Communications

Biphenyl Synthesis

Iron-Catalyzed Aryl–Aryl Cross-Couplings with Magnesium-Derived Copper Reagents**

Ioannis Sapountzis, Wenwei Lin, Christiane C. Kofink, Christina Despotopoulou, and Paul Knochel*

Dedicated to Professor Michael Veith on the occasion of his 60th birthday

Transition-metal-catalyzed cross-coupling reactions are very powerful C–C bond-forming reactions, especially between $C(sp^2)$ centers at which typical S_N2 substitutions cannot operate.^[1] Palladium(0) catalysts are the most widely and reliably used,^[1,2] especially if appropriate ligands such as sterically hindered phosphines are present.^[3] Nickel(0) complexes have also found useful applications, but appear to have

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[*] Dr. I. Sapountzis, Dipl.-Chem. W. Lin, Dipl.-Chem. C. C. Kofink,
C. Despotopoulou, Prof. Dr. P. Knochel
Department Chemie
Ludwig Maximilians-Universität München
Butenandtstrasse 5–13, Haus F,
81 377 München (Germany)
Fax: (+49) 89-2180-77680
E-mail: paul.knochel@cup.uni-muenchen.de
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a less general scope.^[4] Following the pioneering work of Kochi and co-workers,^[5] iron catalysts have recently been very actively investigated for their performance in cross-coupling reactions.^[6] Although highly efficient cross-coupling reactions could be realized between a range of alkyl magnesium reagents and aryl halides or aryl sulfonates, iron-catalyzed cross-coupling between two aryl moieties remained problematic owing to extensive homo-coupling reactions of the aryl magnesium species.^[6,7] We assumed that the homo-coupling side reaction may arise by the formation of ferrate complexes with the highly reactive organomagnesium compounds.^[7] We therefore transmetalated the aryl magnesium species to the corresponding organozinc compounds, which have a lower tendency to form unstable ate complexes.^[8] Unfortunately, no iron-catalyzed cross-coupling reaction of aryl zinc reagents with aryl halides could be observed under various reaction conditions.

We therefore turned our attention to other organometallic species and found that organocopper compounds^[9] of type **1**, prepared by the reaction of functionalized aryl magnesium chlorides $2^{[10]}$ with CuCN·2LiCl,^[11] react with functionalized aryl halides **3** in the presence of catalytic amounts of [Fe(acac)₃] (10 mol%) in DME/THF (3:2) between 25 and 80°C, leading to polyfunctional biphenyls of type **4** (Scheme 1, Table 1 and Table 2).



Scheme 1. Fe-catalyzed cross-coupling of copper reagents 1 with aryl iodides 3. $FG^1 = CO_2Et$, OMe, OTf; $FG^2 = CO_2Et$, COPh, COMe, CN, CONR₂.

Table 1: Cross-coupling of 2-substituted benzophenones with PhCu(CN)MgCl in the presence of [Fe(acac)₃].



Entry	Х	Conversion [%] ^[a]	
1	I	100 (<5) ^[b] , (55) ^[c]	
2	Br	86 (93) ^[d]	
3	Cl	75 (77) ^[d]	
4	OTf	35 (100) ^[e]	
5	OTs	0	

[a] Conversion after 30 min (determined by GC). [b] Conversion in the absence of $[Fe(acac)_3]$ after 30 min. [c] Conversion after 48 h in the absence of $[Fe(acac)_3]$. [d] Conversion after 18 h. [e] Conversion after 2 h in THF.

Table 2: Fe-catalyzed cross-coupling between functionalized aryl copper reagents **1** and aryl iodides **3** to give **4**.

Entry	Aryl copper 1 ^[a]	Aryl iodide 3	Product 4	Yield [%] ^{[b}
1	PhCu	Ph	Ph O Ph	93
	la	3a	4a	
2	PhCu	Ph	Ph	80
	la	3 b	4b	
3	PhCu	Me	Ph O Me	86
	1a	3 c	4c	
4	CO ₂ Et Cu	Ph	Ph Ph	75
	1b	3 a	4d	
5	Cu CO ₂ Me	Bu	Bu	68
	1c	3 d	4e	
6	Cu CO ₂ Et	Ph	Ph EtO ₂ C	86
	٦d	3 a	_4f	
7	Cu	Ph	Ph	76
	le	3 a	4g	
8	Cu CO ₂ Et	CN	EtO ₂ C	72
	٦d	3 e	4 h	
9	Cu	N N	Meq	58
	le	3 f	4i	
10	Cu CO ₂ Et	Ph	EtO ₂ C	50
	1 d	3 b	4 j	
11	Cu	CO ₂ Et		62
	1 f	3 g	4k	

[a] The copper reagent is better represented as ArCu(CN)MgCl. [b] Yield of analytically pure products.

Remarkably, by using organocopper reagents **1**, the amount of homo-coupling is decreased, and the cross-coupling reaction occurs readily. The nature of the leaving

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group of the electrophilic aromatic reagent 3 is also important (Table 1). Thus, the reaction of PhCu(CN)MgCl (1a) with 2iodobenzophenone (3a) is complete within 30 min at 25 °C. In the absence of $[Fe(acac)_3]$, less than 5% of biphenyl 4a is observed after 30 min, and a conversion of approximately 54% only is observed after 48 h (Table 1, entry 1). The corresponding bromide (2-bromobenzophenone; Table 1, entry 2) also reacts fast, but after 30 min leads only to 86% conversion. A reaction time of 18 h only slightly improves the conversion (93%). Similarly, 2-chlorobenzophenone does not lead to complete conversion (75% after 30 min, but only 77% after 18 h). A significantly slower conversion is observed with a triflate substituent (X = OTf), but no reaction is observed with a tosylate (X = OTs) as leaving group. The fact that 2chlorobenzophenone is converted indicates that the mechanism of the reaction does not involve a halogen-copper exchange reaction.^[12,13] Interestingly, the reactivity of aryl copper with aryl halides is the opposite to that observed for the Fe^{III}-catalyzed reaction with alkyl magnesium species, for which aryl iodides are poorer substrates than aryl bromides or chlorides.^[7]

We then investigated the reaction scope and noticed a remarkable functional-group compatibility and chemoselectivity. The reaction of PhCu(CN)MgCl (1a) is especially fast with 2-iodobenzophenone (3a) (30 min) and the corresponding ketone 4a was obtained in 93% yield (Table 2, entry 1). 4-Iodobenzophenone (3b) reacts at 25 °C within 4 h to give the desired ketone 4b in 80% yield (Table 2, entry 2). Remarkably, a methyl ketone, such as 2-iodophenyl methyl ketone (3c) undergoes iron-catalyzed cross-coupling without any competitive deprotonation of the methyl ketone or addition

to the carbonyl function. Functionalized aryl magnesium reagents that bear an ester group at C2 or C4, such as 1b, 1c, or 1d also undergo crosscoupling within a few hours, leading to the expected products **4d**–**f** in 68–86% yield (Table 2, entries 4-6). Thereby, the sterically hindered functionalized 2,2'-substituted biphenyl 4d is prepared in 75% yield (Table 2, entry 4). Also, Grignard reagents that bear an electrondonating group (e.g. 1e) react well to furnish the ketone 4g in 76% yield (Table 2, entry 7). Various aryl iodides that bear electron-withdrawing substituents at C4 (such as a cyanide



Scheme 2. Comparison between 2-, 3-, and 4-substituted substrates in the iron-catalyzed cross-coupling.

considerably. Thus, 4-iodoanisole leads only to some conversion at 80 °C after 12 h. We also compared the crosscoupling rate between 2-, 3-, and 4-substituted ethyl iodobenzoate (3g-i) with PhCu(CN)MgCl in the presence of [Fe(acac)₃] (10 mol%). Interestingly, the 2- and 4-substituted iodobenzoates 3g and 3i react five times faster than the 3substituted ester 3h (Scheme 2). This may indicate that the slow step of the cross-coupling is the nucleophilic attack of the catalytically active species to the benzoates 3g-i.^[14]

Heterocyclic copper compounds are also suitable reagents for this cross-coupling reaction. Thus, organocopper reagents 1g and 1h react under standard conditions with the iodides 3 f and 3e to furnish functionalized indole 4o and pyridine 4p, respectively (Scheme 3).



Scheme 3. Cross-coupling of heterocyclic copper reagents.

(3e), an amide (3f), or a ketone (3b)) undergo smooth crosscoupling and lead to the products 4h-j in 50-70% yield (Table 2, entries 8-10). Remarkably, copper reagent 1 f, which bears a triflate group, reacts with ethyl 2-iodobenzoate 3g to furnish biphenyl 4k in 62% yield (Table 2, entry 11).

We noticed that the presence of an electron-withdrawing substituent at the aryl iodide accelerates the cross-coupling reaction and that donor substituents slow down the reaction In summary, we have shown that the Fe-catalyzed crosscoupling reaction between functionalized heteroaryl and aryl copper reagents derived from the corresponding organomagnesium reagents proceeds readily with functionalized aryl iodides.^[15] The electron-poor electrophilic iodides undergo the cross-coupling reaction more readily. This new procedure presents an economical way (≈ 3 times cheaper than Pdcatalyzed reactions) to perform aryl–aryl cross-couplings. Furthermore, the synergetic effect between copper and iron opens new synthetic possibilities that are being actively investigated in our laboratories.^[16]

Experimental Section

Typical procedure (4h): A 25-mL Schlenk tube equipped with a magnetic stirring bar and a septum was charged with ethyl 4iodobenzoate (855 mg, 3.10 mmol) and DME (5 mL), and the solution was cooled to -20°C. iPrMgCl (3.3 mL, 3.0 mmol, 0.90 M in THF) was then added, and the reaction mixture was stirred at this temperature for 15 min. Subsequently, a solution of CuCN·2LiCl (2.8 mL, 2.8 mmol, 1.0 m in THF) was added, and the reaction mixture was stirred for an additional 10 min. A solution of 4-iodobenzonitrile (3e) (229 mg, 1.00 mmol) and [Fe(acac)₃] (35 mg, 0.10 mmol) dissolved in DME (3 mL) was added in one portion, and the reaction mixture was heated at 80°C for 3 h. The reaction mixture was quenched with saturated aqueous NH4Cl and was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were washed with saturated aqueous NH₄Cl/NH₃ (9:1) (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/Et₂O 9:1) furnished **4h** as a colorless solid (181 mg, 72%).

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- [13] In the absence of the iron catalyst, no reaction was observed for 2-chlorobenzophenone.
- [14] We submitted the substituted iodoesters 3g-i to Pd-and Nicatalyzed cross-coupling and found that in the case of Pd catalysis, 4-iodoester 3i reacts significantly faster than 3g and 3h, whereas under Ni catalysis, the 3-iodoester 3h is the fastest. These results indicate that the mechanism of Ni-, Pd- and Fecatalyzed cross-coupling reactions is significantly different, as electronic and steric effects of the substituents affect them differently (see Supporting Information for details).
- [15] Interestingly, copper reagents made from aryl lithium species can also be used. The reaction proceeds at a similar rate (somewhat faster). The occurrence of an I–Cu exchange reaction is minimized with this type of copper species (ArCu(CN)Li).
- [16] A patent application for this and related crossing-coupling reactions has been filed.

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