DOI: 10.1002/adsc.200606018

To Catalyze or not to Catalyze? Insight into Direct Amide Bond Formation from Amines and Carboxylic Acids under Thermal and Catalyzed Conditions

Kenny Arnold,[a] Bryan Davies,[b] Richard L. Giles,[a] Christophe Grosjean,[a] Gillian E. Smith,[b] Andrew Whiting[a,*]

[a] Department of Chemistry, Durham University, Science Laboratories, South Road, Durham DH1 3LE, United Kingdom
Fax: (+44)-191-386 1127, e-mail: andy.whiting@durham.ac.uk
[b] GlaxoSmithKline Research & Development Ltd., Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

Received: January 13, 2006; Accepted: March 9, 2006

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Kinetic studies show that the direct formation of amides from amines and carboxylic acids without catalyst does occur under relatively low temperature conditions, but is highly substrate dependent. Boric and boronic acid-based catalysts improve the reaction, especially for less reactive acids, and initial results indicate that bifunctional catalysts show even greater potential.

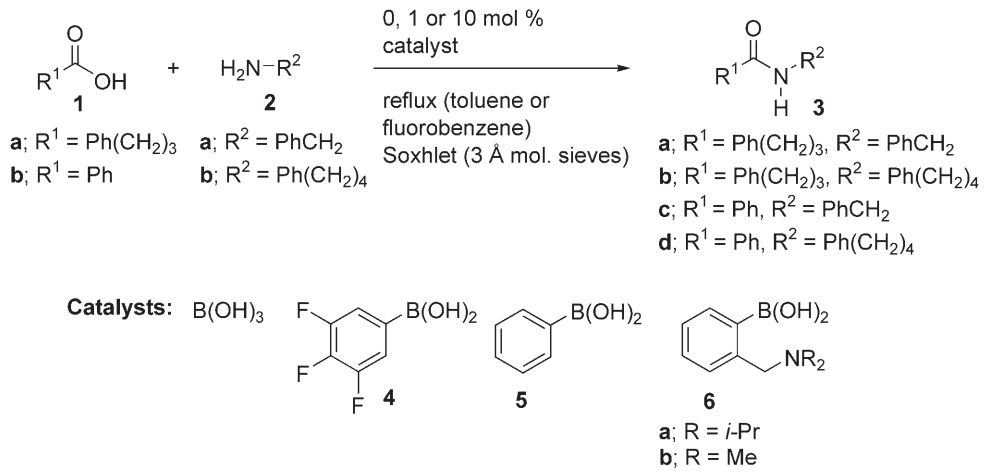
Keywords: amines; bifunctional catalysis; boronate catalysis; carboxylic acids; direct amide formation; green catalysis

Amide bonds are generally formed from carboxylic acid derivatives such as acyl halides or anhydrides, including mixed anhydrides, or active esters.[1] Equivalent reactive entities can also be generated *in situ* using diimide derivatives.[1] Such reagents, however, represent poor atom economy,[2] as does the addition of activating agents or acyl transfer agents, etc.[3] The most desirable method for preparing amides would be a direct condensation between a carboxylic acid and amine, which is generally understood to be impossible due to the formation of an unreactive carboxylate-ammonium salt. Although the direct formation of amide bonds has been known since 1858,[4] this process has found little synthetic utility with a few exceptions.[5] However, the use of boron reagents to assist amide formation directly from carboxylic acids and amines[6,7] has been punctuated by the report[8] that boric acid is similarly effective.

Our recent interests in the development of bifunctional catalysts[9] led us to examine amine-boronic acids as potential amide bond forming catalysts; however, some reactions carried out in the absence of a catalyst gave surprising amounts of amide product under mild conditions. We therefore undertook an investigation into the kinetics of both thermal and boric or boronic acid-catalyzed reactions, in order to compare these results with those derived from bifunctional systems. In this communication we report our unexpected findings.

A parallel series of experiments was carried out as detailed by Scheme 1, in which a carboxylic acid **1** (either **1a** or **b**) was reacted with an amine **2** (either **2a** or **b**) in refluxing toluene in the presence of activated 3 Å molecular sieves (Soxhlet). The thermal reaction was compared with the addition of 1 mol % of each of the catalysts shown in Scheme 1, with direct monitoring from the reaction being carried out at 2 hourly intervals over 22 hours by HPLC. The results are shown in Table 1.

Reaction 1 (**1a** + **2a**, Table 1) shows the highest level of uncatalyzed, thermal reaction (blue line), resulting in a surprisingly high *ca.* 60% yield of **3a** after 22 hours. In comparison, and even more surprisingly, all the catalyzed reactions are only incrementally better than the thermal reaction, with boric acid, **4** and **5** being essentially identical. These results immediately raised the question as to whether much of the catalytic activity observed, albeit only 20% of the yield (i.e., over the thermal reaction), was actually due to the formation of boric acid under these reaction conditions. Boronic acids are known to undergo facile proto-deboronation in the presence of carboxylic acids, especially alkyl carboxylic acids which is a faster process than for more electron-deficient arylboronic acids.[10] However, boronic acids **4**, **5** and **6a** do not seem to show substantial proto-deboronation under the reaction conditions reported herein. In comparison, reactions with **1b** showed a much less impressive thermal amide formation (see Reactions 2



Scheme 1. General equation for direct amide formation and catalyst structures.

and 4, Table 1). For the reaction of **1b** with **2a** (Reaction 2, Table 1), the catalyzed reactions are also poor, however, boric acid does show *ca.* 70% yield over 22 hours, and the only other effective catalyst is the bifunctional system **6a**, which shows 40% yield. Since the catalyst **6a** is stable to proto-deboronation under these conditions, this result raises the question as to whether with this combination of substrates, there is benefit to using the bifunctional catalyst, compared with **4** or **5**. However, the differences again disappear when applied to more reactive systems, i.e., as in Reaction 3, **1a** and **2b** (Table 1), which again shows a substantial thermal reaction (*ca.* 70%), with all catalysts adding only incremental improvement.

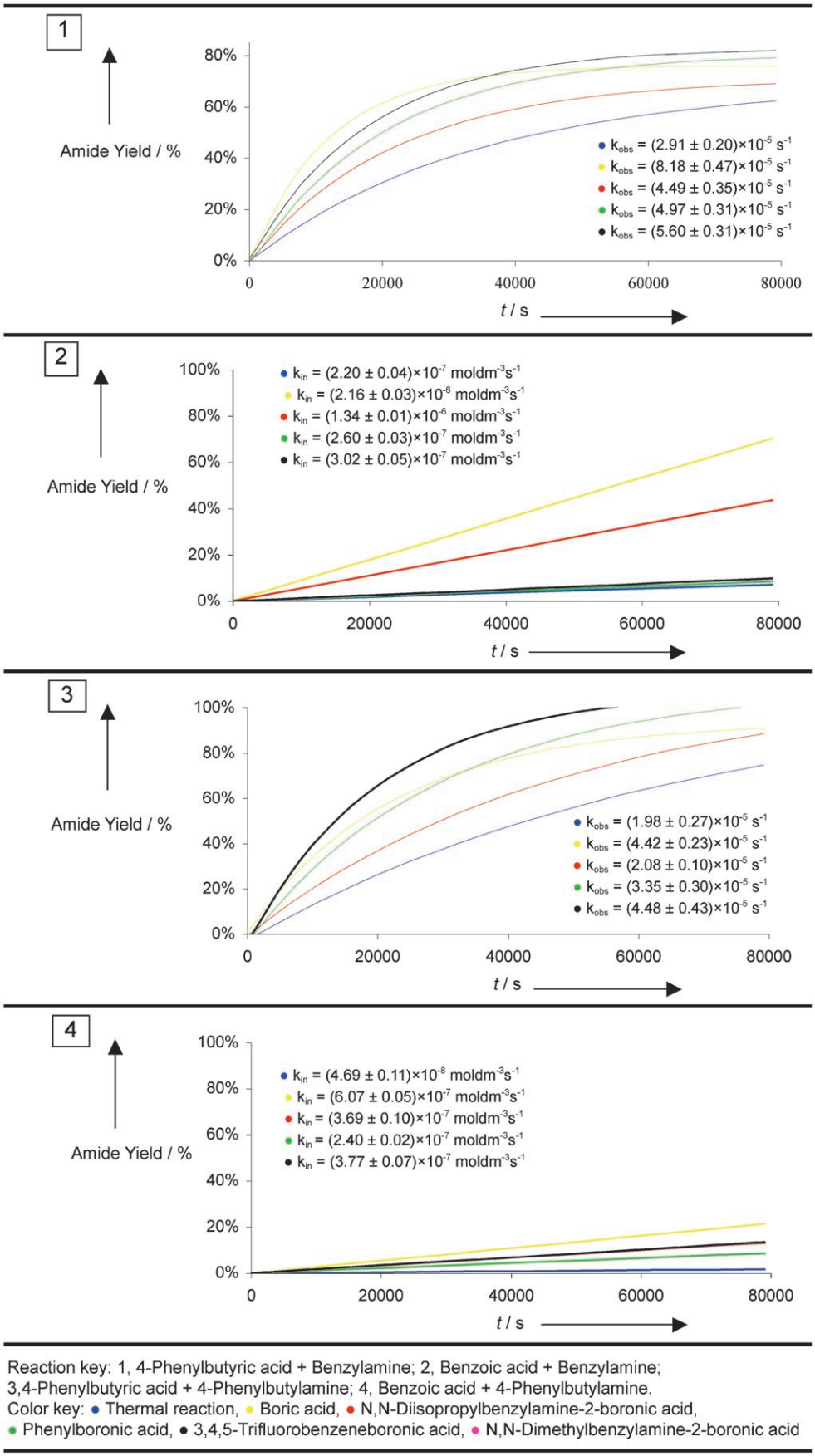
Because of the substantial amide formation observed in the thermal reactions (Reactions 1 and 3, Table 1), it was necessary to separate actual catalytic effects from any other processes. This necessarily meant looking for reaction conditions which minimized the thermal reaction. Hence, a second series of parallel reactions was carried out, but at lower temperature in refluxing fluorobenzene (85 °C), while maintaining azeotropic removal of water. These reactions were carried out as described above and formulated by Scheme 1. Under these lower temperature conditions, catalyst loading had to be increased to 10 mol % in order to obtain reasonable reaction rates. Each of these reactions was monitored by HPLC over 24 to 48 hours. The results of these experiments are shown in Table 2.

Even in fluorobenzene, the thermal conversion of **1a** and **2a** to **3a** is reasonable, i.e., *ca.* 60% over 24 hours (Reaction 1, Table 2). However, under these reaction conditions where there is no evidence of proto-deboronation, the arylboronic acids all show rate improvement over the thermal reaction, with **4** being particularly impressive, showing an initial rapid reaction which levels off at *ca.* 80% yield. Boric acid is generally less effective at the lower temperature, except with **1a** and **2b** where it is similarly active to the arylboronic acids (Reaction 3, Table 2). The similarity of the different catalysts for Reactions 1 and 3 (Table 2) shows that, for certain substrate combinations, catalyst choice is less important. However, once the substrate combination becomes inherently less reactive (Reactions 2 and 4, Table 2), the possible advantage of bifunctional catalysts becomes evident. Hence, in Reaction 2 (Table 2), **6a** is the most active catalyst leading to *ca.* 80% conversion over 48 hours, with the thermal reaction being non-existent over the same time period. Next most reactive is **4**, with boric acid and **5** being similar. Interestingly, using the less basic and less hindered catalyst **6b** results in a drop in activity to a similar level to **4**. It is known that **6a** shows no B–N chelation in both solution and solid states, whereas **6b** only shows B–N chelation under these conditions.[9b] A similar trend is seen in Reaction 4 (Table 2), where again there is essentially no thermal reaction and the more basic and hindered bifunctional catalyst **6a** is the most reactive catalyst, providing *ca.* 60% yield of amide over 48 hours.

The findings demonstrated by Tables 1 and 2 highlight many issues which have not been fully addressed in the literature to date. Firstly, thermolysis of carboxylate-ammonium salts[11] in non-polar solvent conditions alone does produce amide products, however, the efficiency is highly substrate- and temperature-dependent. Presumably, there is a critical balance between the ability of the ammonium salt to act as a general Brønsted acid, and the free amine to act as a reasonable nucleophile on either the protonated carboxylic acid or the anhydride (*vide infra*). This balance seems to result in a "benzylic effect", i.e., benzylamine shows higher amide formation potential than the more nucleophilic amine **2b**, especially when coupled with the more reactive acid **1a**.[12]

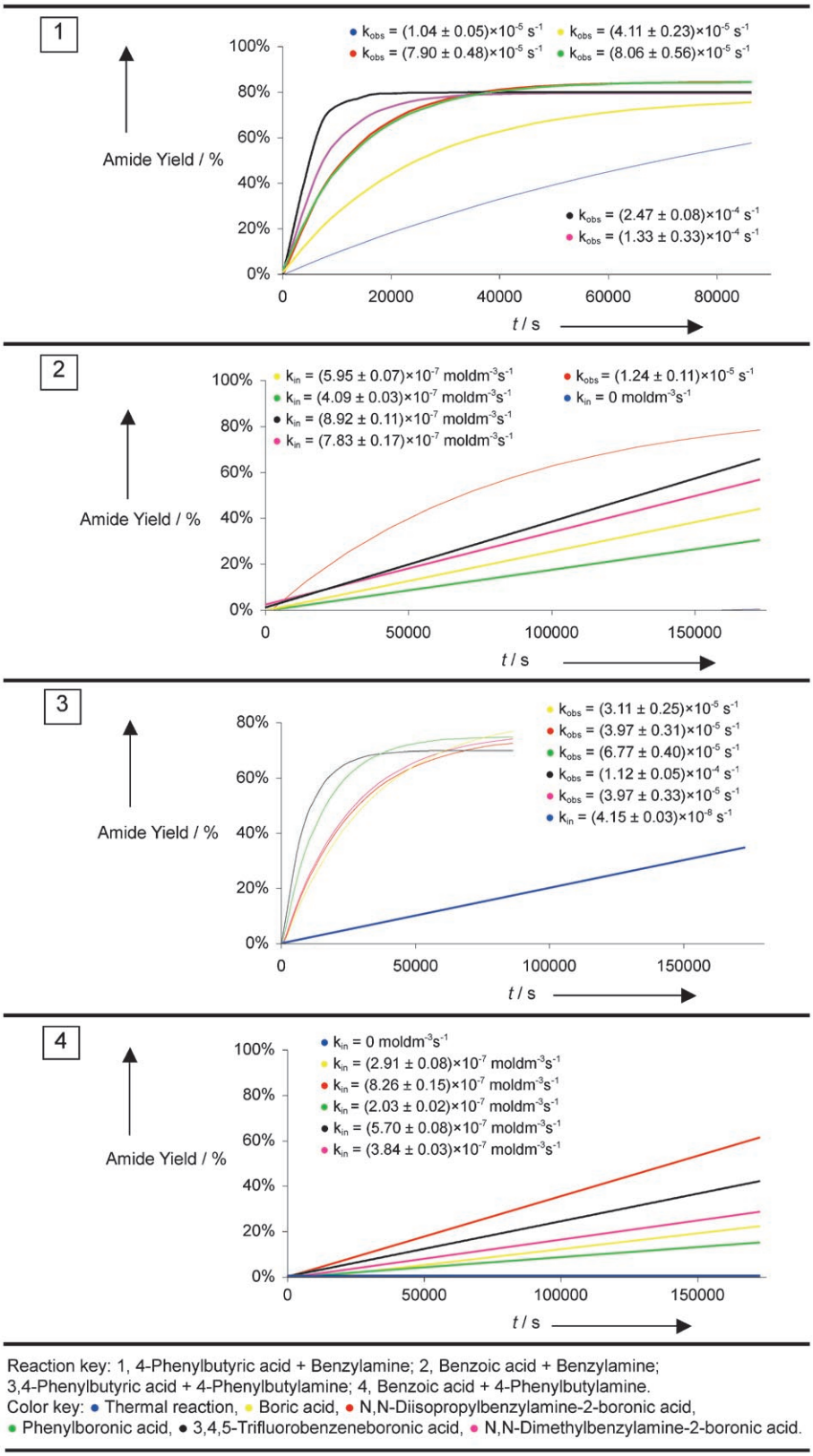
Secondly, the more electron-deficient catalyst **4** is an effective catalyst for amide formation reactions,[7] and indeed, similar to boric acid, which is also a good general catalyst under the higher temperature conditions.

Table 1. Table of yields versus time and rate constants for different carboxylic acid-amine combinations carried out in refluxing toluene.



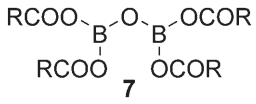
Reaction key: 1, 4-Phenylbutyric acid + Benzylamine; 2, Benzoic acid + Benzylamine; 3,4-Phenylbutyric acid + 4-Phenylbutylamine; 4, Benzoic acid + 4-Phenylbutylamine.
Color key: ● Thermal reaction, ● Boric acid, ● N,N-Diisopropylbenzylamine-2-boronic acid, ● Phenylboronic acid, ● 3,4,5-Trifluorobenzeneboronic acid, ● N,N-Dimethylbenzylamine-2-boronic acid

Table 2. Table of yields versus time and rate constants for different carboxylic acid-amine combinations carried out in refluxing fluorobenzene.



Reaction key: 1, 4-Phenylbutyric acid + Benzylamine; 2, Benzoic acid + Benzylamine; 3,4-Phenylbutyric acid + 4-Phenylbutylamine; 4, Benzoic acid + 4-Phenylbutylamine.
Color key: ● Thermal reaction, ● Boric acid, ● N,N-Diisopropylbenzylamine-2-boronic acid, ● Phenylboronic acid, ● 3,4,5-Trifluorobenzeneboronic acid, ● N,N-Dimethylbenzylamine-2-boronic acid.

Thirdly, the general reactivity of boric acid at higher temperature raises the question as to why this occurs. It is known that boric acid reacts readily under acylating conditions to form tetraacyldiborate systems, i.e., of type **7**,[13] however, triacylboranes have also been shown to react *via* amine complex intermediates to provide amides.[14] It is possible that formation of these species is essential for the catalytic activity of boric acid and that the higher temperature (refluxing toluene) assists catalyst recycling.



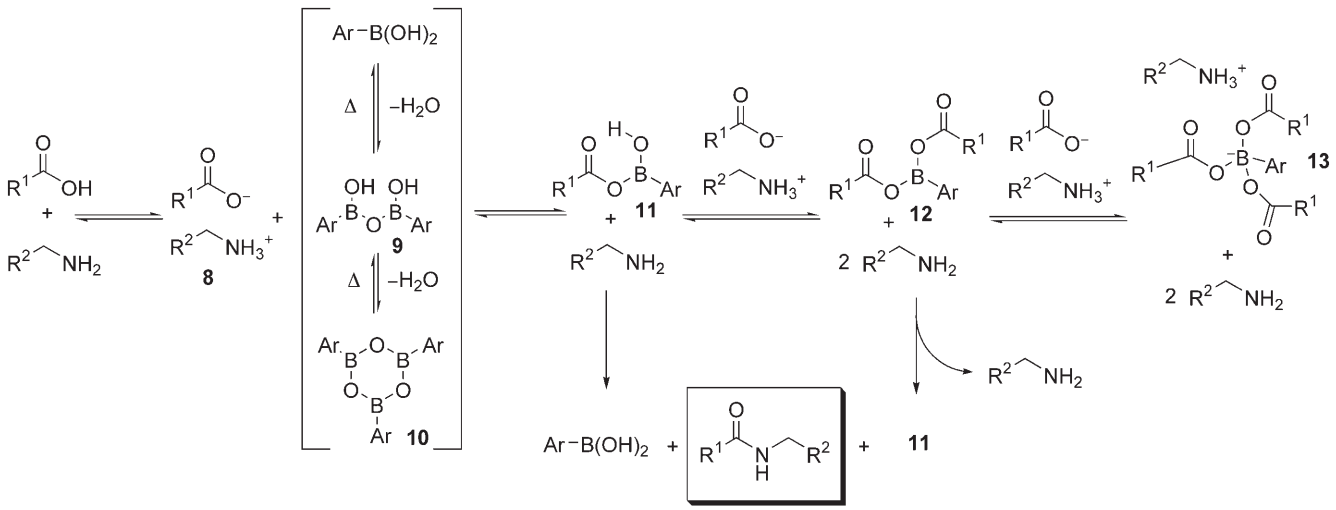
7

Fourthly, we find clear evidence of bifunctional activity assisting certain substrate-dependent reactions. This is shown most graphically at lower temperature (Reaction 2, Table 2). We observe a clear added advantage of the more hindered bifunctional system **6a** over the less hindered **6b**, the non-bifunctional system **5** and the more electron deficient system **4**. It may well be the case that the combination of both electron deficiency and an intramolecular base may provide more active, generally applicable, catalysts in the future. In the interim, we have been able to show that bifunctionality is at the root of the activity of **6a**, as shown by the fact that addition of 10 mol % of diisopropylethylamine to the phenylboronic acid **5**-catalyzed reaction (Reaction 4, Table 2), does not lead to significant enhanced reactivity which approaches that of the bifunctional catalyst **6a** [$k_i = (2.32 \pm 0.04) \times 10^{-7}$ *c.f.* $(2.03 \pm 0.04) \times 10^{-7}$ mol $dm^{-3}\,s^{-1}$ (Table 2)].[15]

Fifthly, NMR (^1H, ^{13}C and ^{11}B) and IR[7a] spectroscopic studies are not sufficient to determine exactly which acylating species are produced in these amide formation reactions. However, using ambient, soft ionization electrospray mass spectrometric techniques, we can gain some insight into the species which are being produced in solution[16] (see Supplementary Information). Hence, for the reaction of catalyst **6a** with **1a**, there is evidence of several species, including boroxine **10**, diboronate **9** and diacyloxyboronate **12**, and the absence of either a monoacyloxyboronate **11** or diacyloxydiboronate (i.e., by diacylation of **9**, see Scheme 2).[17] Overall, this and related evidence[7a] does not categorically point to which is the active acylating species, however, literature precedent[13,14] does suggest that diacyloxyboronate systems in general are acylating agents, i.e., **12** (Scheme 2).

Finally, from Tables 1 and 2, the change in amide concentration with time was found to follow first-order kinetics for **1a**. In the case of **1b**, where the reaction was too slow to be fitted to a particular model, initial rate constants were calculated. Data were fitted to a first order model[18] and initial rate constants were calculated by regression.[19]

In the case of **1a**, first-order kinetics for the catalyzed amide formation are followed (see Tables 1 and 2, entries 1 and 3), which is consistent with the reaction proceeding through an intermediate. These are likely to be either **11** or **12** derived from acylation[20,21] of the boronic acids (a similar intermediate presumably is involved in the case of boric acid) (Scheme 2). In contrast, under thermal conditions (see Scheme 3), the likely intermediate is the anhydride **14** formed by thermolysis,[22] which would explain the subsequent formation of the amide.[23] Indeed, under thermal conditions, the reaction of benzoic anhydride with **2a** shows that the acylation of anhydrides by amines is a fast process (0.5 equivs. benzoic anhydride, 1 equiv. **2a** produces 100% **3d** formation in less than 2 mins). Hence, in the present study, amine acylation is clearly not the rate-determining step on the basis



Scheme 2. Proposed overall mechanism for amide formation involving either boric or arylboronic acid catalysis.

of the large difference in rate between amide formation from the pre-formed anhydride and the thermal reactions shown in Tables 1 and 2. Therefore, for the thermal reaction, formation of the anhydride **14** is likely to be rate-limiting. It is therefore also possible, by analogy with the thermal reactions, that for the catalyzed reactions, amine acylation is also not rate-determining, hence carboxylate activation is likely to be rate-determining and is possibly achieved by formation of either the monoacyloxyboronic acid **11** as proposed by Yamamoto et al.[7a] or, as favoured by us, the diacyloxyboronate **12** (*vide supra*). It is also of interest to note that Brown[20] reported the influence of the substituents on the formation of acyloxyboranes from carboxylic acids and boranes, where carboxylic acids with lower pK_a values were shown to slow the formation of acyloxyborane. This can be related to the difference in the rate of reaction between carboxylic acids **1b** and **1a** towards amide formation ($pK_a = 4.19$ and 4.76, respectively). Therefore, the more electron-rich carboxylic acid **1a** is inherently more reactive towards formation of the acyloxyboronate, and hence, undergoes amide formation more readily. It is also likely that this reactivity is paralleled in the monofunctional catalysts: more electron-deficient boron catalysts would be expected to have higher reactivity towards acylation and, hence, will behave as superior catalysts.[21] This is manifested by the observation that the trifluorophenylboronic acid **4** is a superior catalyst to phenylboronic acid **5**.

In summary, the efficiency of amide formation under thermal and catalyzed conditions is highly substrate-dependent. For alkyl carboxylic acids such as **1a**, the addition of boron-based catalysts does improve reaction rate and yield of amide despite the competing thermal reaction. There is, however, even greater improvement with aryl carboxylic acids such as **1b**, where the thermal reaction is essentially non-existent. Indeed, the use of the amino-boronate catalyst **6a** clearly improves amide formation particularly for aryl carboxylic acids and at lower reaction temperatures. This catalyst has also been demonstrated to act through a bifunctional mechanism, the exact nature of which is yet to be fully elucidated. However, for more difficult amidations this catalyst is superior to other monofunctional boronic acid catalysts. Further studies are underway to examine this process in more detail and to develop improved catalytic systems in the future.

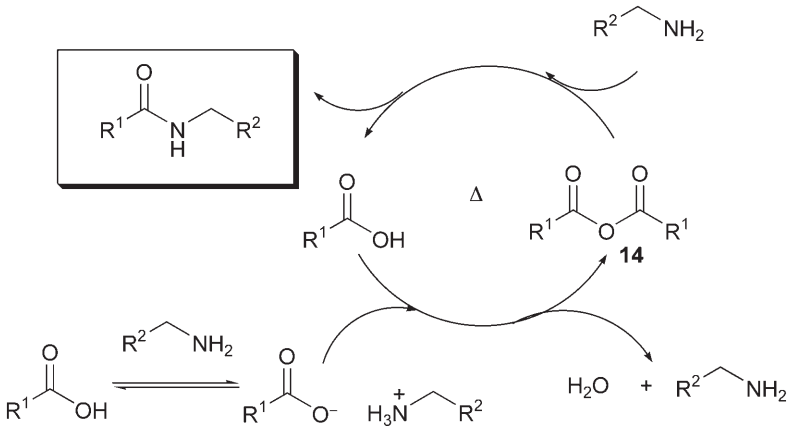
Experimental Section

General Remarks

All ^1H and ^{13}C NMR were recorded with either a Varian Mercury-400, Bruker Avance-400 or Varian Inova-500 spectrometer. ^{11}B NMR were recorded with the Bruker Avance-400 at a frequency of 128 MHz. Chemical shifts are expressed as parts per million (ppm) downfield from the internal standard TMS. Mass spectra were performed with a Micromass Autospec. IR spectra were recorded with a Perkin-Elmer 1615 FTIR spectrometer. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. Melting points were determined using an electrothermal melting point apparatus. All reagents were obtained from Aldrich or Lancaster and were used as received. Molecular sieves were activated by heating to 450 °C under vacuum (<2 mmHg). Reactions were stirred using a magnetic stirrer bar. All parallel reactions were performed on a Gilson 215 Synthesis Workstation equipped with ReactArray racks and heating block, carried out using ReactArrray Control Software (version 3,0,0,3048) and HPLC data were analyzed either directly using Gilson Unipoint (version 5.11) or using ReactArray DataManager (version 1,1,33,0). HPLC conditions were under Gilson Unipoint (version 5.11) control and injections carried out in conjunction with ReactArray DataManager. The HPLC system consisted of Gilson 322 Pump, Gilson 402 Syringe Pump, Agilent 1100 Series UV Diode Array Detector and Phenomenex Gemini C18 5 μm, 150 mm × 4.60 mm column.

General Direct Amide Formation Procedure (Toluene)

To the reaction vessel was added catalyst (1 mol %), followed by assembly of a micro-Soxhlet apparatus loaded with activat-



Scheme 3. Proposed overall mechanism for thermal amide formation.

ed 3 Å molecular sieves. The amine (3.27 mmol) and toluene (5.6 mL) were added and the mixture heated at 120 °C for 22 hours under argon. Samples (100 μL) were removed automatically at 2 h intervals, diluted with MeCN (900 μL), mixed and further diluted sequentially in 2 × 10-fold steps (total 1000-fold dilution). Samples were analyzed by online HPLC [MeCN (0.05% TFA)/water (0.05% TFA) 70:30 for 10 min or gradient MeCN (0.05% TFA)/water (0.05% TFA) 0:100 to 100:0 over 15 min; 1 mL min^{-1}]. Calibration of HPLC-UV response was achieved using external calibration curves and checked by normalization of starting material consumption against product formation. Four or more (typically six) solutions of analyte acid and analyte amide with graduated concentrations covering the concentration range of the amide bond forming experiment in question were produced. Samples were analyzed by the same method as used in the original acquisition and the results plotted to give a calibration curve against which the samples could be calibrated. Peak area data was extracted using Gilson Unipoint peak recognition software.

General Direct Amide Formation Procedure (Fluorobenzene)

The appropriate catalyst (0.233 mmol, 10 mol %) was manually weighed into each reaction vessel, followed by assembly of a micro-Soxhlet apparatus loaded with activated 3 Å molecular sieves under argon. Solid reagents were added using the ReactArray as standard solutions (0.5 M in fluorobenzene). Naphthalene (0.35 mmol, 15 mol %) and amine (2.33 mmol) were added to the reaction vessels at ambient temperature. The appropriate amount of fluorobenzene was then added to each reaction vessel in order to give a final reaction volume of 10 mL. After heating to reflux, carboxylic acid (2.33 mmol) was added to the stirred solution. Reactions were sampled (50 μL) at 2 or 4 h intervals (24 or 48 h reaction time respectively). Samples were quenched with MeCN (950 μL), diluted once (50 μL in 950 μL MeCN) mixed and analyzed by HPLC [gradient MeCN (0.05% TFA)/water (0.05% TFA) 0:100 to 100:0 over 15 or 19 minutes; 1 mL min^{-1}). Naphthalene was used as an internal standard, with response factors calculated automatically by ReactArray DataManager.

General Procedure for Isolation of Amides

A 2-necked round-bottomed flask was equipped with stirrer bar, pressure equalizing dropping funnel (in vertical neck) with a Soxhlet thimble containing CaH_2 (~1 g) inside, followed by a condenser. The appropriate carboxylic acid (5 mmol), followed by fluorobenzene (50 mL), and amine (5 mmol) were added, followed by catalyst **6a** (117.6 mg, 0.5 mmol, 10 mol %). The mixture was allowed to stir at reflux for 24 h, before being concentrated under vacuum. The residue was then redissolved in DCM (25 mL), washed with brine (25 mL), 5% (w/v) HCl (25 mL), brine (25 mL), 5% (w/v) NaOH (25 mL), brine (25 mL), dried over $MgSO_4$, and the solvent evaporated under vacuum.

N-*Benzyl-4-phenylbutyramide* (**3a**):[25] Yield: 0.86 g (68%); HPLC (gradient 15 min, t_r = 10.28 min).

N-*4-Phenylbutyl-4-phenylbutyramide* (**3b**): Yield: 1.03 g (70%); HPLC (gradient 19 min, t_r = 14.21 min); mp 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.56 (m, 2H, CH_2), 1.60–1.69 (m, 2H, CH_2), 1.92–2.01 (m, 2H, CH_2), 2.15 (t, *J* = 7.4 Hz, 2H, CH_2), 2.64 (m, 4H, 2 × $ArCH_2$), 3.26 (m, 2H, CH_2N), 5.44 (br s, 1H, CONH), 7.15–7.22 (m, 6H, ArH), 7.25–7.31 (m, 4H; ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.3 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 35.3 (CH_2), 35.6 (CH_2), 36.0 (CH_2), 39.4 (CH_2), 125.9 (ArC), 126.1 (ArC), 128.45 (ArC), 128.49 (ArC), 128.51 (ArC), 128.6 (ArC), 141.6 (Ar*C*-CH_2), 142.2 (Ar*C*-CH_2), 172.7 (CONH); IR (film): $\tilde{\nu}$ = 3304, 2925, 2861, 1635 (s), 1535 (s), 741 (s), 693 (vs) cm^{-1}; MS (ES): *m/z* (%) = 318.3 (100) $[M+Na]^+$, 296.3 (60) $[M+H]^+$; elemental analysis (%): calcd. for $C_{20}H_{25}NO$: C 81.31, H 8.53, N 4.74; found: C 81.24, H 8.57, N 4.69.

N-*Benzylbenzamide* (**3c**):[26] Yield: 0.53 g (50%); HPLC (gradient 15 mins, t_r = 9.12 min).

Preparation of *N*-4-Phenylbutylbenzamide (3d)

To a stirred solution of benzoyl chloride (0.12 mL, 1 mmol) in dry Et_2O (6 mL) under Ar at 0 °C, was added triethylamine (0.21 mL, 1.5 mmol) and 4-phenylbutylamine (0.16 mL, 1 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 2 hours and then quenched with 5% (w/v) HCl (5 mL). The organic layer was separated and washed again with 5% (w/v) HCl (5 mL), then brine (5 mL), 5% (w/v) NaOH (2 × 5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated under vacuum to afford *N*-4phenylbutylbenzamide as a white solid; yield: 0.25 g (99%); HPLC (gradient 15 min, t_r = 10.83 min); mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60–1.78 (m, 4H, 2 × CH_2), 2.66 (t, *J* = 7.4 Hz, 2H, $ArCH_2$), 3.47 (m, 2H, CH_2N), 6.21 (br s, 1H, CONH), 7.19 (t, *J* = 7.1 Hz, 3H, ArH), 7.28 (t, *J* = 7.6 Hz, 2H, ArH), 7.41 (t, *J* = 7.2 Hz, 2H, ArH), 7.49 (t, *J* = 7.4 Hz, 1H, ArH), 7.75 (dt, 2H, *J* = 7.4, 1.2 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.8 (CH_2), 29.4 (CH_2), 35.6 (CH_2), 40.0 (CH_2N), 126.0 (ArC), 126.9 (ArC), 128.47 (ArC), 128.54 (ArC), 128.7 (ArC), 131.5 (ArC), 134.8 (Ar*C*–CH_2), 142.2 (Ar*C*–CONH), 167.7(CONH); IR (film): $\tilde{\nu}$ = 3328, 2936, 2859, 1633 (s), 1521 (s), 691 (vs) cm^{-1}; MS (ES): *m/z* (%) = 276.5 (100) $[M+H]^+$; elemental analysis (%): calcd. for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53; found: C 80.50, H 7.59, N 5.44.

Acknowledgements

We thank the EPSRC for a research grant (GR/R24722/01), for DTA studentships (for KA and RG) and the National Mass Spectrometry Service at Swansea, and GlaxoSmithKline for CASE funding (KA and RG), S. M. Lynn (GSK, Tonbridge) for information retrieval.

References and Notes

[1] B. M. Trost, I. Fleming, in: *Comprehensive Organic Synthesis*, (Ed.: E. Winterfield), Pergamon, Oxford, **1991**, Vol. 6.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
[3] a) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827; b) Y. R. Mahajan, S. M. Weinreb, in *Science of Synthesis* **2005**, Vol. 21, Thieme, Stuttgart, New York, p 17.
[4] a) J. A. Mitchell, E. E. Reid, *J. Am. Chem. Soc.* **1931**, *53*, 1879 and references cited therein; b) B. S. Jursic, Z. Zdravkovski, *Synth. Commun.* **1993**, *23*, 2761.
[5] L. Perreux, A. Loupy, F. Volatron, *Tetrahedron* **2002**, *58*, 2155.
[6] a) A. Pelter, T. E. Levitt, P. Nelson, *Tetrahedron* **1970**, *26*, 1539; b) R. Latta, G. Springsteen, B. Wang, *Synthesis* **2001**, 1611; c) W. Yang, X. Gao, G. Springsteen, B. Wang, *Tetrahedron Lett.* **2002**, *43*, 6339.
[7] a) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196; b) K. Ishihara, S. Ohara, H. Yamamoto, *Macromolecules* **2000**, *33*, 3511; c) K. Ishihara, S. Kondo, H. Yamamoto, *Synlett* **2001**, 1371; d) K. Ishihara, S. Ohara, H. Yamamoto, *Org. Synth.* **2002**, *79*, 176; e) T. Maki, K. Ishihara, H. Yamamoto, *Org. Lett.* **2005**, *7*, 5043.
[8] P. Tang, *Org. Synth.* **2005**, *81*, 262.
[9] 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; b) S. W. Coghlan, R. L. Giles, J. A. K. Howard, M. R. Probert, G. E. Smith, A. Whiting, *J. Organomet. Chem.* **2005**, *490*, 4784.
[10] a) L. H. Toporcer, R. E. Dessy, S. I. E. Green, *J. Am. Chem. Soc.* **1965**, *87*, 1236; b) K. V. Nahabedian, H. G. Kuivila, *J. Am. Chem. Soc.* **1961**, *83*, 2167.
[11] The formation of the carboxylate-ammonium salt is immediate for all the combinations reported herein, as shown by reaction in fluorobenzene at room temperature. Precipitation of the salt is rapid and quantitative.
[12] Note that aniline is unreactive under all of the relatively ambient reaction conditions reported herein, presumably because both its basicity and nucleophilicity are too low.
[13] A. Dal Negro, L. Ungaretti, A. Perotti, *J. Chem. Soc. Dalton Trans.* **1972**, 1639.
[14] A. Pelter, T. E. Levitt, P. Nelson, *Tetrahedron* **1970**, *26*, 1899.
[15] Diisopropylethylamine alone does not catalyze this reaction.
[16] Electrospray mass spectrometry is recognized as being a sufficiently mild technique to allow the observation of solution phase intermediates which are not a facet of the technique, i. e., caused through heating effects, see: a) A. P. Bruins, T. R. Covey, J. D. Henion, *Anal. Chem.* **1987**, *59*, 2642; b) C. M. Whitehouse, R. N. Dreyer, M. Yamashita, J. B. Fenn, *Anal. Chem.* **1985**, *57*, 675.
[17] See Supporting Information.
[18] Micromath® Scientist® for Windows®, Version 2.02.
[19] Microsoft® Excel, **2003**.
[20] H. C. Brown, T. P. Stocky, *J. Am. Chem. Soc.* **1977**, *99*, 8218.
[21] A. Pelter, M. G. Hutchings, T. E. Levitt, K. W. Smith, *Chem. Commun.* **1970**, 347.
[22] D. Davidson, P. Newman, *J. Am. Chem. Soc.* **1952**, *74*, 1515.
[23] T. Higuchi, T. Miki, A. C. Shah, A. K. Herd, *J. Am. Chem. Soc.* **1963**, *85*, 3655.
[24] It has been reported that 4 Å molecular sieves can catalyze amide formation by direct heating of carboxylic acids and amines between 140 and 180 °C, however, the comparative reactions without sieves was not reported; see: J. Cossy, C. Pale-Grosdemange, *Tetrahedron Lett.* **1989**, *30*, 2771. We have found no evidence of such molecular sieve-catalyzed reactions, however, thermal reactions alone do occur as reported herein.
[25] R. Verma, S. K. Ghosh, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2377.
[26] N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754.

