CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Cu-Catalyzed Desulfonylative Amination of Benzhydryl Sulfones

Authors: Cathleen Marie Crudden, Masakazu Nambo, Yasuyo Tahara, and Jacky C.-H. Yim

To be cited as: *Chem. Eur. J.* 10.1002/chem.201805638

Link to VoR: http://dx.doi.org/10.1002/chem.201805638

Supported by
ACES

WILEY-VCH

10.1002/chem.201805638

COMMUNICATION

WILEY-VCH

Cu-Catalyzed Desulfonylative Amination of Benzhydryl Sulfones

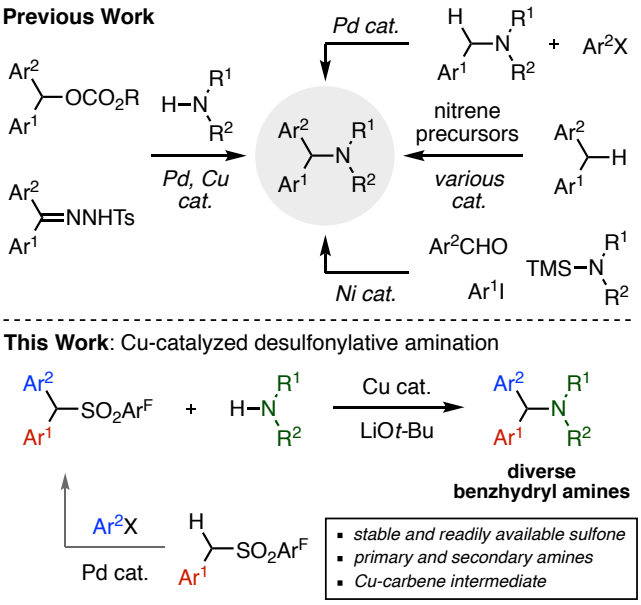
Masakazu Nambo,*[a] Yasuyo Tahara,[a,+] Jacky C.-H. Yim,[a,+] and Cathleen M. Crudden*[a,b]

Abstract: A new method for the synthesis of benzhydryl amines from the reaction of readily available sulfone derivatives with amines is described. The Cu-catalyzed desulfonylative amination not only provides structurally diverse benzhydryl amines in good yields, but is also applicable to iterative and intramolecular aminations. Control experiments suggest the formation of a Cu-carbene intermediate generated from the sulfone substrate, which represents a novel route for desulfonylative transformations.

Methods for the construction of carbon–nitrogen bonds are highly valuable in organic chemistry since amines are frequently found in biologically active molecules.[1] Remarkable progress has been made in the development of catalytic amination reactions, providing useful synthetic strategies routes to complex amine compounds from simple building blocks.[2] Among amine derivatives, the benzhydryl amine is an attractive structural motif that possesses unique biological activities.[3] However, synthetic approaches to this class of molecules still rely heavily on classical methods such as S_N2 reactions on benzhydryl halides with amines, which requires the preparation of relatively unstable and toxic benzhydryl halides. Although reductive amination of diarylketones[4] and nucleophilic addition of organometallic reagents to aldimines[5] are potential alternatives, these methods are not effective for secondary amines due to slow formation of iminium intermediates.[6]

To address these challenges, new synthetic routes have been developed using transition-metal catalyzed cross-coupling[7,8], reductive coupling[9], and C–H amination reactions[10] Recently, Doyle reported an elegant Ni-catalyzed three-component coupling of benzaldehydes, arylhalides, and *N*-silylamines to afford unsymmetric benzhydryl amines.[11] In this communication, we describe new synthetic approach to these important structures that does not require the use of any sensitive reagents or the multistep preparation of the benzhydryl precursors.

Recently, we have developed cross-coupling reactions using benzylic sulfone derivatives as a new class of electrophile in which carbon–sulfonyl bond activation can be accomplished via Pd and Ni catalysis.[12] One significant advantage of sulfone-based electrophiles is that the strongly electron-withdrawing sulfonyl group can direct α-functionalization of simple and readily available sulfone derivatives, permitting the facile preparation of benzylic electrophiles without additional synthetic steps. Activated sulfones bearing 3,5-bis(trifluoromethyl)phenyl sulfones undergo mild desulfonylative cross-coupling reactions to afford multiply-arylated methanes in minimal synthetic steps.[12b] Herein we report the use of inexpensive Cu salts to catalyze desulfonylative aminations yielding benzhydryl amine derivatives in good to excellent yields. A variety of benzhydryl sulfones and amines can be employed, and iterative and intramolecular aminations rapidly afford valuable amine compounds. Control experiments suggest the generation of an electrophilic Cu-carbene as a key intermediate.



Scheme 1. Synthesis of Benzhydryl Amine Derivatives by Transition Metal Catalysis.

We began our investigation by studying the desulfonylative amination of benzhydryl 3,5-bis(trifluoromethyl)phenyl sulfone **1a** with morpholine **2a** as a model reaction (Table 1). In early experiments using LiO*t*-Bu as a base, we found that Pd catalysts, which were effective for desulfonylative cross-coupling reactions in our previous studies[12a-c], did not give any amination product. However, the use of 20 mol % CuCl as a catalyst gave the amination product **3aa** in 81% yield (entry 1). Other Cu(I) salts and $CuCl_2$ were found to be less reactive than CuCl (entries 2-5). Additionally, the presence of common ligands such as 2,2'-bipyridyl (bpy) and *N*-heterocyclic carbene (SIPr) inhibited product formation (entries 6, 7). The effect of the counter cation of the base was crucial: when NaO*t*-Bu and KO*t*-Bu were used instead of LiO*t*-Bu, product yields were significantly decreased (entries 8, 9).

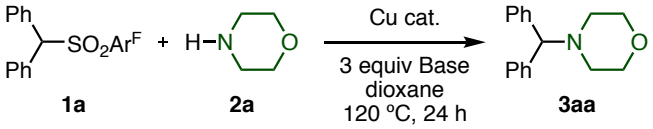
Settling on CuCl and LiO*t*-Bu, we were able to improve the yield to 90% by conducting the reaction at a higher

[a] Prof. Dr. M. Nambo, Y. Tahara, Dr. J. C.-H. Yim, Prof. Dr. C. M. Crudden
Institute of Transformative Bio-Molecules (WPI-ITbM)
Nagoya University, Chikusa, Nagoya, 464-8602 (Japan)
E-mail: mnambo@itbm.nagoya-u.ac.jp
cruddenc@chem.queensu.ca
[b] Prof. Dr. C. M. Crudden
Department of Chemistry
Queen's University, Chernoff Hall, Kingston, Ontario, K7L 3N6 (Canada)
[+] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

concentration (entry 10). Decreasing catalyst loading or lowering the reaction temperature diminished the yield (entries 11, 12), thus 20 mol % CuCl at 120 ºC was selected as our optimal reaction conditions. Finally, benzhydryl phenyl sulfone showed low conversion (entry 13), indicating that 3,5-bis(trifluoromethyl)phenyl group functions is more reactive.

Table 1. Optimization of Cu-catalyzed desulfonylative amination of diphenylmethyl sulfone **1a** with morpholine **2a** (Ar^F = 3,5-$(CF_3)_2C_6H_3$).[a]



1a **2a** **3aa**

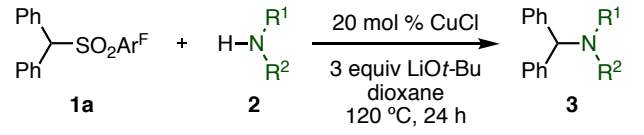
Entry	Cu cat.	Base	Yield [%][b]
1	CuCl	LiO*t*-Bu	81
2	CuBr	LiO*t*-Bu	73
3	CuI	LiO*t*-Bu	27
4	CuOAc	LiO*t*-Bu	72
5	$CuCl_2$	LiO*t*-Bu	52
6	CuCl / bpy	LiO*t*-Bu	33
7	Cu(SIPr)Cl	LiO*t*-Bu	18
8	CuCl	NaO*t*-Bu	8
9	CuCl	KO*t*-Bu	23
10[c]	CuCl	LiO*t*-Bu	90 (89)[d]
11[c,e]	CuCl	LiO*t*-Bu	76
12[c,f]	CuCl	LiO*t*-Bu	62
13[c,g]	CuCl	LiO*t*-Bu	52

[a] Conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), Cu catalyst (20 mol %), ligand (20 mol %), base (3.0 equiv), dioxane (0.33 M). [b] Yields were determined by GC using dodecane as an internal standard. [c] Concentration was 0.5 M. [d] Isolated yield (0.2 mmol scale). [e] 10 mol % of CuCl was used. [f] Reaction was conducted at 100 °C. [g] Benzhydryl phenyl sulfone was used instead of **1a**.

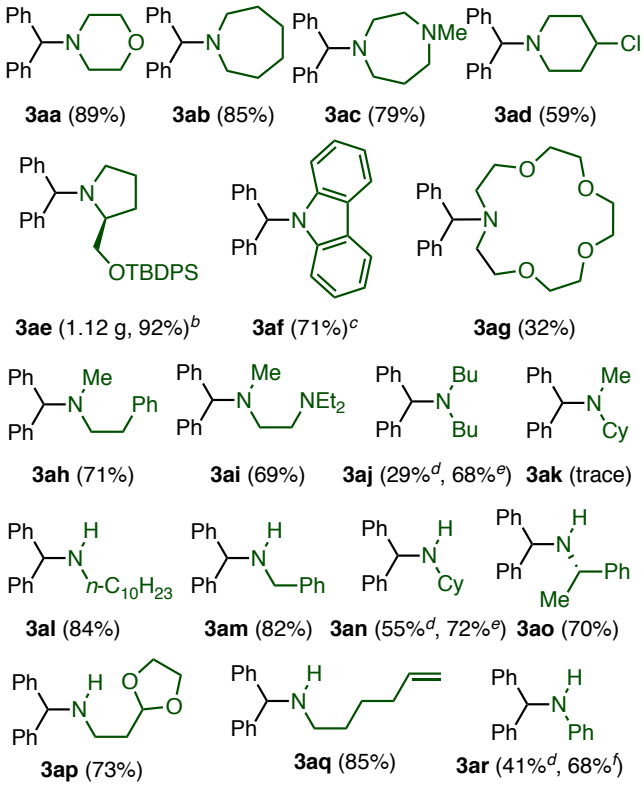
With optimized reaction conditions in hand, the scope of amines was investigated (Table 2). A variety of cyclic amines (**2a**-**e**) were reacted to give the corresponding products in high yields. Notably, compound **3ae** could be produced on gram scale in excellent yield. Carbazole **2f** could also be coupled and even aza-crown ether **2g** afforded the amination product **3ag**, albeit in low yield. Acyclic secondary amines (**2h**-**j**) were also reactive, however dibutylamine **2j** required an excess of amine and base, and the reaction with the more bulky *N*-methylcyclohexylamine **2k** did not afford the desired product.

Primary amines (**2l**-**q**) could also be employed, but aniline **2r** gave a mixture of amination product **3ar** and the corresponding imine. Fortunately, we found that by substituting DPEphos as the ligand and toluene as solvent we could suppress formation of the undesired imine, improving the yield to 68% (See Supporting Information).[9b] With regards to functional groups, protected alcohol, chloro, acetal, and olefin moieties were found to be compatible.

Table 2. Scope of Cu-catalyzed desulfonylative amination of **1a** with amine **2** (Ar^F = 3,5-$(CF_3)_2C_6H_3$).[a]



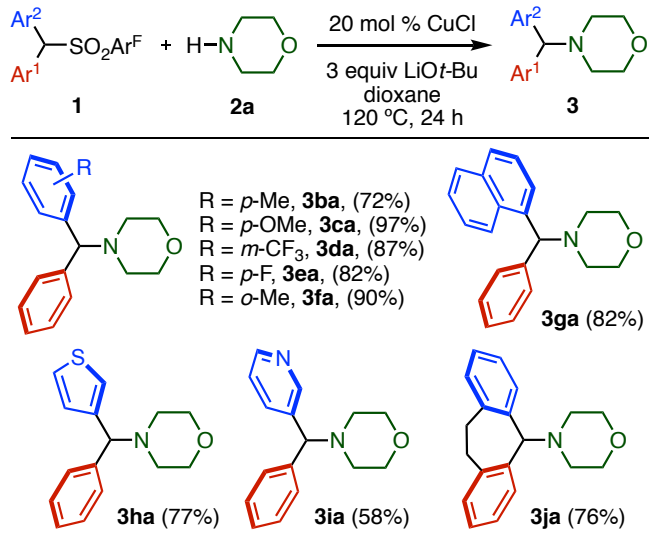
1a **2** **3**



[a] Conditions: **1a** (0.2 mmol), **2** (2.0 equiv), CuCl (20 mol %), LiO*t*-Bu (3.0 equiv), dioxane (0.5 M), 120 ºC, 24 h. Isolated yield was given in parentheses. [b] 2.4 mmol scale. [c] 1.2 equiv of amine was used. [d] Yields were determined by GC using dodecane as an internal standard. [e] 3 equiv of amine and 4 equiv of base were used. [f] DPEphos (20 mol %) and 4 equiv of base were used and reaction was conducted in toluene (0.5 M).

Various sulfone derivatives were easily prepared via Pd-catalyzed α-arylation, and were employed in amination reactions with morpholine **2a** (Table 3). Sulfones bearing electron-donating (**1b**, **1c**) and electron-withdrawing groups (**1d**, **1e**) on one of the arenes reacted with **2a** to afford the corresponding products in high yield. The bulky *o*-tolyl (**1f**) and 1-naphthyl (**1g**) substituents and heteroaromatics such as 3-thienyl (**1h**) and 3-pyridyl (**1i**) were well-tolerated. Interestingly, the dibenzosuberyl group (**1j**), which is important pharmacophore in medicinal chemistry, could be employed in this amination.

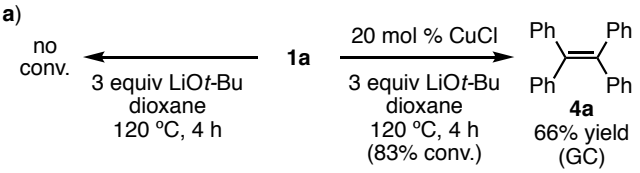
Table 3. Scope of Cu-catalyzed desulfonylative amination of **1** with amine **2a** (Ar^F = 3,5-$(CF_3)_2C_6H_3$).[a]



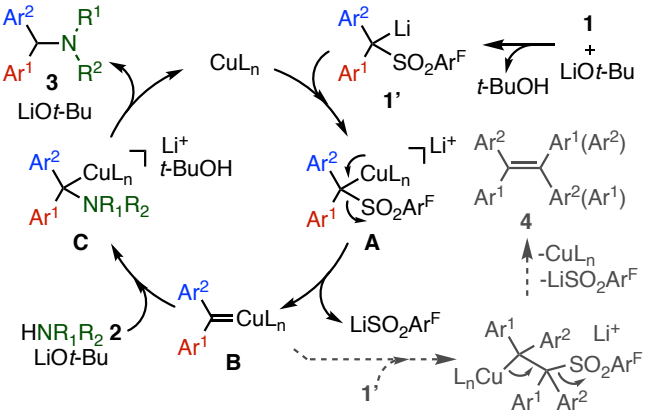
[a] Conditions: **1a** (0.1 mmol), **2** (2.0 equiv), CuCl (20 mol %), LiO*t*-Bu (3.0 equiv), dioxane (0.5 M), 120 °C, 24 h. Isolated yield was given in parentheses.

To gain insight into the Cu-catalyzed desulfonylative amination, several control experiments were carried out. During optimization of the reaction of **1a** with **2a**, we observed tetraphenylethylene **4a** as a by-product. In the absence of amine **2a**, **4a** was formed in 66% GC yield from **1a** (Scheme 2a). In addition, no conversion was observed with base alone, suggesting that a Cu-stabilized carbene intermediate rather than the free-carbene species would be generated from CuCl and α-lithiated **1a**. The Wang group reported the Cu-catalyzed olefination of *N*-sulfonylhydrazones with sulfones, which is proposed to proceed via Cu-carbene species.[13] From the similarities with our reaction conditions, we hypothesized that a similar olefination would occur if the Cu-carbene intermediate is formed from sulfones instead of hydrazones. To examine this hypothesis, we reacted sulfone **1a** with *p*-tolylmethyl phenyl sulfone **5** under our standard conditions (Scheme 2b). This reaction proceeded to give the expected olefination product **6** along with **4a** in 34% and 11% yields, respectively. As dimerization of **5** did not occur, the reaction likely proceeds by preferential generation of Cu- carbene species derived from **1a**, which then reacts with α-lithiated **5** or **1a**. Subsequent desulfination yields **6** or **4a**, respectively.

The proposed catalytic cycle is shown in Scheme 3. Initially, α-lithiated **1** reacts with the Cu catalyst to form species **A**, which then undergoes desulfination to generate Cu-carbene intermediate **B**. Subsequently, the attack of amine **2** on the electrophilic carbene center of **B** forms **C**. Protonation of **C** gives the amination product **3** and regenerates the Cu catalyst. As a side reaction pathway, **B** can react with α-lithiated **1** followed by desulfination to give the olefin **4**.



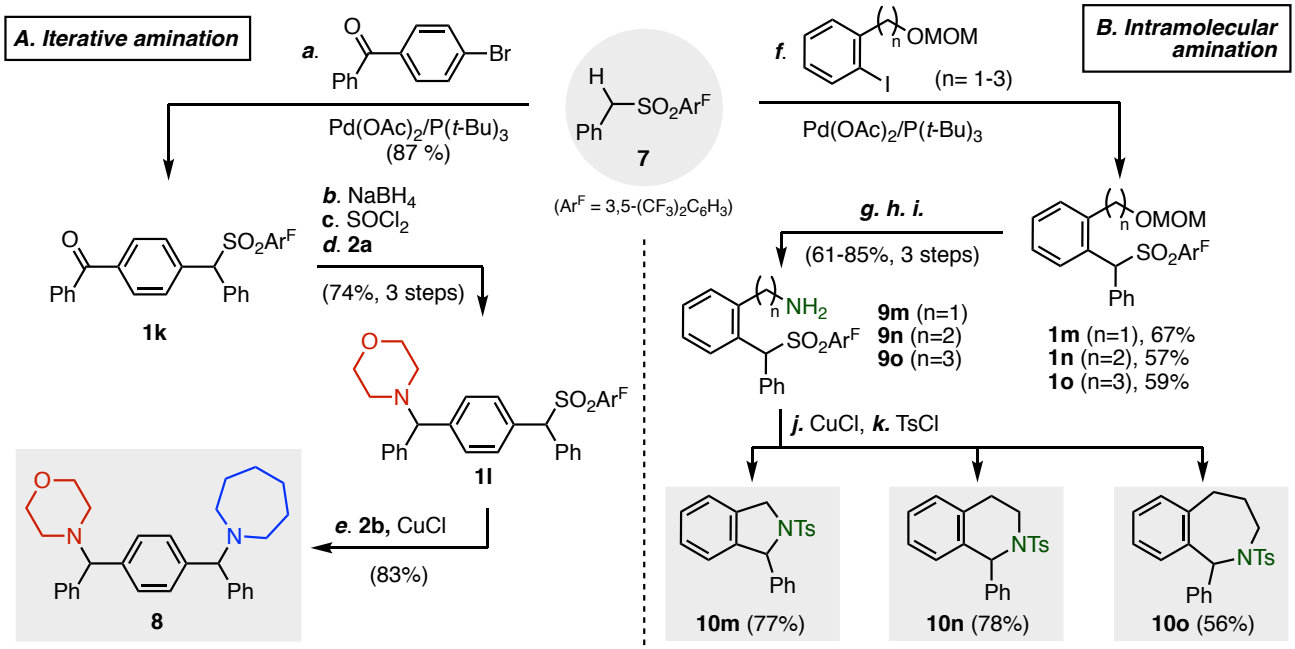
Scheme 2. Control experiments (Ar^F = 3,5-$(CF_3)_2C_6H_3$).[a]



Scheme 3. Proposed catalytic cycle.

Finally, we demonstrated the synthetic utility of this method by employing the α-arylation of benzylsulfones for the concise synthesis of complex amine derivatives (Scheme 4). Iterative amination was carried out using *p*-benzoylbenzhydryl sulfone derivative **1k**, which was easily prepared by the Pd-catalyzed α-arylation of benzyl sulfone **7** (Scheme 4A). Compound **1k** could be converted into **1l** by classical methods without affecting the sulfonyl group. Subsequently, a Cu-catalyzed desulfonylative amination of **1l** with **2b** to give unsymmetric diamine **8**.

Our method can also be employed in an intramolecular sense, leading to the formation of cyclic amines (Scheme 4B). Benzhydryl sulfone derivatives bearing an amino group with different alkyl tether lengths (**9m-o**) by Pd-catalyzed α-arylation of benzyl sulfone **7** with iodoarenes followed by transformation of methoxymethoxy group to amino group. Under standard conditions, compounds **9m-o** were reacted to give various cyclic amines, which were isolated as the corresponding *N*-tosylated products (**10m-o**) in good yields. These results indicate that this method can rapidly provide a variety of functionalized amines, such as **8** and **10**, which are difficult to synthesize by only typical amination processes in short steps.



Scheme 4. Synthetic Applications. Condition: (a) ArBr, $Pd(OAc)_2$, P(*t*-Bu)$_3$, Cs_2CO_3, CPME, 125 °C; (b) $NaBH_4$, THF/MeOH, rt; (c) $SOCl_2$, CH_2Cl_2, 50 °C; (d) **2a**, MeCN, reflux; (e) **2b**, CuCl, LiO*t*-Bu, dioxane, 120 °C; (f) ArI, $Pd(OAc)_2$, P(*t*-Bu)$_3$, Cs_2CO_3, CPME, 145 °C; (g) HCl*aq*, THF/MeOH, 70 °C; (h) phthalimide, PPh_3, DIAD, THF/toluene, rt; (i) hydrazine, EtOH, 80 °C; (j) CuCl, LiO*t*-Bu, dioxane, 120 °C; (k) TsCl, NaOH, CH_2Cl_2/H_2O, rt.

In summary, we have developed a new synthetic method for the preparation of benzhydryl amines by a Cu-catalyzed desulfonylative amination. This strategy represents a novel, modular route for the preparation of biologically active benzhydryl amines. The possibility of generating a reactive Cu-carbene species from stable and readily accessible sulfone derivatives, leading to the exploration of new types of desulfonylative reactions will provide new routes to a variety of complex molecules. Mechanistic investigations and the development of new transformations of organosulfones are ongoing in our laboratory.

Acknowledgements

This work was supported by KAKENHI from JSPS (17K17805 to M.N.). M.N. thanks the Ichihara International Scholarship Foundation for financial support. JSPS and NU are acknowledged for funding of this research through The World Premier International Research Center Initiative (WPI) program.

Conflict of Interest

The authors declare no conflict of interest

Keywords: Desulfonylative Amination • Cu Catalysis • Sulfone • Cu-carbene • Benzhydrylamine

[1] A. Ricci, Amino Group Chemistry: From Synthesis to the Life Sciences; Wiley-VCH: Weinheim, 2008.

[2] Reviews: a) I. P. Beletskaya, A. V. Cheprakov, *Organometallics* **2012**, *31*, 7753–7808. b) P. Ruiz-Castillo, Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564–12649. c) P. Subramanian, G. C. Rudolf, K. P. Kaliappan, *Chem Asian J.* **2016**, *11*, 168–192. d) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301.

[3] a) A. S. Bhatnagar, A. Haüsler, K. Schieweck, M. Lang, R. Bowman, *J. Steroid Biochem. Mol. Biol.* **1990**, *37*, 1021−1027. b) K.-J. Chang, G. C. Rigdon, J. L. Howard, R. W. McNutt, *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852−857. c) M. Kato, K. Komoda, A. Namera, Y. Sakai, S. Okada, A. Yamada, K. Yokoyama, E. Migita, Y. Minobe, T. Tani, *Chem. Pharm. Bull.* **1997**, *45*, 1767–1776. d) H. Hata, N. Toriu, M. Shimazawa, *Cardiovasc. Drug Rev.* **2004**, *22*, 199–214.

[4] Reviews: a) S. Gomez, J. Peter, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037–1057. b) A. F. Abdel-Magid, S. J. Mehrman, *Org. Process Res. Dev.* **2006**, *10*, 971–1031.

[5] For reviews of addition of organoboron reagents to imines, see: a) C. S. Marques, A. J. Burke, *ChemCatChem* **2011**, *3*, 635–645. Selected other examples, see: b) T. Hayashi, M. Ishigedani, *J. Am. Chem. Soc.* **2000**, *122*, 976–977. c) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694; *Angew. Chem.* **2002**, *114*, 3844–3846. d) E. L. Gall, A. Pignon, T. Martens, *Beilstein J. Org. Chem.* **2011**, *7*, 997–1002.

[6] For syntheses of benzhydrylamines by use of organometallic reagents, see: a) H. Böhme, P. Plappert, *Chem. Ber.* **1975**, *108*, 2827−2833. b) T. Murai, F. Asai, *J. Am. Chem. Soc.* **2007**, *129*, 780−781. c) L.-G. Xie, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 7492−7497.

[7] a) G. I. McGrew, C. Stanciu, J. Zhang, P. J. Carroll, S. D. Dreher, P. J. Walsh, *Angew. Chem., Int. Ed.* **2012**, *51*, 11510–11513; *Angew. Chem.* **2012**, *124*, 11678–11681. b) M. Li, B. Yücel, J. Adrio, A. Bellomo, P. J. Walsh, *Chem. Sci.* **2014**, *5*, 2383–2391. c) B. S. Kim, J. Jiménez, F. Gao, P. J. Walsh, *Org. Lett.* **2015**, *17*, 5788–5791. d) G. Gao, Y. Fu, M. Li, B. Wang, B. Zheng, S. Hou, P. J. Walsh, *Adv. Synth. Catal.* **2017**, *359*, 2890–2894.

[8] A. Najib, K. Hirano, M. Miura, *Org. Lett.* **2017**, *19*, 2438–2441.

[9] a) A. Hamze, B. Tréguier, J.-D. Brion, M. Alami, *Org. Biomol. Chem.* **2011**, *9*, 6200–6204. b) J. Aziz, J.-D. Brion, A. Hamze, M. Alami, *Adv. Synth. Catal.* **2013**, *355*, 2417–2429. c) L. Ling, J. Cao, J. Hu, H. Zhang, *RSC Adv.* **2017**, *7*, 27974–27980.

[10] For recent example of C–H amination, see: a) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7652-7655. b) Y. Zhang, B. Feng, C. Zhu, *Org. Biomol. Chem.* **2012**, *10*, 9137–9141. b) H. Wang, G. Tang, X. Li, *Angew. Chem. Int. Ed.* **2015,** *54,* 13049–13052; *Angew. Chem.* **2015**, *127*, 13241–13244. c) A. Wang, N. J. Venditto, W. Darcy, J. M. H. Emmert, *Organometallics* **2017**, *36*,

1259–1268. d) H. Wang, D. Zhang, C. Bolm, *Angew. Chem. Int. Ed.* **2018,** *57,* 5863–5866; *Angew. Chem.* **2018**, *130*, 5965–5968.

[11] C. Heinz, J. P. Lutz, E. M. Simmons, M. M. Miller, W. R. Ewing, A. G. Doyle, *J. Am. Chem. Soc.* **2018**, *140*, 2292–2300.

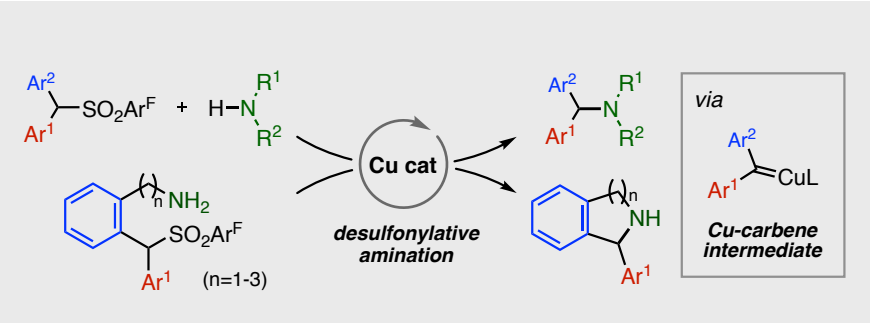
[12] a) M. Nambo, C. M. Crudden, *Angew. Chem. Int. Ed.* **2014,** *53,* 742–746; *Angew. Chem.* **2014**, *126*, 761–765. b) M. Nambo, E. C. Keske, J. P. G. Rygus, J. C.-H. Yim, C. M. Crudden, *ACS Catal.* **2017,** *7*, 1108–1112. c) J. C.-H. Yim, M. Nambo, C. M. Crudden, *Org. Lett.* **2017**, *19*, 3715–2342. d) Z. T. Ariki, Y. Maekawa, M. Nambo, C. M. Crudden, *J. Am. Chem. Soc.* **2018**, *140*, 78–81.

[13] S. Xu, Y. Gao, R. Chen, K. Wang, Y. Zhang, J. Wang, *Chem. Commun.* **2016**, *52*, 4478–4480.

10.1002/chem.201805638

WILEY-VCH

COMMUNICATION



*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title