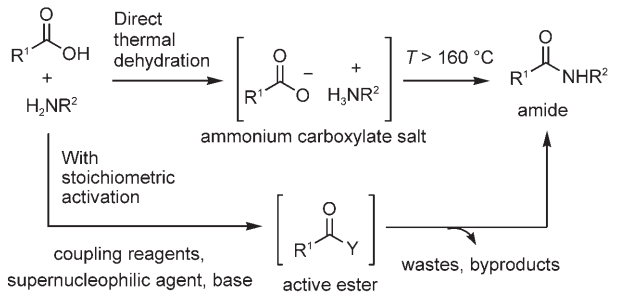
Organocatalysis

DOI: 10.1002/anie.200705468

Direct and Waste-Free Amidations and Cycloadditions by Organocatalytic Activation of Carboxylic Acids at Room Temperature**

*Raed M. Al-Zoubi, Olivier Marion, and Dennis G. Hall**

The amide bond is ubiquitous in nature. It links amino acids to form peptides and proteins and is an important component of many natural products. Furthermore, it has been estimated that as many as 25% of all synthetic pharmaceutical drugs contain an amide unit.[1] Consequently, the development of efficient amidation methods continues to be an important scientific pursuit.[2,3] Despite the favorable thermodynamic stability of the resulting amide bond, the simple thermal dehydration reaction between a carboxylic acid and an amine is plagued by a large activation energy. The initial formation of a stable ammonium carboxylate salt deters the dehydration step, and the intermediate salt collapses to provide the amide product only at very high temperatures (over 160 °C) that are incompatible with most functionalized molecules (Scheme 1).[4] Consequently, there are still no general methods to access amides directly from free carboxylic acids and amines in a simple, green, and atom-economical fashion at ambient temperature.[5] Common means for forming amide bonds involve the use of stoichiometric excesses of expensive and often toxic coupling reagents such as carbodiimides or phosphonium or uronium salts to activate and dehydrate the carboxylic acid.[2] These reagents and their associated co-reagents, including bases, supernucleophiles, and other additives, generate large amounts of wasteful by-products that complicate the isolation of the desired amide product.



Scheme 1. Direct amide formation by reaction of free carboxylic acids and amines.

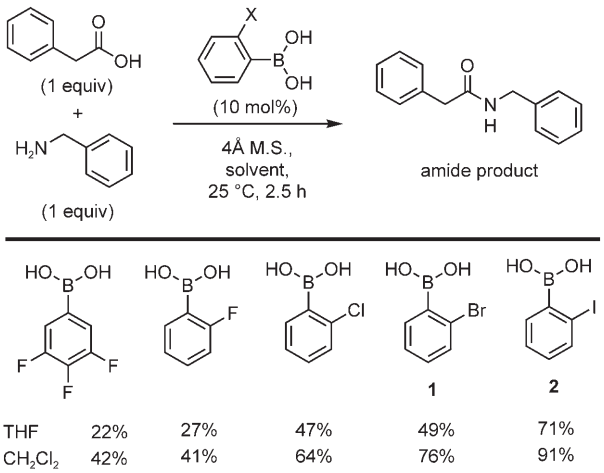
Our interest in the applications of *ortho*-functionalized arylboronic acids[6] led us to examine the catalytic potential of these compounds, with the objective of identifying a catalyst for direct amidation that would function under practical and mild conditions at room temperature. Precedent for this approach was reported in 1996, when Yamamoto and co-workers described the clever use of electron-poor arylboronic acids as catalysts for direct amidations.[7,8] However, even the most efficient boronic acid, 3,4,5-trifluorophenylboronic acid, required heating at reflux in solvent at temperatures over 110 °C for several hours (for other boronic acids, also at high temperatures, see references [9,10]). Using a model amidation reaction between phenylacetic acid and benzylamine, we undertook a systematic evaluation of over 45 *ortho*-functionalized arylboronic acids in different organic solvents (see the Supporting Information for a complete list). A handful were active at room temperature, and in all cases it was found essential to scavenge the water by-product of the reaction, which was conveniently accomplished by the use of molecular sieves.[11] A second round of evaluation of the most promising candidates revealed *ortho*-bromophenylboronic acid (**1**) and the hitherto unknown *ortho*-iodophenylboronic acid (**2**)[12] to be the most efficient catalysts (Scheme 2). The iodo derivative (**2**) in particular was found to give higher yields within shorter reaction times than the commercially available **1**. Both of these catalysts are clearly superior to 3,4,5-trifluorophenylboronic acid[7] and boric acid.[13,14] Further optimization of reaction conditions identified methylene chloride and tetrahydrofuran as the optimal solvents. As excess amine was found to slow down the reactions, it was deemed preferable to use a slight excess of the carboxylic acid.

The examples compiled in Table 1 demonstrate the versatility and scope of the new catalysts **1** and **2** in promoting direct amidations at room temperature. Standard conditions employed the commercially available catalyst **1** in methylene chloride containing 4Å molecular sieves. To ensure reaction completion in the case of slower substrates, a reaction time of 48 h was chosen. Carboxylic acids and primary amines containing aromatic substituents, straight aliphatic chains, or branched aliphatic chains, are suitable substrates (Table 1, entries 1–7). Although an acyclic secondary amine failed to react at room temperature (Table 1, entry 2), cyclic ones

[*] R. M. Al-Zoubi, Dr. O. Marion, Prof. Dr. D. G. Hall
Department of Chemistry
Gunning-Lemieux Chemistry Centre
University of Alberta
Edmonton, Alberta, T6G 2G2 (Canada)
Fax: (+1) 780-492-8231
E-mail: dennis.hall@ualberta.ca
Homepage: http://www.chem.ualberta.ca/~dhall/

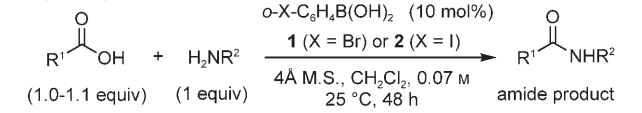
[**] Acknowledgement for financial support of this research is made to the Natural Sciences and Engineering Research Council (NSERC) of Canada (Discovery Grant to D.G.H.) and the University of Alberta. We thank Dr. R. McDonald for the X-ray crystallographic analysis and Prof. F. Dean Toste for helpful suggestions.

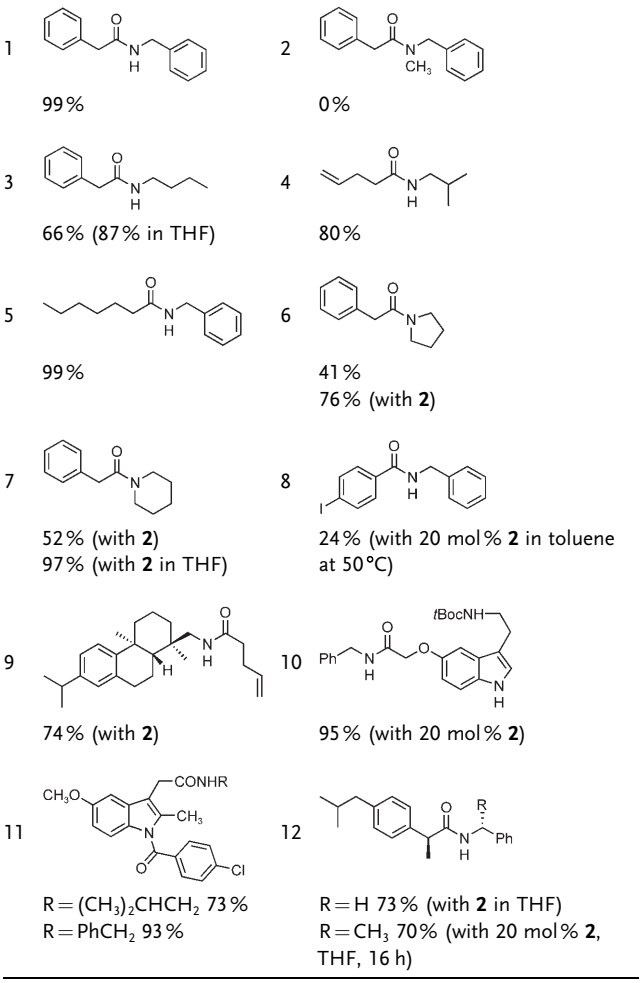
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Comparison of product yields between the most promising *ortho*-substituted arylboronic acid catalysts in a model amidation reaction.

Table 1: Direct amidations between carboxylic acids and amines catalyzed by boronic acids **1** and **2** at room temperature.[a]

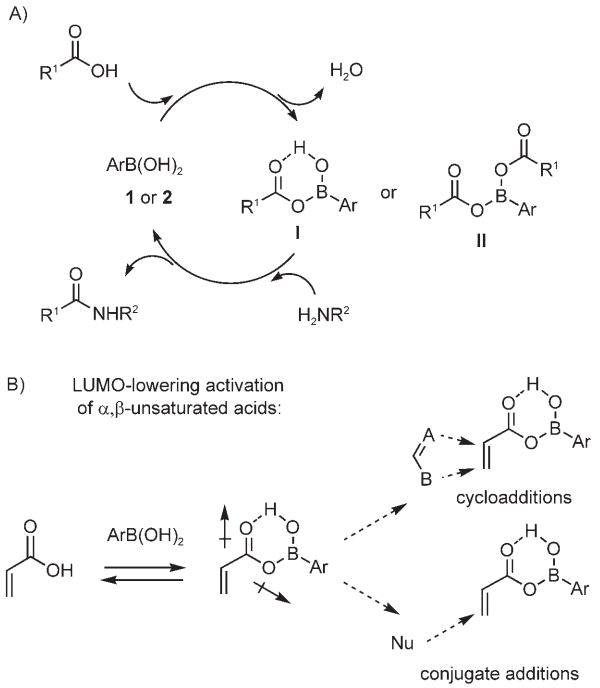




[a] The boronic acid (0.05 mmol), carboxylic acid (0.50-0.55 mmol), and the amine (0.5 mmol) were stirred at 24–25 °C for 48 h in solvent containing powdered activated 4Å molecular sieves (1 g). Unless indicated otherwise, amidations took place in CH_2Cl_2 with catalyst **1** (10 mol%). Product purity was greater than 95% according to ^{1}H NMR spectroscopic analysis. Boc = butoxycarbonyl.

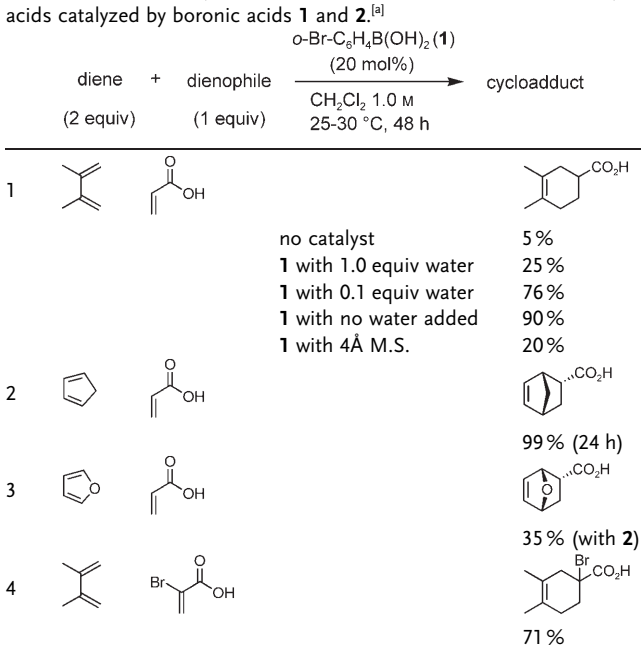
provided the expected tertiary amides (Table 1, entries 6 and 7). Aromatic carboxylic acids were found to require a higher temperature and afforded lower yields after 48 h (Table 1, entry 8). In other difficult cases, such as the formation of cyclic tertiary amides, the superior *ortho*-iodo catalyst **2** is more appropriate (Table 1, entry 6). Likewise, with some substrates the use of THF as solvent gives higher yields (e.g., Table 1, entries 3 and 7). The hindered hydrophobic amine leelamine reacted in good yield (Table 1, entry 9). Highly functionalized substrates were successfully employed to make biologically important amide products using this simple and highly atom-economical process. For example, amides of the drug indomethacin are known to display potent biological properties, such as the inhibition of COX-2 enzymes.[15,16] Considering their reported method of preparation using excess coupling reagents and chromatographic purification, it is remarkable that indomethacin amides can be made with such ease using the new catalysts (Table 1, entry 11). A protected serotonin derivative was prepared in pure form with a high yield (Table 1, entry 10). Ibuprofen amides have been reported to display improved anti-inflammatory activity with less toxicity.[17] In this case, the amidation of optically active (*S*)-ibuprofen with both benzylamine and (*R*)-(+)-α-methylbenzylamine in THF led to the corresponding amides with less than 5% racemization (Table 1, entry 12). Given the propensity of ibuprofen and its amides to racemize,[18] this result provides a clear testimony to the mildness of these low-temperature conditions.[19] These direct catalytic amidations are operationally very simple. They employ equimolar amounts of acid and amine substrates, require no heating or cooling source, generate no by-products, and they afford pure amide products after a simple filtration and acid–base extractions to remove any unreacted substrates and the catalyst. The boronic acid catalyst can be recovered in high yield from the basic aqueous phase.

The previously proposed mechanism for boronic acid catalyzed amidations was supported by the isolation of a monoacyl boronate intermediate **I** (Scheme 3 A),[7] but the reaction may also involve a diacylboronate (**II**).[10] Intermediate **I** would provide electrophilic activation of the carboxylate group through boron conjugation and internal H-bonding.[20] The exceptional activity of *ortho*-iodophenylboronic acid is unexpected and probably not due to steric effects. The fact that the *para* isomer is significantly less effective confirms the crucial importance of the *ortho* position. On the other hand, *o*,*o*′-dihaloarylboronic acids are less effective, which is consistent with the need for one unsubstituted *ortho* position. Because of the reverse trend of efficacy observed in the *ortho*-halide series (I > Br > Cl > F, cf. Scheme 2), inductive effects alone cannot account for the superiority of catalyst **2**. Owing to the size and electron density of the iodo substituent and X-ray crystallographic observations such as the unusual angular



Scheme 3. A) Postulated mechanism for direct amidations with catalysts **1** and **2**. B) Organocatalytic activation of α,β-unsaturated carboxylic acids.

Table 2: Diels–Alder cycloadditions of free α,β-unsaturated carboxylic acids catalyzed by boronic acids **1** and **2**.[a]

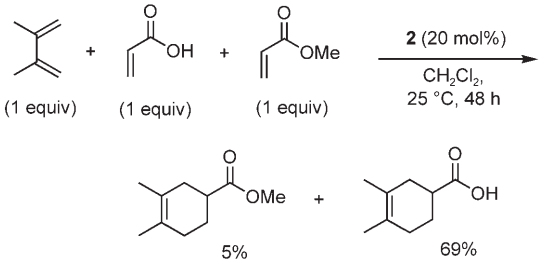


1		no catalyst	5%
		1 with 1.0 equiv water	25%
		1 with 0.1 equiv water	76%
		1 with no water added	90%
		1 with 4Å M.S.	20%
2			99% (24 h)
3			35% (with **2**)
4			71%

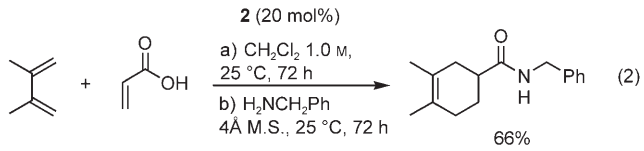
[a] The boronic acid (0.28 mmol), carboxylic acid (1.4 mmol), and diene (2.78 mmol) were stirred at 25 °C in dichloromethane. Unless indicated, the mixture was stirred for 48 h with catalyst **1** (20 mol%). Yields are for purified products.

distortion of the B-C-C bonds (117°, 126°) of boronic acid **2**,[21] subtle electronic or structural effects may be at play.[22]

Beyond direct amidations, the carboxylic acid group tends to be a difficult functional group that is incompatible or unreactive in several important chemical reactions. It can be envisaged that the same catalytic activation mechanism could be exploited in cycloadditions and conjugate additions of unsaturated carboxylic acids (Scheme 3B). Such a concept using boronic acids as organocatalysts would complement the pyrrolidine-catalyzed iminium ion activation of α,β-unsaturated ketones and aldehydes.[23] As a test, we chose the thermal Diels–Alder reactions of α,β-unsaturated carboxylic acids, which are notoriously difficult. Indeed, acrylic acid is known to induce decomposition of functionalized dienes at high temperatures, and it is quite unreactive at low temperatures.[24] We found that boronic acids **1** and **2** catalyze Diels–Alder reactions of acrylic acid and α-bromoacrylic acid in good to high yields at room temperature (Table 2).[25] The reactions proceed in less than 5% yield in the absence of the catalyst. Interestingly, the absence of water (i.e., when using molecular sieves) does not allow catalyst turnover and leads to low yields.[26] Although there are a few reported cases of Lewis acid catalyzed [4+2] cycloadditions of acrylic acid,[27,28] the current system permits a remarkable selectivity over the corresponding esters that would be difficult to achieve with noncovalent catalysis [Eq. (1)]. Furthermore, the possibility to perform cascade reactions with the help of simple organocatalysts is very attractive from the standpoint of step-economy and synthetic efficiency.[29] In this regard, it was found possible to combine the two reactions described herein and promote a remarkable "one-pot" sequential Diels–Alder cycloaddition/amidation with a single catalyst, boronic acid **2** [Eq. (2)].



(1)



(2)

In the past decade, boronic acids have emerged as a very useful and versatile class of organic compounds.[30] Herein, we describe the exceptional ability of *ortho*-bromo- and, especially, *ortho*-iodophenylboronic acid to serve as recoverable catalysts for direct amidations and cycloadditions of carboxylic acids under mild and waste-free conditions at room temperature. With three other ring positions that can be electronically modulated with various substituents, improved catalysts could be designed to further expand the substrate

scope of these reactions. Along with a better mechanistic understanding, this concept of organocatalytic activation of carboxylic acids could become broadly applicable to other important synthetic transformations.

Experimental Section

Example of procedure for organocatalytic amidations (*N*-benzylphenylacetamide): A 25-mL round-bottom flask equipped with a stirbar was charged with phenylacetic acid (0.075 g, 0.55 mmol, 1.1 equiv), *ortho*-bromophenylboronic acid (10 mg, 0.05 mmol, 10 mol%), and activated 4Å molecular sieves (1 g). Dichloromethane (7 mL) was added, and the mixture was stirred for 10 min. Then, benzylamine (55 mL, 0.5 mmol, 1 equiv) was added. The resulting suspension was stirred at room temperature (24–25 °C) for 48 h, after which time it had become homogeneous. The reaction mixture was filtered through a pad of Celite 545. The filtrate was washed with an aqueous acidic solution (pH 4), aqueous basic solution (pH 10–11), and brine. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered, and evaporated to yield the amide product in essentially pure form.

Received: November 29, 2007
Published online: March 5, 2008

Keywords: amides · boronic acids · carboxylic acids · cycloaddition · organocatalysis

[1] A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55–68.
[2] C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852.
[3] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.
[4] B. S. Jursic, Z. Zdravkovski, *Synth. Commun.* **1993**, *23*, 2761–2770.
[5] For alternative approaches not employing carboxylic acids, see: a) N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755; b) W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065; c) N. Carrillo, E. A. Davalos, J. A. Russak, J. W. J. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 1452–1453; d) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792; e) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.
[6] M. Dowlut, D. G. Hall, *J. Am. Chem. Soc.* **2006**, *128*, 4226–4227.
[7] K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197.
[8] T. Maki, K. Ishihara, H. Yamamoto, *Tetrahedron* **2007**, *63*, 8645–8657.
[9] R. Latta, G. Springsteen, B. Wang, *Synthesis* **2001**, 1611–1613.
[10] K. Arnold, B. Davies, R. L. Giles, C. Grojean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813–820.
[11] Molecular sieves were shown to catalyze amidations at very high temperatures: J. Cossy, C. Pale-Grosdemange, *Tetrahedron Lett.* **1989**, *30*, 2771–2774. No such effect was observed under our reaction conditions.
[12] Catalyst **2** was synthesized based on a procedure by Scott and coworkers: H. A. Wegner, H. Reisch, K. Rauch, A. Demeter, K. A. Zachariasse, A. de Meijere, L. T. Scott, *J. Org. Chem.* **2006**, *71*, 9080–9087. See detailed procedure in Supporting Information.
[13] P. Tang, H. Krause, A. Fürstner, *Org. Synth.* **2005**, *81*, 262–267.
[14] R. K. Mylavarapu, G. C. M. K. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya, R. Bandichhor, *Org. Process Res. Dev.* **2007**, *11*, 1065–1068.
[15] A. S. Kalgutkar, A. B. Marnett, B. C. Crews, R. P. Remmel, L. J. Marnett, *J. Med. Chem.* **2000**, *43*, 2860–2870.
[16] C. W. Moth, J. J. Prusakiewicz, L. J. Marnett, T. P. Lybrand, *J. Med. Chem.* **2005**, *48*, 3613–3620.
[17] L. V. Anikina, G. L. Levit, A. M. Demin, Y. B. Vikharev, V. A. Safin, T. V. Matveeva, V. P. Krasnov, *Pharm. Chem. J.* **2002**, *36*, 237–239.
[18] X. Yuchun, L. Huizhou, C. Jiayong, *Int. J. Pharm.* **2000**, *196*, 21–26.
[19] The use of previously reported conditions (toluene, heating at reflux)[7] led to greater than 30% racemization.
[20] The intermediacy of carboxylic acid anhydrides has been ruled out.[10] Further, we observed no formation of acetic anhydride when acetic acid and **2** are mixed alone under the same amidation conditions as in Table 1. Moreover, in the same conditions, butyric anhydride reacted efficiently with *N*-methylbenzylamine, a substrate that failed by direct amidation catalyzed by **2**.
[21] CCDC-664933 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[22] The acidity of **2**, which we measured to have a pK_a of 8.9, is not abnormal (e.g. $PhB(OH)_2$ 8.8) and thus cannot explain its exceptional catalytic activity.
[23] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
[24] For example, the Diels–Alder reactions between acrylic acid and cyclopentadiene and furan require, respectively, one hour at 165 °C and 75 days at 35 °C to achieve reasonable yields of products: a) F. X. Werber, J. E. Jansen, T. L. Gresham, *J. Am. Chem. Soc.* **1952**, *74*, 532–535; b) J. A. Moore, E. M. Partain III, *J. Org. Chem.* **1983**, *48*, 1105–1106.
[25] Phenylboronic acid gave only 25% yield under the same conditions.
[26] Contrary to amidations where attack of the amine regenerates the catalyst (Scheme 3 A), a small amount of water (from condensation of the acid and the catalyst) is required to regenerate the catalyst from the cycloadduct.
[27] K. Furuta, Y. Miza, K. Iwanaga, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 6254–6255.
[28] D. Hyun Ryu, T. W. Lee, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993.
[29] For an excellent essay on cascade catalysis, see: A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477–1489.
[30] *Boronic Acids—Preparation and Applications in Organic Synthesis and Medicine* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**.

