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N-Substituted Imines by the Copper-Catalyzed *N*-Imination of Boronic Acids and Organostannanes with *O*-Acyl Ketoximes

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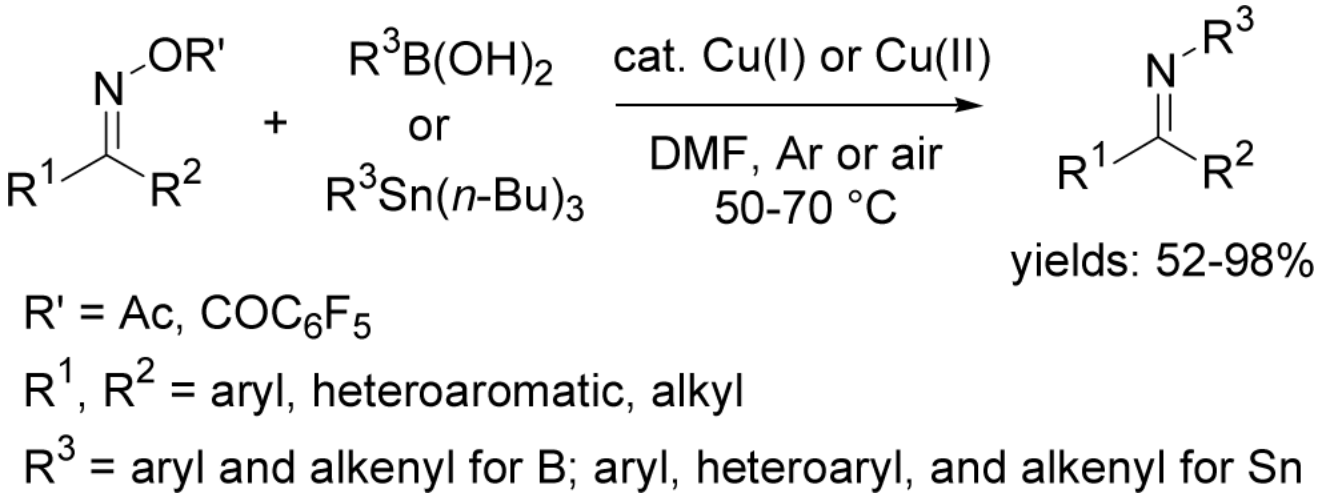
Abstract



Catalytic quantities of copper (I) or copper (II) sources catalyze the *N*-imination of boronic acids and organostannanes through reaction with oxime *O*-carboxylates under non-basic conditions. This method tolerates various functional groups and takes place efficiently using aryl, heteroaryl, and alkenyl boronic acids and stannanes.

Mild metal-catalyzed methods for the formation of carbon-heteroatom bonds have revolutionized the practice of organic synthesis in both academic and industrial settings. [1] Most noteworthy are the palladium- and copper-catalyzed reactions developed by Buchwald and Hartwig and extended by many others. [2] Important complementary reactions that oxidatively couple boronic acids with RXH substrates (X = N, O, S) have been developed by Chan, Evans, Lam, and others.[3]

Although C-X bonds can be easily generated under basic conditions through the Buchwald-Hartwig or oxidative Lam-like conditions, a non-basic and nonoxidative metal-catalyzed protocol could prove highly selective and useful in complex synthetic settings. In pursuit of this goal we initiated an exploration of the metal-catalyzed cross-coupling of nitrogen-heteroatom reagents (N—O, N—S) explicitly with boronic acids and organostannanes as mild, non-basic, and functional group compatible reaction partners (Scheme 1). Related cross-

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Supporting Information Available Complete description of experimental details and product characterization (19 pages) and photocopies of spectra (55 pages). This material is available free of charge via Internet at http://pubs.acs.org.

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couplings have also been studied by Narasaka [4] and Johnson [5] and their coworkers using basic organomagnesium and organozinc reagents. Göttlich and coworkers have explored metal-mediated reactions of *N*-halo compounds and some hydroxylamine derivatives.[6]

The overall reaction chemistry parallels Lam-like reactions of boronic acids, but replaces the requisite oxidant in those transformations (stoichiometric Cu^{II} or air) with the heteroatom-heteroatom bond of the reagent. The unique value of this additional method for carbon-heteroatom bond formation becomes apparent if one contemplates hypothetical synthetic challenges such as the easy and selective manipulation of natural product oximes at the O-N bond for structure activity relationship studies, or the generation of transient, highly reactive imines from oximes for subsequent transformations under mild conditions.

The concept depicted in Scheme 1 led to the disclosure of Cu(I)-catalyzed couplings of boronic acids with *N*-thioimides[7] and with nitrosoaromatics.[8] Extending these studies, we report herein a mild method for the *N*-imination of boronic acids and organostannanes with oxime *O*-carboxylates providing a non-basic, and nonoxidative method for C-N bond formation leading to *N*-substituted imines.[9]

The project was initiated by exploring the cross-coupling of benzophenone oxime *O*-acetate with both *p*-tolylboronic acid and $PhSnBu_3$. After screening a variety of metal catalysts (CuTC, 10 CuOAc, CuCl, CuI, $Pd(PPh_3)_4$), solvents (THF, DMA, DMF), and reaction temperatures (60, 70, 80 °C), this initial effort revealed the effectiveness of 20 mol % CuTC in DMF at 70 °C for the cross-coupling: after 14 h under argon Ph_2C=N-OAc and *p*-tolylboronic acid produced Ph_2C=N-*p*-tolyl in 81% yield, while $PhSnBu_3$ gave Ph2C=N-Ph in 86% yield.

However, upon extending the same reaction conditions to the cross-coupling of alkenyl boronic acids with oxime *O*-acetates (Table 1), the boronic acid homo-coupling (**HC**) side-product (1,3-diene) was observed in significant quantities. Transitioning from *O*-acetyl- to *O*-benzoyl- to *O*-pentafluorobenzoyl- (used by Narasaka in his studies[11]) derived oximes completely suppressed the homo-coupling side-reaction (Table 1, compare entries 1−3). The greater reactivity of the *O*-pentafluorobenzoyl oximes allowed efficient coupling to be carried out with lower catalyst loadings (10 mol % rather than 20 mol % Cu), at lower temperature (50 °C rather than 70 °C), and within 3 h.

Another side-reaction, competitive hydrolysis (**HD**) of the product imines by water generated *in situ* from the boronic acid – boroxine equilibrium[12] was problematic, but this was minimized using DMF as solvent relative to THF, toluene, and dioxane (Table 1, compare entries 3−6). While many different copper sources (CuTC, CuCl, CuBr, CuI, $Cu(OAc)_2$, $CuBr_2$) were effective catalysts for the cross-coupling of oxime *O*-pentafluorobenzoates with aryl and alkenyl boronic acids, no reaction occurred in the absence of the catalyst. Interestingly, the reaction can be carried out in the presence of air using boronic acids as the coupling partners, however, Cu(I) and an inert atmosphere were required when organostannanes were employed.

Using the optimized conditions, the scope of this new methodology was examined as shown in Table 2.[13] A variety of boronic acids and organostannanes react with *O*-acetyl and *O*-pentafluorobenzoyl oximes to generate the *N*-imination products in good to excellent yields. Electron-neutral (entries 1−2), electron-rich (entries 4−6) and electron-deficient (entry 7) arylboronic acids participated efficiently in the reaction. *o*-Tolylboronic acid and 4-methoxy-2-formylphenyl boronic acid, the two *ortho*-substituted arylboronic acids investigated in this study gave acceptable yields of the products under the conditions investigated (entries 3 and 8). Unprotected phenolic and aldehydic functional groups were well-tolerated using this method (entries 5, 7 and 8) suggesting that interesting functionalized imine intermediates could be prepared by this mild synthetic method. Although providing somewhat lower yields of *N*-substituted imine products, heteroaromatic organostannanes and alkenylstannanes were also

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suitable reaction partners in this chemistry (entries 9−12). Synthetically useful 2-azadienes [14] are easily and efficiently produced when alkenylboronic acids are the reactants (entries 13−16).

When coupling with boronic acids the *O*-pentafluorobenzoyl oximes generally gave better results than *O*-acetyl oximes probably due to the milder conditions using the former reactants (lower temperature and shorter reaction time). However, when using organostannanes as reaction partners, the *O*-acetyl oximes performed better than *O*-pentafluorobenzoyl oximes because the more reactive *O*-pentafluorobenzoyl oximes suffered a competitive Beckmann rearrangement.[15]

The scope of oxime *O*-carboxylate substrates was also probed. Oxime *O*-carboxylates derived from aryl-heteroaryl, aryl-alkyl and alkyl-alkyl ketones were suitable substrates, but the imines derived from alkyl substituted oximes were typically unstable to workup and isolation. Rather than carrying out direct isolation of these imines, a reductive workup using $NaCNBH_3$ allowed a more convenient isolation of the corresponding amines (entries 20−23). Unfortunately, aldoxime *O*-carboxylates did not produce the desired aldimines; rather, they suffered β-elimination to give the corresponding nitrile products under the reaction conditions (Scheme 2).

Under the conditions studied to date this new reaction is not appropriate for the stereodefined synthesis of imines, since separate treatment of each stereoisomeric *E*-and *Z*-oxime *O*-carboxylate derived from phenyl-2-furyl ketone with 3-hydroxyphenylboronic acid produces the same 2:1 mixture of product imines (Table 2, entry 18; Scheme 3).

A reasonable mechanistic pathway for the copper catalyzed coupling of ketoxime *O*-carboxylates with boronic acids or organostannanes is shown in Scheme 4. Oxidative additions to N–O bonded species are precedented.[11, 16] In the current study strong support for oxidative addition of the oxime *O*-carboxylate to Cu(I) comes from the formation of benzophenone imine in 90% yield after a mixture of benzophenone oxime *O*-acetate and 1 equiv of CuTC in DMF was subjected to workup after 30 min. Transmetallation of either the boronic acid or the organostannane to the putative Cu(III) intermediate followed by reductive elimination would produce the desired C-N bond and regenerate a catalytically active Cu(I). The requisite Cu(I) catalyst is either added to the reaction system or generated *in situ* through reduction of a Cu(II) precatalyst by the coupling agent.

In summary, a general copper-catalyzed *N*-imination of boronic acids and organostannanes has been developed. The reaction uses oxime *O*-carboxylates as iminating agents and proceeds under non-basic and non-oxidizing conditions thus complementing existing C-N bond forming reactions. A simple, modular synthesis of highly substituted pyridines, a powerful extension of this new method, will be reported shortly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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13. **Typical Experimental Procedure**. To benzophenone oxime *O*-pentafluorobenzoate (0.1 mmol), *E*-β-styrylboronic acid (0.12 mmol) and CuTC (2 mg, 0.01 mmol) in a Schlenk tube flushed with argon was added dry DMF (2 mL). The reaction mixture was stirred at 50 °C for 3 h and diluted with EtOAc (30 mL). The copper catalyst was removed by passing the reaction mixture through a short pad of silica gel that was buffered with triethylamine. After evaporation of the solvent, the residue was subjected to flash chromatography (silica gel, buffered by triethylamine, eluted with 40 : 1 hexanes : EtOAc) giving the desired product as a yellow oil in 90% yield.
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15. The Beckmann rearrangement may be facilitiated by the organostannane: reaction of the same substrate under the same reaction conditions with the analogous boronic acid does not cause formation of the Beckmann product.
16. For the oxidative addition of oxime derivatives to metals such as Re, Pd and Cu, see:a Kusama H, Yamashita Y, Uchiyama K, Narasaka K. Bull. Chem. Soc. Jpn 1997;70:965. b Ferreira CMP, Guedes da Silva MFC, Kukushkin VY, Fraústo da Silva JJR, Pombeiro AJL. J. Chem. Soc., Dalton Trans 1998:325. c Tsutsui H, Narasaka K. Chem. Lett 2001:526. d Kitamura M, Zaman S, Narasaka K.

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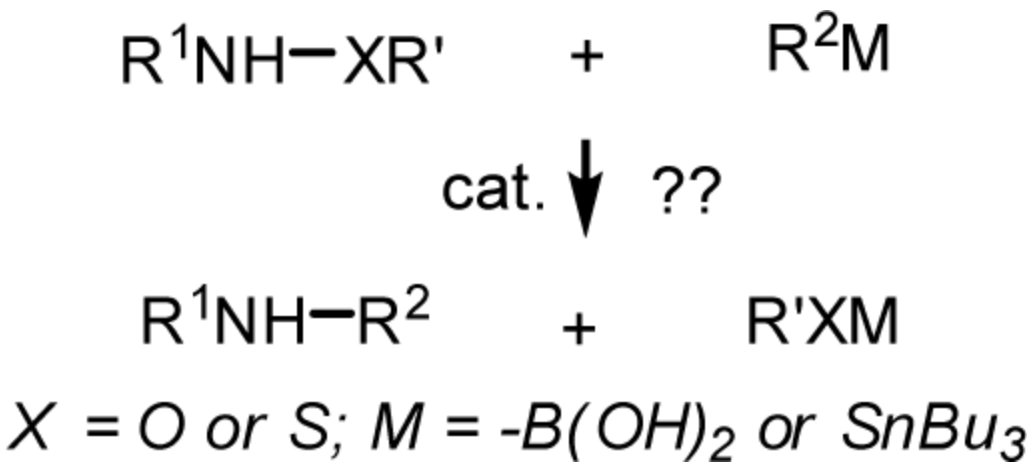

Scheme 1.
Cross-Coupling Concept

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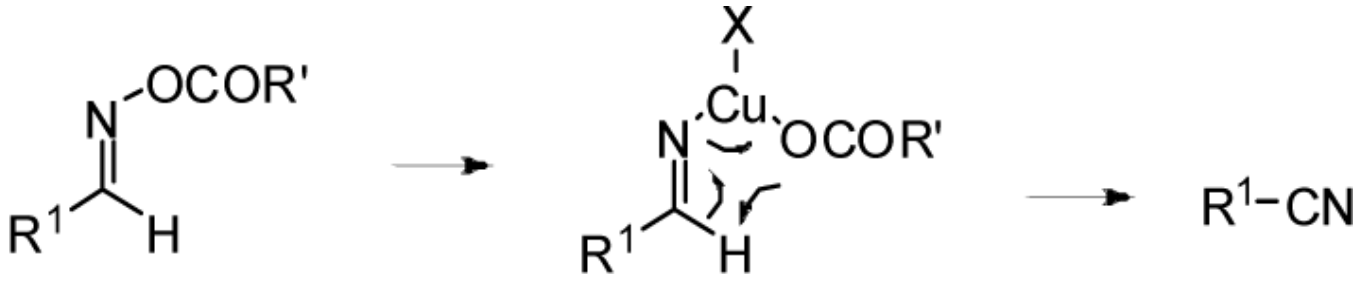

Scheme 2.
Formation of Nitriles from Aldoximes

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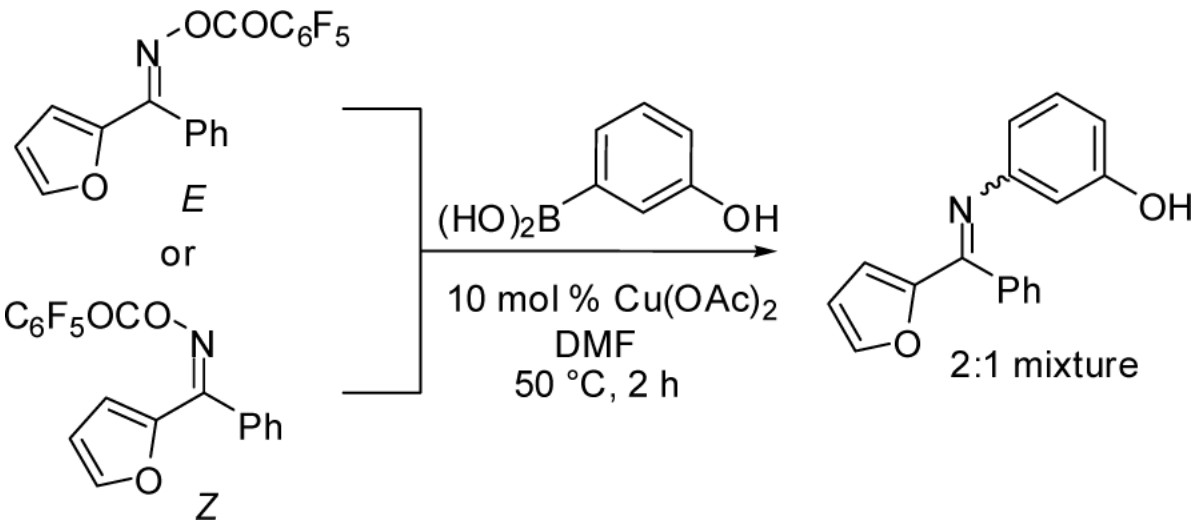

Scheme 3.
Stereochemistry of the Cross-Coupling

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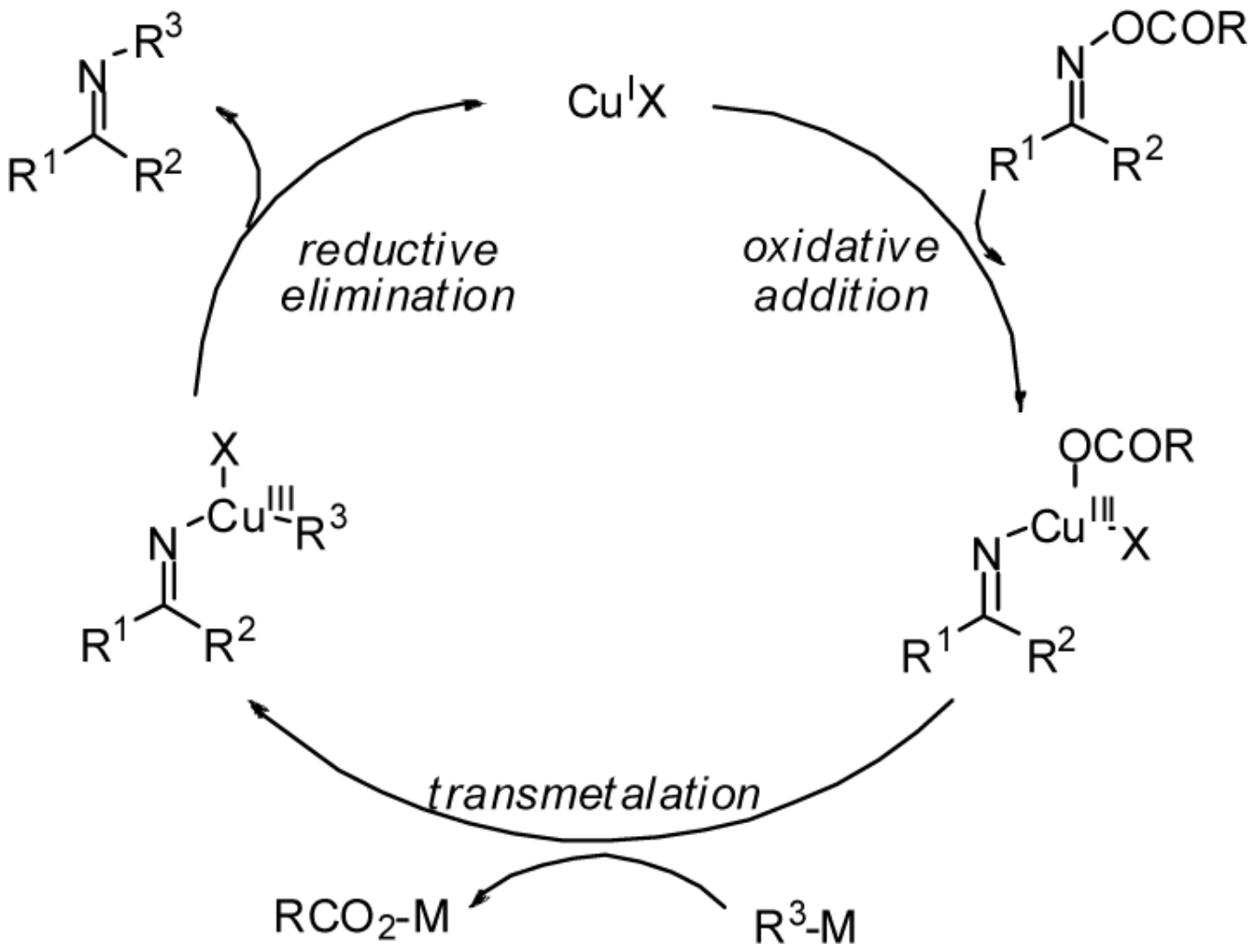

Scheme 4.
Suggested Mechanism

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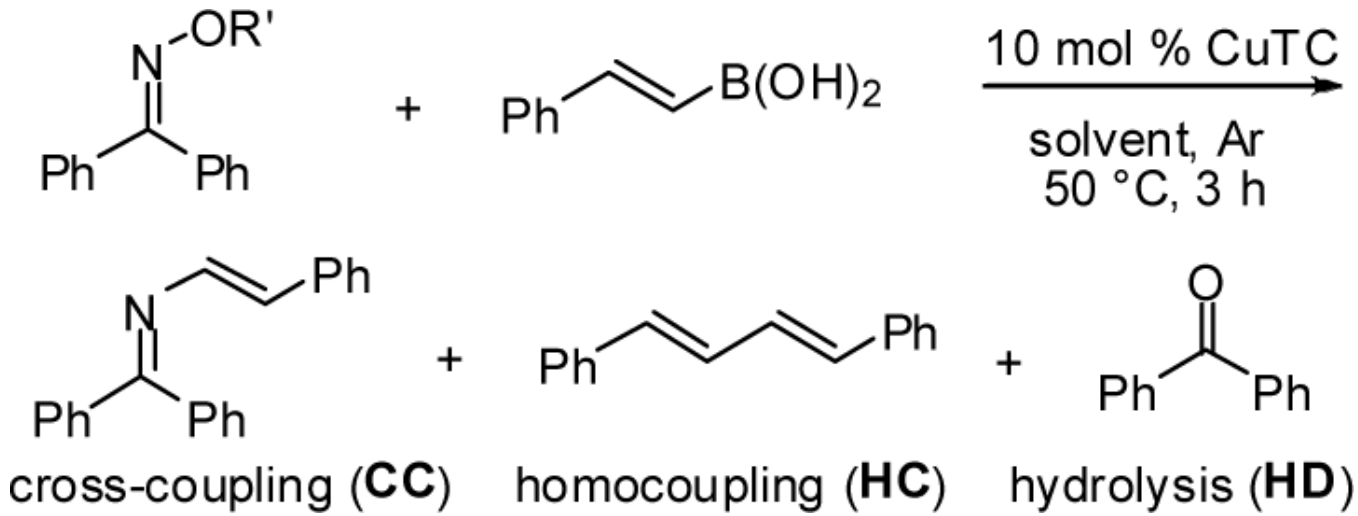
Table 1

Optimization Studies



entry	R'	solvents	yield (%)[a]		
			CC	HC	HD
1	Ac	DMF	41	12	9
2	COPh	DMF	63	9	12
3	COC_6F_5	DMF	86	0	5
4	COC_6F_5	THF	81	0	12
5	COC_6F_5	toluene	41	0	38
6	COC_6F_5	dioxane	39	0	38

[a] ^{1}H NMR yield, *para*-dimethoxybenzene as internal standard.

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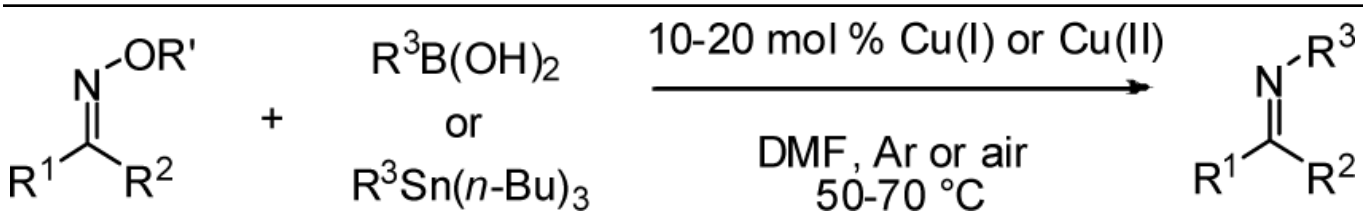
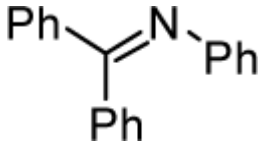
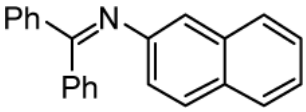
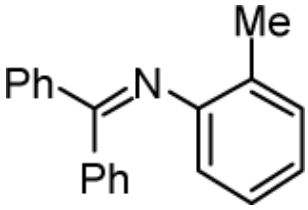
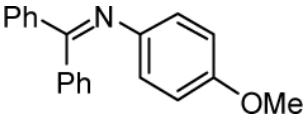
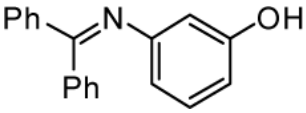
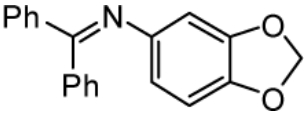
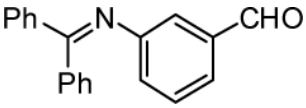
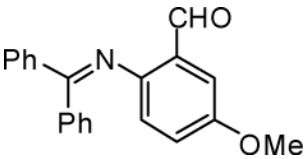
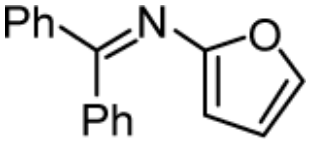
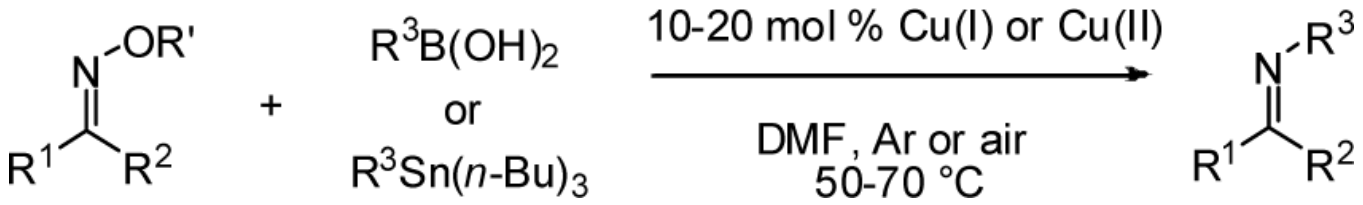
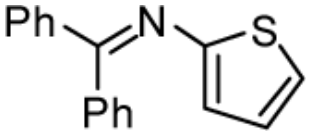
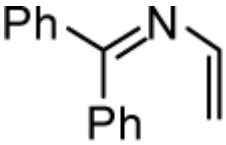
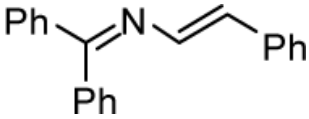
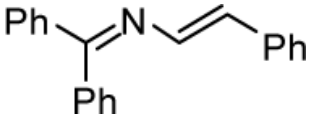
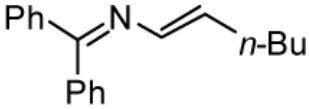
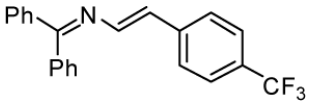
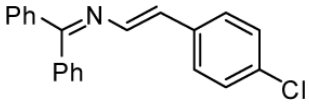
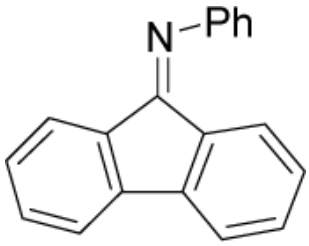
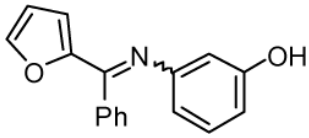
Table 2

Cu-Catalyzed *N*-Imination of Boronic Acids and Organostannanes



entry	R'	R^3M	product	yield[i] (%)
1[a]	Ac	$PhB(OH)_2$ $PhSn(n\text{-}Bu)_3$		82 86
2[a]	Ac	2-naphthyl-$B(OH)_2$		72
3[a]	Ac	*o*-tolyl-$B(OH)_2$		59
4[b]	COC_6F_5	4-methoxyphenyl-$B(OH)_2$		96
5[b]	COC_6F_5	3-hydroxyphenyl-$B(OH)_2$		93
6[b]	COC_6F_5	3,4-methylenedioxyphenyl-$B(OH)_2$		89
7[c]	COC_6F_5	3-formylphenyl-$B(OH)_2$		86
8[d]	COC_6F_5	4-methoxy-2-formylphenyl-$B(OH)_2$		55
9[a]	Ac	2-furyl-$Sn(n\text{-}Bu)_3$		52



entry	R'	R^3M	product	yield[i] (%)
10[a]	Ac	2-thiophenyl-Sn(*n*-Bu)$_3$		56
11[e]	Ac	vinyl-Sn(*n*-Bu)$_3$		61
12[e]	Ac	*E*-β-styryl-Sn(*n*-Bu)$_3$		53
13[f]	COC_6F_5	*E*-β-styryl-B(OH)$_2$		90
14[f]	COC_6F_5	*trans*-1-hexen-1-yl-B(OH)$_2$		98
15[b]	COC_6F_5	*trans*-2-[4-(trifluoromethyl)phenyl]vinyl-B(OH)$_2$		88
16[b]	COC_6F_5	*trans*-2-(4-chlorophenyl)vinyl-B(OH)$_2$		94
17[a]	Ac	PhB(OH)$_2$		86
18[b]	COC_6F_5	3-hydroxyphenyl-B(OH)$_2$		95

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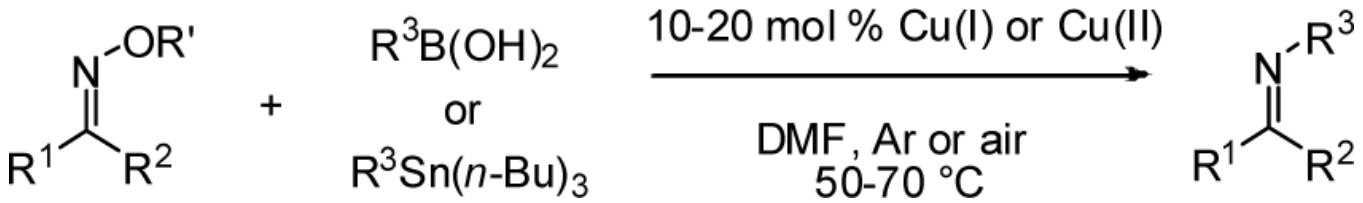
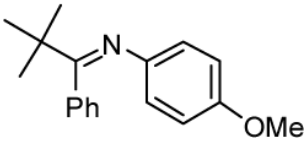
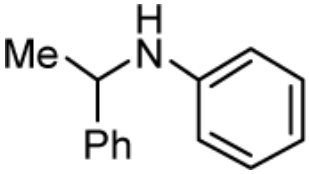
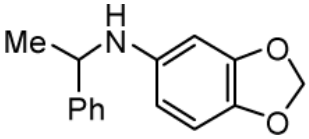
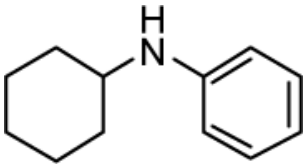
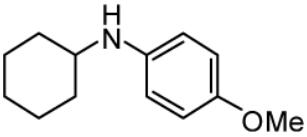


entry	R'	R^3M	product	yield[i] (%)
19[b]	COC_6F_5	4-methoxyphenyl-$B(OH)_2$		69
20[g]	COC_6F_5	$PhB(OH)_2$		94
21[g]	COC_6F_5	3,4-methylenedioxyphenyl-$B(OH)_2$		76
22[h]	COC_6F_5	$PhB(OH)_2$		75
23[h]	COC_6F_5	4-methoxyphenyl-$B(OH)_2$		53

[a] 20 mol % CuTC, Ar, 70 °C, 14 h.

[b] 10 mol % $Cu(OAc)_2$, air, 50 °C, 2−3 h.

[c] 20 mol % $Cu(OAc)_2$, air, 50 °C, 1 h.

[d] 20 mol % CuTC, Ar, 50 °C, 2 h.

[e] 20 mol % CuTC, Ar, 50 °C, 18 h.

[f] 10 mol % CuTC, Ar, 50 °C, 2−3 h.

[g] 10 mol % CuTC, Ar, 50 °C, 2−3 h; $NaBH_3CN$ (3 equiv) / CF_3COOH (2 equiv), 0 °C, 2 h.

[h] 10 mol % CuTC, 4 Å mol sieves., Ar, 50 °C, 1−2 h; $NaBH_3CN$ (3 equiv) / CF_3COOH (2 equiv), 0 °C, 2 h.

[i] Isolated yield.

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