

View Article Online View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Mailig, R. P. Rucker and G. Lalic, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC03565A.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/chemcomm

Melrose Mailig,^a Richard P. Rucker,^a and Gojko Lalic^{*a}

Journal Name

ARTICLE



Practical Catalytic Method for Synthesis of Sterically Hindered Anilines.

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A practical catalytic method for the synthesis of sterically hindered anilines is described. The amination of aryl and heteroar ytheoronic 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 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 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 Ullman³ 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 electrophiles¹⁵⁻¹⁸ 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 significant¹/ limited its practical utility: 1) The pre-catalyst, $(CuOt-Bu)_{4}$, is hard to prepare,²⁰ is extremely air sensitive, and has to k is handled in a glovebox; 2) The use of LiOt-Bu as a turnove, 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*-alk is anilines is not possible. In this communication, we report a practical method for the synthesis of both secondary an is tertiary sterically hindered anilines that addresses all of these limitations.

Scheme 1. Synthesis of sterically hindered anilines.

Previous work



LiOt-Bu strong base

R₂NOBz limited to N,N-dialkyl-O-benzoylhydroxylamines

In the reaction shown in Scheme 1, the choice of the cata vst precursor was dictated by the turnover reagent. Previously, vehave shown that LiOt-Bu reacts with *N*,*N*-dialkyl-*O*-benzo hydroxylamines at a significant rate in all but the high 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 precatalyst, although a small amount of toluene still had to be used to facilitate the preparation of the active catalyst. Base.¹ on this analysis of the problems associated with the reaction

 ^{a.} Department of Chemistry, Unioversity of Washington, Seattle, WA 98195, USA
 [†] Footnotes relating to the title and/or authors should appear here.
 Electronic Supplementary Information (ESI) available: Characterization data for all new compounds, experimental procedures. See DOI: 10.1039/x0xx00000x

Journal Name

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

 Table 1. Catalytic amination of aryl boronic esters.

ARTICIF

Bneop	+	<i>i</i> -Pr ₂ NOBz	CuOTf 1/2C ₆ H ₆ (2.5 mol %) 4 (3.5 mol %)	i-Pr _N -i-Pr Me
			CsF (3.0 equiv) THF, 66 °C, 6 h	

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>i</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), BzONR₂ (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 tgethine and could be used to prepare a wide wide solution of the successful heteroaryl anilines (Table 2). The reaction can be successful performed in the presence of esters, nitriles, aldehy is ketones, carbamates, iodo arenes, bromo arenes and nitriarenes. 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 by successfully used in the reaction. Finally, even the extreme. / hindered anilines such as **19** are made in excellent yields and under relatively mild reaction conditions. It is also wort i pointing out that the catalyst precursor, copper(I) triflat : benzene complex, is commercially available and sufficientry stable to be weighted in air. Similarly, ligand **4** is commercial' available and air stable. Overall, the reaction condition. described in Table 2 are practical and can be applied to a wⁱ 'e 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 attemption attemption

2 | J. Name., 2012, 00, 1-3

This journal is © The Royal Society of Chemistry 20xx

Journal Name

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 welldocumented, most notably by Shibasaki²³ and more recently by Giri.²¹ As a result, we focused on the C-N bond forming stepline the reaction. DOI: 10.1039/C5CC03565A Scheme 3. Proposed mechanism.



We showed that copper(I) aryl complexes supported or diphosphine ligands react with N,N-dialkyl-O-benzov 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-benzov hydroxylamines.



Figure 1. Yield of the aniline product as a function of time. Reaction conditions: 4-BrC₆H₄Bneop (1.2 equiv), *i*-Pr₂NOBz (1.0 equiv), CuOT^f $1/2C_6H_6$ (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 achiever. 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 organisolvents. In this scenario, the turnover limiting step of the catalytic cycle would be the formation of the copper fluorid intermediate **33**, and the catalyst resting state would be the copper benzoate intermediate **35**.

Conclusions

This journal is © The Royal Society of Chemistry 20xx

Journal Name

DOI: 10.1039/C5CC03565A

ARTICLE

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 airstable 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

Financial support by NSF (NSF CAREER award #1254636) is gratefully aknowledged.

Notes and references

- 1 B. Schlummer and U. Scholz, Adv. Synth. Catal., 2004, 346, 1599-1626.
- J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, Org. 2 Biomol. Chem., 2006, 4, 2337-2347.
- 3 F. Ullmann, Ber. Dtsch. Chem. Ges., 1903, 36, 2382.
- 4 A. S. Guram, R. A. Rennels and S. L. Buchwald, Angew. Chem. Int. Ed., 1995, 34, 1348-1350.
- J. Louie and J. F. Hartwig, Tetrahedron Lett., 1995, 36, 3609-5 3612.
- S. V. Ley and A. W. Thomas, Angew. Chem. Int. Ed., 2003, 42, 6 5400-5449.
- F. Monnier and M. Taillefer, Angew. Chem. Int. Ed., 2009, 48, 7 6954-6971.
- D. S. Surry and S. L. Buchwald, Angew. Chem. Int. Ed., 2008, 8 **47**, 6338-6361.
- 9 D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura and S. L. Buchwald, Chem. Sci., 2011, 2, 57-68.
- 10 J. F. Hartwig, Acc. Chem. Res., 2008, 41, 1534-1544.
- 11 For state-of-the-art in synthesis of sterically hindered anilines see: P. Ruiz-Castillo, D. G. Blackmond and S. L. Buchwald, J. Am. Chem. Soc., 2015, 3085-3092.
- 12 A. V. Del, S. R. Dubbaka, A. Krasovskiy and P. Knochel, Angew. Chem. Int. Ed., 2006, 45, 7838-7842.
- 13 E. R. Biehl, S. M. Smith and P. C. Reeves, J. Org. Chem., 1971, 36. 1841-1842.
- 14 J. L. Bolliger and C. M. Frech, Tetrahedron, 2009, 65, 1180-1187.
- 15 A. M. Berman and J. S. Johnson, J. Am. Chem. Soc., 2004, 126, 5680-5681.
- 16 A. M. Berman and J. S. Johnson, J. Org. Chem., 2006, 71, 219-224

15598-15599.

53. 6473-6476. 23 R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai and N. Shibasaki, J. Am. Chem. Soc., 2006, 128, 7687-7691.

17 T. J. Barker and E. R. Jarvo, J. Am. Chem. Socyiev2009.

18 C. Zhu, G. Li, D. H. Ess, J. R. Falck and L. Kürti, J. Am. Chen

19 R. P. Rucker, A. M. Whittaker, H. Dang and G. Lalic, Angev.

20 T. H. Lemmen, G. V. Goeden, J. C. Huffman, R. L. Geerts and

G. Caulton, Inorg. Chem., 1990, 29, 3680-3685.

Soc., 2012, 134, 18253-18256.

Lett., 2014, 16, 1264-1267.

Chem. Int. Ed., 2012, 51, 3953-3956.

24 For a more detailed description of the results, see ESI.

²² H. Dang, M. Mailig and G. Lalic, Angew. Chem. Int. Ed., 2014.