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Selective Formation of Secondary Amides via the Copper-Catalyzed Cross-Coupling of Alkylboronic Acids with Primary Amides

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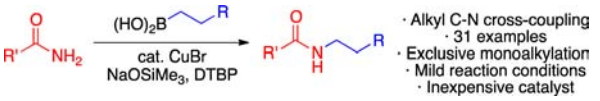
ABSTRACT



For the first time, a general catalytic procedure for the cross-coupling of primary amides and alkylboronic acids is demonstrated. The key to the success of this reaction was the identification of a mild base ($NaOSiMe_3$) and oxidant (di-*tert*-butyl peroxide) to promote the copper-catalyzed reaction in high yield. This transformation provides a facile, high-yielding method for the monoalkylation of amides.

Over the past two decades, the preparation of nitrogen-containing molecules has been revolutionized by the advent of transition metal-catalyzed cross-coupling procedures for constructing C_{sp^2}–N bonds. Both aryl halide/amine cross-couplings (palladium- and nickel-catalyzed Buchwald–Hartwig[1] and copper-catalyzed Ullmann-type couplings[2]), as well as arylboronic acid/amine cross-couplings (copper-catalyzed Lam–Chan reactions)[3−5] are used to an extraordinary extent in preparing biologically active compounds and pharmaceutical agents. In contrast to these methods, the development of transition-metal-catalyzed C_{sp^3}–N bond construction has lagged significantly behind. The difficulty in developing alkyl C–N bond forming reactions stems from the lack of reactivity of alkyl halides and alkylboronic acids with transition metal catalysts, as well as the propensity of intermediate alkylmetal complexes to undergo competitive β-hydride elimination (eq 1, Figure 1).[6]

Traditionally, the conversion of alkyl boronates to alkylamines has been a challenging process requiring highly electrophilic boronate reagents and electrophilic nitrogen sources.[7,8] An alkyl variant of the Lam–Chan protocol

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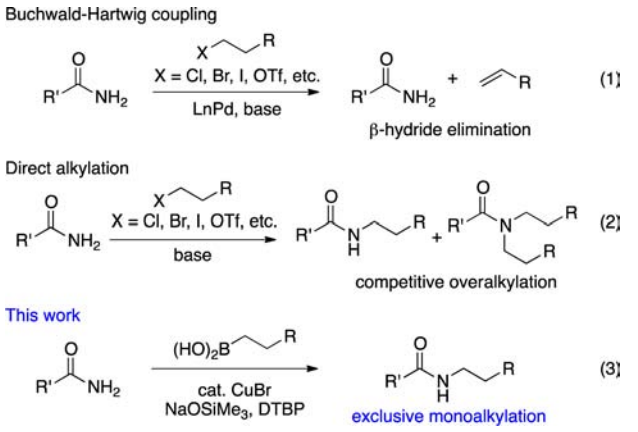

Figure 1. Strategies for monoalkylation of primary amides.

has been recognized as a potential solution to this long-standing problem.[4b] To date, however, only a handful of alkyl Lam–Chan reactions involving alkyl boronates have been reported,[9] and most are limited to the use of methyl or cyclopropylboronates.[9a–d] Notably, both of these substrate classes lack hydrogen atoms suitable for β-elimination.[10] Additionally, most of these protocols require stoichiometric or superstoichiometric copper promoters.[9a,b] Only a single report of a catalytic reaction has been described, and the yields are often inferior compared to reactions employing stoichiometric copper.[9c] The Cruces group has recently reported a series of more general protocols for alkylation of anilines using a range of alkylboronic acids. These procedures require a large excess of both copper and boronic acid (up to 4 equiv each).[9e,f] The large excess of alkylboronic acid required in these reactions may be consistent with partial degradation of the starting material via β-elimination pathways.[11]

Our interest in developing catalytic alkyl carbon–nitrogen bond-forming reactions has led us to explore the cross-coupling of primary amides with alkylboronic acids to provide secondary amides selectively. Secondary amides are important functional groups in organic chemistry, as they comprise the backbones of all natural peptides and proteins and are widely found in therapeutic small molecules and synthetic intermediates.[12] Further, although secondary amides can readily be prepared by acylation of a primary amine, the complementary monoalkylation of a primary amide with an alkyl halide remains a difficult reaction to control and often provides modest selectivity with respect to overalkylation (eq 2).[13]

Herein, for the first time, we report a general protocol for the copper-catalyzed monoalkylation of primary amides using alkylboronic acids (eq 3). The key to this reaction is the discovery that the combination of a mild base (sodium trimethylsilanolate, $NaOSiMe_3$, $pK_a' = 12.7$)[14] and di-*tert*-butyl peroxide (DTBP) as the oxidant is uniquely effective in promoting the catalytic cross-coupling reaction of primary amides and primary boronic acids.[11] This reaction is completely tolerant of β-hydrogen atoms and, in most cases, requires only a small excess of alkylboronic acid. This protocol offers a simple method for preparing secondary amides, while providing a rare example of catalytic alkyl C–N cross-coupling.[8a,9c,15]

We began by examining the reaction of benzamide and isobutylboronic acid (Table 1). Under typical Lam–Chan reaction conditions, employing $Cu(OAc)_2$ as the catalyst and air (or dry oxygen) as the oxidant with a mild base, only traces of the desired secondary amide **1** were observed (entries 1 and 2). The use of ligand additives, such as 2,2′-bipyridine, did not positively affect the reaction (not shown). In contrast, the use of stoichiometric $Cu(OAc)_2$ (4 equiv) under air did lead to a small, but measurable, increase in the yield of the product (up to 5% as determined by NMR, not shown). We suspected that this result might indicate ineffective catalyst turnover. Accordingly, we examined the role of the oxidant in the reactions conducted under a nitrogen atmosphere. Whereas a range of common oxidants such as (diacetoxyiodo)benzene, benzoquinone, hydrogen peroxide, *meta*-chloroperbenzoic acid, and *tert*-butyl hydrogen peroxide (entries 3–7) were completely ineffective, the use of di-*tert*-butyl peroxide (DTBP, entry 8) provided discernibly more product under catalytic conditions. A stronger base (NaO^tBu, entry 9) and optimization of the solvent to ^{t}BuOH (entry 10) provided further increases in the yield.[16] Interestingly, with the use of ^{t}BuOH as the solvent, the use of $NaOSiMe_3$ provided a significant increase in yield (87%, entry 11). With this weaker base, the equilibrium concentration of deprotonated amide is expected to be lower, which we suspect might prevent competitive ligation of the copper catalyst. Finally, we elected to examine the use of other copper salts as precatalysts; CuBr proved to be slightly more effective, leading to a 92% assay yield under optimized conditions.[17]

(10) β-Hydride elimination from metal cyclopropanes has been shown to be a highly unfavorable process. See: Nuzzo, R. G.; McCarthy, T. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 3404–3410.

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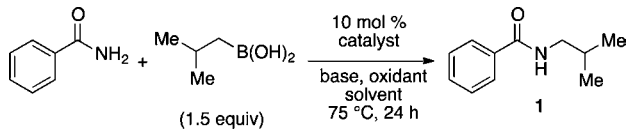
(16) Other solvents were also examined in this reaction; see Supporting Information for details.

(17) Further attempts to optimize the reaction (varied temperature, time, concentration, and equivalents of reagents) lead to lower yields of **1**.

The reaction is completely selective for monoalkylation; in no case was any dialkylated product detected.

Table 1. Identification of Reaction Conditions

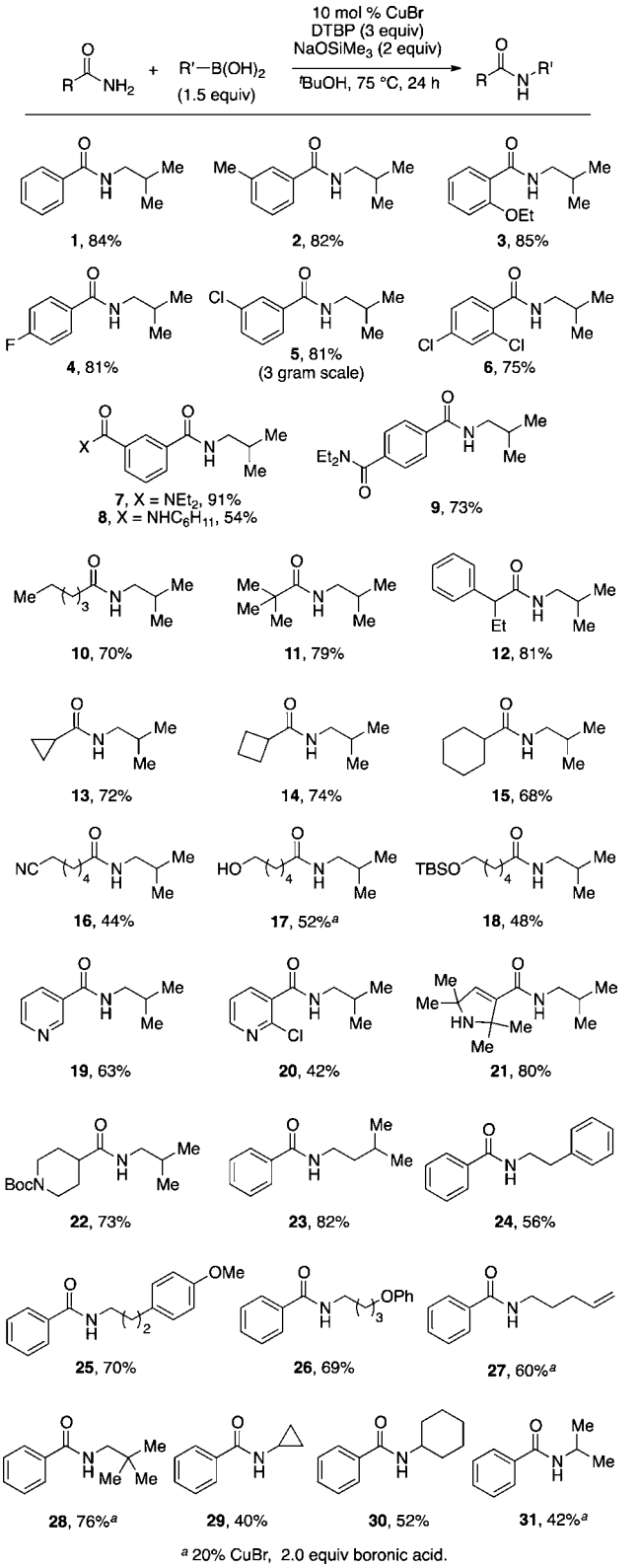


entry	catalyst	base	oxidant	solvent	yield[a]
1	$Cu(OAc)_2$	Na_2CO_3	air	DCE	trace
2	$Cu(OAc)_2$	Na_2CO_3	O_2	DCE	trace
3	$Cu(OAc)_2$	Na_2CO_3	$PhI(OAc)_2$	DCE	0%
4	$Cu(OAc)_2$	Na_2CO_3	BQ	DCE	0%
5	$Cu(OAc)_2$	Na_2CO_3	H_2O_2	DCE	0%
6	$Cu(OAc)_2$	Na_2CO_3	*m*-CPBA	DCE	0%
7	$Cu(OAc)_2$	Na_2CO_3	TBHP	DCE	0%
8	$Cu(OAc)_2$	Na_2CO_3	DTBP	DCE	5%
9	$Cu(OAc)_2$	Na^tOBu	DTBP	DCE	31%
10	$Cu(OAc)_2$	Na^tOBu	DTBP	^{t}BuOH	36%
11	$Cu(OAc)_2$	$NaOSiMe_3$	DTBP	^{t}BuOH	87%
12	Cu(OAc)	$NaOSiMe_3$	DTBP	^{t}BuOH	71%
13	CuCl	$NaOSiMe_3$	DTBP	^{t}BuOH	70%
14	CuI	$NaOSiMe_3$	DTBP	^{t}BuOH	88%
15	CuBr	$NaOSiMe_3$	DTBP	^{t}BuOH	92%

[a] Yield determined using NMR. DCE = 1,2-dichloroethane; BQ = benzoquinone; *m*-CPBA = *meta*-chloroperbenzoic acid; TBHP = *tert*-butyl hydrogen peroxide; DTBP = di-*tert*-butyl peroxide.

Under preparative conditions, amide **1** was isolated in 84% yield (1 mmol scale, Scheme 1).[18] Significantly, the reaction conditions developed for this substrate proved highly general with respect to both amide and alkylboronic acid. As shown in Scheme 1, a variety of substituents on the amide were well tolerated, including alkyl groups (**2**), aromatic ethers (**3**), and tertiary amides (**7** and **9**), as well as alkyl nitriles (**16**), alcohols (**17**), and silyl ethers (**18**). As expected from the high selectivity for monoalkylation, secondary amides were inert under the alkylation conditions (**8**). Electron-rich (**3**), as well as mildly electron-deficient (**4** and **9**), amides were highly effective substrates. However, benzamides bearing electron-withdrawing groups stronger than *p*-dialkylamides failed to react. While aryl fluorides (**4**) and chlorides (**5** and **6**) were well tolerated, we found that reactions involving aromatic bromides were less effective, providing only low yields of the desired product. Unfortunately, esters (both aromatic and alkyl) proved incompatible with the reaction conditions due to competitive hydrolysis.[19] In contrast, aliphatic amides were excellent substrates for the reaction. This includes linear amides such as hexanoamide (**10**), as well as those containing branching α to the carbonyl, such as in **11** and benzylic amide **12**. Amides containing carbocyclic rings were also were well tolerated, including those containing

Scheme 1. Substrate Scope for Amide Alkylation



cyclopropyl, cyclobutyl, and cyclohexyl units (**13**–**15**). Significantly, heterocyclic amides were also suitable substrates in the reaction. This includes both heteroaromatic compounds, such as those leading to **19** and **20**, as well as

(18) All reported isolated yields are the average of at least two runs.

(19) The incompatibility of ester under the reaction conditions appears to be due to the combination of the mildly basic conditions with the Lewis acidic catalyst. Control experiments showed that esters decomposed only when base and catalyst were present.

nonaromatic heterocycles (**21** and **22**). The latter two examples demonstrate that both protic and protected amines can also be tolerated in the reaction. Finally, the reaction also proved to be highly scalable; amide **5** was prepared on a 3-g scale (ca. 20 mmol) in 81% yield, which was nearly identical to that obtained on a 1-mmol scale.

The copper-catalyzed alkylation reaction is not limited to the use of isobutylboronic acid. As demonstrated by the preparation of amides **23**–**31**, a wide range of boronic acids can be utilized as alkylating reagents. This includes those bearing functional groups, such as arenes, ethers, and alkenes (**24**–**27**), as well as more sterically demanding primary alkylboronic acids, such as neopentylboronic acid (**28**). Taken together with the examples above, the coupling reaction displays wide functional group tolerance.

Finally, we have examined the scope with respect to more substituted boronic acids. Whereas tertiary boronic acids (such as *tert*-butylboronic acid, not shown) were not successful substrates for the cross-coupling reaction, some secondary boronic acids did undergo coupling. For example, cyclopropyl- and cyclohexylboronic acids both underwent coupling, giving rise to **29** and **30** in modest yield. However, other similar secondary boronic acids were less successful. For example, the use of isopropylboronic acid required excess reagent and catalyst to afford a modest yield. We believe that this difference in yield corresponds to the low stability of isopropylboronic acid relative to the others.

In conclusion, we have developed a mild, inexpensive, functional group tolerant method for the synthesis of secondary amides via the cross-coupling of primary amides with alkylboronic acids. We demonstrated that the Lam–Chan-type reaction can be carried out efficiently using a catalytic amount of copper, and for the first time,[11] DTBP was discovered as an effective oxidant for the process. Moreover, the application of alkylboronic acids in the cross-coupling significantly broadens the scope of Lam–Chan-type reactions in organic synthesis. Further efforts will be directed toward investigation of the detailed reaction mechanism[20] and expansion of the generality of the transformation.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.