

Amide Synthesis

Formamide Synthesis through Borinic Acid Catalysed Transamidation under Mild Conditions

Tharwat Mohy El Dine, David Evans, Jacques Rouden, and Jérôme Blanchet*^[a]

Abstract: A highly efficient and mild transamidation of amides with amines co-catalysed by borinic acid and acetic acid has been reported. A wide range of functionalised formamides was synthesized in excellent yields, including important chiral α -amino acid derivatives, with minor racemisation being observed. Experiments suggested that the reaction rely on a cooperative catalysis involving an enhanced boron-derived Lewis acidity rather than an improved Brønsted acidity of acetic acid.

Formamides are important pharmacophore in various drugs, such as leucovorin,^[1a] formoterol^[1b] and orlistat^[1c] (Figure 1). They are also used in the synthesis of valuable heterocycles, such as quinolone^[2a] or imidazole,^[2b] and as precursors of isocyanides^[3a-c] and formamidines.^[3d] Formamides are also used as Lewis base organocatalysts in allylation and hydrosilylation

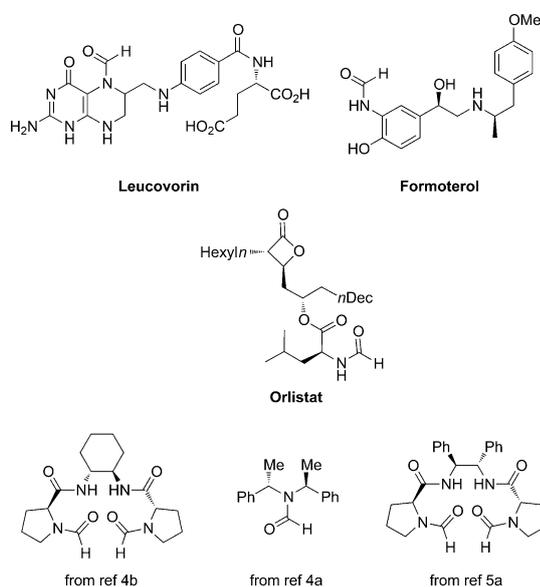


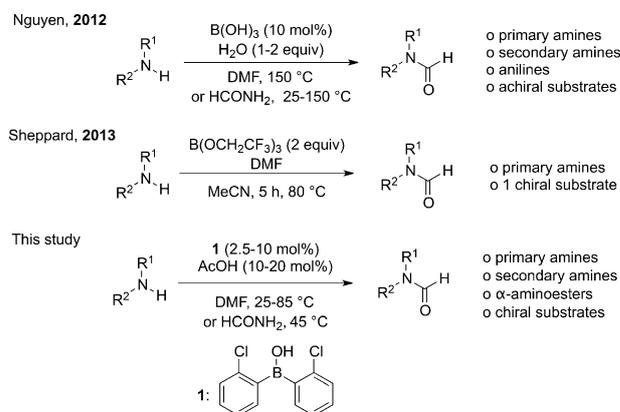
Figure 1. Relevant formamide-containing molecules.

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reactions^[4] and other transformations.^[5] Moreover, the formyl group is a useful protecting group of the amine functionality.^[6]

Beside the use of formic acid and its derivatives as amine formylating reagents,^[7] recent developments focused on the use of sub-stoichiometric amounts of a catalyst and a simpler formyl donor, such as methanol,^[8a-c] carbon monoxide^[8d-e] and CO₂.^[8f-i] However, these methodologies are significantly restricted to the use of expensive transition metals and high pressure of toxic gases. Alternatively, transamidation^[9] has been established by recent formylating methodologies reported by Williams,^[10a-b] Gamba-Sánchez^[10c] and other groups.^[10d-f] Unfortunately, despite of the advances achieved, most of the methods require excess amounts of activating reagents, high temperatures or extended reaction times to attain reasonable conversions along with a limited scope. In this context, the use of boron-based catalysts has appeared as an appealing approach (Scheme 1).^[11] Evidences on the acceleration of intramolecular



Scheme 1. Formylating transamidations promoted by boron-based catalysts.

transamidation of glutamine by sodium borate were reported as early as 1949.^[12] More recently, Sheppard reported a useful fluorinated boronate, which is able to promote chromatography-free synthesis of formamides.^[11b] Nevertheless, in both previous reports, the boron reagent had to be used in large excess. The first transamidation catalysed by sub-stoichiometric amount of a boron derivative was reported by Nguyen in 2012 (10 mol% boric acid, solvent-free conditions).^[11a] However, in most of the cases, temperatures as high as 150 °C were required, limiting the scope to stable achiral amine substrates.^[13]

In continuation to our recent developments in the field of boron-based catalysis aiming at developing metal-free alternatives for key chemical transformations,^[14] we recently reported

the borinic acid **1** as an efficient catalyst capable of achieving the challenging coupling between two non-activated amino acids.^[14b]

Herein, we report the remarkable efficiency of borinic acid **1** in catalyzing the transamidation of DMF with amines. As a first reaction, a combination of 10 mol% of **1** with 20 mol% of acetic acid was found to promote the unusual transamidation of DMF with benzylamine at room temperature in 73% isolated yield. Intriguingly, under such conditions, the amide synthesis involving acetic acid was found to be completely unproductive^[15] (Table 1, entry 1).^[16] Notably, the result obtained

its higher Brønsted acidity (entry 14), thus rendering unlikely the initial hypothesis about the improvement of Brønsted acidity through the coordination of acetic acid with **1**.

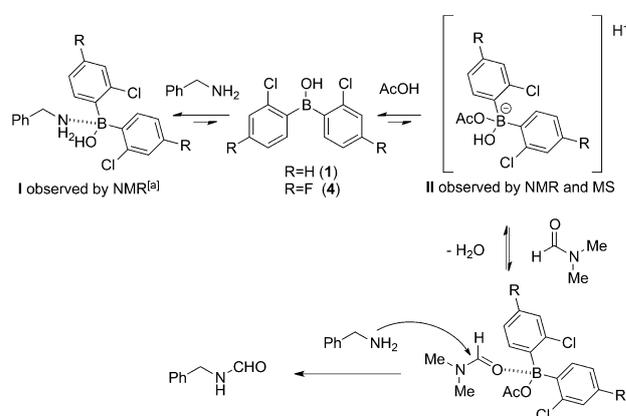
In order to gain insight into the mechanism, the reaction was monitored using borinic acid **4** as a fluorinated probe. Accordingly, aliquots of the reaction mixture were sequentially examined by means of ¹⁹F NMR spectroscopy after the stepwise addition of the reagents. After the addition of acetic acid to borinic acid **4** in DMF, a single signal was observed at $\delta = -110$ ppm, corresponding to pure **4**. However, upon the addition of benzylamine (**2a**), a new signal immediately appeared at $\delta = -115.3$ ppm, likely corresponding to the amine-borinic acid complex **I** (Scheme 2) that remained as the only detectable signal during 24 h at 65 °C. A possible proto-deboronation of **4** during the reaction was ruled out because 2-chloro-4-fluorophenyl boronic acid **6** displayed a different signal at $\delta = -108.3$ ppm under similar conditions.^[18]

Table 1. Optimisation of the transamidation of DMF with benzylamine.

Entry	Deviation from standard conditions	Yield [%] ^[a]
1	none	73
2	2-Cl-4-F-(C ₆ H ₃) ₂ B(OH) ₂ 4 ^[b]	54
3	Ph ₂ B(OH) 5 ^[b]	6
4	2-Cl-C ₆ H ₄ B(OH) ₂ 6 ^[b]	22
5	reaction run for 72 h	82
6	reaction run at 45 °C	98
7	reaction run at 65 °C for 4 h	99
8	no 1 , no AcOH	0
9	only 1	34
10	only AcOH	19
11	only BnCO ₂ H ^[c]	15
12	only HCO ₂ H ^[c]	11
13	only CCl ₃ CO ₂ H ^[c]	9
14	only CF ₃ CO ₂ H ^[c]	1

[a] Isolated yields. [b] Instead of **1**. [c] Instead of AcOH.

under very mild conditions compared favorably with the state of art and prompted us to further investigate this reaction in details. The efficiency of catalyst **1** was found to be significantly superior to that of borinic acids **4** and **5** (entries 2 and 3) as well as its analogue 2-chlorophenyl boronic acid **6** (entry 4). After optimisation, a gentle warming to 45 °C provided a quantitative yield, whereas the duration of the reaction could be decreased to 4 h upon warming to 65 °C (entries 6 and 7). In the course of optimising the different reaction parameters, several test experiments were carried out and suggested a synergistic mechanism between the borinic acid **1** and acetic acid. In the absence of both acids, no conversion was observed (entry 8). However, the presence of borinic acid **1** alone resulted in a low yield of 34%, whereas acetic acid alone led to an even further decrease in the yield. (entries 9–10). These results suggested a cooperation between the two acids and that a Lewis acid-assisted Brønsted acid (LBA) catalytic system could be at play.^[17] However, upon examining the reactivity of different Brønsted acids (entries 11–14), the strongest trifluoroacetic acid afforded a barely detectable conversion despite of



Scheme 2. Second mechanistic hypothesis for the transamidation of DMF.

Borinic acid **1** displayed a ¹¹B NMR signal at $\delta = 38.7$ ppm in [D₇]DMF, representative of a trivalent boron species, indicating the absence of any detectable interaction between DMF and the boron centre. Interestingly, upon the addition of two equivalents of acetic acid, a new signal appeared at $\delta = 5.5$ ppm in a 1:1 ratio, consistent with a tetravalent boron centre.^[19] Any attempts to isolate this intermediate yielded back borinic acid **1**, but direct ESI-TOF mass analysis of the mixture displayed a peak at 309.0 *m/z* corresponding to [M–H][–] of **1** complexed with acetic acid (**II**; Scheme 2). Unfortunately, no species involving the activation of DMF by the borinic acid **1** was detected. However, the observation of complex **II** suggested a mechanism where the borinic acid **1** was first converted to a mixed borinic-acetic anhydride possessing a higher Lewis acidity. Species **II** would then activate DMF and promote the addition of benzylamine (Scheme 2).

With the optimal conditions in hand, the scope of DMF transamidation was further examined, and it appeared that borinic acid **1** was efficiently able to formylate a wide range of amines. The formylation of various primary amines was achieved at room temperature with good to excellent 77–99% yields (Table 2, entries 1–5). It is worth noting that only five equivalents of DMF were found to be sufficient for achieving

Table 2. Scope of the transamidation of DMF with different amines.^[a]

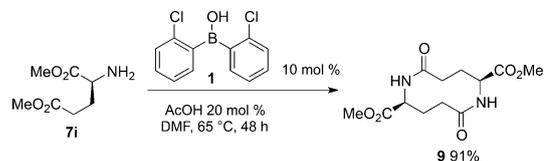
Entry	Formamide	T [°C]	t [h]	Yield [%] ^[b]	Entry	Formamide	T [°C]	t [h]	Yield [%] ^[b]		
1		3 a	20	72	86 ^[c] (99) ^[d]	10		3 j	65	12	99
2		3 b	20	72	77 ^[c]	11		3 k	65	12	96 ^[f]
3		3 c	20	72	86 ^[c]	12		3 l	65	12	97 ^[f]
4		3 d	20	72	98 (90) ^[e]	13		3 m	65	12	99 ^[f]
5		3 e	20	72	99	14		3 n	65	12	98 ^[f]
6		3 f	65	12	99	15		3 o	65	24	99 ^[f]
7		3 g	65	12	99	16		3 p	65	12	99 ^[f]
8		3 h	65	24	89	17		3 q	65	12	98 ^[f]
9		3 i	65	24	96	18		3 r	85	24	26 ^[f,g]

[a] Reaction conditions: Borinic acid **1** (10 mol %), acetic acid (20 mol %), DMF (5 equiv). [b] Isolated yields. [c] Quantitative yield at 65 °C. [d] Run on 5 mmol scale at 65 °C. [e] Run on 5 mmol scale at 20 °C. [f] DMF was used as solvent. [g] NMR conversion.

room temperature formylation of primary amines functionalised with a pyridine, indole, unprotected alcohol or methyl thioether (entries 2–5). More difficult substrates required warming to 65 °C to attain acceptable reaction rates. At this temperature, α -substituted primary and secondary amines gave 89–99% yields within 12–24 h (entries 6–10). In some occasions, the starting amine was found to be poorly soluble in the reaction media, resulting in the absence of conversion. However, in such cases, dilution with DMF led to higher yields. Thus, piperazine, cyclohexylamine and other amine substrates afforded excellent 96–99% yields with DMF being used in excess amounts (entries 11–17). Among the tested primary amines, the hindered *tert*-butylamine was the only to behave sluggishly, thus illustrating that steric hindrance played a significant role during the reaction (entry 18).

Next, our attention was focused on the formylation of the more challenging α -amino esters. Indeed, this class of functionalised and racemisable substrates is generally less investigated with no precedent for a boron-derived catalysis so far reported for the synthesis of *N*-formyl- α -amino ester formamides.^[20] As anticipated, glycine methyl ester reacted slowly at room temperature but afforded a quantitative yield at 65 °C. Encouraged by this result, several substituted chiral α -amino esters were tested. However, less reactive derivatives of alanine, phenylalanine, leucine, valine, methionine and proline re-

quired a considerable increase in the reaction temperature (up to 85 °C) to achieve yields of 78–99% (not reported in this paper).^[21] However, significant racemisation was recorded as formamides **8b**, **8c** and **8e** were obtained with enantiomeric excesses of 25, 47 and 80%, respectively. Interestingly, the methyl glutamate diester provided the macrolactam **9** in 91% yield instead of the expected formamide **8i**, suggesting an unexpected activation of the side chain involving the ester moiety (Scheme 3).^[22]

**Scheme 3.** Synthesis of lactam **9** from the aspartic acid derivative.

Consequently, milder conditions were sought and optimised to decrease racemisation during the transamidation process. Formamide (HCONH₂) was identified^[23] as a useful alternative to DMF allowing transamidation at a lower temperature (45 °C) and using a lower catalyst loading (2.5 mol% of **1**).^[24] Upon using the new set of conditions, the reactions were noticeably faster with yields generally superior to 91% (Table 3, entries 1–

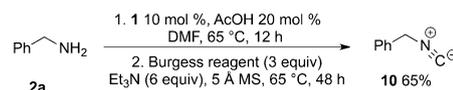
Table 3. Scope of the transamidation of HCONH₂ with α -aminoesters.^[a]

Entry	Formamide	Yield [%] ^[b]
1		99
2		99
3		98
4		97
5		96 (97) ^[c]
6		91
7		99
8		99
9		57

[a] Reaction conditions: Borinic acid **1** (2.5 mol%), acetic acid (10 mol%), HCONH₂ (5 equiv). [b] Isolated yields. [c] Run on 5 mmol scale (with 656 mg of **7e**).

8). It is worth mentioning that these milder conditions strongly limited the racemization, with enantiomeric excesses of 94, 92 and 99% obtained for formamides **8b**, **8c** and **8e**, respectively (determined by chiral HPLC, see the Supporting Information). Additionally, racemisation in the case of formamides **8f** and **8i** was notably reduced (*ee* values >90%). Remarkably, this method also afforded a quantitative yield of the acid sensitive Boc-protected lysine **8h** (entry 8). Additionally, the methyl glutamate diester led chemoselectively to the desired formamide **8i**; however, in a moderate yield of 57% with no traces of the cyclic dimer **9** detected by TLC or NMR (entry 9).

Finally, our study was completed by taking advantage of the mildness of our catalytic conditions to develop a one-pot procedure for the direct preparation of isocyanide **10** from benzylamine.^[25] Among the various possible reagents that are able to dehydrate a formamide, the Burgess reagent^[26] was foreseen as being the most compatible upon using DMF as the solvent. Indeed, when Burgess reagent and triethylamine were added after completion of the transamidation step of DMF with benzylamine and further reacted for 48 h, the corresponding benzyl isocyanide **10** was isolated in 65% yield (Scheme 4). Furthermore, when other amines were tested (α -methylbenzylamine, decylamine and cyclohexylamine), high conversions were observed by NMR. Unfortunately, the corresponding iso-



Scheme 4. One-pot synthesis of isocyanide **10** from benzylamine.

cyanides rapidly decomposed invariably upon different purification attempts.

In conclusion, a new method for the *N*-formylation of amines using catalytic amounts of borinic acid **1** and acetic acid was reported. A short mechanistic study pointed towards a cooperative involvement of both species and a reactivity based on an improved Lewis acidity of the boron centre. More specifically, the *N*-formylation of amines was examined with a wide range of primary and secondary amines as well as functionalised α -amino esters. In the case of chiral substrates, the observed racemisation led to a switch of the formyl donor from DMF to HCONH₂ in order to keep racemisation at a low level. Additionally, our catalytic system was successfully extended to one-pot synthesis of isocyanides from primary amines.

Experimental Section

General Procedure for the *N*-formylation of Amines using DMF

To a round-bottom flask kept under an argon atmosphere were added 2-chlorophenylborinic acid **1** (12.5 mg, 0.05 mmol, 0.1 equiv), acetic acid (6 μ L, 6 mg, 0.10 mmol, 0.2 equiv) and dry DMF (0.19 mL or 7 mL as indicated). The mixture was vigorously stirred for 15 min at 25 °C, 65 °C or 85 °C, as indicated, and the amine (0.50 mmol, 1 equiv) was then slowly added using a gastight syringe. The resulting mixture was stirred for a further 12–72 h, as reported in Table 2. DMF was removed using Kugelrohr distillation apparatus (55 °C) and the crude mixture was further purified by column chromatography to give the corresponding title compounds. For the amines with low boiling points, the reaction was conducted in a sealed tube.

General Procedure for the *N*-formylation of Amines using HCONH₂

To a sealed tube were added 2-chlorophenylborinic acid **1** (3 mg, 0.0125 mmol, 0.025 equiv), HCONH₂ (0.10 mL, 2.5 mmol, 5 equiv) and acetic acid (3 μ L, 3 mg, 0.05 mmol, 0.1 equiv). The mixture was vigorously stirred for 15 min at 45 °C and α -amino methyl ester amine (0.50 mmol, 1 equiv) was then slowly added using a gastight syringe. The resulting mixture was stirred for a further 24 h. The crude was purified using column chromatography to yield the corresponding title compounds.

Procedure for the One-Pot Synthesis of Isocyanide from Benzylamine

To a round-bottom flask kept under an argon atmosphere were added 2-chlorophenylborinic acid **1** (12.5 mg, 0.05 mmol, 0.1 equiv), acetic acid (6 μ L, 6 mg, 0.10 mmol, 0.2 equiv) and dry DMF (7 mL) at 65 °C. The mixture was vigorously stirred for 15 min and benzylamine (0.50 mmol, 1 equiv) was then slowly added using a gastight 100 μ L syringe. The resulting mixture was stirred

for 12 h at 65 °C. After 12 h, Burgess reagent (360 mg, 1.5 mmol, 3 equiv), triethylamine (418 μ L, 3 mmol, 6 equiv) and 5 Å powdered molecular sieves (1 g) were added and stirring was maintained for further 48 h. The reaction was quenched with water and extracted five times with Et₂O, washed with brine, dried over anhydrous MgSO₄ and concentrated under vacuum. Crude isocyanide **10** was purified by column chromatography.

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Keywords: amides · amines · boronic acid · synthetic methods · transamidation

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