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Practical Catalytic Method for Synthesis of Sterically Hindered Anilines.

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A practical catalytic method for the synthesis of sterically hindered anilines is described. The amination of aryl and heteroaryl boronic esters is accomplished using a catalyst prepared in situ from commercially available and air-stable copper(I)triflate and diphosphine ligand. For the first time, the method can be applied to the synthesis of both secondary and tertiary anilines in the presence of a wide range of functional groups. Esters, aldehydes, alcohols, aryl halides, ketones, nitriles, and nitro arenes are all compatible with the reaction conditions. Finally, even the most sterically hindered anilines can be successfully prepared under mild reaction conditions. Overall, the new method addresses significant practical limitations of a transformation previously developed in our lab, and provides a valuable complement to the existing methods for the synthesis of anilines.

Aromatic and heteroaromatic amines have important applications in medicinal chemistry and the pharmaceutical industry.[1, 2] As a result, several catalytic transformations have been developed to facilitate access to this important class of organic compounds. The most general and commonly used are copper-catalyzed Ullman[3] and palladium-catalyzed Buchwald-Hartwig[4, 5] cross coupling reactions, which have an excellent scope and provide access to a wide range of anilines from readily available starting materials.[6-10] However, some important challenges remain. The most notable one is the synthesis of highly sterically hindered anilines, which are difficult to access using the common catalytic methods.[11]

There are very few methods useful for the synthesis of sterically hindered anilines. Knochel reported an oxidative coupling of aryl Grignard reagents with amines, using a stoichiometric amount of a copper salt and an oxidant.[12] Sterically hindered anilines can also be prepared in reactions of highly reactive benzyne intermediates.[13, 14] In a rare instance of a *catalytic* method used in the synthesis of hindered anilines, Johnson reported three examples of electrophilic amination of aryl zinc reagents by hindered electrophiles[15-18] This method requires the use of a significant excess (>2 equiv) of an aryl lithium reagent. Recently, we have reported a related catalytic method for electrophilic amination of aryl and heteroaryl boronic esters (Scheme 1).[19] Our method avoids the use of highly reactive intermediates, and allows the synthesis of a wide range of functionalized anilines, including iodo, bromo, or nitro anilines. Most importantly, our method proved to be well suited for the

synthesis of even the most sterically hindered anilines, such as compound **3**.

Unfortunately, several features of our method significantly limited its practical utility: 1) The pre-catalyst, (CuOt-Bu)$_4$, is hard to prepare,[20] is extremely air sensitive, and has to be handled in a glovebox; 2) The use of LiOt-Bu as a turnover reagent prevents the use of protic functional groups in either coupling partner; 3) The method can be used only in the synthesis of N,N-dialkyl anilines, and the synthesis of N-alkyl anilines is not possible. In this communication, we report a practical method for the synthesis of both secondary and tertiary sterically hindered anilines that addresses all of these limitations.

Scheme 1. Synthesis of sterically hindered anilines.

Previous work

neop = neopentyl glycol

80% yield
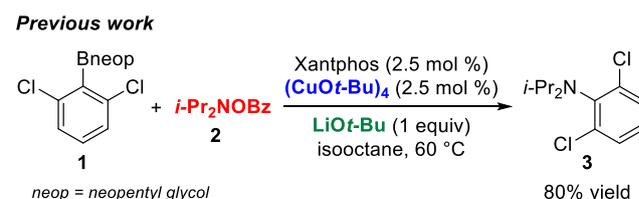
Limitations

(CuOt-Bu)$_4$	*extremely air and moisture sensitive, difficult synthesis*
LiOt-Bu	*strong base*
R$_2$NOBz	*limited to N,N-dialkyl-O-benzoylhydroxylamines*

In the reaction shown in Scheme 1, the choice of the catalyst precursor was dictated by the turnover reagent. Previously, we have shown that LiOt-Bu reacts with N,N-dialkyl-O-benzoylhydroxylamines at a significant rate in all but the highly nonpolar solvents, such as isooctane.[19] The low polarity of the solvent, in turn, severely limits the choice of a precatalyst. We found that in isooctane, (CuOt-Bu)$_4$ is uniquely effective as a precatalyst, although a small amount of toluene still had to be used to facilitate the preparation of the active catalyst. Based on this analysis of the problems associated with the reaction

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shown in Scheme 1, we focused on finding a new turnover reagent.

Table 1. Catalytic amination of aryl boronic esters.
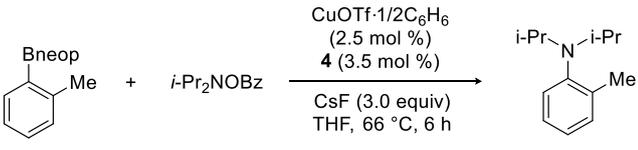
entry[a]	Change from the standard conditions	yield[b]
1.	none	96%
2.	[Cu(MeCN)$_4$]OTf instead CuOTf·1/2C$_6$H$_6$	79%
3.[c]	[Cu(MeCN)$_4$]BF$_4$ instead CuOTf·1/2C$_6$H$_6$	86%
4.[c]	CuCO$_3$ instead CuOTf·1/2C$_6$H$_6$	1%
5.	Cu(i-BuCO$_2$)$_2$ instead CuOTf·1/2C$_6$H$_6$	60%
6.	Xantphos instead **4**	84%
7.	BINAP instead **4**	<5%
8.	KF instead CsF	<5%
9.	2-Me-THF instead THF	95%
10.	1,4-dioxane instead THF	83%
11.	MeCN instead THF	16%
12.	Toluene instead THF	6%

[a] ArB(OR)$_2$ (1.2 equiv), BzONR$_2$ (1.0 equiv), neop = neopentyl glycol, [b] determined by GC, [c] 1.5 equivalent of sodium ascorbate used.
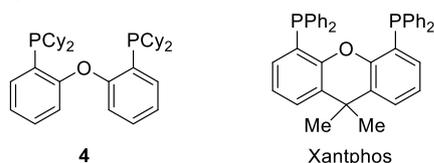
In a preliminary experiment, we found that CsF is compatible with *N,N*-dialkyl-*O*-benzoylated-hydroxylamines in a wide range of solvents, even at elevated temperatures. However, when CsF was used instead of LiO*t*-Bu as a turnover reagent in the reaction shown in Scheme 1, 72 h were required for complete conversion.[19] More importantly, no product formation occurred in reactions with a significant number of substrates. As a result, we decided to reinvestigate all aspects of the reaction and explore the electrophilic amination of aryl boronic esters using a wide range of copper precatalysts, in combination with a number of phosphine ligands, in several organic solvents. Through the standard optimization of the reaction parameters, we found that the best results are obtained using a catalyst prepared in situ from copper(I) triflate benzene complex and ligand **4**, in THF (Table 1).

During the reaction optimization we found that several other copper(I) salts can also serve as a catalyst precursor, although yields were generally lower. We also found that copper (II) salts can be used as precursors in the presence of sodium ascorbate. Interestingly, with copper(II) precursors there was a considerable induction period, suggesting that the reduction of copper(II) precursor may limit the overall rate of the reaction. Diphosphine ligand **4** and Xantphos ligand gave comparable results. However, other common bidentate phosphine ligands with a smaller bite angle, gave inferior results. Finally, in addition to THF, 2-Me-THF or 1,4-dioxane can also be used as a solvent, while the other common organic solvents gave inferior results.

The optimized reaction conditions proved to be quite general and could be used to prepare a wide range of aryl and heteroaryl anilines (Table 2). The reaction can be successfully performed in the presence of esters, nitriles, aldehydes, ketones, carbamates, iodo arenes, bromo arenes and nitro arenes. As demonstrated by the synthesis of compound **18**, even protic functional groups are compatible with the reaction conditions.

Table 2. Synthesis of tertiary amines.[a]

[a] Reactions performed on 0.5 mmol scale. Yields of isolated products are reported. neop = neopentyl glycol.

Heteroaromatic boronic esters, such as pyrrole, thiophene, pyrimidine, and pyridine boronic esters could also be successfully used in the reaction. Finally, even the extremely hindered anilines such as **19** are made in excellent yields and under relatively mild reaction conditions. It is also worth pointing out that the catalyst precursor, copper(I) triflate benzene complex, is commercially available and sufficiently stable to be weighted in air. Similarly, ligand **4** is commercially available and air stable. Overall, the reaction conditions described in Table 2 are practical and can be applied to a wide range of substrates.

We were especially interested in expanding the scope of this reaction to the synthesis of *N*-alkyl anilines. In previous attempts, using *N*-alkyl-*O*-benzoyl hydroxylamines as electrophiles we never observed the formation of the desired *N*-alkyl anilines; furthermore the reaction conditions described in Table 1 proved equally ineffective in the synthesis of secondary anilines.

We identified the presence of acidic protons in both the electrophile and the desired *N*-alkyl aniline products as a potential source of the problem. We further speculated that deprotonation of either the electrophile or the product by an aryl copper intermediate leads to the formation of a copper anilide and results in inactivation of the catalyst. To provide experimental evidence for this hypothesis, we exposed an isolated copper aryl complex **25** to *N-tert*-butyl-*O*-benzoyl hydroxylamine (Scheme 2). To our surprise, the stoichiometric reaction resulted in a formation of the desired *N*-alkyl aniline in excellent yield, indicating that the presence of acidic protons does not affect the C-N bond-forming step of the catalytic reaction.

Scheme 2. Stoichiometric synthesis of N-alkyl anilines.
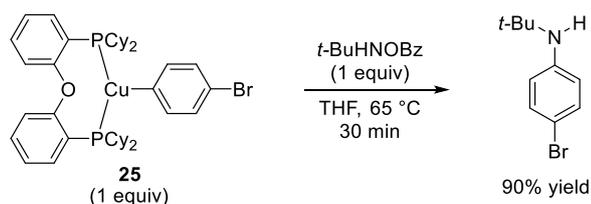
Intrigued by the result of the stoichiometric experiment, we decided to explore slow addition of the electrophile over the course of the reaction. We found that by adding *N*-alkyl-*O*-benzoyl hydroxylamine electrophiles to the reaction mixture over three hours, we can accomplish the desired transformation using the otherwise standard reaction conditions described in Table 2.

Table 3. Synthesis of secondary amines.[a]
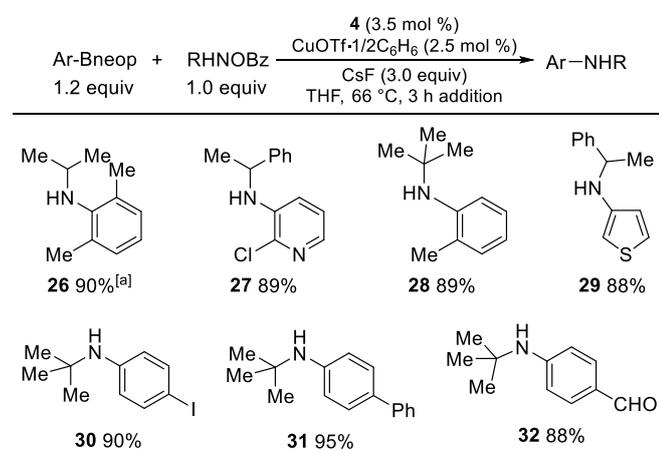
[a] Reactions performed on 0.5 mmol scale. Yields of isolated products are reported. neop = neopentyl glycol. See supporting information for a detailed experimental procedure.

As shown in Table 3, a range of hindered *N*-alkyl anilines and heteroanilines can be prepared using this procedure. Not surprisingly, the transformation can still be performed in the presence of sensitive functional groups, such as aryl iodides and aldehydes.

We propose that the catalytic amination of boronic esters proceeds according to the mechanism shown in Scheme 3. The formation of the copper fluoride complex from various other copper salts in the presence of CsF or KF has been demonstrated.[21, 22] Similarly, transmetalation involving copper fluoride complexes and organoboron compounds is well-documented, most notably by Shibasaki[23] and more recently by

Giri.[21] As a result, we focused on the C-N bond forming step of the reaction.

Scheme 3. Proposed mechanism.
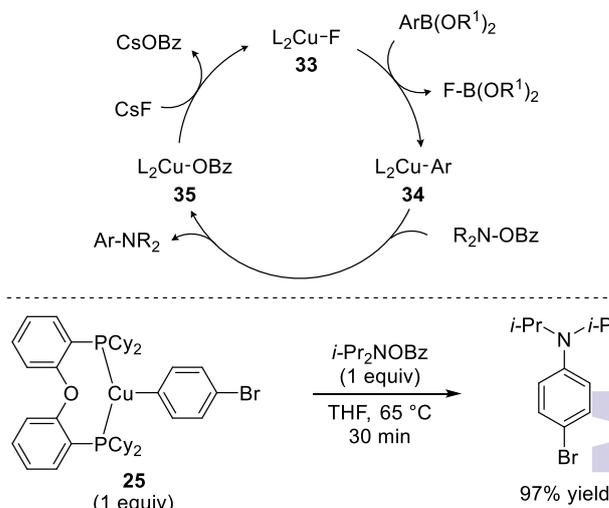
We showed that copper(I) aryl complexes supported by diphosphine ligands react with *N,N*-dialkyl-*O*-benzoyl hydroxylamines at 65 °C, and within 0.5 hours produces the expected aniline product in excellent yield (Scheme 3). The reaction shown in Scheme 2 demonstrates that the same stoichiometric reaction is feasible with *N*-alkyl-*O*-benzoyl hydroxylamines.
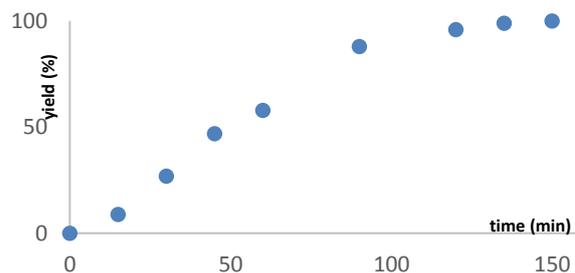

Figure 1. Yield of the aniline product as a function of time. Reaction conditions: 4-BrC$_6$H$_4$Bneop (1.2 equiv), *i*-Pr$_2$NOBz (1.0 equiv), CuOTf·1/2C$_6$H$_6$ (2.5 mol %), 4 (3.5 mol %), CsF (3 equiv), 80 °C, THF.

We have also explored the kinetics of the reaction. Initially, we monitored the change in the concentration of the product with time until the full conversion of the electrophile was achieved. Somewhat surprisingly, we found that the overall rate of the reaction does not significantly change during the course of the reaction (Figure 1). Furthermore, we found that the initial rate of the reaction does not depend on the concentration of either the aryl boronic ester or the concentration of the electrophile.[24] These observations are all consistent with the rate of the reaction being limited by the low solubility of CsF in organic solvents. In this scenario, the turnover limiting step of the catalytic cycle would be the formation of the copper fluoride intermediate **33**, and the catalyst resting state would be the copper benzoate intermediate **35**.

Conclusions

We have developed a practical method for the synthesis of highly sterically hindered anilines through electrophilic amination of aryl and heteroaryl boronic esters. The copper catalyst is prepared in situ from commercially available and air-stable precursors. The method can be applied to the synthesis of both secondary and tertiary anilines, and is compatible with a wide range of functional groups, including carboalkoxy, formyl, cyano, and hydroxyl. Furthermore, aryl iodides and aryl bromides are also compatible with the reaction conditions, making this method complementary to the other cross-coupling reactions commonly used in the synthesis of anilines. Finally, even the most sterically hindered anilines can be successfully made under relatively mild reaction conditions. Overall, the readily available catalyst precursors, mild reaction conditions and exceptionally broad substrate scope make this method a valuable tool for the synthesis of sterically hindered anilines.

Acknowledgements

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