

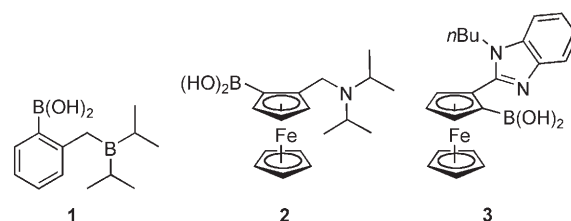
Amidation

Asymmetric Direct Amide Synthesis by Kinetic Amine Resolution: A Chiral Bifunctional Aminoboronic Acid Catalyzed Reaction between a Racemic Amine and an Achiral Carboxylic Acid**

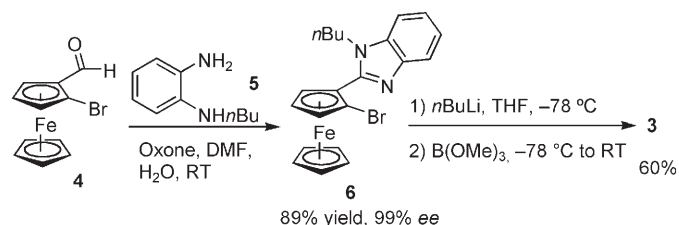
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The formation of amide bonds by direct reaction of amines with carboxylic acids by thermal^[1,2] or catalytic methods^[2–5] is generally a high temperature process. There have been no reports to date of any reactions that involve asymmetric induction during direct amide formation, with the exception of an enzyme-catalyzed process.^[6] Lower temperatures are often preferred for any reaction as it can reduce the amount of reagent, reactant, or thermal product degradation. A more important consideration is that asymmetric induction processes are usually more efficient at lower temperatures because small differences in energy between diastereoisomeric transition states are amplified; however, there are an increasing number of examples where this is not the case and improved asymmetric induction can be obtained at higher temperatures.^[7] With these considerations in mind, we endeavored to develop a catalytic direct amide formation under mild conditions, though still well above room temperature. The current limiting temperature appears to be 85 °C, the temperature at which reactions can be carried out with bifunctional aminoboronic acid catalysts by using azeotropic water removal in fluorobenzene.^[2] Although these reaction conditions are relatively mild compared to all other direct amide formation reactions with boron-derived catalysts,^[4,5] they do not completely preclude the thermal direct amide formation with the more reactive carboxylic acid/amine combinations.^[2] Though the prospect of developing asymmetric catalysts for amide formation may not look promising,^[7] we report herein preliminary results that demonstrate asymmetric processes are possible under elevated temperatures with the development of a planar chiral ferrocene-derived bifunctional aminoboronic acid catalyst.

Our recent interests in the development of bifunctional aminoboronic acids as potential catalysts^[8] led to the development of *N,N*-di-*iso*-propylbenzylaminoboronic acid type catalysts^[2] such as commercially available **1** and planar chiral



ferrocene analogue **2**. We recently reported using a (–)-sparteine-directed metallation to provide **2** in 96% *ee*.^[9] Attempts to prepare other planar chiral aminoboronic acids such as **3** were hindered by the lack of direct access by asymmetric deprotonation methods of ferrocene benzimidazole precursors.^[8d] However, this was circumvented by the synthesis of **3** from the known^[10] (*pS*)-bromoferrocene aldehyde **4** (Scheme 1).



Scheme 1. Synthesis of the (*pS*)-2-(2-boronoferrocenyl)-*N*-*n*-butylbenzimidazole (**3**).

Coupling aldehyde **4** with diamine **5**^[8c] in the presence of Oxone gave bromoferrocenylbenzimidazole **6** in 89% yield and 99% *ee* (determined by chiral HPLC methods, see the Supplementary Information), which compares with a literature value of 98% *ee* for aldehyde **4**.^[10] Subsequent lithium-halogen exchange of **6** provided enantioenriched catalyst **3** (60% yield).

A series of parallel experiments were conducted with catalysts **2** and **3**, in which carboxylic acids **7a–b** were reacted with amines **8a–c** in refluxing fluorobenzene by using activated 3-Å molecular sieves in a Soxhlet (solvent drying system). The uncatalyzed (background) reaction was com-

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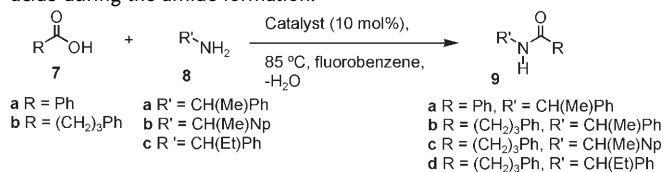
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[**] We thank the EPSRC for research grants (GR/R24722/01, GR/S85368/01, and GR/T22759/01) and GlaxoSmithKline Pharmaceuticals for a CASE award (K.A.). We also thank the EPSRC mass-spectroscopy service, Swansea.

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pared with the reactions having 10 mol % catalyst (either **2** or **3**); the reactions were monitored every four hours over a 48 hour period by HPLC methods (Table 1 and Figures 1 and 2).

Table 1: Evaluation of the catalysts with different amines and carboxylic acids during the amide formation.



Entry	Catalyst	7	8 (equiv)	Conversion [%]	ee [%] ^[a]	Product 9
1 ^[a]	background	a	a(1)	0(48 h)	n.a.	a
2 ^[a]	1	a	a(1)	52(48 h)	n.a.	a
3 ^[a]	2	a	a(1)	38(48 h)	0	a
4 ^[a]	3	a	a(1)	21(48 h)	41(S)	a
5 ^[a]	3	a	a(2)	13(48 h)	18(S)	a
6 ^[a]	background	b	a(1)	11(48 h)	n.a.	b
7 ^[a]	3	b	a(1)	34(12 h), 73(48 h)	29(S) ^[c] , 19(S) ^[d]	b
8 ^[a]	3	b	a(2)	67(48 h)	15(S)	b
9 ^[a]	background	b	b(1)	13(48 h)	n.a.	c
10 ^[a]	3	b	b(1)	85(48 h)	9(S)	c
11 ^[a]	3	b	b(2)	64(48 h)	6(S)	c
12 ^[a]	background	b	c(1)	12(48 h)	n.a.	d
13 ^[a]	3	b	c(1)	65(48 h)	7(S)	d
14 ^[a]	3	b	c(2)	63(48 h)	8(S)	d
15 ^[b]	background	b	a(1)	< 1(48 h)	n.a.	b
16 ^[b]	3	b	a(1)	21(48 h)	16(S)	b

[a] Reaction carried out in refluxing fluorobenzene with 1 equiv **7**. Np = naphthyl; n.a. = not applicable. [b] Reaction carried out in *i*Pr₂O with 1 equiv **7**. [c] The ee value after 12 h. [d] The ee value after 48 h. [e] Absolute configuration indicated in parentheses.

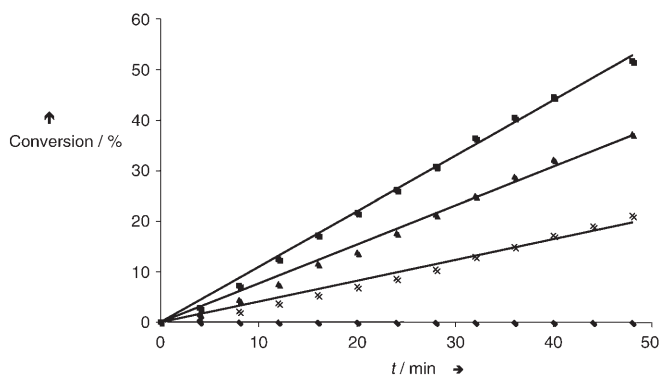


Figure 1. Formation of (1-phenylethyl)benzamide **9a** versus time. ♦ = background; ■ = catalyst **1**; ▲ = catalyst **2**; × = catalyst **3**.

Catalyst **2** is more active than **3** (Figure 2), as we expected on the basis of previous investigations involving the corresponding phenyl-derived bifunctional catalysts;^[2] however, **2** is less reactive than corresponding phenyl-derived catalyst **1**. There is no background reaction for the formation of amide **9a** under these reaction conditions (Table 1, entry 1). Amide **9a** is obtained in a 38 % yield in the presence of catalyst **2**, and

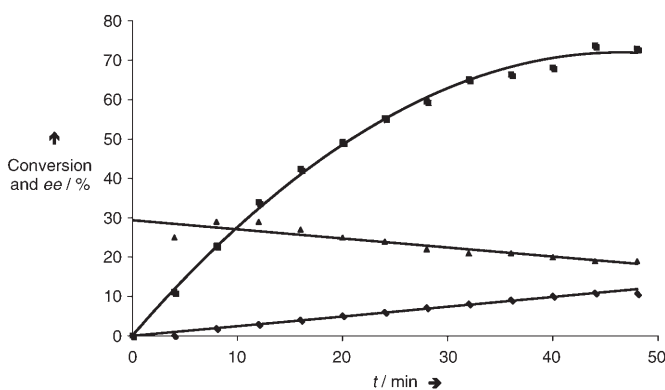
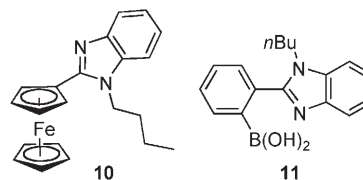


Figure 2. Formation and ee value of (1-phenylethyl)-4-phenylbutyramide **9b** versus time relative to the thermal reaction ♦ = background; ■ = catalyst; ▲ = ee value).

in a 52 % yield with catalyst **1** (Table 1, entry 3 versus entry 2) without any asymmetric induction. In contrast, catalyst **3** provides amide **9a** in 41 % ee (Table 1, entry 4), albeit with a reduced conversion of 21 %, which is approximately two turnovers in 48 hours for the 10 mol % catalyst loading used. The concentration of the amine substrate was increased to two equivalents in an attempt to increase the potential for kinetic resolution (Table 1, entry 5), however, this did not increase the asymmetric induction and, more problematically, it retarded the reaction. Additional examination of catalyst **3** with other racemic α -alkylbenzylamines (Table 1, entries 7, 8, 10, 11, 13 and 14) did not reveal higher levels of asymmetric induction. However, as expected,^[2] the conversions to amides were considerably increased when the more reactive carboxylic acid **7b** was used. Asymmetric induction was still observed, with the highest being 29 % ee after only 12 hours (Table 1, entry 7).

The lower asymmetric induction observed when employing more reactive carboxylic acid **7b** can be explained by examining Figure 2. As the conversion increases, the background reaction contributes 11 % to the formation of product amide **9b**, and therefore, the ee value drops from an initial 29 % to 19 %. Also notable is that during all of the reactions involving catalyst **3** (Table 1), partial degradation of **3** by proto-deboronation to form **10** was observed^[11] when using

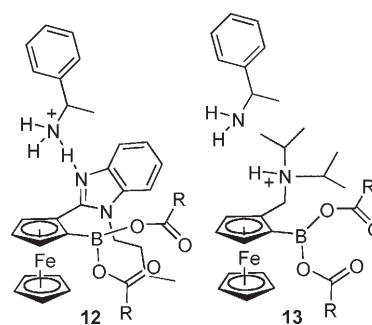


phenylbutyric acid **7b** (re-isolation of 35–40 % of intact catalyst **3**) and benzoic acid **7a** (70–80 % of intact catalyst **3** isolated; see the Supporting Information). This competing side reaction may reduce the asymmetric efficiency of the reaction because of the slow increase in the concentration of boric acid,^[5] particularly in the reactions with phenylbutyric

acid, which may increase the formation of the racemic amide product (above any direct background contributions).^[2a,5] Hence, the low enantiomeric excess observed might be explained by the competitive formation of boric acid, coupled with direct background contributions for the more reactive carboxylic acid (**7b**). Although boric acid is being produced in these reactions, the boric acid is only a more efficient catalyst at higher temperatures than employed herein.^[2] Therefore, the major contributions to asymmetric induction are from the actual catalyst and the background reaction as indicated in Figure 2. Over time the concentration of catalyst **3** is decreases and the background reaction increasingly contributes to product formation. To examine whether it was possible to overcome the competitive effects of both catalyst **3** decomposition and the background contribution to the formation of amide **9b**, an alternative lower boiling solvent for azeotroping water was examined. Parallel reactions were carried out in *i*Pr₂O (68°C). The background reaction was essentially negligible under the lower temperature conditions (Table 1, entry 15), and the reaction with catalyst **3** (Table 1, entry 16) had a conversion of 21% (73% in fluorobenzene) and the asymmetric induction was 16%. Although a drop in boiling point did result in preventing background contributions to the reaction, it did not result in improved asymmetric induction.

Since *N,N*-diisopropylbenzylamine-2-boronic acid (**1**) is a more active catalyst than ferrocene analogue **2**, phenylbenzimidazole boronic acid **11** was screened to see if the same would hold true in the benzimidazole series. However, phenylbenzimidazole boronic acid **11** did not have any activity in any the direct formation of amide bonds, including those reported herein. This could be due in part to B–N chelation, which is not present in diisopropylamine-derived catalysts **1** and **2**, and ferrocene benzimidazole **3** show. In contrast, phenylbenzimidazole boronic acid **11** exists as a mixture of B–N chelates, free boronic acid, and boroxine in solution as evidenced by ¹¹B NMR spectroscopy. Also boroxine shows partial B–N interactions in the solid state^[8c] (two of the three boron atoms are partially tetrahedral or four-coordinate). In addition, the benzimidazole moiety is closer to the boronic acid group in **11** than in **3**, suggesting that the benzimidazole is acting as more than just a steric blocking group and that the distance between the boron and nitrogen atoms is crucial for an efficient reaction involving proton transfer, and therefore catalysis. One explanation for the observed asymmetric induction obtained from catalyst **3** is that the benzimidazole group does not deprotonate the ammonium salt, but preferentially selects (*S*)-amine **8** by hydrogen bonding and effectively delivers the incoming nucleophile to activated diacylboronate^[12] **12**.^[13] In contrast, the lack of asymmetric induction afforded by corresponding catalyst **2** may result from the increased basicity of the *N,N*-diisopropylamine group, which simply deprotonates the salt to allow either enantiomer of an uncomplexed free amine substrate to approach the acylating agent (**13**).

Although direct amide formation has been known and employed for 150 years, asymmetric direct amide formation is less well-known, and the reaction itself has attracted remarkably little attention until recent years. This demonstrates that



this unpromising, yet green reaction may be manipulated to achieve good enantioselectivity and engender new interest in this old process. The discovery that catalyst **3** is able to react with one enantiomer of a chiral α -substituted benzylamine with low to moderate selectivity, and couple it to a moderately activated acylating agent demonstrates the major potential of this type of process. The current challenges are to develop more reactive catalysts that are capable of producing higher asymmetric induction, and to examine alternative methods of removing water from these reactions to drive them efficiently to completion. Developments in these directions will be reported in due course.

Received: December 10, 2007

Published online: February 27, 2008

Keywords: boronates · homogeneous catalysis · kinetic resolution · selectivity

- [1] a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1882**, 15, 977–978; b) J. A. Mitchell, E. E. Reid, *J. Am. Chem. Soc.* **1931**, 53, 1879–1883; c) D. Davidson, P. Newman, *J. Am. Chem. Soc.* **1952**, 74, 1515–1516; d) B. S. Jursic, Z. Zdravkovski, *Synth. Commun.* **1993**, 23, 2761–2770.
- [2] a) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, 348, 813–820; b) K. Arnold, A. S. Batsanov, B. Davies, A. Whiting, *Green Chem.* **2008**, 10, 124–134.
- [3] a) Y. I. Leitman, M. S. Pevzner, *Zh. Prikl. Khim.* **1963**, 36, 632–639; b) W. Walter, H. Besendorf, O. Schnider, *Helv. Chim. Acta* **1961**, 44, 1546–1554.
- [4] a) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1996**, 61, 4196–4197; b) K. Ishihara, S. Ohara, H. Yamamoto, *Macromolecules* **2000**, 33, 3511–3513; c) K. Ishihara, S. Kondo, H. Yamamoto, *Synlett* **2001**, 1371–1374; d) K. Ishihara, S. Kondo, H. Yamamoto, *Org. Synth.* **2002**, 79, 176–185; e) T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, 7, 5043–5046; f) T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, 8, 1431–1434.
- [5] P. Tang, *Org. Synth.* **2002**, 81, 262–272.
- [6] V. Gotor, *Bioorg. Med. Chem.* **1999**, 7, 2189–2197.
- [7] a) D. Enders, H. Gielena, J. Runsinka, K. Breuerb, S. Brodeb, K. Boehnb, *Eur. J. Inorg. Chem.* **1998**, 913–919; b) Y.-G. Wang, M. Ueda, X. Wang, Z. Han, K. Maruoka, *Tetrahedron* **2007**, 63, 6042–6050; c) P. Bachu, J. S. Gibson, J. Sperry, M. A. Brimble, *Tetrahedron: Asymmetry* **2007**, 18, 1618–1624; d) A. T. Axtell, J. Klosin, K. A. Abboud, *Organometallics* **2006**, 25, 5003–5009.
- [8] a) R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2003**, 680, 257–262; b) S. W. Coghlan, R. L. Giles, J. A. K. Howard, M. R.

- Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2005**, 690, 4784–4793; c) A. J. Blatch, O. V. Chetina, J. A. K. Howard, L. G. F. Patrick, C. A. Smethurst, A. Whiting, *Org. Biomol. Chem.* **2006**, 4, 3297–3302; d) D. Hérault, K. Aelvoet, A. J. Blatch, A. Al-Majid, C. A. Smethurst, A. Whiting, *J. Org. Chem.* **2007**, 72, 71–75.
- [9] A. S. Batsanov, D. Hérault, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, A. Whiting, *Organometallics* **2007**, 26, 2414–2419.
- [10] a) O. Riant, O. Samuel, H. Kagan, *J. Am. Chem. Soc.* **1993**, 115, 5835–5836; b) O. Riant, O. Samuel, T. Flessner, S. Taudien, H. B. Kagan, *J. Org. Chem.* **1997**, 62, 6733–6745.
- [11] a) H. C. Brown, D. Basavaiah, S. U. Kulkarni, *J. Org. Chem.* **1982**, 47, 3808–3810; b) H. C. Brown, D. Basavaiah, S. U. Kulkarni, H. D. Lee, E.-I. Negishi, J.-J. Katz, *J. Org. Chem.* **1986**, 51, 5270–5276.
- [12] The intervention of a diacylboronate species as the active acylating agent is not proven, but this type of intermediate has been detected by electrospray mass-spectrometry. a) Alternatively a monoacylboronate could be involved; see reference [4a].
- [13] Although hydrogen bonds become weaker at higher temperatures (see C. Czeslik, J. Jonas, *Chem. Phys. Lett.* **1999**, 302, 633–638), the interaction shown in **12** would be enhanced by a positive-charge-assisted hydrogen bond (see P. Gilli, V. Bertolasi, V. Ferretti, G. Gilli, *J. Am. Chem. Soc.* **1994**, 116, 116–122).
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