Rhodium-catalysed addition reaction of aryl- and alkenylboronic acids to isocyanates†

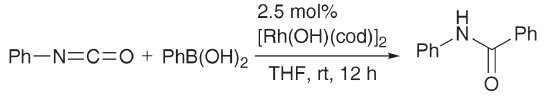
Tomoya Miura, Yusuke Takahashi and Masahiro Murakami*

Received (in Cambridge, UK) 18th June 2007, Accepted 10th July 2007
First published as an Advance Article on the web 2nd August 2007
DOI: 10.1039/b709203b

The addition reaction of aryl- and alkenylboronic acids to isocyanates is catalysed by a rhodium(I) complex, affording secondary amides under mild conditions.

The rhodium-catalysed addition reaction of organoboron reagents to electrophilic organic compounds is attracting increasing attention as a useful method for carbon–carbon bond formation in organic synthesis.[1] Organorhodium(I) species, generated by transmetalation between boron and rhodium, are considerably less polar nucleophiles than conventional organometallic reagents like Grignard and organolithium reagents. Nevertheless, organorhodium(I) species are reactive enough to add intermolecularly to various unsaturated compounds. Polar unsaturated electrophiles such as aldehydes,[2] imines[3] and nitriles[4] are supposedly less reactive toward organorhodium(I) species than less polar unsaturated substrates like electron-deficient alkenes[5] and alkynes,[6] although few experimental results are available for a direct comparison of the reactivities of these electrophiles. Mori demonstrated that, despite their highly polar nature, isocyanates can act as good electrophilic substrates in reactions with organorhodium(I) species generated from organotin reagents by transmetalation.[7] As precursors to organorhodium(I) species, organoboron reagents, organoboronic acids in particular, possess advantages over organotin reagents in terms of commercial availability, toxicity and ease of post-treatment.[8] In addition, organoboron reagents are readily available with a wide variety of functional groups due to the recent development of direct preparative methods that do not require the use of highly reactive Grignard and organolithium reagents.[9] We now report the rhodium-catalysed addition reaction of aryl- and alkenylboronic acids to isocyanates, forming secondary amides under mild conditions.[10]

Phenyl isocyanate (**1a**, 1.0 equiv.) was treated with phenylboronic acid (**2a**, 1.5 equiv.) in the presence of $[Rh(OH)(cod)]_2$ (5 mol% Rh, cod = cycloocta-1,5-diene) in THF (0.1 M) at room temperature under an argon atmosphere [eqn (1)]. Unlike the case of organotin reagents, which required heating at 70 °C,[7] the addition reaction of **2a** to **1a** proceeded smoothly at room temperature to consume **2a** in 12 h. However, hydrolysis of intermediate phenylrhodium(I) species **A** (*vide infra*) occurred concomitantly, and chromatographic isolation on silica gel afforded the secondary amide **3aa** in only moderate yield (49%). The use of three equivalents of **2a** improved the yield of **3aa** to 82%.



(1)

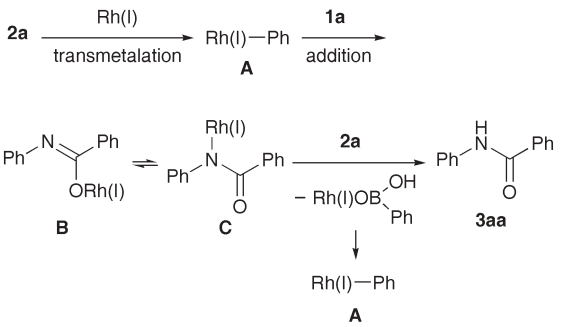
1a	2a	3aa
(1.0 equiv.)	(1.5 equiv.)	49%
	(3.0 equiv.)	82%

A potential reaction pathway is depicted in Scheme 1. Initially, phenylrhodium(I) species **A** is generated by transmetalation between phenylboronic acid (**2a**) and rhodium(I).[11] The phenylrhodium(I) species **A** then adds to the isocyanato group of **1a** to form *O*-bound and/or *N*-bound rhodium(I) complex (**B** and/or **C**). Protonolysis with **2a** releases the product **3aa** together with rhodium(I) boronate, which regenerates **A** through β-aryl elimination.[12] The use of other organoboron reagents such as phenylboroxine (**2a′**) and 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane in place of **2a** gave **3aa** in lower yield under the same reaction conditions.

For comparison, 4-$CH_3C_6H_4SnBu_3$ (3.0 equiv.) was reacted with **1a** *at room temperature* in the presence and absence of phenol.[13] No adduct **3ab** was produced in either case. It is likely that the rate of the entire addition reaction largely depends on the rate of transmetalation generating the arylrhodium(I) species **A**.

Various combinations of isocyanates **1** and organoboronic acids **2** were examined for the synthesis of amides **3** (Table 1).‡ The catalytic process worked well with electron-rich arylboronic acids **2b**–**2d** (entries 1–3). Even the hindered *o*-tolylboronic acid (**2c**) afforded the corresponding amide **3ac** in high yield. On the other hand, electron-poor arylboronic acids **2e** and **2f** were less reactive (entries 4 and 5). 3-Thienylboronic acid (**2g**) and the alkenylboronic acids **2h** and **2i** also participated in the addition reaction (entries 6–8).

Three regio-isomeric tolyl isocyanates **1b**–**1d** all afforded the corresponding adducts **3ba**–**3da** in good yield (entries 9–11). A



Scheme 1 A plausible mechanism for the catalysed addition reaction.

Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto, 615-8510, Japan.
E-mail: murakami@sbchem.kyoto-u.ac; Fax: +81 75 383 2748;
Tel: +81 75 383 2747

† Electronic supplementary information (ESI) available: General experimental information and spectral data. See DOI: 10.1039/b709203b

Table 1 Rh(I)-catalysed reaction of isocyanates **1** (R^1NCO) with organoboronic acids **2** ($R^2B(OH)_2$)[a]

Entry	1	R^1	2	R^2	3	Yield (%)[b]
1	**1a**	Ph	**2b**	4-MeC_6H_4	**3ab**	88
2	**1a**	Ph	**2c**	2-MeC_6H_4	**3ac**	90
3	**1a**	Ph	**2d**	3-$MeOC_6H_4$	**3ad**	84
4	**1a**	Ph	**2e**	3-BrC_6H_4	**3ae**	58
5	**1a**	Ph	**2f**	3-ClC_6H_4	**3af**	21
6	**1a**	Ph	**2g**	3-Thienyl	**3ag**	94
7	**1a**	Ph	**2h**	β-Styryl	**3ah**	91
8	**1a**	Ph	**2i**	(*E*)-Pent-1-enyl	**3ai**	73
9	**1b**	4-MeC_6H_4	**2a**	Ph	**3ba**	84
10	**1c**	3-MeC_6H_4	**2a**	Ph	**3ca**	84
11	**1d**	2-MeC_6H_4	**2a**	Ph	**3da**	68
12	**1e**	4-$MeOC_6H_4$	**2a**	Ph	**3ea**	78
13	**1f**	4-ClC_6H_4	**2a**	Ph	**3fa**	76
14	**1g**	4-$EtO_2CC_6H_4$	**2a′**	Ph ($R^2BO)_3$	**3ga**	83[c]
15	**1h**	3-$O_2NC_6H_4$	**2a′**	Ph ($R^2BO)_3$	**3ha**	74[c]
16	**1i**	2-(1-Pent-1-enyl)-C_6H_4	**2a**	Ph	**3ia**	90
17	**1j**	*n*-Hexyl	**2a**	Ph	**3ja**	75
18	**1k**	Cyclohexyl	**2a**	Ph	**3ka**	62
19	**1k**	Cyclohexyl	**2a′**	Ph ($R^2BO)_3$	**3ka**	93[c]

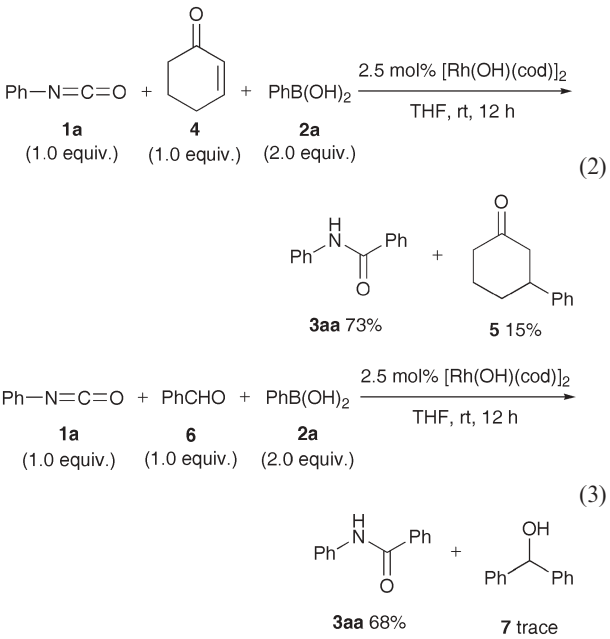
[a] **1** (0.2 mmol), **2** (0.6 mmol), $[Rh(OH)(cod)]_2$ (5 mol% Rh) in THF (0.1 M) at room temperature for 12 h under Ar unless otherwise noted. [b] Isolated yields of products with >95% purity after chromatography. [c] **1** (0.2 mmol), phenylboroxine (**2a′**, 0.2 mmol, 3.0 equiv. of B), $[Rh(OH)(cod)]_2$ (5 mol% Rh) in dioxane (0.1 M) at 100 °C for 12 h under Ar.

wide range of substituents were tolerated on the aryl group of **1** (entries 12–16). Substrates **1g** and **1h** possessing electron-withdrawing ester and nitro groups on the benzene rings, respectively, were reacted with phenylboroxine (**2a′**) in place of **2a** in order to suppress a potentially competitive hydrolysis–decarboxylation pathway that would generate the corresponding aniline derivatives (entries 14 and 15). The successful results obtained with **1g** and **1h** demonstrated that ester and nitro groups, which would be affected by Grignard reagents, are compatible with the present reaction conditions. In addition, alkyl isocyanate **1j** and **1k** also reacted with either **2a** or **2a′** (entries 17–19).

We next carried out the following competitive experiments to directly assess the reactivity of a phenylrhodium(I) species toward an isocyanate, an electron-deficient alkene and an aldehyde. Thus, a mixture of phenyl isocyanate (**1a**, 1.0 equiv.) and cyclohex-2-en-1-one (**4**, 1.0 equiv.) was treated with phenylboronic acid (**2a**, 2.0 equiv.) in the presence of $[Rh(OH)(cod)]_2$ (5 mol% Rh). After the reaction mixture was stirred for 12 h *at room temperature*, the corresponding adducts **3aa** and **5** were isolated in 73% and 15% yields, respectively [eqn (2)]. Contrary to our expectation on the basis of functional group polarity, the isocyanate **1a** was a better acceptor for phenylrhodium(I) species than cyclohex-2-en-1-one (**4**). An analogous competition experiment using **1a** and benzaldehyde (**6**) resulted in the formation of **3aa** in 68% yield and a trace of **7** [less than 5% yield, eqn (3)]. These results indicate that the electrophilic reactivities toward phenylrhodium(I) nucleophiles are approximately isocyanate > electron-deficient alkene ≫ aldehyde.

In summary, the rhodium-catalysed addition reaction of organoboronic acids to isocyanates provides a convenient method for the construction of secondary amides. Further synthetic applications of the present reaction are currently under way.

This work was supported in part by a Grant-in-Aid for Young Scientists (B) 18750084 and Scientific Research on Priority Areas 18032040 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.



Notes and references

‡ *General procedure*: To an oven-dried flask was added $[Rh(OH)(cod)]_2$ (2.3 mg, 5.0 μmol, 5 mol% Rh), organoboronic acid **2** (0.60 mmol, 3.0 equiv.) and a solution of isocyanate **1** (0.20 mmol, 1.0 equiv.) in dry THF (2.0 mL). The reaction mixture was stirred at room temperature for 12 h under an argon atmosphere, and then quenched with addition of water (2.0 mL). The resulting aqueous solution was extracted with ethyl acetate (4 × 10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (chloroform–ethyl acetate 20 : 1 or 10 : 1) to give the corresponding amide **3**.

1 For reviews, see: (*a*) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169; (*b*) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; (*c*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217.

2 (*a*) M. Sakai, M. Ueda and N. Miyaura, *Angew. Chem., Int. Ed.*, 1998, **37**, 3279; (*b*) M. Pucheault, S. Darses and J.-P. Genêt, *J. Am. Chem. Soc.*, 2004, **126**, 15356; (*c*) S. U. Son, S. B. Kim, J. A. Reingold, G. B. Carpenter and D. A. Sweigart, *J. Am. Chem. Soc.*, 2005, **127**, 12238; (*d*) K. Suzuki, K. Kondo and T. Aoyama, *Synthesis*, 2006, 1360.

3 (*a*) M. Ueda, A. Saito and N. Miyaura, *Synlett*, 2000, 1637; (*b*) M. Kuriyama, T. Soeta, X. Hao, Q. Chen and K. Tomioka, *J. Am. Chem. Soc.*, 2004, **126**, 8128; (*c*) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584; (*d*) M. A. Beenen, D. J. Weix and J. A. Ellman, *J. Am. Chem. Soc.*, 2006, **128**, 6304; (*e*) R. B. C. Jagt, P. Y. Toullec, D. Geerdink, J. G. de Vries, B. L. Feringa and A. J. Minnaard, *Angew. Chem., Int. Ed.*, 2006, **45**, 2789.

4 (*a*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2005, **7**, 2229; (*b*) H. Shimizu and M. Murakami, *Chem. Commun.*, 2007, 2855.

5 (*a*) M. Sakai, H. Hayashi and N. Miyaura, *Organometallics*, 1997, **16**, 4229; (*b*) J.-F. Paquin, C. Defieber, C. R. J. Stephenson and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 10850; (*c*) C. G. Frost, S. D. Penrose, K. Lambshead, P. R. Raithby, J. E. Warren and R. Gleave, *Org. Lett.*, 2007, **9**, 2119; (*d*) W.-L. Duan, H. Iwamura, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2007, **129**, 2130 and references therein.

6 (*a*) T. Hayashi, K. Inoue, N. Taniguchi and M. Ogasawara, *J. Am. Chem. Soc.*, 2001, **123**, 9918; (*b*) M. Murakami and H. Igawa, *Helv. Chim. Acta*, 2002, **85**, 4162; (*c*) M. Lautens and M. Yoshida, *Org. Lett.*, 2002, **4**, 123; (*d*) E. Genin, V. Michelet and J.-P. Genêt, *Tetrahedron Lett.*, 2004, **45**, 4157.

7 T. Koike, M. Takahashi, N. Arai and A. Mori, *Chem. Lett.*, 2004, **33**, 1364.
8 *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005.
9 For selected recent examples, see: (*a*) J. Takagi, K. Takahashi, T. Ishiyama and N. Miyaura, *J. Am. Chem. Soc.*, 2002, **124**, 8001; (*b*) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr. and M. R. Smith, III, *Science*, 2002, **295**, 305; (*c*) M. Suginome, M. Shirakura and A. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 14438.
10 For addition of Grignard reagents to isocyanates, see: J. M. Brown and S. K. Armstrong, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon Press, Oxford, 1995, vol. 11, pp. 139–141.
11 T. Hayashi, M. Takahashi, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 2002, **124**, 5052.
12 P. Zhao, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 1876.
13 Phenol was an effective additive in the rhodium-catalysed addition reaction of organotin reagents[7].