

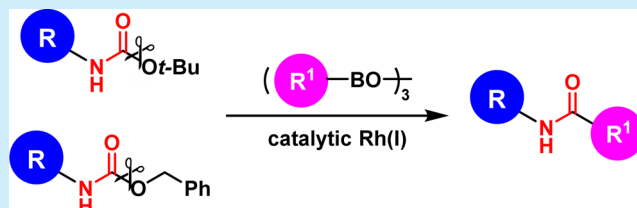
Direct Amidation of *N*-Boc- and *N*-Cbz-Protected Amines via Rhodium-Catalyzed Coupling of Arylboroxines and Carbamates

Diane S. W. Lim, Tedrick T. S. Lew, and Yugen Zhang*

Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669, Singapore

S Supporting Information

ABSTRACT: *N*-Boc- and *N*-Cbz-protected amines are directly converted into amides by a novel rhodium-catalyzed coupling of arylboroxines and carbamates, replacing the traditional two-step deprotection–condensation sequence. Both protected anilines and aliphatic amines are efficiently transformed into a wide variety of secondary benzamides, including sterically hindered and electron-deficient amides, as well as in the presence of acid-labile and reducible functional groups.



Amide bond formation ranks as one of the most utilized chemical reactions in drug discovery.¹ While traditional amide synthesis by dehydrative condensation of a carboxylic acid and an amine has proven suitable for the majority of amides, this approach relies on stoichiometric amounts of coupling reagents, raising economic and environmental concerns.² Added to the limited success this disconnection has achieved in constructing sterically hindered and electron-deficient amides,³ the search for new catalytic modes of amide bond formation remains an ongoing challenge.

In recent years, extensive work in the field of three-component carbonylations of halides, amines, and carbonyl source has produced notable advances in metal-catalyzed amidations.⁴ However, practical applications are hampered by the risks of handling of gaseous CO, while the alternative pathway of carbon nucleophile addition to carbamoyl-based electrophiles requires added steps of converting amines into reactive carbamoyl chlorides⁵ or isocyanates⁶ utilizing toxic phosgene-based reagents. In contrast, no metal-catalyzed amidation has been developed for carbamates despite the prevalence of this compound class as a protecting group in multistep syntheses, possibly owing to the poor electrophilicity of the sp²-hybridized carbon center.^{7,8} In particular, carbamates with *tert*-butyl and benzyl *O*-substitution, better known as Boc and Cbz groups, are widely employed as amine protecting groups in medicinal and process chemistry,¹ and a direct catalytic amidation of such carbamates would be of interest to the synthetic community, achieving in a single step the same overall transformation as a deprotection–condensation sequence traditionally applied to protected amines (Figure 1).

During the course of developing a copper(I)-catalyzed amidation of isocyanates with boronic esters activated by alkoxides, we observed carbamate intermediate **1** (Table 1). On extended reaction times, consumption of this intermediate corresponded to increased amide yields.^{6d} Encouragingly, when we submitted carbamate **1** to identical reaction conditions with boronic ester **2a**, a low yield of amide **3a** was obtained along

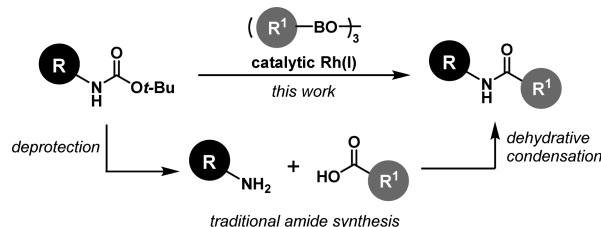
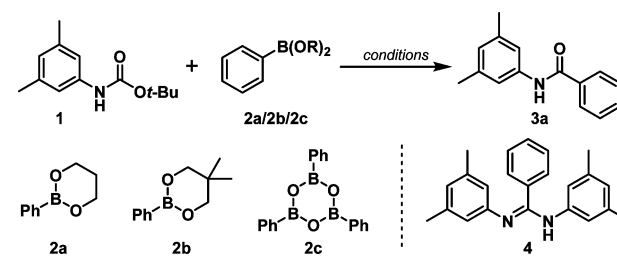


Figure 1. One-step conversion of *N*-Boc-protected amines to amides.

with significant amounts of amidine **4** and 3,5-dimethylaniline (entry 1). A survey of different combinations of boronic acid derivatives and transition-metal complexes revealed that both amidine formation and carbamate deprotection could be suppressed by employing arylboroxine **2c** in conjunction with dimeric rhodium(I) complexes when the reaction was conducted in 1,4-dioxane (entries 2–5). Surprisingly, none of the boronic esters included in our study were reactive under these conditions and were recovered as biphenyl homocoupled side products (entry 3). Exchanging sodium *tert*-butoxide for potassium hydroxide resulted in carbamate hydrolysis, yielding 3,5-dimethylaniline (entry 6), while potassium fluoride returned an excellent yield of amide **3a** (entry 7). Interestingly, employing cesium fluoride, the more commonly employed albeit costly and moisture-sensitive base, resulted in no product formation, and carbamate **1** was recovered unchanged (entry 8). Reducing the amount of organoboron nucleophile to 1.2 equiv resulted in minimal loss of isolated amide product (entry 9).

The scope of the reaction was investigated with a variety of arylboroxines and *N*-Boc-anilines with the results summarized in Figure 2. Arylboroxines with electron-rich substituents in the *para* position underwent smooth coupling with carbamate **1** to

Received: October 22, 2015

Table 1. Optimization of Reaction Conditions^a


entry	PhB(OR) ₂	catalyst ^b	base	solvent (temp, °C)	yield ^c (%)
1	2a	IPrCuCl	NaOt-Bu	DMF (140)	16 ^d
2	2b	SIPrCuCl	NaO- <i>t</i> -Bu ^e	DMF (140)	30 ^f
3	2a/2b	[Cl(cod)Rh] ₂	NaOt-Bu	dioxane (110)	0
4	2c	[Cl(cod)Rh] ₂	NaOt-Bu	dioxane (110)	37
5	2c	[Cl(nbd)Rh] ₂	NaOt-Bu	dioxane (110)	25
6	2c	[Cl(cod)Rh] ₂	KOH	dioxane (100)	0
7	2c	[Cl(cod)Rh] ₂	KF	dioxane (100)	89
8	2c	[Cl(cod)Rh] ₂	CsF	dioxane (100)	0
9 ^g	2c	[Cl(cod)Rh] ₂	KF	dioxane (100)	86

^aStandard reaction conditions: **1** (0.25 mmol), **2** (**2a/2b**: 0.50 mmol, **2c**: 0.17 mmol), base (0.25 mmol), solvent (0.5 mL), 16 h. ^b5 mol % of Cu or Rh. ^cYield of isolated product. ^d9% of **4**. ^e0.13 mmol. ^f20% of **4**. ^g0.10 mmol of **2c**. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. nbd = norbornadiene. cod = 1,5-cyclooctadiene.

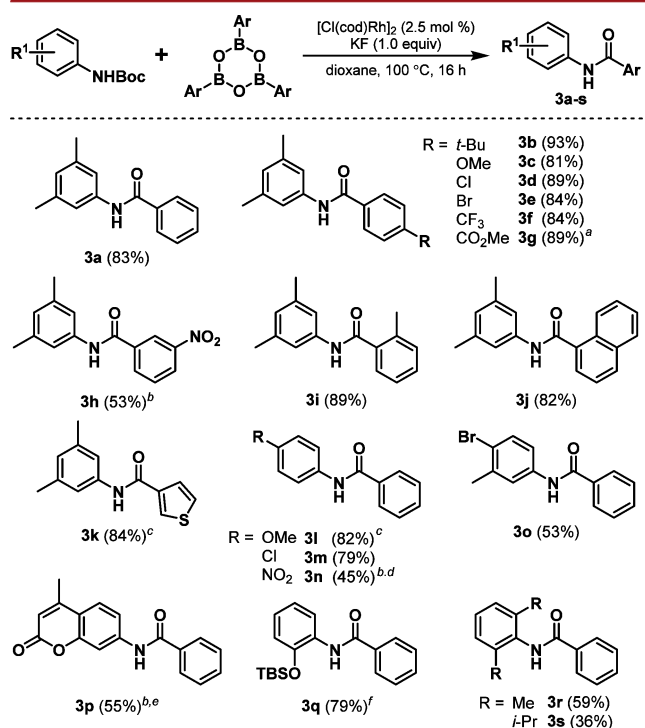


Figure 2. Coupling of *N*-Boc-protected anilines and arylboroxines. Reaction conditions: *N*-Boc-aniline (0.50 mmol), arylboroxine (0.20 mmol), [Cl(cod)Rh]₂ (13 μmol), KF (0.50 mmol), 1,4-dioxane (1 mL), 100 °C, 16 h: (a) 12 h reaction time; (b) 24 h reaction time; (c) 0.60 mmol of tris(thiophene-3-yl)boroxine; (d) recovered 26% *N*-Boc-aniline; (e) recovered 12% *N*-Boc-aniline; (f) 120 °C. Boc = *tert*-butyloxycarbonyl. TBS = *tert*-butyldimethylsilyl.

afford benzamides **3b** and **3c** in excellent yields, as did halide-substituted arylboroxines to yield chloro- and bromoarenes **3d** and **3e**. Although electron-deficient boronic acids have been reported to undergo homocoupling and protodeboronation under similar conditions, we were pleased to achieve good to satisfactory yields of amides **3f–h** with boroxine coupling

partners bearing electron-withdrawing trifluoromethyl, ester, and nitro groups in the *para* or *meta* positions.^{6b,9} The amidation conditions tolerate both an *ortho* substitution and extended aromatic system on the boroxine partner (**3i,j**), while successful coupling of a heteroarylboroxine with carbamate **1** for the synthesis of thiophenecarboxamide **3k** was achieved with a three-fold excess of the organoboron coupling partner.

A similar pattern of reactivity was observed when substitution on the *N*-Boc-aniline was varied: electron-rich and halide-substituted arenes underwent efficient conversion to amides **3l**, **3m**, and **3o**, while an electron-withdrawing nitro substituent resulted in a modest yield of amide **3n** even after an extended reaction time. Coumarin-based amide **3p** was prepared in a moderate yield and notably contains a Michael acceptor as a competing site for the organoboron nucleophile to undergo 1,4-addition.¹⁰ Despite the use of fluoride base, suitably bulky silyl ethers were not degraded, as evinced by the isolation of silyl-protected phenol **3q**. Carbamates in sterically congested environments also proved to be competent substrates, allowing the bulky amides **3r** and **3s** to be prepared using this method. In addition to *tert*-butyl carbamates, benzyl carbamates (Cbz) were transformed into benzamides under identical reaction conditions (Figure 3). The reaction profiles of *N*-Cbz-amines were generally cleaner than that of their *N*-Boc counterparts and corresponded to improved yields of amide products from boroxine and carbamate substrates that had proved challenging (**3h**, **3n**, and **3o**).

We next investigated *N*-Boc-protected aliphatic amines as coupling partners and were delighted to find that this could be accomplished by exchanging dimeric rhodium(I) complex [Cl(cod)Rh]₂ for monomeric catalyst (cod)₂Rh(OTf) (Figure 4). Under these conditions, Boc-protected benzylic amines with primary and secondary substitution and amines appended to (poly)cyclic scaffolds were efficiently coupled with trisphenylboroxine to form benzamides **3t–x** in excellent yields. The conversion of primary aliphatic carbamates to amides **3y** and **3z** required slightly elevated temperatures, which resulted in partial lactamization of amide **3y**. For the design of synthetic routes,

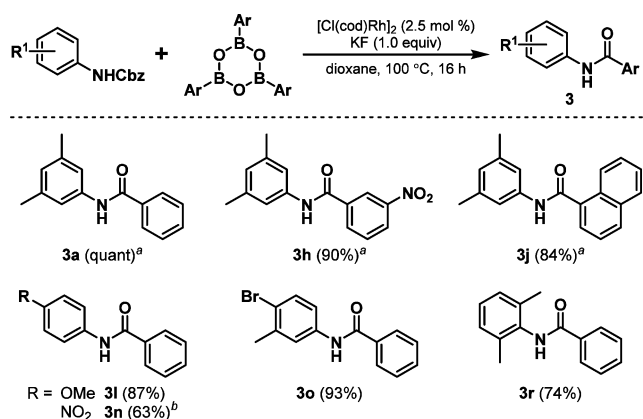


Figure 3. Coupling of *N*-Cbz-protected anilines and arylboroxines. Reaction conditions: *N*-Cbz-aniline (0.50 mmol), arylboroxine (0.20 mmol), [Cl(cod)Rh]₂ (13 μmol), KF (0.50 mmol), 1,4-dioxane (1 mL), 100 °C, 16 h; (a) 24 h reaction time; (b) recovered 9% *N*-Cbz-aniline. Cbz = benzyloxycarbonyl.

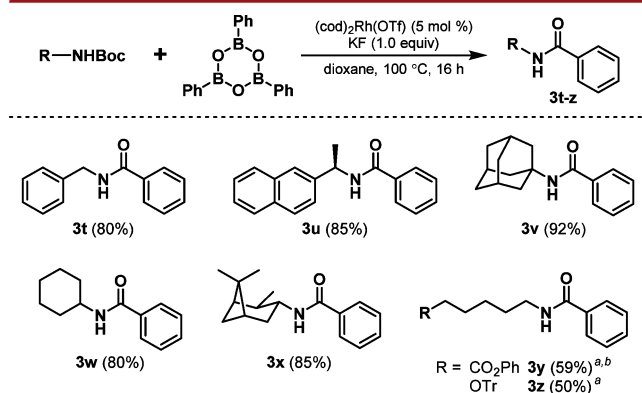


Figure 4. Coupling of *N*-Boc-protected alkylamines and arylboroxines. Reaction conditions: *N*-Boc-amine (0.50 mmol), arylboroxine (0.20 mmol), (cod)₂Rh(OTf) (25 μmol), KF (0.50 mmol), 1,4-dioxane (1 mL), 100 °C, 16 h; (a) 120 °C; (b) 8:1, amide/lactam. Tr = trityl.

this method tolerates the conversion of *N*-Boc-protected amines to amides in the presence of an acid-labile *O*-trityl functional group (3z), which is incompatible with the strong acid conditions required for Boc deprotection.

Initially, the coupling was thought to proceed via addition of a boroxine-derived organorhodium species to the isocyanate generated by elimination of *tert*-butyl alcohol from *tert*-butyl carbamate. However, it was ruled out by the absence of isocyanate intermediate by ¹H NMR spectroscopy.¹¹ With that, the following mechanism is proposed for the reaction (Figure 5): fluoride-induced ring opening of trisarylboroxine 2c releases mixed boronate A,¹² which upon transmetalation with rhodium complex generates arylrhodium(I) species B. Addition (or carborhodation) of nucleophilic B at the sp²-hybridized carbon of carbamate–borate complex C affords alkoxyrhodium(I) complex D.¹³ Subsequent β-alkoxy elimination¹⁴ and borate dissociation yields the amide product and returns rhodium(I) alkoxide for the next catalytic turnover. This pathway is supported by the following observations: (i) the unique reactivity of boroxines over boronic esters and acids, implicating mixed borate of type E as a critical intermediate, (ii) secondary and cyclic carbamate systems are unreactive, suggesting complexation is required to enhance the electrophilicity of the carbamate coupling partner, and (iii) detection

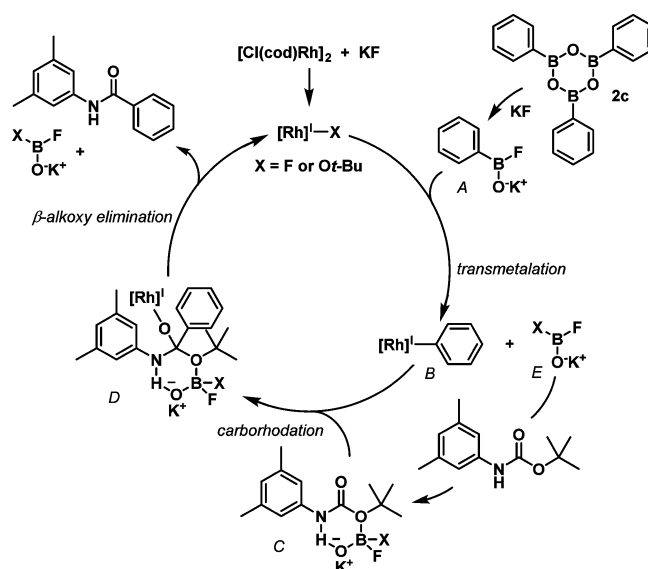


Figure 5. Possible mechanism for boroxine–carbamate coupling.

of hydrogen-bonding interactions between borate A and carbamate 1 by an upfield shift of the N–H signal in the ¹H NMR spectrum of the mixture compared to that of the isolated carbamate.¹¹

In conclusion, we have reported a novel rhodium(I)-catalyzed coupling of boroxines and *tert*-butyl or benzylcarbamates in the presence of fluoride to afford benzamides in good yield. This method provides a direct route for converting *N*-Boc- and *N*-Cbz-protected amines to amides and is tolerant of acid-sensitive and reducible functional groups, thereby offering an attractive alternative to the two-step deprotection–condensation sequence traditionally employed for these amines. Finally, evidence for carbamate activation by a borate intermediate suggests the coupling may be extended to other classes of carbon nucleophiles. Studies in this area are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03061.

Experimental procedures, extended optimization experiments, characterization, ¹H and ¹³C NMR spectra of new substrates and products, and mechanistic studies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ygzhang@ibn.a-star.edu.sg.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research (A*STAR), Singapore).

REFERENCES

- (1) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
- (2) (a) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (b) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
- (3) (a) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (b) Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9173.
- (4) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867.
- (5) For representative metal-catalyzed carbamoyl chloride amidations, see: (a) Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* **2004**, *6*, 3703. (b) Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342. (c) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792.
- (6) For representative metal-catalyzed isocyanate amidations with organometallic reagents, see: (a) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 3577. (b) Kianmehr, E.; Rajabi, A.; Ghanbari, M. *Tetrahedron Lett.* **2009**, *50*, 1687. (c) Correa, A.; Martin, R. J. *Am. Chem. Soc.* **2014**, *136*, 7253. (d) Lew, T. T. S.; Lim, D. S. W.; Zhang, Y. *Green Chem.* **2015**, DOI: 10.1039/C5GC01374G. For representative metal-catalyzed isocyanate amidations via C–H activation, see: (e) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (f) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (g) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 4262. (h) Zhou, B.; Hou, W.; Yang, Y.; Li, Y. *Chem. - Eur. J.* **2013**, *19*, 4701. (i) Hou, W.; Zhou, B.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* **2013**, *15*, 1814. (j) De Sarkar, S.; Ackermann, L. *Chem. - Eur. J.* **2014**, *20*, 13932. (k) Shi, X.-Y.; Renzetti, A.; Kundu, S.; Li, C.-J. *Adv. Synth. Catal.* **2014**, *356*, 723. (l) Shi, X.-Y.; Liu, K.-Y.; Fan, J.; Dong, X.-F.; Wei, J.-F.; Li, C.-J. *Chem. - Eur. J.* **2015**, *21*, 1900. (m) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400. (n) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8551.
- (7) Previous additions of carbon nucleophiles to carbamate have overcome this via two methods. (i) Employing organometallic reagents in excesses of 6–8-fold: (a) El Kaim, L.; Grimaud, L.; Lee, A.; Perroux, Y.; Tirla, C. *Org. Lett.* **2004**, *6*, 381. (b) Latorre, A.; Rodríguez, S.; Izquierdo, J.; González, F. V. *Tetrahedron Lett.* **2009**, *50*, 2653. (ii) Tethering or stabilizing the carbon nucleophile: (c) Tay, M. K.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Tetrahedron* **1989**, *45*, 4415. (d) White, J. D.; Blakemore, P. R.; Milicevic, S.; Choudhry, S. C.; Cupano, J.; Serico, L. *Org. Lett.* **2002**, *4*, 1803. (e) Hernandez, N. M.; Sedano, M. J.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett.* **2003**, *44*, 4035. (f) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *J. Org. Chem.* **2009**, *74*, 782. (g) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron* **2011**, *67*, 2206. (h) Gibson, S.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett.* **2011**, *52*, 887. (i) Aboussafy, C. L.; Clive, D. L. J. *J. Org. Chem.* **2012**, *77*, 5125.
- (8) (a) Adachi, S.; Onozuka, M.; Yoshida, Y.; Ide, M.; Saikawa, Y.; Nakata, M. *Org. Lett.* **2014**, *16*, 358. (b) Kurouchi, H.; Kawamoto, K.; Sugimoto, H.; Nakamura, S.; Otani, Y.; Ohwada, T. *J. Org. Chem.* **2012**, *77*, 9313. (c) Sumita, A.; Kurouchi, H.; Otani, Y.; Ohwada, T. *Chem. - Asian J.* **2014**, *9*, 2995.
- (9) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591.
- (10) (a) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285. (b) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350.
- (11) See the [Supporting Information](#) for further details.
- (12) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156.
- (13) *N*-Boc-protected amines on their own have previously been shown to be stable under rhodium(I)-catalyzed boronic acid/ester additions: (a) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706. (b) Tsui, G. C.; Menard, F.; Lautens, M. *Org. Lett.* **2010**, *12*, 2456. (c) He, Z.-T.; Tian, B.; Fukui, Y.; Tong, X.; Tian, P.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 5314. (d) Li, Y.; Zhu, D.-X.; Xu, M.-H. *Chem. Commun.* **2013**, *49*, 11659.
- (14) (a) Tonogaki, K.; Itami, K.; Yoshida, J.-i. *Org. Lett.* **2006**, *8*, 1419. (b) Miyamura, S.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 2255.