

One-Pot Amidation of Olefins through Pd-Catalyzed Coupling of Alkylboranes and Carbamoyl Chlorides[†]

Yoshizumi Yasui, Sayo Tsuchida, Hideto Miyabe, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

takemoto@pharm.kyoto-u.ac.jp





A one-pot synthesis of C_1 -elongated amides starting from olefins and carbamoyl chlorides has been developed. Alkylboranes, generated by hydroboration of terminal olefins with 9-BBN-H, underwent smooth coupling with carbamoyl chlorides in the presence of palladium catalyst and Cs_2CO_3 .

Amides have a fundamental importance in organic chemistry due to their biological significance and synthetic utility. Generally, amides are formed through condensation of amines and carboxylic acids (Figure 1, path a).¹ However, this method is not always efficient, especially when the availability of the carboxylic acid is limited. Therefore alternative methods have been developed for the synthesis of a broad range of amides. Recent examples include oxidative coupling of alkynes with amines,² hydrative condensation of alkynes and sulfonyl azides,³ and iridium-catalyzed conversion of alcohols to amides via oximes.⁴ The transition-metal-catalyzed amidation of multiple C-C bonds with formamide derivatives (X-CO-NR'₂) is a unique strategy, which enables the use of the corresponding onecarbon-less olefins and acetylenes as the amide precursors (Figure 1, path b). Our recent studies showed that rhodiumcatalyzed intramolecular hydroamidation (X = H) of alkynes⁵ and palladium-catalyzed intramolecular cyanoamidation (X =



FIGURE 1. Strategy for amide formation.

CN) of alkynes and alkenes⁶ followed such transformations.^{7,8} Expanding these methods to intermolecular reactions is an ongoing task, with the difficulties of finding an effective catalyst and controlling the regiochemical course of the reaction.^{9,10}

The direct amidation of organometallic reagents with formamide derivatives is also an attractive method owing to its simplicity and reliability (Figure 1, path c); however, the organometallic reagents used for such an approach have been limited mainly to magnesium or lithium reagents.¹¹ It would be useful to develop the amidation of less reactive metallic reagents, to allow the presence of various functional groups.^{12,13} In this paper, we report a one-pot amidation of olefins through hydroboration, and subsequent coupling of the resulting alkylboranes with carbamoyl chlorides (X = Cl), which allows olefins to be precursors for amide synthesis (path d \rightarrow path c). For the hydroboration, 9-BBN-H was chosen as a reagent due

(8) Intramolecular carbonylative amidation of unsaturated amines is an equivalent transformation, see: (a) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219 and references cited therein. (b) Ye, F.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1855.

(9) Similar problems were reported on the related intermolecular hydroamidation, see: (a) Tsuji, Y.; Yoshii, S.; Ohsumi, T.; Kondo, T.; Watanabe, Y. J. Organomet. Chem. **1987**, *331*, 379. (b) Kondo, T.; Okada, T.; Mitsudo, T. Organometallics **1999**, *18*, 4123. (c) Ko, S.; Han, H.; Chang, S. Org. Lett. **2003**, *5*, 2687.

(10) A few regioselective intermolecular amidations are known. For carbamoylstannation, see: (a) Hua, R.; Onozawa, S.; Tanaka, M. Organometallics **2000**, 19, 3269. For carbonylative selenoamidation, see: (b) Knapton, D. J.; Meyer, T. Y. J. Org. Chem. **2005**, 70, 785. For carbonylative radical amidation, see: (c) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. Angew. Chem., Int. Ed. **2005**, 44, 1075.

(11) (a) Blicke, F. F.; Zinnes, H. J. Am. Chem. Soc. 1955, 77, 4849. (b)
Mills, R. J.; Taylor, N. J.; Snieckus, V. J. Org. Chem. 1989, 54, 4372. (c)
Lemoucheux, L.; Rouden, J.; Lasne, M.-C. Tetrahedron Lett. 2000, 41, 9997.
(d) Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.;
Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. J. Am. Chem. Soc. 2006, 128, 9722. For amidation of Cu, K, Ti, and Zn reagents, see: (e) Lemoucheux, L.; Rouden, J.; Lasne, M.-C. Org. Lett. 2004, 6, 3703 and references cited therein.

10.1021/jo070724u CCC: \$37.00 © 2007 American Chemical Society Published on Web 06/20/2007

[†] Dedicated to the memory of Professor Yoshihiko Ito.

^{(1) (}a) Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002. (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.

⁽²⁾ Chan, W.-K.; Ho, C.-M.; Wong, M.-K.; Che, C.-M. J. Am. Chem. Soc. 2006, 128, 14796.

^{(3) (}a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. J. Am. Chem. Soc. **2005**, *127*, 16046. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. Angew. Chem., Int. Ed. **2006**, *45*, 3154.

⁽⁴⁾ Owston, N. A.; Parker, A. J.; Williams, J. M. J. Org. Lett. 2007, 9, 73.

⁽⁵⁾ Kobayashi, Y.; Kamisaki, H.; Yanada, K.; Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* **2005**, *46*, 7549.

^{(6) (}a) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. Org. Lett. 2006, 8, 2711. (b) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. Tetrahedron 2007, 63, 2978.
(7) For related intramolecular amidation of formamide derivatives, see:

⁽⁷⁾ For related intramolecular amidation of formamide derivatives, see:
(a) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. J. Am. Chem. Soc. 2005, 127, 9706. (b) Anwar, U.; Fielding, M. R.; Grigg, R.; Sridharan, V.; Urch, C. J. J. Organomet. Chem. 2006, 691, 1476.

⁽¹²⁾ For amidation of aryl- and vinyltin reagents, see: (a) Balas, L.; Jousseaume, B.; Shin, H.; Verlhac, J.-B.; Wallian, F. *Organometallics* **1991**, *10*, 366. (b) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, 163.

⁽¹³⁾ Amidation of arylboron reagents was recently reported, see: (a) Duan, Y.-Z.; Deng, M.-Z. *Synlett* **2005**, 355. (b) Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2005**, *70*, 5342.

 TABLE 1. Optimization of the Palladium-Catalyzed Amidation

 Reaction of Alkylborane^a



entry	catalyst	base ^b	cosolvent	yield (%)
1c	Pd(PPh ₃) ₄	CsF		36 ^d
2	Pd(PPh ₃) ₄	K_3PO_4		8^e
3	$Pd(PPh_3)_4$	K_2CO_3		f
4	$Pd(PPh_3)_4$	Cs_2CO_3		78
5^g	$Pd(PPh_3)_4$	Cs_2CO_3		80
6^h	Pd ₂ (dba) ₃ , ^t Bu ₃ P	Cs_2CO_3		33
7	PdCl ₂ (dppf)	Cs ₂ CO ₃	toluene	31
8	Pd(PPh ₃) ₄	Cs ₂ CO ₃	toluene	72
9	Pd(PPh ₃) ₄	Cs_2CO_3	1,4-dioxane	75
10	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	52
11	Pd(PPh ₃) ₄	Cs_2CO_3	DME	55

^{*a*} Unless otherwise indicated, reactions were carried out on a 1.2–1.3 mmol scale under Ar; isolated yields based on **3a** are reported. ^{*b*} Dried by heating under vacuum before use. ^{*c*} Styrene (**1a**) (1.0 equiv), **9**-BBN-H (1.0 equiv), **3a** (1.5 equiv), and CsF (3.0 equiv) were used; yield is based on **1a**. ^{*d*} 30% (based on **3a**) of *N*,*N*-dibenzylfluoroformamide was isolated.^{*e*} 63% of **3a** was recovered. ^{*f*} 81% of **3a** was recovered. ^{*s*} Reaction was carried out for 40 h. ^{*h*} Pd₂(dba)₃ (2.5 mol %) and 'Bu₃P+HBF₄ (15 mol %) were used.¹⁸

to its well-established regioselectivity and high functional group tolerance. In the second step, the viability of the coupling reaction of alkylborane with carbamoyl chlorides was expected to be a novel contribution to the growing alkylborane coupling chemistry.^{14,15}

To optimize the reaction conditions, styrene (1a) and N,Ndibenzylcarbamoyl chloride $(3a)^{16}$ were chosen as substrates (Table 1). Hydroboration of styrene (1a) with 9-BBN-H was carried out in THF. Carbamoyl chloride 3a, palladium catalyst (5 mol %), and inorganic base were added, and the mixture was heated to reflux. To avoid hydrolysis of carbamoyl chloride, anhydrous basic conditions rather than aqueous conditions were chosen for the coupling. The combination of Pd(PPh₃)₄ with CsF was tested (entry 1). After refluxing for 16 h, the desired amide, 4aa, was isolated in only 36% yield, and a considerable amount of N,N-dibenzylcarbamoyl fluoride was obtained.17 Other inorganic bases, K₃PO₄, K₂CO₃, and Cs₂CO₃ were tested in the presence of $Pd(PPh_3)_4$. A large amount of chloride **3a** was recovered from the reactions with use of K₃PO₄ and K₂-CO₃: 63% and 81%, respectively (entries 2 and 3). However, when Cs₂CO₃ was used, the reaction proceeded smoothly to give the desired amide 4aa in 78% yield (entry 4). Although this yield was quite acceptable considering the difficulty of the coupling reactions of alkylborane reagents,^{14,15} this reaction was studied further. Increasing the reaction time improved the yield slightly (entry 5). A quick investigation of palladium catalysts showed that the frequently utilized 'Bu₃P or dppf complexes were not suitable for the current coupling (entries 6 and 7). The effect of solvent was examined by adding cosolvents to the THF solution after the hydroboration reaction. The addition of either toluene, 1,4-dioxane, DMF, or DME did not improve the yield (entries 8–11).

By using the following conditions, $Pd(PPh_3)_4$ (5 mol %) and Cs_2CO_3 (1.5 equiv) in THF, and refluxing for 16 h, a broad range of amides was obtained in good yield (Table 2). Starting materials were not only simple olefins (entry 1), but also olefins possessing functionalities such as the trimethylsilyl group (entry 2), benzyl ether (entry 3), acetal (entry 4), and ester (entry 5). 1,1-Disubstituted olefins were amidated with no problem (entry 5). Carbamoyl chlorides derived from dialkyl and cyclic amines proved to be good coupling partners (entries 6 and 7). Moreover, a carbamoyl chloride derived from an amino acid underwent amidation without any problem (entry 8). These results clearly indicate the advantage of the current methodology: functionalized amides can be synthesized directly from the corresponding one-carbon-less olefins.

This protocol was not limited to alkylboranes generated from olefins. Without optimization, triethylborane, phenylboronic acid, and styrylboronic acid underwent the amidation reaction in excellent yields (eqs 1-3). It is worth noting that the latter



two examples are the first copper-free coupling reactions of boronic acids with carbamoyl chlorides. By comparing the current conditions [cat. $Pd(PPh_3)_4$, Cs_2CO_3] and Deng's conditions [cat. $Pd(PPh_3)_4$, cat. Cu_2O , K_3PO_4],¹⁹ the superior promotion of the reaction by Cs_2CO_3 is highlighted.

A working model for the reaction mechanism was proposed based on the well-accepted mechanism of Suzuki–Miyaura coupling (Scheme 1).²⁰ Of particular mechanistic interest is the possibility of several chemical species corresponding to **B**, from which oxidative addition may proceed. The simplest is chloride **B**¹, which is subjected to the reaction. But if attack of carbonate on **B**¹ occurred, anion **B**², which can be described as a mixed anhydride of carbonic acid and carbamic acid, could be generated.²¹ Considering the significant presence of borane in the reaction mixture, anion **B**² could be trapped as borate **B**³.

⁽¹⁴⁾ Palladium-catalyzed coupling reaction of alkylboranes with aryl or vinyl halides, which is called *B*-alkyl Suzuki–Miyaura coupling, is widely applied in synthesis. For a review, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

⁽¹⁵⁾ Acylation of alkylborane with carboxylic acid derivatives was reported, see: (a) Kabalka, G. W.; Malladi, R. R.; Tejedor, D.; Kelley, S. *Tetrahedron Lett.* **2000**, *41*, 999. (b) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554.

⁽¹⁶⁾ Carbamoyl chlorides 3a and 3d can be obtained easily from corresponding amine and triphosgene, see the Supporting Information.

⁽¹⁷⁾ Kristensen et al. reported similar fluorination, see ref 13b.

⁽¹⁸⁾ Netherton, M. R.; Fu, G. C. Org. Lett. 2001, 3, 4295.

⁽¹⁹⁾ Deng et al. reported that they obtained *N*,*N*-dibutylbenzamide in 93% yield from phenyl boronic acid and *N*,*N*-dibutylcarbamoyl chloride (ref 13a). The reaction was carried out in the presence of Pd(PPh₃)₄ (3 mol %), Cu₂O (6 mol %), and K₃PO₄ (3.3 equiv) in toluene at 80 °C for 24 h. (20) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

⁽²¹⁾ Surprisingly, *O-tert*-butylated analogues of structure \mathbf{B}^2 are known to be isolatable in some cases from the reactions of amines with Boc₂O, see: (a) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368. (b) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. J. Org. Chem. **2004**, *69*, 2367.

 TABLE 2.
 One-Pot Amidation of Olefins through

 Palladium-Catalyzed Coupling of Alkylboranes and Carbamoyl
 Chlorides^a





 a Reactions were carried out on a 1.6–3.8 mmol scale under Ar; isolated yields based on carbamoyl chlorides are reported.

Although the reactivity of \mathbf{B}^2 or \mathbf{B}^3 toward transition metal complexes has never been discussed to our knowledge, oxidative addition of carboxylic acid anhydrides toward palladium complexes has been shown to be involved in some coupling reactions.²² Efforts are underway to elucidate the mechanistic details of the current reaction.

SCHEME 1. Plausible Mechanism for Alkylborane Amidation.



In conclusion, we have demonstrated a one-pot amidation of olefins through the first reported palladium-catalyzed coupling reaction of carbamoyl chlorides with alkylboranes. With use of this reaction protocol, one-carbon-less olefins are promising synthetic precursors for amides. Under the same reaction conditions, the first copper-free coupling reaction of boronic acids with carbamoyl chlorides was demonstrated. Additionally, the possibility of mixed anhydrides of carbonic acids and carbamic acids as a substrate for oxidative addition to palladium complexes was proposed, which may be a starting point for new transition-metal-catalyzed reactions.

Experimental Section

Typical Procedure for One-Pot Amidation of Olefins. To styrene (1a) (220 µL, 1.92 mmol) at 0 °C was added 9-BBN-H (0.5 M solution in THF, 4.20 mL, 2.10 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. N,N-Dibenzylchloroformamide (3a) (343 mg, 1.32 mmol) in anhydrous THF (3 mL), Cs₂CO₃ (636 mg, 1.95 mmol), and Pd(PPh₃)₄ (77.0 mg, 0.0666 mmol) were added sequentially at 0 °C. After the solution was stirred for 16 h at reflux, water was added at 0 °C, and the product was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by silica gel column chromatography (hexane/EtOAc = $9/1 \rightarrow 5/5$), followed by trituration from hexane, and drying under vacuum gave N,N-dibenzyl-3-phenylpropanamide **4aa** (339 mg, 78%) as a white solid: $R_f 0.48$ (hexane/Et₂O = 5/5); mp 104.5-105.0 °C; ¹H NMR (CDCl₃) δ 7.35-7.24 (m, 8H), 7.20-7.17 (m, 5H), 7.07 (d, 2H, J = 7.4 Hz), 4.60 (s, 2H), 4.37(s, 2H), 3.05 (t, 2H, J = 3.1 Hz), 2.72 (t, 2H, J = 3.1 Hz); ¹³C NMR (ô, CDCl₃) 173.0, 141.4, 137.5, 136.6, 129.1, 128.8, 128.7, 128.6, 128.5, 127.8, 127.6, 126.5, 126.3, 50.0, 48.4, 35.1, 31.7; IR (KBr) 1633 cm⁻¹; HRMS (EI) calcd for C₂₃H₂₃NO (M⁺) 329.1779, found 329.1773. Anal. Calcd for C23H23NO: C, 83.85; H, 7.04; N, 4.25. Found: C, 84.15; H, 7.20; N, 4.24.

Acknowledgment. This work was supported by grants from the 21st Century COE Program, (Knowledge Information Infrastructure for Genome Science) and a Grant-in-Aid for Scientific Research on Priority Areas 17035043, from The Ministry of Education, Culture, Sports, Science and Technology.

Supporting Information Available: Detailed experimental procedures and characterization data of key compounds. This material is available free of charge via the Internet at http:// pubs.acs.org.

JO070724U

^{(22) (}a) Yamamoto, A. J. Organomet. Chem. **2004**, 689, 4499 and references cited therein. (b) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. J. Am. Chem. Soc. **2005**, 127, 11102.