Cu-Catalyzed Cross-Coupling of Nitroarenes with Aryl Boronic Acids to Construct Diarylamines
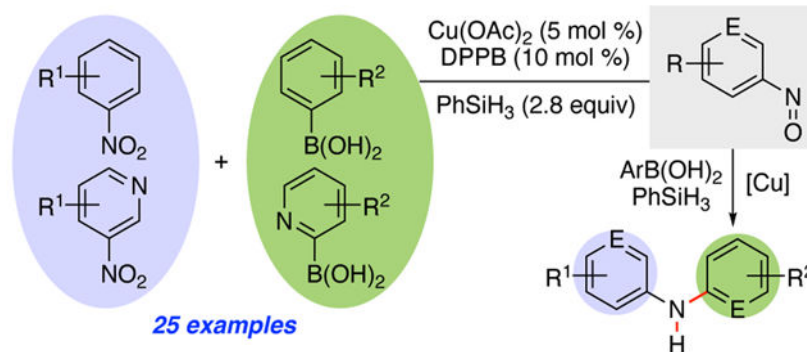
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Abstract

The development and study of a simple copper-catalyzed reaction of nitroarenes with aryl boronic acids to form diarylamines that uses phenyl silane as the stoichiometric terminal reductant is described. This cross-coupling reaction requires as little as 2 mol % of CuX and 4 mol% of diphosphine for success and tolerates a broad range of functional groups on either the nitroarene or the aryl boronic acid with to afford the amine in good yield. Mechanistic investigations established that the cross-coupling reaction proceeds via a nitrosoarene intermediate and that copper is required to catalyze both the deoxygenation of the nitroarene to afford the nitrosoarene and C–NAr bond formation of the nitrosoarene with the aryl boronic acid.

Graphical Absract

Keywords

nitroarene; nitrosoarene; aryl boronic acid; cross-coupling; copper

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Author Contributions

The manuscript was written through contributions of all authors.

Supporting Information

Experimental procedures, spectroscopic and analytical data for the products (PDF) are available free of charge via the Internet at http://pubs.acs.org.

Experimental details and spectral data (PDF)

The ubiquitous nature of *N,N*-diarylamines in molecules that exhibit important biological- and material activities has spurred considerable research in developing efficient catalytic reactions to construct this important scaffold.[1,2] While transition metal-catalyzed cross-coupling reactions that form C–N bonds are legion,[3] few examples exist of their use to make secondary *N,N*-diarylamines from nitroarenes. Our laboratory has developed a series of transition metal-catalyzed reactions that exploit the reactivity embedded in nitroarenes for the construction of C–NAr bonds via nitrosoarene reactive intermediates,[4] and we were curious if a nitroarene could serve as the nitrogen component of the cross-coupling reaction.[5] In 2002, Sapountzis and Knochel reported that diarylamines **3** could be constructed from nitroarenes via the nucleophilic addition of Grignard reagents to nitrosoarenes followed by an iron-mediated reduction of the N-oxide product.[6,7] After this seminal report, the development of reductive intermolecular cross-coupling reactions of nitroarenes lay dormant until 2015 when Baran and co-workers reported that 30 mol % of Fe(acac)$_3$ catalyzed a reductive hydroamination reaction between a nitroarene and an olefin using superstoichmetric amounts of PhSiH3 and Zn(0) as the reductant (Scheme 1).[8] The authors proposed that this reaction occurred through the addition of benzyl radical **5** to nitrosoarene **1**. For this reaction, the transition metal catalyst was not involved in the formation of the C–NAr bond but functioned to facilitate deoxygenation of the nitroarene to the nitrosoarene. This report spurred a surge in interest in using nitroarenes to construct C–NAr bonds in reductive amination reactions.[9] Recently, Radosevich and co-workers reported an organophosphorous-catalyzed reductive coupling of nitroarenes and aryl boronic acids using phenyl silane as the stoichiometric reductant.[10] Critical to the success of this transformation was the strained nature of the phosphacyclobutane catalyst **6**, which enables the P(III)-P(V)=O redox manifold.[10] In 2019, a Mo-catalyzed reductive coupling of nitroarenes and boronic acids that used triphenylphosphine as the terminal reductant was reported by Suaréz-Pantiga, Sanz and co-workers.[11] This transformation required only 5 mol % of MoO$_2$Cl$_2$(dmf)$_2$ and bipyridine and a slight excess of either an aryl- or alkyl boronic acid for success and was proposed by the authors to proceed via metallocycle **10**. We hoped to build on these results by developing a catalytic system that used a commercially available and earth abundant first row transition metal and ligand and a mild reductant. Herein, we report the development of a Cu-catalyzed cross-coupling reaction of nitroarenes and aryl boronic acids that uses phenyl silane as the stoichiometric reductant. Our data suggests that copper catalyzes both the deoxygenation of nitroarene to nitrosoarene and subsequent formation of the C–NAr bond.

To determine if a first-row transition metal catalyzed reductive cross-coupling reaction of nitroarenes and aryl boronic acids could be achieved we examined the reactivity of 4-methoxyphenylboronic acid and methyl-4-nitrobenzoate (Table 1). While only aniline formation was observed using an iron- or nickel catalyst,[12] we found that the combination of 10 mol % of Cu(OAc)$_2$ and DPPB as the ligand afforded diarylamine **3a**, but reduction to aniline was observed to be competitive (entry 1). While changing the oxidation state of copper resulted in no aniline formation, the yield of **3a** was severely attenuated (entry 2). After control experiments established that both copper and the silane were required for the formation of diarylamine **3a**,[12] we turned our attention to improving the ratio of cross-coupling product **3a** to aniline. Changing the ratio of the nitroarene to aryl boronic

acid from 1.5:1 to 1:1.5 reduced the amount of aniline significantly (entry 3). A solvent screen was performed,[12] and the amount of aniline was reduced in acetonitrile (entries 4 – 6). The catalyst loading was investigated using this reaction medium, and we observed that 5 mol % of $Cu(OAc)_2$ could be used without attenuating the ratio of **3a** to aniline (entry 7). The catalyst could be reduced to as little as 2 mol % without adversely affecting the reaction outcome (entry 8). While changing the counterion on copper did not have a positive effect on the cross-coupling reaction (entries 9 – 11),[11] reducing the temperature of the reaction to 60 °C improved the ratio of **3a** to aniline to almost 2:1 (entry 12). At this temperature, we surveyed a range of co-solvents,[11] and using a 1:1 mixture of acetonitrile and toluene produced 76% of **3a**, which was accompanied by only 18% of aniline (entry 13). Using this solvent mixture and temperature, we found that changing the identity of the silane or ligand had a negative effect on the reaction outcome and did not improve the amount diarylamine **3a** formed (entries 14 – 18). The larger effect of changing the substituents on silane prompted us to examine the concentration of $PhSiH_3$, and we found that using 2.8 equivalents of $PhSiH_3$ afforded the highest ratio of diarylamine **3a** to aniline (entries 19 and 20).

Using the optimal conditions, the scope and limitations of our Cu-catalyzed reductive cross-coupling reaction was investigated with respect to the nitroarene (Table 2). The influence of electronic nature of the nitroarene on the reaction outcome was examined by changing the identity of the R^1-substituent (entries 1 – 6). We found the reaction worked best with electron-deficient nitroarenes, but diarylamines could be accessed from nitrobenzene albeit with a diminished yield. Electron-rich nitroarenes, however, such as 4-nitroanisole resulted in no reaction (entry 5).[13] This result could be leveraged by using 1,4-dinitrobenzene, which resulted in coupling of the aryl boronic acid to only one of the two nitro groups to produce **3f**, albeit in a slightly attenuated yield (entry 6). The effect of meta-substitution was investigated, and diarylamines **3g** – **3i** were formed in good yield irrespective of whether the R^2-substituent was a F_3C-, Me- or MeO-group (entries 7 – 10). To our surprise, the cross-coupling reaction exhibited a broad tolerance to the identity of the *ortho*-substituent (entries 10 – 13): high yields of diarylamine **3** were obtained with a potentially coordinating nitrile R^3-substituent, an alkyl group and even an electron-donating methoxy R^3-substituent, which inhibited the reaction when it was present in the *para*-position. The success of nitroarene **3j** spurred us to examine other potentially coordinating heteroarenes, and we were delighted to see that 3-nitropyridines were competent substrates enabling access to **3o** (entry 15). These results illustrate that diarylamines can be efficiently formed from a broad range of nitroarenes and heteroarenes.

The scope with regards to the aryl boronic acid was also surveyed (Table 3). Modifying the electronic nature of the aryl boronic acid was investigated by examining the effect of a variety of R^1- and R^2-substituents on the cross-coupling reaction (entries 1 – 6), and we observed that the yield of **12** was high irrespective of whether the substituent was an electron-donating- or an electron-withdrawing group. In contrast, the cross-coupling reaction was sensitive to the identity of the *ortho*-substituent. While a methoxy substituent was tolerated, no diarylamine was formed from an aryl boronic acid bearing an ethyl R^3-substituent (entries 8 and 9).[14] While this effect could be attributed to the increased steric

environment around the reaction center, we found 1-napthylboronic acid to be a good partner to afford diarylamine **12i** (entry 9). Our cross-coupling reaction also tolerated a coordinating heterocycle in the boronic acid component to afford 2-pyrimidine amine **12j**, albeit in an attenuated yield in comparison to pyridyl **3o** (entry 10). While our method enables access to a broad range of *N,N*-diarylamines, neither nitroalkanes nor alkyl boronic acids are tolerated as substrates using our reaction conditions despite their use in Radosevich's or Suaréz-Pantiga and Sanz's methods.[10,11]

To provide insight into the mechanism of the reaction, several control experiments were performed (Scheme 2). To validate that the cross-coupling reactions proceeded via a nitrosoarene intermediate, an excess of 2,3-dimethylbutadiene was added to the reaction of 2-bromonitrobenzene and 4-methoxyphenyl boronic acid. Although the excess of diene inhibited this reaction, analysis of the reaction mixture after approximately 10% conversion using ^{1}H NMR spectroscopy revealed that oxazine **13** and diarylamine **3k** were both present.[15,16] The observation of oxazine **13** indicates that cycloaddition of the nitrosoarene intermediate with 2,3-dimethylbutadiene is competitive with the cross-coupling process. Because anilines are well established as competent substrates for C–N bond cross-coupling reactions,[17] we were curious to determine if C–NAr bond formation in our reaction occurred via a nitrosoarene or aniline. While no diarylamine formation was obtained using an aniline, submission of nitrosoarene **14** to reaction conditions afforded diarylamine **3p** in 56%. Our data suggests that copper is required to trigger C–NAr bond formation. No reaction was observed when copper acetate was omitted from the reaction of nitrosoarene **14** and the aryl boronic acid. Our investigations also uncovered that the hydroxyl substituent of the aryl boronic acid plays a critical role for a successful reaction outcome. When an aryl boronic pinacolate ester or an aryl trifluoroborate were submitted to reaction conditions only reduction to aniline was observed.

Together these experiments suggest that the catalytic cycle for this cross-coupling reaction requires the copper catalyst for both the deoxygenation and C–NAr bond formation (Scheme 3). Deoxygenation of nitroarene by a copper hydride produces nitrosoarene and a copper hydroxide, which is reduced by silane.[18] The observation of oxazine **13** when 2,3-dimethylbutadiene is present suggests that the nitrosoarene dissociates from the copper hydroxide complex before the subsequent C–NAr bond forming steps. If the copper remained coordinated to ArNO then only a nitroso-ene product would have been observed.[19] Our control experiments indicate that copper also catalyzes the carbon–nitrogen bond formation. This could occur through coordination of copper to either the aryl boronic acid to form **15** or via copper nitrosoarene **16**.[19a,19b,20] Reaction with the coupling partner—ArNO **1** or ArB(OH)$_2$—forms metallocycle **17**,[21] which triggers a 1,2-aryl shift to establish the C–N bond and produce **18**. Reduction of **18** with copper hydride produces the diarylamine and regenerates the copper catalyst.[22,23]

Alternatively, diarylamine **3** could form via a copper aryl intermediate. This species could be generated following a mechanism proposed by Liebeskind and co-workers for the cross-coupling of nitrosoarenes with aryl boronic acids:[24] reaction of copper(I) complex **19** with ArNO **1** to afford side-on formal copper(III) complex **20**.[25] Transmetalation by the aryl

boronic acid would form **21**, and reductive elimination would generate the C–NAr bond. Reduction of **22** by silane would form diarylamine **3** and generate the copper catalyst.

The C–NAr bond could also be formed through a mechanism similar to the Chan–Evans–Lam reaction. Coordination of the aryl boronic acid to the copper hydroxide substituent affords **23**, which triggers transmetalation to produce Cu(II) intermediate **24** and boric acid. Coordination of nitrosoarene **1** affords **25**, which undergoes a 1,2 insertion to produce **26**. Reduction of **26** with silane produces diarylamine 3 and regenerates the copper catalyst. This mechanism appears less likely because formation of copper aryl species **24** should occur for aryl boronic pinacolate esters or trifluoroborate salts.[26,27]

In conclusion, we have discovered a mild copper-catalyzed reaction that couples nitroarenes or nitroheteroarenes and aryl boronic acids using phenyl silane as the stoichiometric reductant. Our reaction requires as little as 2 mol % of copper and tolerates a broad range of functionality on both the nitroarene and aryl boronic acid to furnish the amine product. Our preliminary mechanistic investigations reveal that the cross-coupling reaction proceeds via a nitrosoarene intermediate and that copper is required for to catalyzed both the deoxygenation and the C–NAr bond forming steps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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12. Refer to the Supporting Information for more details.

13. Raising the temperature of the reaction did not result in the formation of diarylamine **3e.3e.**

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27. While the Chan–Evans–Lam reaction of aryl amines with boronic pinacolate esters requires modified conditions for high yields, Watson and co-workers reported in ref 25e that using Cu(OAc)$_2$ in combination with Et$_3$N in MeCN at 60 °C produced diarylamine from 4-
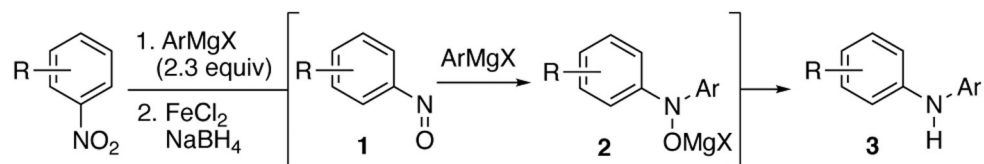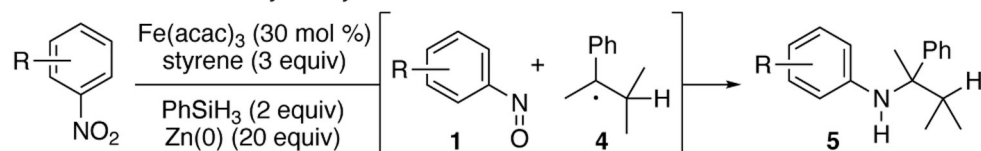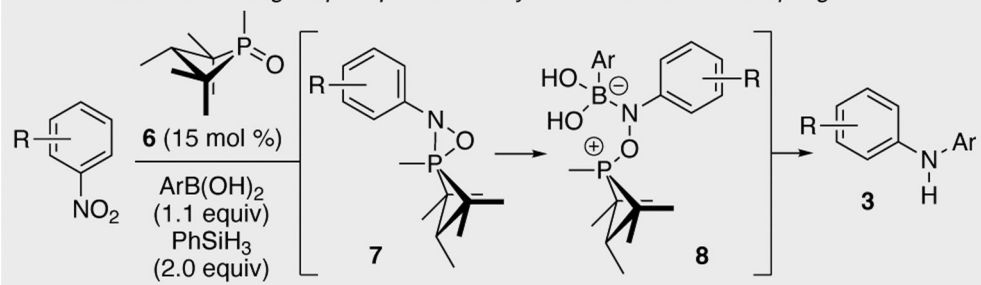
phenylbenzene boronic pinacolate ester and aniline, albeit in a reduced yield. Consequently, some diarylamine **3** would be expected using ArBpin as a coupling partner.[23] **3**

2002 *Knochel — Nucleophilic addition of RMgX*

2015 *Baran — Fe-catalyzed hydroamination*

2018 *Radosevich — Organophosphorus-catalyzed reductive C–N coupling*

2019 *Sanz — Mo-catalyzed reductive coupling*
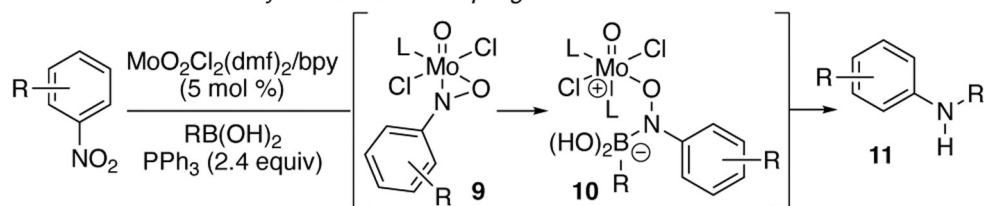
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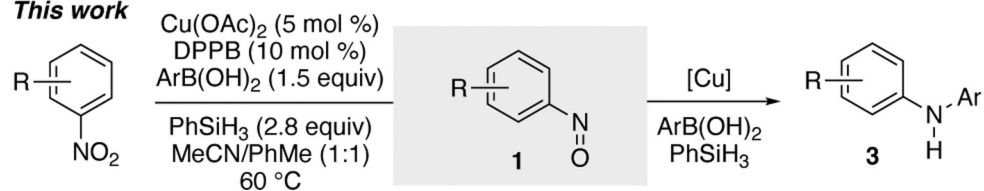
Scheme 1.
Progress towards the development of efficient catalysis of cross-coupling reactions of nitroarenes to access diarylamines.

Evidence for ArNO intermediate

~10% conversion

(1.5 equiv)   (10 equiv)

13, ~3%   +   **3k**, ~6%
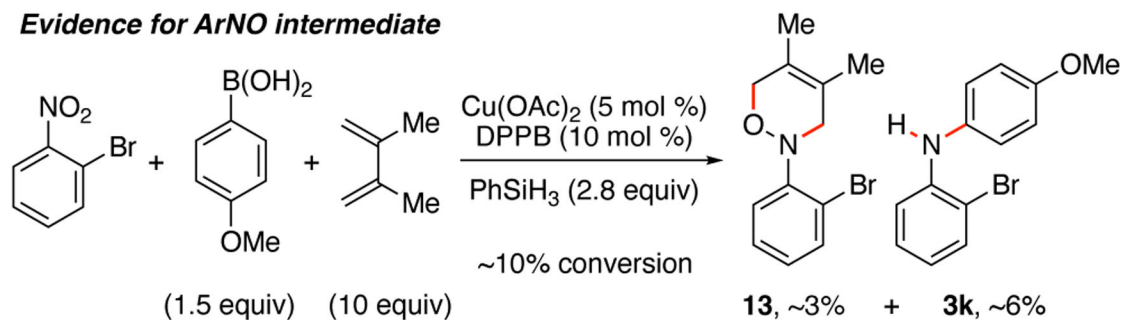
Nonreactivity of aniline reactive intermediate

(1 equiv)   (1 equiv)   (1.5 equiv)

3a, 56%
3b, *not observed*

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14   (1.5 equiv)

3p, 56%   +   28%

no reaction observed in the absence of Cu(OAc)$_2$
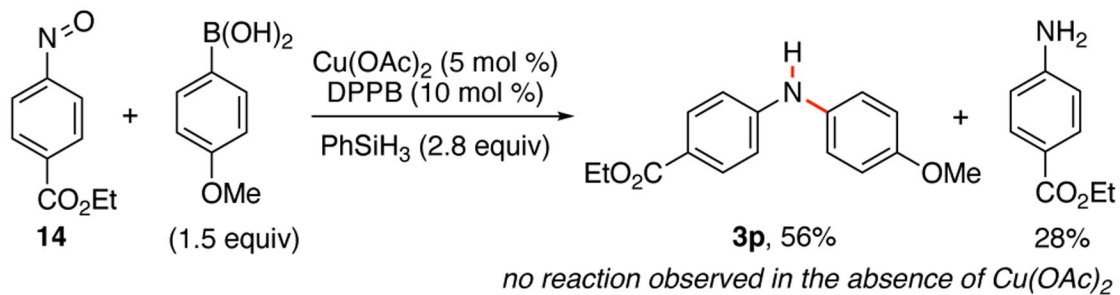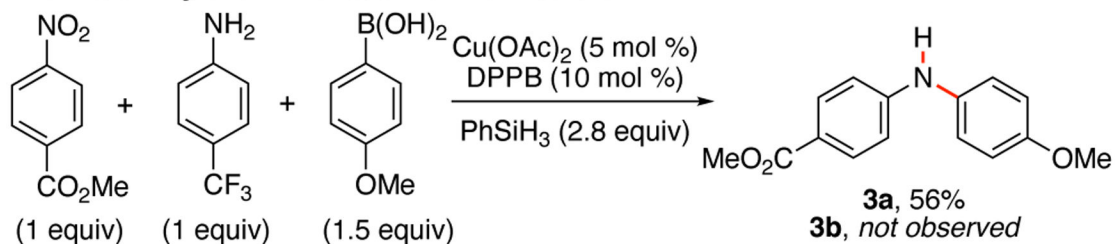
Critical nature of boronic acid hydroxy substituents

BR$_n$	3a	aniline
Bpin	0%	40%
BF$_3$K	0%	85%
B(OH)$_2$	83%	16%
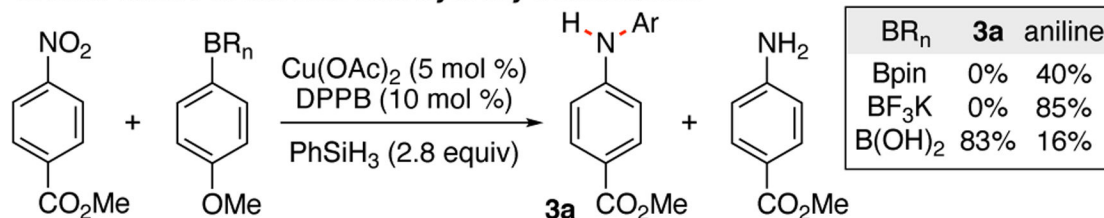
Scheme 2.
Mechanistic experiments.

Scheme 3.
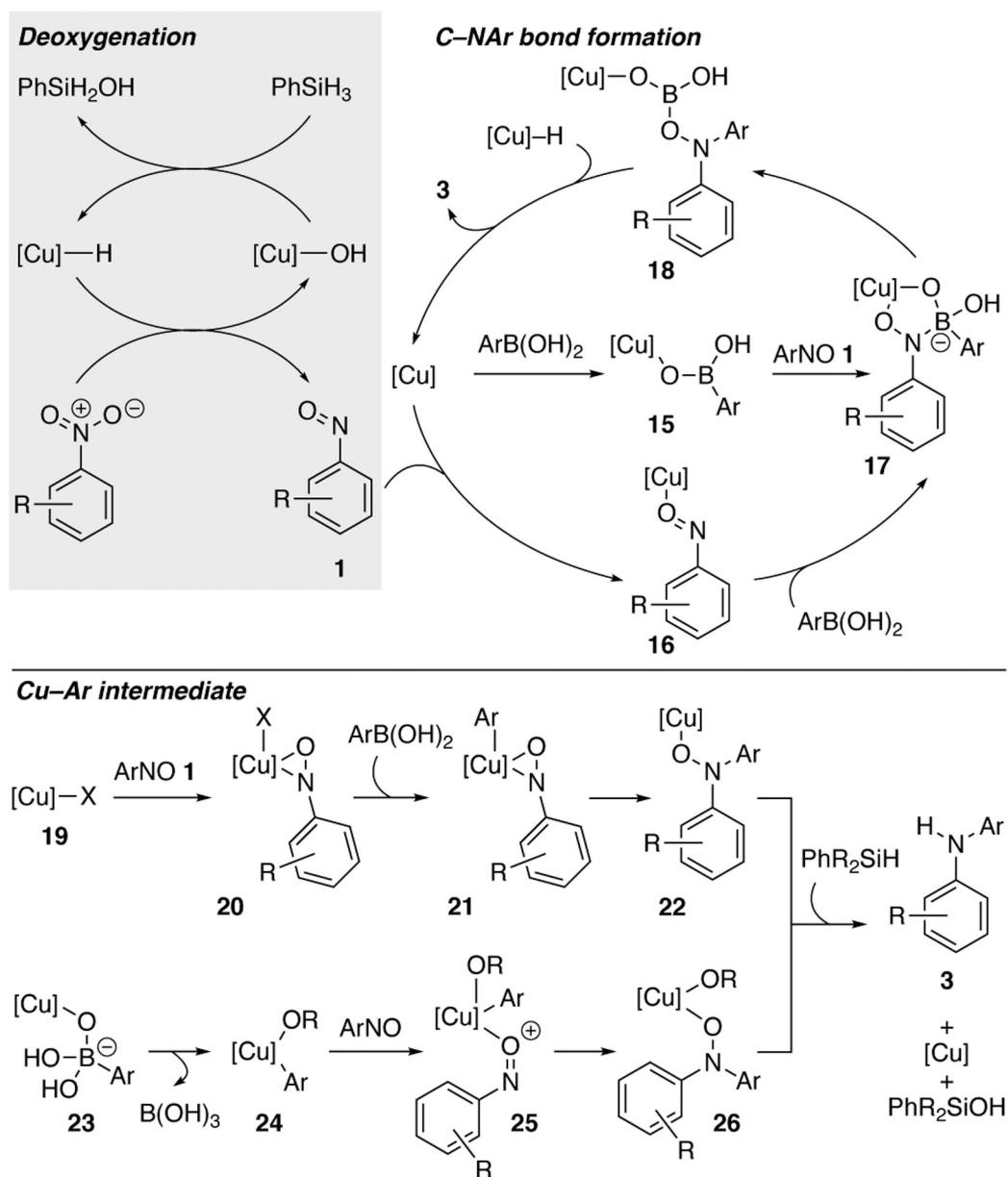Potential catalytic cycle.

Table 1.

Development of optimal conditions.

entry	Cu salt (mol %)	ligand (mol %)	silane (equiv)	solvent	T (°C)	yield 3a, %[a]	yield aniline, %[a]
1[b]	Cu(OAc)$_2$ (10)	DPPB (20)	PhSiH$_3$ (3)	PhMe	100	42	54
2[b]	CuCl (10)	DPPB (20)	PhSiH$_3$ (3)	PhMe	100	25	0
3	Cu(OAc)$_2$ (10)	DPPB (20)	PhSiH$_3$ (3)	PhMe	100	65	32
4	Cu(OAc)$_2$ (10)	DPPB (20)	PhSiH$_3$ (3)	1,4-dioxane	100	56	40
5	Cu(OAc)$_2$ (10)	DPPB (20)	PhSiH$_3$ (3)	DCE	100	52	42
6	Cu(OAc)$_2$ (10)	DPPB (20)	PhSiH$_3$ (3)	MeCN	100	52	28
7	Cu(OAc)$_2$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN	100	55	26
8	Cu(OAc)$_2$ (2)	DPPB (4)	PhSiH$_3$ (3)	MeCN	100	50	31
9	CuCl$_2$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN	100	35	50
10	Cu(tfacac)$_2$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN	100	45	28
11	CuSO$_4$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN	100	36	34
12	Cu(OAc)$_2$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN	60	63	33
13	Cu(OAc)$_2$ (5)	DPPB (10)	PhSiH$_3$ (3)	MeCN/PhMe (1:1)	60	76	18
14	Cu(OAc)$_2$ (5)	DPPB (10)	iPr$_3$SiH (4)	MeCN/PhMe (1:1)	60	0	0
15	Cu(OAc)$_2$ (5)	DPPB (10)	(MeO)$_2$MeSiH (3)	MeCN/PhMe (1:1)	60	27	48
16	Cu(OAc)$_2$ (5)	DPPP (10)	PhSiH$_3$ (3)	MeCN/PhMe (1:1)	60	55	27
17	Cu(OAc)$_2$ (5)	BINAP (10)	PhSiH$_3$ (3)	MeCN/PhMe (1:1)	60	33	37
18	Cu(OAc)$_2$ (5)	1,1-phen (10)	PhSiH$_3$ (3)	MeCN/PhMe (1:1)	60	0	90
19	Cu(OAc)$_2$ (5)	DPPB (10)	PhSiH$_3$ (2.8)	MeCN/PhMe (1:1)	60	83	16
20	Cu(OAc)$_2$ (5)	DPPB (10)	PhSiH$_3$ (2.6)	MeCN/PhMe (1:1)	60	80	20

[a] As determined using ^{1}H NMR spectroscopy using CH$_2$Br$_2$ as the internal standard.

b1.5 equiv of ArNO$_2$ and 1.0 equiv of ArB(OH)$_2$ used.

Table 2.

Scope and limitations with regards to the nitroarene.
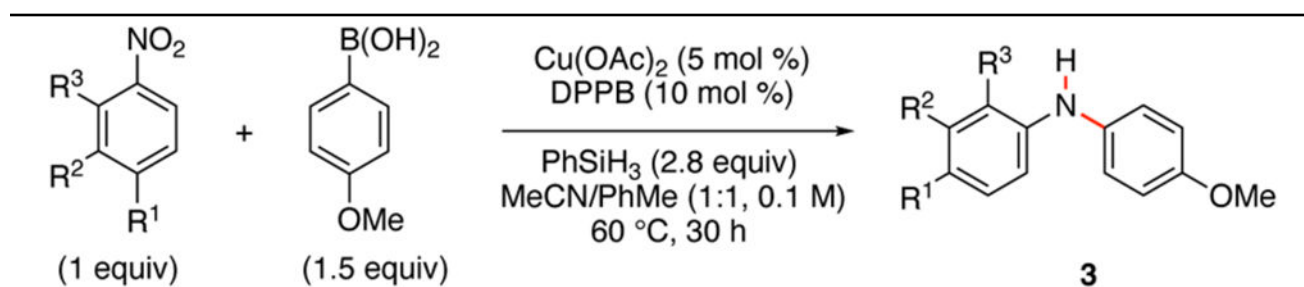
entry	R¹	R²	R³	3	yield, %^{a}
1	MeO₂C	H	H	**a**	83 (81)^b
2	F₃C	H	H	**b**	84
3	H	H	H	**c**	66
4	Cl	H	H	**d**	85
5	MeO	H	H	**e**	n.r.
6	O₂N	H	H	**f**	59
7	H	F₃C	H	**g**	89
8	H	Me	H	**h**	73
9	H	MeO	H	**i**	85
10	H	H	NC	**j**	83
11	H	H	Br	**k**	89
12	H	H	Et	**l**	82
13	H	H	OMe	**m**	72
14		−HC=CH−CH=CH−	H	**n**	96

Reaction scheme: A nitroarene bearing R^3, NO_2, R^2, R^1 (1 equiv) plus 4-methoxyphenylboronic acid B(OH)$_2$/OMe (1.5 equiv) with Cu(OAc)$_2$ (5 mol %), DPPB (10 mol %), PhSiH$_3$ (2.8 equiv), MeCN/PhMe (1:1, 0.1 M), 60 °C, 30 h, giving product **3**.

entry	R¹	R²	R³	3	yield, %ᵃ
15				o	75

ᵃIsolated after silica gel chromatography.

ᵇ1 mmol reaction scale.

Table 3.

Scope and limitations with regards to the boronic acid.
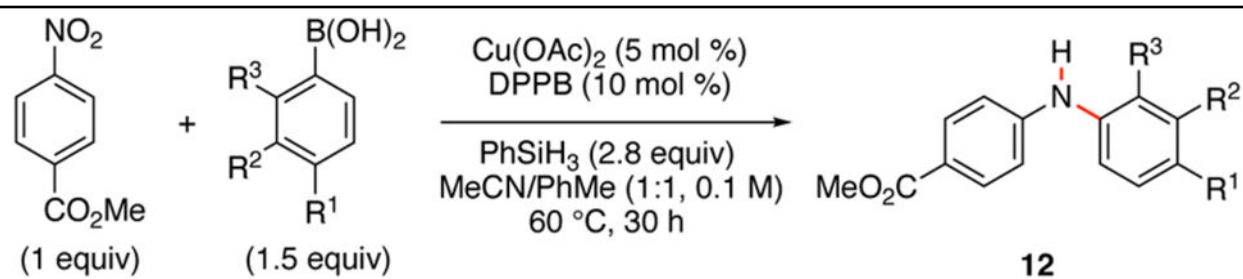
entry	R¹	R²	R³	13	yield %ᵃ
1	F₃C	H	H	a	90
2	F	H	H	b	97
3	Me	H	H	c	90
4	H	F	H	d	88
5	H	MeO	H	e	92
6	H	Me	H	f	88
7	H	H	MeO	g	85
8	H	H	Et	h	n.r.
9	H	–HC=CH–CH=CH–		i	83
10				j	59

ᵃIsolated after silica gel chromatography.