

## Copper(I)-Catalyzed Amidation Reaction of Organoboronic Esters and Isocyanates

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**A simple and efficient methodology for the preparation of amides from easily available organoboronic esters and isocyanates has been accomplished using cost-effective copper(I) catalyst. The reaction system demonstrated excellent functional group tolerance and provided convenient access to a wide variety of secondary amides.**

Amide bonds are one of the most important chemical building blocks in nature. Not only do they constitute the backbone of peptides and proteins, but they are also found extensively in synthetic polymers, fine chemicals and pharmaceutically active molecules.<sup>[1]</sup> Despite their ubiquity, most amides are prepared through the traditional approach of condensation reaction between carboxylic acids and amine in the presence of stoichiometric amounts of coupling reagents, making the overall process wasteful and expensive.<sup>[2,3]</sup> It is therefore not surprising that a catalytic and more atom-economical approach for amide formation was recently highlighted as the top challenge in green chemistry research.<sup>[4]</sup> Aside from economic and environmental concerns, the preparation of sterically-hindered and electron-deficient amides from carboxylic acid-amine condensation is also widely recognized to be a long-standing challenge.<sup>[5]</sup>

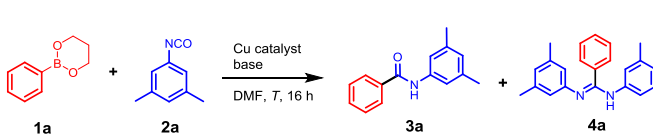
In recent years, there have been significant efforts to explore more atom-economical reaction pathways for amide synthesis from different starting materials using transition metals as the catalysts.<sup>[3, 6-12]</sup> More recently, the use of organoboron reagents in transition metal-catalyzed addition reactions with isocyanates to form secondary amides has been developed.<sup>[13]</sup> These reactions are particularly useful for the synthesis of various functionalized amides because of the wide availability of organoboron reagents with different functional groups, and new protocols for their convenient preparation without the use of highly reactive Grignard or

organolithium reagents.<sup>[14]</sup> In addition, organoborons are non-toxic and highly stable.<sup>[15-16]</sup> However, the activation of organoboron reagents in amidation reactions has thus far been the domain of precious rhodium<sup>[13a]</sup> and palladium<sup>[13b]</sup> catalysts, thereby limiting its industrial applications. Furthermore, in Rh or Pd catalyst systems, organoboron homo-coupling side reaction is unavoidable, leading to the use of a large excess of organoboron reagents for the Rh system and low amide yield in Pd system.<sup>[13]</sup> The preparation of sterically-hindered and electron-deficient amides in synthetically-useful yields is also difficult to achieve with these precious metal catalyst systems. On the other hand, the use of cost-effective and environmentally-benign first row transition metals such as copper as catalysts for amidation reactions has attracted great attention.<sup>[17]</sup> Herein we report an efficient copper-catalyzed system for an amidation reaction between arylboronates and isocyanates. Some of the notable features of our approach include: 1) the use of cheap and earth-abundant copper catalysts, 2) broad substrate scope of both arylboronates and isocyanates, which includes sterically-encumbered and electron-deficient substrates, and 3) suppression of organoboron homo-coupling side reaction.

We began our investigation by using phenylboronic 1,3-propanediol ester (**1a**) and 3,5-dimethylphenyl isocyanate (**2a**) as the model substrates for the amidation reaction. It was encouraging to find that in the presence of IPrCuCl (10 mol%), NaOt-Bu (1 equiv.) and DMF (2 mL) at 120 °C, the desired product (**3a**) was detected after 16 hours, albeit in a low yield (Table 1, entry 1). Two of the notable side products which were observed are amidine **4a** and the carbamate formed from the reaction between **2a** and NaOt-Bu. As the reaction time was extended to 48 h, the carbamate intermediate was consumed and this was accompanied by a substantial increase in the amide yield. When the reaction temperature was increased to 140 °C, the yield of amide **3a** increased significantly (Table 1, entry 2) while there was only trace amount of carbamate detected. This suggests that the carbamate formation is reversible and that it decomposes at extended reaction time or higher temperature to give **2a** and the base. However, at temperatures above 140 °C (Table 1, entry 3), isocyanate **2a** decomposes through reaction with DMF.<sup>[18]</sup> No phenylboronic ester homo-coupling side product (biphenyl) was observed in the reaction mixture.

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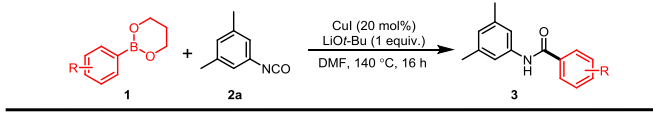
**Table 1** Optimization of reaction conditions for Cu-catalyzed amidation of organoboronate ester and isocyanate<sup>a</sup>


Entry	Catalyst (mol%)	Base	T (°C)	Yield <b>3a</b> (%) <sup>b</sup>
1	(IPr)CuCl (10)	NaOt-Bu	120	16
2	(IPr)CuCl (10)	NaOt-Bu	140	34
3	(IPr)CuCl (10)	NaOt-Bu	160	23
4	CuCl (10)	NaOt-Bu	140	40
5	CuCl (20)	NaOt-Bu	140	53
6	CuI (20)	NaOt-Bu	140	60
7	CuCN (20)	NaOt-Bu	140	52
8	CuOAc (20)	NaOt-Bu	140	34
9	CuCl <sub>2</sub> (20)	NaOt-Bu	140	35
10	CuBr <sub>2</sub> (20)	NaOt-Bu	140	15
11	CuI (20)	LiOt-Bu	140	64
12	CuI (20)	KOt-Bu	140	-
13	CuI (20)	LiOMe	140	45
14	CuI (20)	CsF	140	17
15	CuI (20)	KF	140	42
16	CuI (20)	Cs <sub>2</sub> CO <sub>3</sub>	140	-
17	CuI (20)	K <sub>3</sub> PO <sub>4</sub>	140	-
18 <sup>c</sup>	<b>CuI (20)</b>	<b>LiOt-Bu</b>	<b>140</b>	<b>82</b>
19	CuI (20)	-	140	-
20	-	LiOt-Bu	140	-

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base (0.5 mmol), DMF (2 mL), 16 h, Ar atmosphere, unless otherwise noted. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> Reaction was carried out using 1.5 equivalents (0.75 mmol) of **1a**.

Various copper catalysts were then screened. To our delight, ligand-free CuI catalyst was found to be the most efficient catalyst for this reaction and the formation of amidine **4a** was significantly suppressed (Table 1, entries 4 - 6). Other Cu(I) catalysts were found to be less effective than CuI, while the use of Cu(II) catalysts led to significant formation of undesirable biphenyl side product, thereby resulting in lower amide yields (Table 1, entries 5-10). Further optimization also revealed that LiOt-Bu gave the highest yield of **3a** among the different bases screened (Table 1, entries 6, 11-17). A slight excess of **1a** (1.5 equivalents) was found to further improve the yield of **3a** to 82% by compensating for the loss of arylboronate ester to background protodeboronation. The use of other organoboron reagents in place of **1a** gave the product in a lower yield under the same reaction conditions (Table S1 in the ESI). Both the Cu catalyst and the base were crucial for the formation of the amide as no product was formed in the absence of either reagent (Table 1, entries 19 and 20).

With the optimized reaction conditions, the scope of arylboronate esters was investigated (Table 2). The reaction

**Table 2** Substrate scope of arylboronate esters **1** for Cu-catalyzed amidation reaction with isocyanates<sup>a,b</sup>


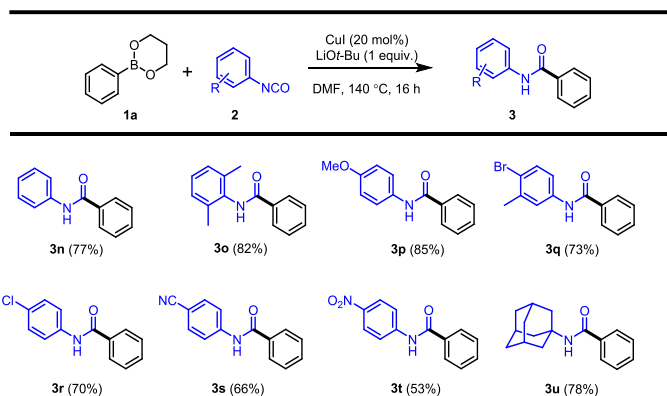
<b>3a</b> (80%)	<b>3b</b> (81%)	<b>3c</b> (65%)	<b>3d</b> (80%)
<b>3e</b> (74%)	<b>3f</b> (55%)	<b>3g</b> (70%)	<b>3h</b> (62%)
<b>3i</b> (70%)	<b>3j</b> (83%)	<b>3k</b> (72%)	<b>3l</b> (58%)
<b>3m</b> (40%, 56% <sup>c</sup> )			

<sup>a</sup> Conditions: **1** (0.75 mmol), **2a** (0.5 mmol), CuI (20 mol%), LiOt-Bu (0.5 mmol), DMF (2 mL), 140 °C, 16 h, Ar atmosphere, unless otherwise noted.

<sup>b</sup> Isolated yields. <sup>c</sup> 48 h reaction time.

proceeded well with sterically-hindered arylboronate esters, giving the corresponding amides in moderate to excellent yields (**3b-3c**). A range of arylboronate esters bearing electron-donating groups (e.g. OMe), as well as electron-withdrawing substituents (e.g. halides, CN, CF<sub>3</sub>), could provide the amide products in good yields (**3d-3j**). We were particularly pleased to find that **3i** could be efficiently prepared by this protocol as trifluoromethyl-substituted amides serve as important building blocks in the preparation of a wide variety of agrochemicals and pharmaceuticals.<sup>[19]</sup> Importantly, the Cu(I)-catalyzed system was not restricted to aromatic substrates. Heteroaromatic substrates, such as pyridyl and thienyl derivatives, also furnished moderate yields of the desired amides (**3k-3l**). Although a lower yield of 40% was initially obtained from the alkenyl boronic ester (**3m**), extending the reaction time to 48 hours resulted in a modest yield of 56%.

With good reactivity for organoboronate esters in hand, the substrate scope of the isocyanate was then screened (Table 3). Sterically-hindered substrates and aryl isocyanates bearing an electron-donating group readily underwent amidation, resulting in excellent product yields (**3o-3p**). In the condensation reaction conventionally employed for amide synthesis, the preparation of amides derived from electron-deficient amines is often difficult because of the decreased nucleophilicity of the amines. On the other hand, isocyanates bearing electron-withdrawing halide groups were efficiently transformed into the desired amide products through this Cu(I)-catalyzed reaction system (**3q-3r**). Various functional groups such as cyano and nitro substituents were also well tolerated under the reaction conditions and the desired products were obtained in modest yields (**3s-3t**). Notably, the bulky adamantanyl isocyanate also proved to be an excellent substrate to

**Table 3** Substrate scope of isocyanates **2** for Cu-catalyzed amidation reaction with phenylboronic 1,3-propanediol ester<sup>a,b</sup>

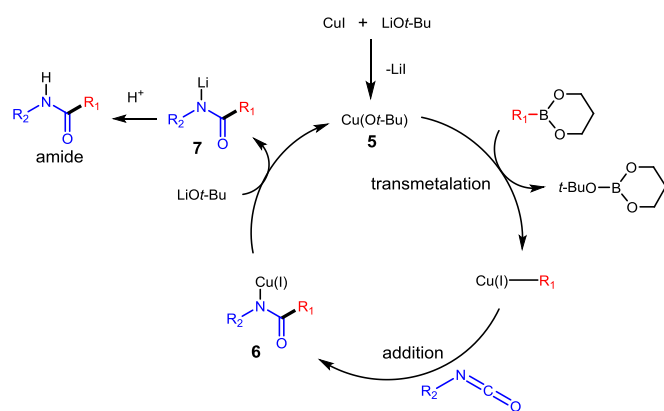
<sup>a</sup> Conditions: **1a** (0.75 mmol), **2** (0.5 mmol), CuI (20 mol%), LiOt-Bu (0.5 mmol), DMF (2 mL), 140 °C, 16 h, Ar atmosphere, unless otherwise noted.

<sup>b</sup> Isolated yields.

provide the corresponding sterically-hindered amide in high yield (**3u**), highlighting the versatility and efficacy of Cu(I)-catalytic system for amide formation.

The amidation reaction may follow a similar mechanism to that of the Cu-catalyzed carboxylation of organoboronic esters with CO<sub>2</sub> reported by Hou and co-workers,<sup>[20]</sup> with the major difference being isocyanate as the carbon source instead of CO<sub>2</sub>. The arylboronate ester will first undergo a transmetalation reaction with the alkoxide complex **5** formed by the metathesis reaction between CuI and LiOt-Bu (Scheme 1). The resulting organocopper complex would then participate in an addition reaction with the electrophilic isocyanate to form intermediate **6**, which subsequently undergoes metathesis reaction with LiOt-Bu to regenerate the complex **5**. Simultaneously, this metathesis reaction produces lithium salt **7** which, upon protonation, gives the desired amide product.

In summary, we have demonstrated an efficient copper-catalyzed system for the amidation reaction between widely available organoboronate esters and isocyanates. The broad substrate scope and excellent functional group tolerance of this system showcase the versatility and ability of earth-abundant and

**Scheme 1** Proposed catalytic cycle for amidation reaction between organo-boronic esters and isocyanates.

environmentally-benign copper catalysts to mediate this type of synthetic transformation which has previously been achieved only by the use of precious metal catalysts. Furthermore, this approach also provides an alternative route to access amides which are difficult to synthesize through a conventional condensation reaction. This new method would be of significant use in cost-effective and more atom-economical amide preparation for pharmaceuticals, agrochemicals and materials synthesis.

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## Notes and references

- (a) J. Zabicky, *The Chemistry of Amides*, Wiley-Interscience, New York, 1970; (b) A. Greenberg, C. M. Breneman and J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, John Wiley & Sons: New York, NY, 2000; (c) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337-2347; (d) T. J. Deming, *Prog. Polym. Sci.*, 2007, **32**, 858-875.
- (a) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606-631; (b) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451-3479.
- (a) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405-3415. (b) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453-7465; (c) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714-2742.
- D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411-420.
- (a) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471-479; (b) G. Schafer, C. Matthey and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 9173-9175.
- Representative examples for amidation of aldehydes: (a) A. Tillack, I. Rudloff and M. Beller, *Eur. J. Org. Chem.*, 2001, 523-528; (b) J. W. W. Chang and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1138-1140; (c) S. Y. Seo, T. J. Marks, *Org. Lett.*, 2008, **10**, 317-319; (d) A. M. Whittaker, V. M. Dong, *Angew. Chem., Int. Ed.*, 2015, **54**, 1312-1315; (e) B. Zhou, J. Du, Y. Yang and Y. Li, *Org. Lett.*, 2013, **15**, 2934-2937; (f) W. J. Yoo, C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064-13065.
- Representative examples for amidation of alcohols: (a) C. Gunanathan, Y. Ben-David, D. Milstein, *Science*, 2007, **317**, 790-792; (b) C. Chen, Y. Zhang and S. H. Hong, *J. Org. Chem.*, 2011, **76**, 10005-10010; (c) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Lett.*, 2009, **11**, 2667-2670; (d) T. Zweifel, J.-V. Naubron and H. Gruetzmacher, *Angew. Chem., Int. Ed.*, 2009, **48**, 559-563; (e) N. Ambreen, T. Wirth, *Euro. J. Org. Chem.*, 2014, **34**, 7590; (f) L. U. Nordstrom, H. Vogt, R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672; (g) Y. Wang, D. Zhu, L. Tang, S. Wang, Z. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8917-8921.
- Representative examples for amidation of alkenes: (a) R. Shi, H. Zhang, L. Lu, P. Gan, Y. Sha, H. Zhang, Q. Liu, M. Beller and

- A. Lei, *Chem. Commun.*, 2015, **51**, 3247-3250; (b) X. H. Yang, K. Li, R. J. Song and J. H. Li, *Eur. J. Org. Chem.*, 2014, 616-623; (c) Z. M. Deng, J. L. Wei, L. H. Liao, H. Y. Huang, X. D. Zhao, *Org. Lett.*, 2015, **17**, 1834-1837; (d) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040-1052.
- 9 Representative examples for amidation of alkynes: (a) Y. Uenoyama, T. Fukuyama, O. Nobuta, H. Matsubara and I. Ryu, *Angew. Chem., Int. Ed.*, 2005, **44**, 1075-1078; (b) J. H. Park, S. Y. Kim, S. M. Kim and Y. K. Chung, *Org. Lett.*, 2007, **9**, 2465-2468; (c) M. Kumar, S. Devari, A. Kumar, S. Sultan, Q. N. Ahmed, M. Rizvi, B. A. Shah, *Asian J. Org. Chem.*, 2015, **4**, 438-441; (d) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833-835; (e) H. Liu, G. P. S. Lau and P. J. Dyson, *J. Org. Chem.*, 2015, **80**, 386-391.
- 10 Representative examples for amidation of aryl halides: (a) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2007, **46**, 8460-8463; (b) S. Kathiravan, S. Ghosh, G. Hogarth, Ian A. Nicholls, *Chem. Commun.*, 2015, **51**, 4834-4837; (c) X.-F. Wu, H. Neumann and M. Beller, *Chem.-Asian J.*, 2010, **5**, 2168-2172; (d) N. Saito, T. Taniguchi, N. Hoshiya, S. Shuto, M. Arisawa and Y. Sato, *Green Chem.*, 2015, **17**, 2358-2361.
- 11 Representative examples for amidation of nitriles: (a) E. Tomas-Mendivil, F. J. Suarez, J. Diez and V. Cadierno, *Chem. Commun.*, 2014, **50**, 9661-9664. (b) R. S. Ramon, N. Marion and S. P. Nolan, *Chem. Eur. J.*, 2009, **15**, 8695-8697; (c) K. Yasuda, Y. Obara, *J. Organomet. Chem.*, 2015, **775**, 33-38; (d) Y.-M. Liu, L. He, M.-M. Wang, Y. Cao, H.-Y. He and K.-N. Fan, *ChemSusChem*, 2012, **5**, 1392-1396.
- 12 Representative examples for amidation of isocyanates: (a) X.-Y. Shi, K.-Y. Liu, J. Fan, X.-F. Dong, J.-F. Wei and C.-J. Li, *Chem.-Eur. J.*, 2015, **21**, 1900-1903; (b) X.-Y. Shi, A. Renzetti, S. Kundu and C.-J. Li, *Adv. Synth. Catal.*, 2014, **356**, 723-728. (c) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430-11433; (d) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202-209; (e) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Org. Lett.*, 2012, **14**, 4262-4265; (f) J. R. Hummel and J. A. Ellman, *Org. Lett.*, 2015, **17**, 2400-2403; (g) J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 1-5; (h) C. Gurtler, K. Danielmeier, *Tetrahedron Lett.*, 2004, **45**, 2515-2521.
- 13 (a) T. Miura, Y. Takahashi and M. Murakami, *Chem. Commun.*, 2007, 3577-3579; (b) E. Kianmehr, A. Rajabi and M. Ghanbari, *Tetrahedron Lett.*, 2009, **50**, 1687-1688.
- 14 Selected examples of organoboron preparations without Grignard or organolithium reagents: (a) T. Ishiyama, M. Murata and N. Miyauro, *J. Org. Chem.*, 1995, **60**, 7508-7510; (b) G. A. Molander, S. L. J. Trice and S. D. Dreher, *J. Am. Chem. Soc.*, 2010, **132**, 17701-17703; (c) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka and M. R. Smith, *Science*, 2002, **295**, 305-308; (d) S. Shimada, A. S. Batsanov, J. A. K. Howard and T. B. Marder, *Angew. Chem., Int. Ed.*, 2001, **40**, 2168-2171.
- 15 D. G. Hall, *Boronic Acids*, Wiley-VCH, Weinheim, 2005.
- 16 For reviews see: (a) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829-2844; (b) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217-224.
- 17 (a) C. Zhang, N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28-29; (b) Q. Kang, Y. Zhang, *Green Chem.*, 2012, **14**, 1016-1019; (c) S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai, A. Chen, *J. Org. Chem.*, 2012, **77**, 8007-8015.
- 18 M. L. Weiner, *J. Org. Chem.*, 1960, **25**, 2245-2247.
- 19 (a) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827-856; (b) K. Mueller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886; (c) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214-231; (d) P. Jeschke, *ChemBioChem*, 2004, **5**, 570-589
- 20 T. Ohishi, M. Nishiura and Z. Hou, *Angew. Chem., Int. Ed.*, 2008, **47**, 5792-5795.