C–C Coupling

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Efficient Cobalt-Catalyzed Formation of Unsymmetrical Biaryl Compounds and Its Application in the Synthesis of a Sartan Intermediate

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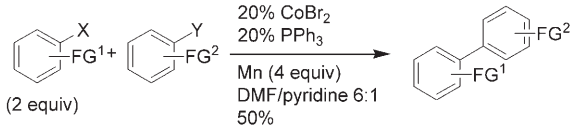
Unsymmetrical biaryl compounds are of considerable interest in organic chemistry. The biaryl structural motif is encountered in a wide variety of organic processes, from supramolecular chemistry[1] to natural products synthesis.[2] Among the innumerable methods for the construction of aryl–aryl bonds, transition-metal-mediated reactions constitute one of the main strategies used.[3] Generally, such reactions involve the coupling of an organometallic reagent (ArM; M = B,[4] Sn,[5] Si,[6] Zn,[7] Mg,[8] Mn[9]) with an aryl halide or pseudohalide. They all require the preparation of a stoichiometric organometallic reagent and typically the presence of a Ni or Pd complex as a catalyst. More recently, it has been shown that iron[10] and cobalt[11] catalysts might be employed as alternatives to expensive precious metals, such as palladium, or toxic metals, such as nickel,[12] in coupling reactions with organometallic reagents. Studies within the realms of metal catalysis have provided several direct aryl–aryl bond-forming transformations for organic synthesis. Catalytic direct arene C–H cross-coupling[13] and the decarboxylative coupling of aromatic carboxylates[14] with aryl halides can be very efficient; however, these methods often require the use of a base, high temperatures, and expensive catalysts. Other reaction pathways include the palladium-catalyzed reductive coupling of two aryl halides in combination with a reducing agent.[15]

In an attempt to couple two different aryl halides, we previously developed electrochemical methods involving either Ni[16] or Co[17] catalysis. However, the transformation is less efficient with aryl chlorides than with aryl bromides, and no reaction was observed with aryl pseudohalides. Moreover, nickel is environmentally hazardous, and a large quantity of the catalyst was required when a cobalt catalyst was used. Motivated by the interest in cobalt-catalyzed reactions[18] and our early success in the use of new cobalt-catalyzed direct procedures[19] as an efficient alternative to electrochemical methods, we carried out studies aimed at broadening the use of this type of catalyst in the direct cross-coupling of aryl compounds. These transformations with aryl halides or even aryl triflates are of particular interest owing to their high functional-group tolerance and the ready availability of the aryl species. In line with our previous experience in cobalt-mediated coupling reactions, we found that the low-valent cobalt species generated from the chemical reduction of a cobalt halide associated with a ligand can activate functionalized aryl (or heteroaryl) halides or triflates in an unprecedented manner to provide unsymmetrical biaryl compounds. The results of our previous studies demonstrated the activation efficiency of a cobalt halide associated with 2,2′-bipyridine in dimethylformamide in the presence of pyridine.[19a,c] Herein, we describe the details of a similar cobalt-catalyzed cross-coupling reaction, in which another cobalt complex is used in combination with manganese dust as a reducing agent, and establish its scope and synthetic utility for the efficient formation of a variety of unsymmetrical biaryl compounds (Scheme 1).



Scheme 1. Cross-coupling of two aryl halides. DMF = *N*,*N*-dimethylformamide, FG = functional group.

Our initial studies involving an activated aryl bromide and a non-activated aryl iodide were highly encouraging. We determined that [$CoBr_2(PPh_3)$] (0.1 equiv) in the presence of manganese dust (4 equiv) activated by traces of acid promoted the cross-coupling of the two aryl halides in DMF/pyridine at 50 °C within 12 h. However, we chose to increase the amount of [$CoBr_2(PPh_3)$] to 0.2 equivalents to reduce the reaction time to 5 h.

The choice of ligand had a substantial impact on the course of the reaction. In contrast to other cross-coupling reactions of aryl compounds, the product was produced in higher yield when triphenylphosphane was used as the ligand than with any other ligand tested; 1,2-bis(diphenylphosphanyl)ethane and 2,2′-bipyridine were less effective. In the absence of PPh_3 or with only 5 mol% of the catalyst, the desired product was still formed, although more slowly. An increase in the temperature led to the formation of the product in lower yield despite a coinciding decrease in the

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reaction time. From an extensive survey of solvents, a 6:1 mixture of DMF and pyridine emerged as the best choice. The cross-coupling was not efficient in pure DMF, acetonitrile, THF, or other solvent mixtures, such as acetonitrile/pyridine. Interestingly, in contrast to other cobalt-catalyzed reactions developed recently, zinc (used instead of manganese) was not able to reduce the phosphine-associated cobalt species in this solvent mixture to form either the biaryl compound or the organozinc species. Not surprisingly, the results depended on the amount of manganese dust used. After a few attempts, we found that the minimum manganese loading required for the conversion of all aryl halides into the corresponding products in optimal yields was 4 equivalents with respect to the limiting halogenated aryl substrate. In contrast to palladium-catalyzed reactions,[15] the more reactive aryl halide was used in excess (2 equiv).

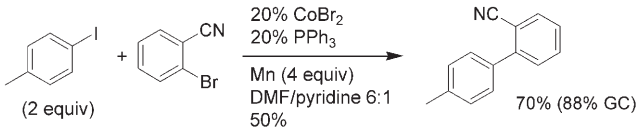
This novel method generally gives the expected cross-coupling product in good yield with good selectivity, both when an aryl bromide and an aryl iodide are used (Table 1, entries 1–5) and with two aryl bromide substrates (Table 1, entries 8–16). However, a significant difference in the reactivity of the two substrates results in a decrease in the yield of the product when an aryl bromide and an aryl iodide are used (Table 1, entry 6).

These results prompted us to attempt the synthesis of 2-(4-tolyl)benzonitrile, a key intermediate in the synthesis of sartan derivatives (Scheme 2). Chemical modifications of the resulting biaryl compound, which was isolated in 70% yield, lead to a large range of biologically active compounds, such as losartan, irbesartan, and valsartan.[20]

Table 1: Cross-coupling of various aryl halides.[a]

Entry	FG^1 (Ar^1)	X	FG^2 (Ar^2)	Y	Ar^1–Ar^2 Yield [%][b]	Ar^2–Ar^2 Yield [%][c]
1	*p*-OMe	I	*p*-CO_2Et	Br	77	8
2	H	I	*m*-CO_2Et	Br	70	19
3	H	I	*p*-CN	Br	46 [72][c]	10
4	*p*-OMe	I	*p*-CN	Br	54 [88][c]	10
5	*p*-CO_2Et	I	*p*-CN	Br	57 [75][c]	15
6	*p*-CO_2Et	I	OMe	Br	[48][c]	60
7	H	I	OMe	Br	[47][c]	40
8	*p*-OMe	Br	H	Br	73	13
9	*p*-CO_2Et	Br	*p*-CF_3	Br	68	14
10	*p*-CO_2Et	Br	*p*-F	Br	63	12
11	*p*-CO_2Et	Br	*p*-CN	Br	56 [75][b]	15
12	*p*-CO_2Et	Br	*o*-CN	Br	60 [92][b]	3
13	*m*-CO_2Et	Br	*p*-OMe	Br	60	19
14	*o*-CO_2Et	Br	*p*-OMe	Br	52	7
15	*p*-CO_2Et	Br	*m*-OMe	Br	64	16
16	*p*-CO_2Et	Br	*o*-OMe	Br	65	9
17	*p*-OMe	Br	*p*-CO_2Me	Cl	84	6
18	*p*-NMe_2	Br	*p*-CO_2Me	Cl	71	12
19	H	Br	*p*-CO_2Me	Cl	70	12
20	*m*-OMe	Br	*p*-CO_2Me	Cl	72	12
21	*o*-OMe	Br	*p*-CO_2Me	Cl	89	3
22	*p*-Me	Br	*o*-CN	Cl	72	10
23	*p*-CO_2Me	Cl	*p*-CN	Cl	47 [72][b]	13
24	*p*-CO_2Me	Cl	*o*-CN	Cl	66	6
25	*p*-CO_2Me	Cl	*p*-CF_3	Cl	60 [73][b]	24
26	*p*-CO_2Me	Cl	*m*-CF_3	Cl	50	32
27	*m*-CO_2Me	Cl	*p*-CF_3	Cl	63	24
28	*o*-CO_2Me	Cl	*p*-CF_3	Cl	71	13
29	*p*-SO_2Me	Cl	*p*-CO_2Me	Cl	60	17

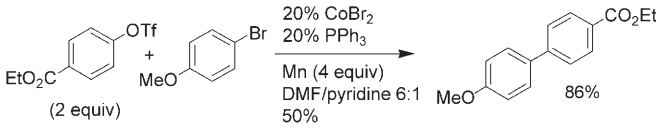
[a] See Scheme 1. [b] Yield of the isolated product. [c] Yield determined by GC.



Scheme 2. Synthesis of a key intermediate for the preparation of sartan derivatives.

An array of aryl bromides and chlorides also underwent the desired coupling reaction with one another (Table 1, entries 17–22). Indeed, activated aryl chlorides can be coupled successfully with non-activated aryl bromides and activated aryl chlorides, albeit in modest yields in the latter case. To the best of our knowledge, this is the first example of a chemical cross-coupling reaction of two aryl chlorides (Table 1, entries 23–29).

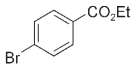
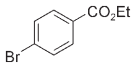
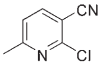
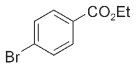
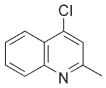
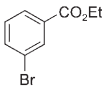
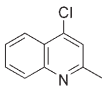
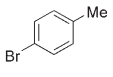
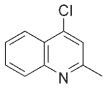
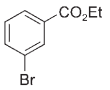
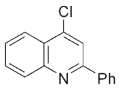
Recently, we reported that phenol derivatives react with low-valent cobalt complexes with a 2,2′-bipyridine ligand either to form an aryl zinc species[19d] or to form an intermediate that undergoes conjugate addition to activated olefins.[19c] Cobalt bromide associated with PPh_3 is also a suitable catalyst for the formation of an aryl cobalt species upon treatment with an aryl triflate. The resulting organometallic reagent can undergo cross-coupling with an aryl bromide to provide a biaryl compound in very good yield (Scheme 3). Efforts are currently under way towards the comprehensive development of this aryl bromide–aryl triflate coupling.



Scheme 3. Cross-coupling of 4-trifluoromethanesulfonyloxybenzoic acid ethyl ester with 4-bromoanisole.

As a further test of the flexibility of this cobalt-catalyzed synthesis of unsymmetrical biaryl compounds, we investigated the suitability of heteroaromatic halides as substrates in reactions with aryl bromides (Table 2). The cross-coupling of aryl bromides with an electron-withdrawing or electron-donating substituent with 4-chloroquinoline derivatives afforded the desired products in good to excellent yields, regardless of the position of the substituent (Table 2, entries 3–6). However, moderate yields were observed with 3-bromothiophene and a 2-chloropyridine derivative (Table 2, entries 1 and 2). The lower yields can be rationalized by the propensity of the heteroaromatic ring to act as a strong ligand in the reaction medium for reduced cobalt (Co^I or Co^0) and prevent it undergoing oxidative addition at a sufficient rate. Studies are in progress towards the extension of these

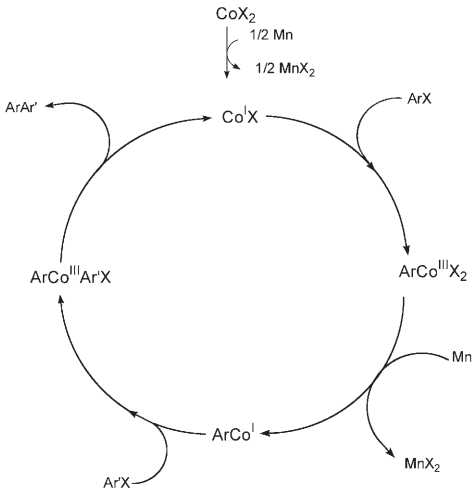
Table 2: Cross-Coupling of aryl bromides with heteroaryl halides.

Entry	ArBr	HetArX	Ar–HetAr [%][a]	HetAr–HetAr [%][b]
1			50	2
2			49	10
3			60	21
4			71	19
5			70	20
6			94	2

[a] Yield of the isolated product. [b] Yield determined by GC.

cross-coupling reactions to other heteroaromatic halide substrates.

The proposed mechanism in Scheme 4 is comparable to that described for the nickel-catalyzed formation of biaryl compounds, which is favored in the presence of excess reductant.[21] A radical pathway can be ruled out; however, the presence of a radical inhibitor (galvinoxyl free radical) leads to similar results.



Scheme 4. Proposed mechanism for the cobalt-catalyzed formation of biaryls.

In conclusion, we have devised an expedient route to functionalized biaryl and heteroaryl–aryl compounds on the basis of cobalt catalysis. The tolerance of our protocol toward a wide variety of functional groups enables the synthesis from commercially available chemicals of a broad spectrum of valuable compounds, including heterocyclic biaryl compounds, in satisfactory to high yields under simple and mild conditions. This catalytic process involves a simple, inexpensive, and environmentally friendly cobalt halide salt and the ligand triphenylphosphane. This combination affords an extremely powerful catalyst for the coupling of a large variety of aromatic reagents, which range from halides to triflates, functionalized with reactive groups. Further studies are in progress to elucidate the mechanism of this reaction and to extend this process to vinylic and other heterocyclic systems.

Experimental Section

General procedure: A mixture of $CoBr_2$ (20 mol%; 220 mg, 1 mmol) and PPh_3 (20 mol%; 262 mg, 1 mmol) in DMF (6 mL) and pyridine (1 mL) was stirred at room temperature for 15 min. Manganese powder (20 mmol, 1.098 g) and the two aryl halides (5 mmol for less reactive and 10 mmol for more reactive compounds) were added successively to the resulting deep blue solution. The manganese dust was activated with trifluoroacetic acid (100 μL), and the mixture was stirred at 50°C. The amounts of the corresponding heterocoupling, homocoupling, and reduction products were measured by GC by using an internal reference (dodecane, 200 μL). The reaction mixture was poured into a solution of 2 N HCl and extracted with diethyl ether. The organic layer was washed with a saturated solution of NaCl, and dried over $MgSO_4$. Evaporation of the solvents and purification by column chromatography on silica gel (pentane/ethyl acetate) afforded the corresponding unsymmetrical biaryl compound, which was characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

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