bromoacetophenone (**1f**) reacted smoothly with various aryl copper reagents to

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Table 1: [Co(acac)₂]-catalyzed reaction of aryl copper derivatives **2** with aryl bromides **1** to give products **3**.

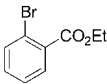
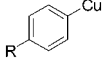
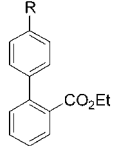
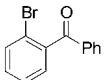
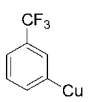
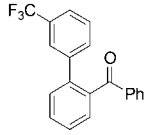
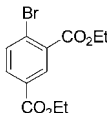
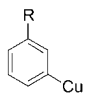
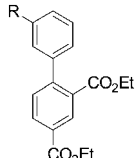
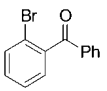
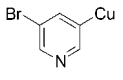
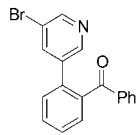
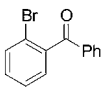
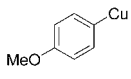
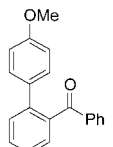
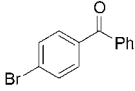
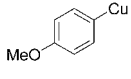
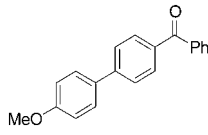
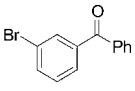
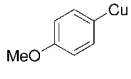
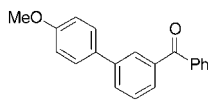
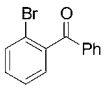
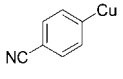
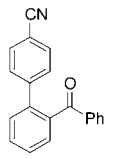
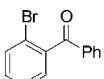
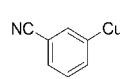
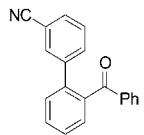
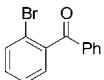
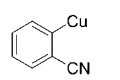
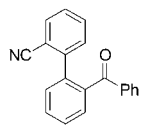
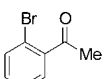
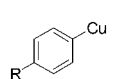
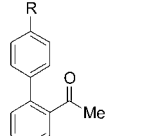
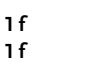
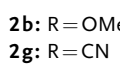
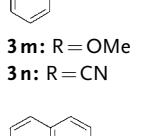
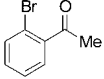
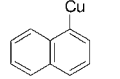
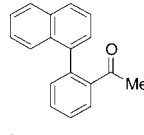
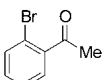
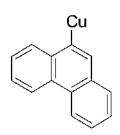
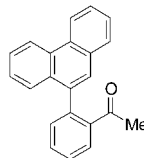
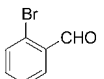
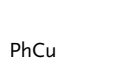
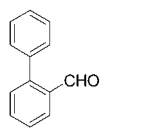
Entry	Aryl bromide 1	Aryl copper reagent 2 ^[a]	Product 3	Conditions [°C, h]	Yield [%] ^[b]
1 2				80, 0.25	77
			3a: R = H 3b: R = OMe	80, 0.25	79
3				80, 3	62
4 5				80, 0.5	65
			3e: R = CO ₂ Et	80, 18	54
6				80, 16	62
7				RT, 1	89
8				RT, 7.5	73
9				RT, 24	25
10				RT, 0.5	90

Table 1: (Continued)

Entry	Aryl bromide 1	Aryl copper reagent 2 ^[a]	Product 3	Conditions [°C, h]	Yield [%] ^[b]
11				RT, 0.5	80
12				RT, 2.5	74
13				RT, 0.5	90
14				RT, 1	77
15				RT, 15	83
16				RT, 0.25	70
17				RT, 0.25	42

[a] The copper reagent is better represented as ArCu(CN)MgCl. [b] Yield of analytically pure product. RT = room temperature.

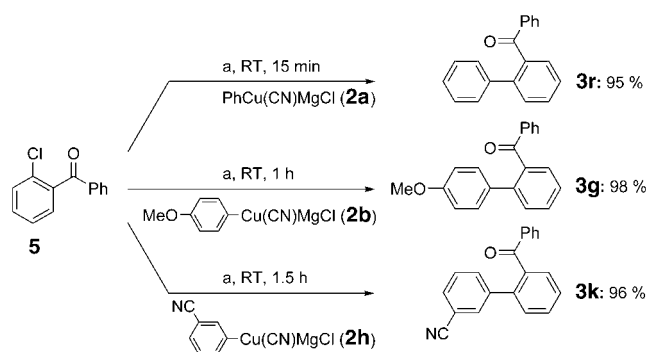
give the polyfunctional ketones **3m–p** in 70–90% yield (Table 1, entries 13–16). An unexpected reactivity difference was observed between the 9-phenanthrylcopper reagent **2k** and the 1-naphthylcopper reagent **2j**. Whereas **2k** reacted with **1f** within 15 min at room temperature, **2j** required a reaction time of 15 h at the same temperature (Table 1, entries 15 and 16). Finally, we found a remarkable compatibility of the reaction conditions with an aldehyde functionality. Thus, 2-bromobenzaldehyde (**1g**) reacted readily with **2a** to provide 2-phenylbenzaldehyde (**3q**) in 42% yield (Table 1, entry 17).

The excellent reactivity of aryl bromides with electron-withdrawing substituents led us to examine cross-coupling reactions with aryl chlorides. The reaction of 2-chlorobenzo-

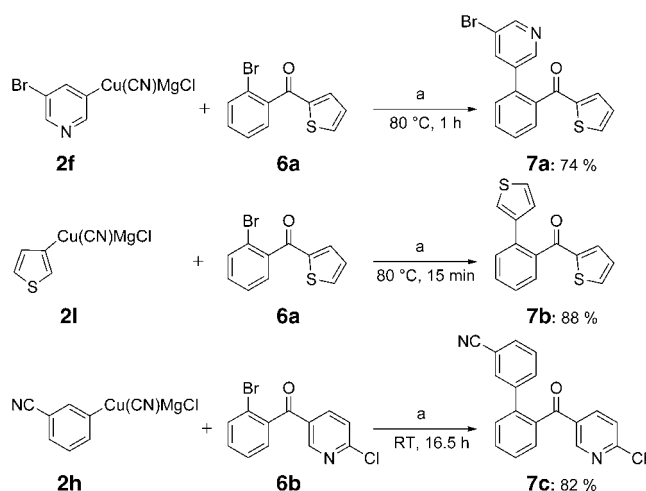
phenone (**5**) with the aryl copper compounds **2a**, **2b**, and **2h** proceeded smoothly at 25 °C within 15 min to 1.5 h under our typical reaction conditions and furnished the expected ketones **3r**, **3g**, and **3k** in almost quantitative yield (Scheme 2).

In further experiments to establish the scope of this method, we investigated the cross-coupling of bromoketones **6a,b** with heterocyclic substituents. An efficient cross-coupling reaction took place with **2h**, as well as with the heteroaromatic copper reagents **2f** and **2l**; the products **7a–c** were formed in 74–88% yield (Scheme 3).

In summary, we have shown that [Co(acac)₂] catalyzes the cross-coupling of functionalized aryl copper reagents with a variety of chloro- and bromoaryl ketones and bromoaryl



Scheme 2. Cobalt-catalyzed cross-coupling reactions of 2-chlorobenzophenone (**5**) with aryl copper compounds: a) **5** (1 equiv), **2** (1.7 equiv), [Co(acac)₃] (7.5 mol%), DME/THF/DMPU (3:2:1), **4** (20 mol%), Bu₄Ni (1 equiv).



Scheme 3. Cobalt-catalyzed cross-coupling reactions of heterocycle-substituted bromoaryl ketones **6** with heteroaryl and aryl copper compounds: a) **6** (1 equiv), **2** (1.7 equiv), [Co(acac)₃] (7.5 mol%), DME/THF/DMPU (3:2:1), **4** (20 mol%), Bu₄Ni (1 equiv).

esters in a DME/THF/DMPU solvent mixture in the presence of the promoters 4-fluorostyrene and Bu₄Ni. The reaction leads to polyfunctional biphenyl derivatives and heterocyclic analogues. The remarkable functional-group compatibility of organocopper reagents with esters, ketones, and even aldehydes should make this cross-coupling method especially attractive for multistep syntheses, as it should be possible to avoid the extensive use of protecting groups.

Experimental Section

Typical procedure: **3j**: 4-Bromobenzonitrile (309 mg, 1.70 mmol) was added to *i*PrMgCl·LiCl (1.73 mL, 1.70 mmol, 0.98 M in THF) at –20 °C in a 25-mL Schlenk tube equipped with a magnetic stirring bar and a septum. The reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h. A solution of CuCN·2LiCl (1.9 mL, 1.9 mmol, 1 M in THF) was then added, and the mixture was stirred for an additional 10 min. DME (6.0 mL), DMPU (2.0 mL), Bu₄Ni (370 mg, 1.00 mmol), 4-fluorostyrene (25 mg, 0.20 mmol), [Co(acac)₃] (19.3 mg, 0.075 mmol), and 2-bromobenzophenone (261 mg, 1.00 mmol) were then added, and the reaction mixture was stirred

for 0.5 h at room temperature, then quenched with a saturated, aqueous solution of NH₄Cl/NH₃ (9:1; 50 mL). The organic phase was washed a second time with a saturated, aqueous solution of NH₄Cl/NH₃ (9:1; 50 mL), and the combined aqueous phases were extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO₄, and filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography on silica gel (pentane/diethyl ether 4:1) furnished **3j** as a light-yellow solid (256 mg, 0.90 mmol, 90%; m.p.: 91.4–92.3 °C).

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