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Copper-Catalyzed Oxidative sp^3 C−H Bond Arylation with Aryl Boronic Acids

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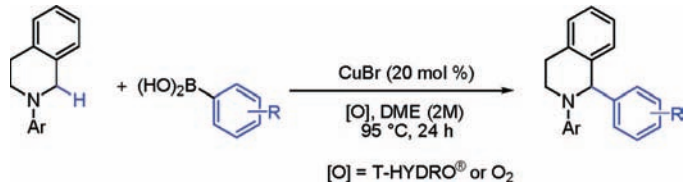
ABSTRACT



An efficient method was developed for arylation of sp^3 C−H bonds using copper bromide as catalyst in absence of directing group with arylboronic acids. The oxidative arylation provides easy access to biologically active tetrahydroisoquinoline derivatives and can either use peroxide or molecular oxygen as oxidant.

Environmental consciousness has given rise to much interest in the direct arylation of selective C−H bonds.[1] Analogous catalytic functionalization processes provide an economical alternative to traditional organic chemistry.[2] Recent efforts have been made toward direct cross-coupling using sp^3 C−H bonds, and in particular, palladium-catalyzed regioselective phenylation and arylation of sp^3 C−H bonds has frequently been reported.[3] An alternative to the use of palladium was recently reported by Sames and co-workers in which α-arylation of saturated cyclic amine was efficiently achieved using low-valent ruthenium catalyst with boronic esters directed by removable amidine protecting group.[4] Herein we wish to describe a different approach for the arylation of sp^3 C−H bonds adjacent to a nitrogen atom using simple copper salts as catalysts with free arylboronic acids.

Due to its low cost and low toxicity, using a copper catalyst for C−H bond functionalization is particularly attractive. There exist few examples in which copper is used as a catalyst for such transformations.[5] We previously reported a copper-catalyzed reaction of indoles with tetrahydroisoquinoline via cross-dehydrogenative coupling (CDC).[6] Tetrahydroisoquinoline derivatives mediate useful pharmacological and physiological effects. As representative examples, 1-phenyl-1,2,3,4-tetrahydroisoquinoline displays high affinity to the PCP binding site of the NMDA receptor[7] and also constitutes the starting building block for synthesizing attractive estrogen receptor modulators.[8] We envisioned a direct arylation of the sp^3 C−H bond adjacent to the nitrogen atom to synthesize these biologically active molecules via the coupling of phenylboronic acid (**2a**) with *N*-phenyltetrahydroisoquinoline (**1a**). Similar to a Petassis borono-Mannich reaction, we postulated the nucleophilic addition of the arylboronic acid to an in situ generated iminium-

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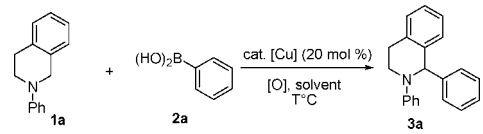
Table 1. Copper-Catalyzed Arylation of Tetrahydroisoquinoline[a]



entry	**2a**	cat.[Cu]	[O] (equiv)	solvent (concn)	T (°C)	**3a**[c] (%)
1	1.2	CuBr	TBHP (1.2)	DME (1 M)	95	15
2	1.2	CuBr	T-HYDRO (1.2)	DME (1 M)	95	75
3	1.2	CuBr	T-HYDRO (1.2)	DME (1 M)	120	50
4	1.2	CuBr	TBHP (1.2)	DME (+ 5 μL of H_2O)	95	65
5	1.2	CuBr	TBHP (1.2)	H_2O	95	<5
6	1.2	CuI	T-HYDRO (1.2)	DME (1 M)	95	10[b]
7	1.5	CuBr	T-HYDRO (1.5)	DME (1 M)	95	80
8	1.5	CuBr	T-HYDRO (1.6)	DME (1 M)	95	85
9	**1.6**	**CuBr**	**T-HYDRO (1.6)**	**DME (2 M)**	**95**	**90**
10	1.5	CuBr	T-HYDRO (1.6)	neat	95	30

[a] Reactions scale: tertiary amine (0.1 mmol). [b] Use of other copper(I) salts resulted in decreased yield. [c] NMR yields based on tetrahydroisoquinoline using an internal standard.

type intermediate via oxidation of the tertiary amine in the presence of a peroxide and a copper salt.[5d] The key challenge was the absence of a neighboring heteroatom directing group generally required in the Petasis reaction to form the more active tetracoordinate borate species.[9] We reasoned that copper would compensate for this absence.[10,11] Considering previous work on transition-metal-catalyzed sp^3 C−H bond activation for C−C bond formation, we began our investigation using *tert*-butyl hydroperoxide (TBHP) as a stoichiometric oxidant.[12] While optimizing the reaction conditions, we discovered the critical role of water in the oxidative arylation reaction. In the absence of water, only 15% of the benzylic α-arylated product was obtained when the CuBr/TBHP system was tested in DME (dimethoxyethane) at 95 °C (Table 1, entry 1). Very interestingly, when the solvent of the oxidant was switched from decane to water, the efficiency of the reaction dramatically increased, providing the arylated product in 75% yield (Table 1, entry 2). Increasing the reaction temperature to 120 °C lowered the yield due to an increase of biphenyl byproduct formation (Table 1, entry 3). Instead of using *tert*-butyl hydroperoxide, 70 wt % in water (T-HYDRO), adding a small amount of water with anhydrous TBHP in decane is also effective (entry 4). However, a large amount of water prevents the reaction from occurring (Table 1, entry 5).

It is also important to note that no product was obtained when **2a** was replaced by its corresponding ester.[13] The optimized reaction conditions required 1.6 equiv of phenylboronic acid in the presence of an equivalent amount of T-HYDRO in DME (2 M) at 95 °C (Table 1, entry 9).

Next, we examined the scope of the oxidative arylation reaction with a variety of substituted aryl boronic acids (Scheme 1). Both electron-withdrawing and electron-donating substituted arylboronic acids were successfully coupled to tetrahydroisoquinolines. Both *N*-phenyl-protected and *N*-PMP-protected tetrahydroisoquinolines were effective for this transformation. *N*-PMP can easily be deprotected to give the α-arylated free N−H tetrahydroisoquinoline.[14] Interestingly, the very sterically hindered 2-naphthylboronic was coupled in good yields under the optimized conditions.

Futhermore, we considered the use of molecular oxygen for the oxidative arylation reaction.[15] Unfortunately, no product could be detected under the previously reported $CuBr/O_2$/water system (Table 2, entry 1).[5e] Nevertheless, when the reaction was performed in DME as solvent, 20% of the desired arylated product was obtained (entry 2). The role of water was also critical under aerobic conditions. In fact, addition of a small amount of water to the previous conditions increased the yield to 60% (entry 3). The yield was further improved to generate 80% of the desired product when a catalytic amount of peroxide was used (Table 2, entry 4).

To have a better understanding of the reaction mechanism and since the biological potency of 1-phenyl-1,2,3,4-tetrahydroisoquinoline is highly enantioselective,[7] we briefly investigated the asymmetric oxidative arylation reaction. Very interestingly, lowering the temperature to 50 °C together with

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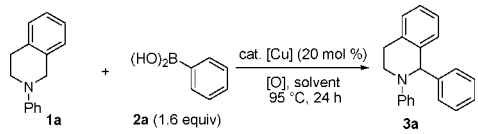
(15) Caution: peroxides are potentially explosive.

Table 2. Aerobic Oxidative Arylation



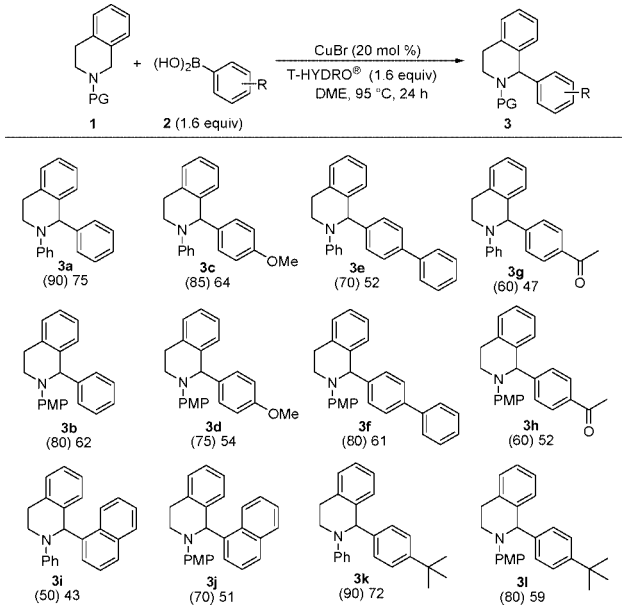
entry	[O] (equiv)	solvent	**3a**[a] (%)
1	O_2 (1 atm)	H_2O	<5
2	O_2 (1 atm)	DME	20
3	O_2 (1 atm)	DME (+ 5 μL H_2O)	60
4	**O_2 (1 atm) + 20 mol % of T-HYDRO**	**DME (+ 5 μL of H_2O)**	**80**

[a] NMR yields based on tetrahydroisoquinoline using an internal standard.

addition of (*R*,*R*)-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine ligand (PhPyBox) provided the desired product with 30% ee and a 50% conversion. After CuBr was replaced by CuOTf, the enantiomeric excess was further improved to provide the α-arylation product with 44% ee (Scheme 2).[12e]

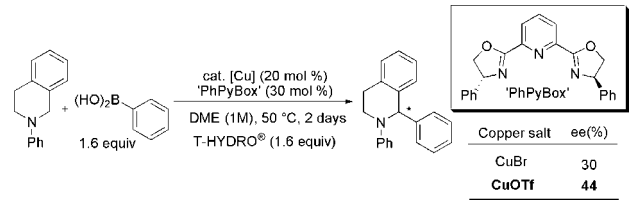
The mechanism of the oxidative arylation reaction remains uncertain at this time. Nevertheless, two possible pathways can be considered (Scheme 3). At first, a well-established iminium-type intermediate **4** is generated by the oxidation of the tertiary amine **1** in the presence of peroxide and copper catalyst.[5d,12] The possibility of a stabilized radical and/or cation intermediate may explain the regioselectivity observed for the benzylic position over the aliphatic one. In pathway A, nucleophilic attack of **4** by a water molecule would generate the α-hydroxy amine intermediate **5**. This intermediate could

Scheme 1. Scope of the Oxidative Arylation Reaction[a]

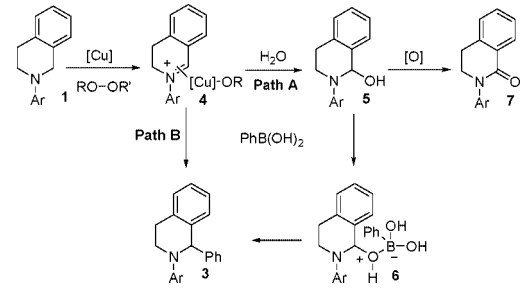


[a]Tetrahydroisoquinolines (0.2 mmol). NMR yields using an internal standard presented in parentheses.

Scheme 2. Asymmetric Oxidative Arylation[16]



Scheme 3. Mechanistic Proposal for the Oxidative Arylation Reaction



either be further oxidized to the observed amide **7** byproduct or react with arylboronic acid to form boronate **6**. Intermediate **6**, through an addition−elimination-type mechanism that results in an overall ipso substitution, would produce product **3**.[9b,17] Alternatively in pathway B, **4** reacts directly with arylboronic acid catalyzed by copper.[10] Pathway B, which involves [Cu] with C−C bond formation, would more easily account for the enantioselectivity obtained in presence of chiral ligands.

In summary, an unprecedented copper-catalyzed arylation of sp^3 C−H bonds adjacent to a nitrogen atom in the absence of a directing group with boronic acids was developed. This new method provides a simple way to synthesize potential biologically active 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives. The method has numerous advantages: the use of minimally toxic and relatively cheap copper salt as catalyst, high regioselectivity, ready generation of free amine, and potential asymmetric synthesis. The scope, applications, and mechanism of this reaction are under investigation.

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Note Added after ASAP Publication. There was an error in the structure of PhPybox in Scheme 2 and the Supporting Information in the version published ASAP July 29, 2008; the corrected version was published ASAP August 28, 2008.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Unoptimized conditions (see the Supporting Information).

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