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Copper-Catalyzed Arene C-H Bond Cross-Coupling

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Abstract

A highly regioselective, one-pot sequential iodination/copper-catalyzed cross-coupling of arene C-H bonds has been developed affording an efficient method for biaryl synthesis.

Copper complexes have been known to promote carbon-carbon bond formation for more than a century.¹ However, the development of the corresponding catalytic processes has started only in the last decade. Efficient copper-catalyzed cross-coupling reactions have been developed for the formation of carbon-carbon bonds.² Unfortunately, copper is underutilized as a catalyst for the functionalization of carbon-hydrogen bonds. We have recently developed a general method for copper-catalyzed arylation of sp^2 C-H bonds possessing pK_a 's below 35 (in DMSO).³ A variety of electron-rich and electron-poor heterocycles such as azoles, thiophenes, benzofuran, pyridine oxides, pyridazine, and pyrimidine can be arylated. Furthermore, arenes possessing electron-withdrawing fluorine, chlorine, nitro, and cyano substituents can also be arylated. Aryl iodides, aryl bromides, and even some activated aryl chlorides can be used as the coupling partners. These reactions can be described as a carbon-hydrogen/carbon-halogen bond coupling that results in the formation of a biaryl or polyaryl (Scheme 1A). From atom-economy and generality viewpoints it would be advantageous if one could employ unfunctionalized coupling partners by coupling two C-H bonds to form a carbon-carbon bond. Several recent examples involve palladium-catalyzed arylation of directing-group-containing arenes or electron-rich heterocycles by simple benzenes.⁴ Unfortunately, regioselectivity with respect to the simple arene coupling component is difficult to achieve and often only symmetric arenes can be used for the arylations (Scheme 1B). We reasoned that a C-H/C-H coupling could be achieved by employing a combination of regioselective halogenation with copper-catalyzed arylation (Scheme 1C).

We report here an electrophilic halogenation followed by a copper-catalyzed arylation that allows a highly regioselective heterocoupling of arene C-H bonds.

For accomplishing the C-H/C-H coupling, two sequential carbon-hydrogen bond functionalizations are required. A halogenation of an sp^2 C-H bond should be followed by copper-catalyzed C-H bond arylation. It has been shown previously that the Cu-catalyzed arylation is highly regioselective with the most acidic C-H bond arylated exclusively.³ Consequently, a highly regioselective and efficient iodination procedure that is compatible with Cu-catalyzed arylation was needed. Iodine chloride has been employed for arene halogenation for at least 130 years.⁵ High iodination regioselectivities have been reported.⁶ The halogenation mechanism has been extensively studied by Kochi.⁷ Several issues that had to be considered are as follows. First, competing substrate chlorination is often observed.⁷

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Second, incomplete iodination of the less reactive substrates may result in lower conversions. Kochi has reported that ICl is more reactive in nonpolar solvents such as CH₂Cl₂, but the selectivity for iodination over chlorination is higher in polar aprotic solvents.⁷ A mixture of those solvents is most likely to deliver the optimal compromise of rate and selectivity. In some cases, relatively stable cation radicals are formed by reaction of arenes with ICl.⁷ The cation radicals were shown to react with I₂ forming iodinated products. Thus, addition of iodine to the reaction mixture may result in higher reactivity and/or selectivity for the iodination. Third, iodination procedure should be compatible with subsequent copper-catalyzed cross-coupling reaction. An excess of ICl may retard the coupling by oxidizing catalytically active Cu species. *p*-Dimethylaminobenzene reacts with ICl forming a haloarene that is relatively inactive in the copper-catalyzed arylation step. Thus, in cases where full consumption of ICl was not observed or an excess of halogenating reagent was required, *p*-dimethylaminobenzene was added.

The scope of the reaction is presented in Table 1. Electron-rich heterocycles such as thiophenes (entries 1, 9), *N*-methylindole (entry 3), and *N*-methylpyrazole (entry 6) can be coupled with electron-deficient arenes such as pentafluorobenzene, tetrafluoropyridine, 3,5-difluorobenzonitrile, and 1,3-dinitrobenzene. 2-Bromothiophene (entry 1) is diarylated by substituting both the bromide and newly introduced iodide. Electron-rich arenes such as biphenyl, alkylbenzenes, diphenyl ether, anisole, naphthalene derivatives, and azulene can be coupled with polyfluorobenzenes (entries 2, 8, 10, and 11), acidic electron-rich heterocycles (entries 4 and 5), and terminal alkynes (entry 12). Entry 1 was run on a 10 mmol scale.

The first component of the cross-coupling reaction is an electron-rich aromatic compound. The regioselectivity of iodination step is dictated by the rules of electrophilic aromatic substitution.⁹ In most cases, only a single product isomer was observed. However, anisole derivatives and alkylbenzenes are halogenated with selectivities ranging from 12/1 (entry 7, anisole) to 32/1 (entry 8, *t*-butylbenzene). The second coupling component can be an arene (or alkyne) possessing a C-H bond with DMSO pK_a's below 35 (in DMSO).¹⁰ The regioselectivity with respect to the second coupling component (R-H in Table 1) is dependent on the acidity of the arene. The most acidic position is functionalized exclusively. Either potassium phosphate or lithium *t*-butoxide base can be employed in the second step. Choice of base depends on the acidity of the second coupling component. Less acidic substrates such as methyltriazole (entry 5) and dichloropyridine (entry 7) require use of a stronger LiO*t*Bu base. For obtaining reproducible yields fresh ICl should be used since older samples disproportionate to chlorine gas and iodine.⁷

In conclusion, we have developed a one-pot procedure for a highly regioselective cross-coupling of arene carbon-hydrogen bonds. A variety of electron-rich arenes such as alkyl- and arylbenzenes, anisole derivatives, azulene, and five membered heterocycles can be coupled with electron-poor arenes possessing at least two electron-withdrawing groups on a benzene ring, thiophenes, triazoles, and alkynes. The cross-coupling reaction is performed by an initial electrophilic iodination of an electron-rich arene followed by a copper-catalyzed arylation of a carbon-hydrogen bond.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. **General procedure:** A 15 mL recovery flask was equipped with a magnetic stir bar was charged with iodine (25.4 mg, 0.1 mmol), DCM/DMF mixture, and ICl. The flask was fitted with a reflux condenser. To the stirred mixture was **quickly added in one portion** the first substrate through the condenser. The reaction mixture was stirred at 50°C (bath temperature) for 2.5 hours followed by CH₂Cl₂ removal under reduced pressure. In most cases, *N,N*-dimethylaniline (121 mg, 1.0 mmol) was added followed by stirring for another 30 minutes. Commercial, non-anhydrous DMF (0.6 mL) was added to reaction mixture followed by transfer to a 1 dram vial. It is important to use the specified vial caps due to volatility of some reactants. Phenanthroline (18.0 mg, 0.1 mmol) and the second substrate (1.0-3.0 mmol) were subsequently added. The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added CuI (19 mg, 0.1 mmol) and base. The sealed vial was taken out of the glovebox, stirred at 50 °C for 5 min and placed in a preheated oil bath (125-135 °C) for indicated time. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (50 mL). The resulting solution was washed with brine (1 × 15 mL), dried over anhydrous MgSO₄, and concentrated under vacuum to a volume of about 2 mL. The mixture containing the product was subjected to flash chromatography on silica gel (hexanes followed by appropriate solvent to elute the products). After concentrating the fractions containing the product, the residue was dried under reduced pressure.
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1A. Previously Reported Cu-catalyzed Arylation **1B. Atom-Economical C-H/C-H Coupling** **1C. This Work**

Scheme 1.
Carbon-Hydrogen Bond Arylation

Table 1Copper-catalyzed Cross-Coupling of C-H Bonds^a

Entry	Ar-H
1 ^b

Entry	Ar-H
2 ^c	Biphenyl

Entry	Ar-H
3
4 ^{c,d}	m-Xylene

Entry	Ar-H
5 ^c	Diphenyl ether

Entry**Ar-H**

6

Entry	Ar-H
7 ^{c,e}
8 ^{c,f}

Entry**Ar-H**

 9^c

Entry	Ar-H
10 ^c	<chem>COc1cccc2ccccc12</chem>

Entry**Ar-H**

11

Entry	Ar-H
12 ^g

^a See Experimental Section and Footnote 8 for stoichiometry. Yields are isolated yields of pure regioisomer.

^b Ten mmol scale reaction

^c Dimethylaminobenzene added after step 1.

^d Crude isomer ratio: 12/1.

^e Crude isomer ratio: 12/1.

^f Crude isomer ratio: 32/1.

^g Crude isomer ratio: 24/1.