INTRODUCTION

Amide linkages are at the basis of all life processes, as the key connections in proteins. Although their importance is well recognized in chemistry as a common motif in pharmaceuticals and polymeric materials (1), their synthesis is often overlooked as a contemporary challenge. Improved methods for the synthesis of amide functionality are key to the sustainable future of chemical synthesis and manufacturing, especially if they can offer high efficiency and reduced environmental impact. This is a consequence of the fact that amide formation is typically achieved using inefficient and often hazardous reagents, which generate large quantities of waste products leading to high disposal costs (2). Accordingly, there have been recent calls from numerous major pharmaceutical companies for research into methods for “amide bond formation avoiding poor atom economy reagents” (3).

Despite recent reports of new strategies for amide bond formation from alcohols, aldehydes, or alkynes (4–6), direct condensation of a carboxylic acid and amine remains the most common approach to amide bond formation, owing to the ubiquity and stability of these functional groups. Conventional methods for direct amidation (Fig. 1A) formally proceed via a two-step sequence involving activated carboxylic acid derivatives, which then undergo aminolysis (7, 8). Indirect amide formations of this sort are expensive and waste-intensive and often suffer from functional group incompatibilities. The ideal approach would involve direct condensation of a carboxylic acid and amine in the presence of a catalyst because the only by-product of the reaction would be water. Direct thermal reaction without a catalyst has a relatively limited scope and usually requires high temperatures (9, 10). In recent years, the use of group IV metal salts or boron compounds as catalysts has enabled amidation reactions to take place at lower temperatures (10–24). However, the use of these catalytic reactions in an industrial context is rare because of their limited reactivity with functionalized substrates and the inefficient procedures used [high dilution conditions and large quantities of waste-intensive molecular sieves (0.8 to 2.5 kg/mol)] (Fig. 1B) (10–24). Only boric acid has been applied as an amidation catalyst to any great extent on an industrial scale, but it is effective only for relatively reactive acid/amine combinations (25).

To address this key issue of sustainability, we sought to develop an operationally simple catalytic method for direct amidation of the carboxylic acid/amine pair at high concentrations in “industrially preferred” solvents and without the need for any additives or dehydrating agents (26, 27). Our interest in the application of borate esters in stoichiometric amidation reactions led us to explore the use of these compounds as amidation catalysts, with a view to their suitability for application of preparing multigram quantities of amide. Here, we disclose a novel efficient protocol for amidation using a borate ester catalyst (Fig. 1C), with an unprecedented substrate scope. This method offers significant improvements in terms of safety and ease of setup and leads to a large reduction in the overall waste generated in an amidation reaction [process mass intensity (PMI)].

RESULTS AND DISCUSSION

Development of a highly versatile method for amidation

Borate esters have been demonstrated to mediate amidation reactions of functionalized carboxylic acids and amines (28, 29), yet a priori it was uncertain whether effective catalytic turnover could be achieved because the partially hydrolyzed borate ester 1 could readily undergo decomposition to leave a poorly reactive oligomeric boron oxide (Fig. 2A). Pleasingly, it was observed that effective turnover could be achieved using a Dean-Stark apparatus as an economical and efficient method for water removal, hence avoiding the need for wasteful molecular
confirmed that a commercially available borate ester $\text{B(OCH}_2\text{CF}_3\text{)}_3$ was proved to yield amides due to their importance as low-cost renewable raw materials that can be applied to the synthesis of many biologically active targets. As such, the compatibility of our methodology with this type of building block was an important aspect to examine because many of the existing catalytic amidation methods are unsuccessful with these compounds (11–24). Coupling of N-Boc–protected amino acids with a range of amines, including both simple aliphatic amines (36 to 39) and functionalized examples (34 and 35), gave the corresponding amines in excellent yields. The synthesis of dipeptides (40 to 44) and even a tripeptide (45) was also demonstrated successfully. Pleasingly, the free hydroxyl functionality of threonine did not require protection, and the corresponding amino amides (35 and 38) and dipeptides (43 and 44) were obtained in excellent yields. No detectable racemization was observed for any of the amino acid derivatives.

**Amidation with unprotected amino acids**

In an effort to address the unmet need for novel chemoselective strategies in chemical synthesis and thereby further prevent the generation of unnecessary waste by-products, we sought to test the application of our catalytic amidation reaction with unprotected amino acids. Protecting group manipulations and amide bond formation account for about a third of the reactions carried out in the synthesis of pharmaceutical intermediates (30, 31), so overcoming these synthetic hurdles could pave the way toward greater sustainability in the chemical industry. Perhaps the most impressive feat of this methodology, catalytic amidation of unprotected amino acids, could be achieved in a chemoselective manner, thereby circumventing the need for protection/deprotection of the amino group (Fig. 4) (32). This represents a novel, practical, and more atom-economical route to primary amino acid derivatives, which are a well-documented class of potent anticonvulsants and agents for neuropathic pain treatment (33, 34). Owing to the unreactive/insoluble nature of free amino acids, a higher catalyst loading and a slight excess of amine were necessary for this type of reaction to go to completion. This unique catalytic and chemoselective amide bond formation displayed a broad substrate scope with a variety of functionalized free amino acids and amines. Simple unfunctionalized amino acids (47, 48, 50, 51, and 53 to 59) were obtained in high yields. Diverse functional groups, including hydroxyl groups (52), heterocycles (46), and sulfides (49), were well tolerated. A β-amino acid could also be converted to the corresponding amide, albeit in lower yield (55). Pleasingly, glutamic acid underwent a tandem cyclization/amidation to give the corresponding pyroglutamide (60) in good yield. This method provides a highly efficient route for the catalytic synthesis of amino amides directly in one step from readily available free amino acids.

**Scope of the reaction**

To evaluate the reaction scope, we explored the preparation of a selection of amides (Fig. 3). A variety of primary amines were successfully coupled with simple carboxylic acids to give secondary amides 2 to 13 in excellent yields. In contrast to existing catalytic amidation reactions, a range of tertiary amines could also be prepared, including examples derived from both cyclic (14, 15, 20, and 21) and acyclic (16 to 19) secondary amines, the latter being particularly difficult compounds to prepare via catalytic amidation. Furthermore, challenging amines were prepared from functionalized/heterocyclic carboxylic acids or amines (22 to 33), demonstrating the unprecedented scope of this catalytic amidation reaction. It was even possible to acylate a poorly nucleophilic sulfonamide to give the corresponding derivative 30, albeit in moderate yield. Naturally occurring carboxylic acids such as biotin (32) and lithocholic acid (33) were also amenable to amide bond formation. Non-steroidal anti-inflammatory ibuprofen also smoothly reacted to form the corresponding amide 31. Our studies also suggested that B(OMe)$_3$ was a reasonably effective and very low-cost catalyst for synthesizing relatively unfunctionalized amides when PhMe is used as solvent (6, 17, 25, and 37).

We next directed our efforts to amidation reactions of amino acids due to their importance as low-cost renewable raw materials that can be applied to the synthesis of many biologically active targets. As such, the compatibility of our methodology with this type of building block was an important aspect to examine because many of the existing catalytic amidation methods are unsuccessful with these compounds (11–24). Coupling of N-Boc–protected amino acids with a range of amines, including both simple aliphatic amines (36 to 39) and functionalized examples (34 and 35), gave the corresponding amides in excellent yields. The synthesis of dipeptides (40 to 44) and even a tripeptide (45) was also demonstrated successfully. Pleasingly, the free hydroxyl functionality of threonine did not require protection, and the corresponding amino amides (35 and 38) and dipeptides (43 and 44) were obtained in excellent yields. No detectable racemization was observed for any of the amino acid derivatives.

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One-pot sequential condensations

Given that B(OCH2CF3)3 has previously been shown to promote imine formation when used stoichiometrically, we also explored a one-pot unprotected amino acid amidation/condensation reaction to provide access to imidazolidinones in a single step. Using this approach, we were able to prepare a Macmillan-type organocatalyst and a Seebach-type auxiliary, as well as cyclohexanone derivative, in one-pot procedures starting from the unprotected amino acid. Furthermore, we were also able to synthesize the natural product (±)-Tricladin A from alanine in a two-step, rather than a one-step, sequence:

The one-pot sequential direct amidation/condensation with 2-butanone provided in 81% yield, which could then be converted into the racemic natural product via a literature oxidation method.

Synthetic applications of the reaction

We then went on to explore the application of our methodology to the synthesis of active pharmaceutical ingredients (APIs) (Fig. 5). The amide bond formation steps within the syntheses of several top-selling pharmaceuticals, including Valsartan (Diovan), Bunazosin (Andante), GVS-111 (Noopept), Atorvastatin (Lipitor), Granisetron, and others, were achieved in a two-step sequence.

Fig. 3. Scope of borate-catalyzed amide bond formation. (A) Secondary amides. (B) Tertiary amides. (C) Challenging acids/amines. (D) Amino acid amides and dipeptides.
and Sitagliptin (Januvia) (71 and 72), and all, proceeded well using our new amidation procedure. Similarly, Fasoracetam (73) was synthesized in one step from glutamic acid, a cheap and readily available chemical feedstock.

Because our goal was to develop a highly efficient and scalable amidation protocol, we sought to demonstrate the efficiency of our method by benchmarking it against other known catalytic amide bond formation processes. The PMI \([\text{PMI} = \frac{\text{raw material input}}{\text{bulk product output}}]\) provides a widely used measure for the efficiency of a chemical process and was used to compare a selection of recently reported catalytic amidation reactions with the present method (Fig. 6) (37). The synthesis of phenylacetamide 10 is ubiquitous in the amidation literature,

Fig. 4. Chemoselective amide bond formation from amino acids. (A) Chemoselective amino acid couplings. (B) Sequential amidation/condensation to form imidazolidinones. \(dr\), diastereomeric ratio. Reactions run according to general procedures B and C for 24 hours unless stated otherwise. *Using 30 mol % \(\text{B(OCH}_2\text{CF}_3)_3\). †Using 2 equiv. of amine. ‡Using 1.2 equiv. of benzylamine.

Fig. 5. Application to the synthesis of APIs. Reactions run according to general procedures A or B for 24 hours unless stated otherwise. *Using 1.5 equiv. of homopiperazine. †Using 2 equiv. of \(\text{H-Gly-O}^\text{tt}\text{Bu}\). ‡Using 1.0 equiv. of \(\text{B(OCH}_2\text{CF}_3)_3\).
so this compound was selected for comparison (12–24, 38). Pleasingly, our procedure showed clear improvements over existing catalytic amidation methods with regard to the PMI for both (i) the reaction conditions (more concentrated; no additives or molecular sieves) and (ii) the workup (no liquid-phase extraction). The PMI values were also calculated for two further large-scale borate-catalyzed amide syntheses. Although the solid-phase workup procedure is still highly efficient on a multigram scale (36), direct crystallization of the amide product from the reaction mixture leads to a further improvement in the PMI (74).

### Mechanism of the reaction

Because the alkoxy group present on the borate ester exerts a significant effect on the catalytic activity (Fig. 2B), at least one of these groups must remain attached to the boron atom during the catalytic cycle. Analysis of the contents of the Dean-Stark trap by $^{19}$F nuclear magnetic resonance (NMR) showed that less than 1 equivalent of trifluoroethanol was removed from the reaction mixture over the course of the amidation reaction, suggesting that the active catalyst has a general structure $XB(OCH_2CF_3)_2$.

Using a graphical method involving variable time normalization developed by Burés (39, 40), we were able to elucidate the reaction orders from concentration profiles of the reaction. As expected, analysis of the reaction kinetics for the formation of amide 6 suggests a positive dependence on the concentration of borate ester catalyst (0.8th order). This is consistent with a reaction that is first-order in catalyst, but with some competitive decomposition of the active species (41). The reaction rate was independent of amine concentration (0th order) but displayed a positive correlation with acid concentration (0.5th order). The non-integer reaction order with respect to the carboxylic acid could be explained by off-cycle equilibria, for example, reversible formation of the amine carboxylate salt 75 (equil. 1) (Fig. 7A) (41).

As a consequence of these observations, we propose that the active acylating agent is likely to be an acyloxyboron compound (76) bearing two trifluoroethoxy groups, related to the intermediates previously suggested for stoichiometric amidation reactions mediated by alkoxyboron compounds (42, 43). The $^{11}$B NMR of the reaction mixture only showed that tetrahedral boron species are present, so 76 is likely present as a Lewis base adduct 77 with the amine or solvent ($L = \text{amine, trifluoroethanol, or TAME}$). The former is more likely because the amine is a stronger Lewis base. Note that the first-order dependence on catalyst does not preclude an active species containing two or more boron atoms with bridging carboxylate ligands (for example, [76]$_2$) (41, 44).

On the basis of the kinetic data, we propose a catalytic cycle as shown (Fig. 7A), in which condensation of the carboxylic acid with the monohydroxyboron species 78, with concomitant water removal, is the turnover limiting step.

Finally, an alternative pathway in which a trifluoroethyl ester, such as 80, acts as the acylating species (45, 46) was excluded on the basis that ester 80 is not a competent acylating agent for poorly nucleophilic amines such as aniline (Fig. 7B). Further work is under way to fully elucidate the mechanism of this amidation reaction to facilitate the design of more active catalysts.
CONCLUSIONS
Our new borate-catalyzed amide coupling reaction has many advantages over existing methods for amidation: It uses a simple, commercially available catalyst, and the protocol proceeds with high efficiency (low PMI value), with a remarkably broad substrate scope, including application to the synthesis of many pharmaceutically relevant compounds. The procedure can easily be performed on a multigram scale, and the products can be isolated either via a filtration workup or by direct crystallization from the reaction mixture. We anticipate that this method will find many applications in the synthesis of amides in a wide range of fields.

MATERIALS AND METHODS

General amidation procedure A
A stirred suspension of an amine (5.0 to 5.5 mmol) and carboxylic acid (5.0 mmol) in TAME (5 ml) was heated to reflux (bp, 86°C) in Dean-Stark apparatus (side arm filled with TAME), and B(OCH2CF3)3 (0.5 mmol; 5 ml of a 0.1 M solution in TAME) was added into the reaction mixture through the Dean-Stark apparatus. An air condenser was fitted, and the reaction mixture was stirred for 2 to 36 hours. Upon completion, the reaction mixture was cooled down to room temperature and concentrated in vacuo. The crude mixture was dissolved in dimethyl carbonate (10 ml) and H2O (0.5 ml); Amberlite IRA743 (0.25 g) and Amberlyst A15 (0.5 g), and Amberlyst A-26(OH) (0.5 g) resins were added; the resulting suspension was stirred for 30 min. After the disappearance of any remaining starting materials [monitored by thin-layer chromatography (TLC)], MgSO4 (~0.5 g) was added. The reaction was filtered, the reaction flask was washed with dimethyl carbonate (2 × 10 ml), and the combined filtrates were concentrated in vacuo to give pure amide.

General amidation procedure B for unprotected amino acids
A stirred suspension of an amine (7.5 mmol) and unprotected amino acid (5 mmol) in TAME (2.5 ml) was heated to reflux (bp, 86°C) in a Dean-Stark apparatus (side arm filled with TAME), and B(OCH2CF3)3 (1 mmol; 2.5 ml of a 0.1 M solution in TAME) was added through the Dean-Stark apparatus. An air condenser was fitted, and the reaction mixture was stirred for 24 hours. Upon completion, the reaction mixture was concentrated in vacuo and dry-loaded onto silica gel for column chromatography.

General procedure C for synthesis of imidazolidinones
Following general procedure B, after heating to reflux for 24 hours, a solution of aldehyde or ketone (10 mmol) in TAME (5 ml) was added dropwise over 10 min into the reaction mixture (fig. S2). The reaction was left to stir for 1 hour. If the reaction was not complete, as seen by the disappearance of the intermediate amide amine by TLC (revealed with ninhydrin stain) or high-performance liquid chromatography (HPLC), a further portion of aldehyde or ketone (5 mmol) in TAME (2 ml) was added dropwise over 5 min into the reaction mixture, which was left to stir for another hour. Once complete, the reaction was cooled to room temperature and concentrated in vacuo. The product was purified by flash column chromatography.

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/9/e1701028/DC1

General methods
Optimization of reaction parameters

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Borate esters: Simple catalysts for the sustainable synthesis of complex amides
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