Recent Developments in Amide Synthesis: Direct Amidation of Carboxylic Acids and Transamidation Reactions

Rachel M. Lanigan[a] and Tom D. Sheppard*[a]

Keywords: Amides / Amines / Carboxylic acids / Amidation / Transamidation

The synthesis of amides is of huge importance in a wide variety of industrial and academic fields and is of particular significance in the synthesis of pharmaceuticals. Many of the well established methods for amide synthesis involve reagents that are difficult to handle and lead to the generation of large quantities of waste products. As a consequence, there has been a considerable amount of interest in the development of new approaches to amide synthesis. Over the past few years a wide range of new reagents and catalysts for direct amidation of carboxylic acids have been reported. In addition, the interconversion of amide derivatives through transamidation is emerging as a potential alternative strategy for accessing certain amides. This microreview covers recent developments in the direct amidation of carboxylic acids and the interconversion of amides through transamidation. The advantages and disadvantages of the various methods are discussed, as well as the possible mechanisms of the reactions.

Introduction

Amide bonds are present in a vast array of useful molecules including numerous industrially important compounds, as well as a wide selection of bioactive natural products. The synthesis of amides is hugely important in the preparation of compounds in a wide variety of industries, with amide synthesis attaining particular significance in the pharmaceutical industry: amides are present in around 25% of top-selling pharmaceuticals and in many other medicinally important compounds.[1] Despite the huge importance of amides in organic chemistry, most of the well-established methods for their formation are relatively inefficient, with large quantities of potentially hazardous waste products being produced, leading to adverse environmental impacts and difficulties in purification of the desired amide products. As a consequence, there have been several articles written by representatives of the pharmaceutical industry (such as the ACS Green Chemistry Institute Pharmaceutical Roundtable), which have identified amide bond formation as perhaps the most important synthetic transformation for which improved methods are required.[2]

The environmental aspects of a variety of established amide formation reactions have also been evaluated in several recent articles from representatives of the pharmaceutical industry.[3] The industrial importance of amide synthesis has stimulated increased interest from the research community in the development of new and efficient approaches, and many new developments have been reported over the past decade.[4]

Amides can be prepared from a wide variety of precursors by a range of different reaction pathways. Although recent progress has been made in oxidative amidation reactions employing alcohol or aldehyde precursors, by far the most common approach is condensation between a carbox-
ylic acid and an amine. This is usually achieved by the use of a coupling reagent, which activates the carboxylic acid component and drives the dehydration reaction. More recently, the discovery of effective catalysts for direct amidation has led to processes that offer considerably increased efficiency, although as yet they often have relatively limited substrate scope. Nevertheless, over the next few years it is likely that catalytic amidation reactions will become increasingly competitive with the more traditional coupling reagent approaches. Alternative strategies that employ esters or amides as acyl donors have also begun to emerge, and in some cases such strategies might offer advantages over carboxylic acid activation methods.

A number of recent reviews of the area have covered metal-catalysed amide bond formation and the use of more traditional coupling reagents. This microreview highlights recently reported developments both in the direct amidation of carboxylic acids and in the interconversion of amides through transamidation.

Amidation of Carboxylic Acids

The direct thermal condensation of carboxylic acids and amines in the absence of reagents or catalysts has traditionally been viewed as an unviable approach, due to the presumed formation of ammonium carboxylate salts (Scheme 1), and extremely harsh conditions have been reported to be required. However, thermal amidation has recently attracted renewed interest because it has become apparent that ammonium carboxylate salt formation does not always readily take place, and need not necessarily prevent condensation from occurring. Indeed, the degree of ammonium carboxylate salt formation is strongly dependent both on the substrates employed and on the reaction conditions.

Scheme 1. Ammonium carboxylate salt formation versus condensation.

In a recent experimental and computational study of the mechanism of thermal amidation reactions in nonpolar solvents, a strong correlation between the acidity of a carboxylic acid and its reactivity was observed, with more acidic systems being largely unreactive. This was attributed to the high degree of ammonium carboxylate salt formation observed with stronger acids. Trends in the reactivity of the amine component were much more difficult to identify, and amine reactivity was thought to be down to a complex balance of steric and electronic effects. On the basis of a computational study it was proposed that the key step of the reaction mechanism is nucleophilic attack of the amine on a hydrogen-bonded carboxylic acid dimer (Scheme 2).

The general reactivity trends identified in this mechanistic study have been corroborated by several recent papers on thermal amidation, which are discussed below. Similar reactivity trends have also been observed in amidation reactions mediated by a variety of reagents and catalysts.

The direct thermal condensation of carboxylic acids and amines at 160 °C under neat conditions in the presence of 3 Å molecular sieves (MS) to remove the water generated in the reaction has been described (Scheme 3). During optimisation of this method it was observed that molecular sieves were not necessary for good conversion, although they were still employed in order to limit any pressure build-up in the sealed reaction vessel. Only a limited selection of functionalised acids and amines were explored, but free alcohols and phenols were tolerated under the reaction conditions.

Scheme 3. Direct high-temperature thermal amidation. [a] Reaction time 24 h. [b] Reaction time 12 h.

The use of radiofrequency heating to promote direct amidation under solvent-free conditions has also been reported (Scheme 4). Nickel ferrite nanoparticles act as a radiofrequency-absorbing material that can generate localised heat in the reaction flask when exposed to alternating current (AC) magnetic fields. This method benefits from fast reaction times (<20 min) and easy removal of the nickel ferrite particles by magnetic separation. A range of substrates in-
cluding α-chiral acids, benzoic acids, anilines and secondary amines can be used, and no drop in stereochemical purity was observed during the amidation of N-Boc- or N-Cbz-L-proline. Acid-sensitive protecting groups and free phenols were also tolerated in these reactions.

Scheme 4. Examples of radiofrequency-mediated amidation.

The direct amidation of carboxylic acids was reported to occur for many substrates on heating in PhMe at 110 °C (Scheme 5).[15] This method does not require active water removal (Dean–Stark, etc.), but anhydrous reaction conditions were employed. Because of the nonpolar nature of the solvent, ammonium carboxylate salt formation is disfavoured. This method works well for secondary amines, aliphatic, aromatic and heteroaromatic amines and a range of carboxylic acids. In one case an amidation reaction was successfully performed on a 400 mmol scale to give 93 g of product. Less reactive systems such as anilines and benzoic acids gave lower yields under the standard conditions, although yields from less reactive substrates could be improved by increasing the reaction temperature to 150 °C (xylenes) or by the addition of a zirconium catalyst (ZrCl₄ or Cp₂ZrCl₂). An amidation product derived from N-Boc-proline was determined to have >99% ee.

Scheme 5. Examples of thermal and Zr-catalysed amidation.

A ZrCl₄-catalysed direct amidation was also reported by another research group at the same time.[16] In this case, 4 Å MS were employed as a dehydrating agent and the reaction could be carried out at a lower temperature (70 °C) under anhydrous conditions (Scheme 6). No racemisation was observed in the coupling of two N-protected amino acids, and acid-sensitive N-protecting groups were tolerated. Alkyl, aromatic and heteroaromatic acids and amines underwent amidation in moderate to excellent yield under these conditions. Less active substrates such as benzoic acids and secondary amines, however, required a higher reaction temperature of 100 °C. This method was also shown to be suitable for larger-scale synthesis (>5 g of amide). In terms of functional group compatibility, a few examples of functionalised substrates, including compounds containing acetals/ketals and nitro groups, were investigated. The background reaction observed under these conditions for the reaction between phenylacetic acid and benzylamine was low (10–13%) in comparison with the catalysed reaction (99%).

Scheme 6. Examples of ZrCl₄-catalysed amidation. [a] 1.5 equiv. amine at 100 °C.

It has been proposed that zirconium catalysts activate the carboxylic acid through several different coordination modes (Figure 1), including: a) Lewis acid activation of the carbonyl group either in the acid or in the hydrogen-bonded dimer, b) Lewis acid activation of the carbonyl group with simultaneous activation of the leaving group by hydrogen bonding, and c) zirconium activation of the carboxylate oxygen as a leaving group.

Figure 1. Proposed carboxylic activation modes in Zr catalysis.

In a similar fashion, Ti(OiPr)₄ was also reported to be a suitable catalyst for direct amidation,[17] under reaction conditions related to those reported for ZrCl₄ (Scheme 7). Amidation reactions with both primary and secondary amines in combination with aliphatic acids, unsaturated acids, aromatic acids or heteroaromatic acids proceeded well...
under the reaction conditions. A selection of α-chiral acids were explored: no racemisation was observed with Boc-L-proline or Boc-L-alanine, but some epimerisation was observed with ibuprofen (83% ee). Acid-sensitive groups including Boc-protected nitrogens and ketals were tolerated under the reaction conditions. A range of transition-metal chlorides and alkoxides were also found to act as suitable amidation catalysts, although Ti(OiPr)₄ was judged to be the most suitable candidate due to its ready availability and low price. This reaction probably proceeds by a mode of activation similar to that of the Zr-mediated processes (Figure 1). The background reaction between benzylamine and phenylacetic acid under these reaction conditions was lower (10%) than in the Ti(OiPr)₄-catalysed process (91%).

Scheme 7. Examples of Ti(OiPr)₄-catalysed amidation. [a] Ti(OiPr)₄ (20 mol-%) at 100 °C.

Scheme 8. Proposed AlMe₃-mediated amidation mechanism.

Scheme 9. Selected examples of AlMe₃-mediated amidation.

Scheme 10. Examples of XtalFluor-E-mediated amidation.

A PPh₃/I₂ combination has also been shown to be effective for the direct amidation of carboxylic acids under inert conditions,[20] when used along with an excess of Hünig’s base to facilitate acid deprotonation. However, more challenging substrates require up to two equivalents of the reagents and the products must be separated from the phosphane oxide byproduct by recrystallisation, chromatography or a polymer-supported phosphane must be used.

1-tert-Butoxy-2-tert-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI, Scheme 11) has been reported as a new coupling reagent that can mediate amidation reactions effectively at room temperature.[21] The carboxylic acid is activated as the mixed anhydride after elimination of the isoquinoline leaving group and tBuOH. This procedure is car-
ried out in CH₂Cl₂ and requires an excess of both the BBDI and the amine. Aliphatic amines, anilines and secondary amines could, however, be coupled with aliphatic, benzoic, heteroaromatic and unsaturated acids effectively under the reaction conditions (Scheme 12). Lower yields were observed for bulky acids and amines such as adamantane-carboxylic acid and tert-butylamine, but these reactions could be improved by increasing the reaction temperature to reflux. Low levels of racemisation were observed for some α-chiral acids, but measured enantiopurities were not reported for all chiral amides synthesised.

Scheme 11. Mechanism of BBDI-mediated amidation.

Scheme 12. Examples of amides prepared by BBDI-mediated coupling. [a] Reaction time of 5 h. [b] No enantiopurity reported.

Sulfated tungstate has been reported as a heterogeneous catalyst for the direct preparation of amides. This method requires azeotropic reflux in PhMe or xylene in the presence of excess carboxylic acid (Scheme 13). The synthesis of amides derived from primary/secondary aliphatic amines and anilines by condensation with aliphatic, unsaturated and aromatic carboxylic acids was described. However, only a few functionalised systems were examined. There is a significant background reaction reported in some cases, which can be expected in view of the high temperatures involved. This heterogeneous catalyst offers a considerable advantage in terms of purification because it can easily be separated from the reaction mixture by filtration, and the catalyst can be reused up to four times with only a small loss in amide yield. After catalyst removal, the amide product was purified by aqueous workup.


The use of boron-based reagents and catalysts for direct amidation has attracted significant attention. In very early reports on organoboron chemistry, the ability of boronic acids to promote acylation of amines was noted. For example, catalytic reduction of o-nitrobenzeneboronic acid (1, Scheme 14) in acetic acid led to the formation of a compound tentatively assigned the structure 2, which upon deboronation gave acetanilide 3. More recent work has found further evidence to support this proposed structure of 2. It was hypothesised that a mixed anhydride 4 was generated between the boronic acid group and acetic acid, and that this then reacted with the amine to give 2.

Scheme 14. Boron-mediated acylation reaction during the reduction of 2-nitrobenzeneboronic acid in AcOH.

Subsequently, the direct formation of amides with the aid of a variety of boron reagents including BF₃·OEt₂, borane, catechol boranes and tris-(dialkylamino)boranes has been reported. However, these reagents require anhydrous reaction conditions due to the sensitivity of the reagents towards moisture, and in some cases an excess either of the amine or of the carboxylic acid is also needed.

Borate esters are potentially attractive amidation reagents because they are readily prepared and easy to handle. The use of B(OMe)₃ as a direct amidation reagent in the presence of sulfonic acid was reported for a single example in the early 1970s. More recently we have explored this process in considerable detail and found that B(OMe)₃ and B(OCH₂CF₃)₃ are highly effective reagents for direct amidation reactions in MeCN, in the absence of any added acid. Background experiments were carried out to demonstrate that the thermal amidation rates were largely insignificant under the reaction conditions. Both B(OMe)₃ and B(OCH₂CF₃)₃ are available commercially, and the latter compound can be easily prepared on a 50 g scale from...
B₂O₃ and trifluoroethanol.[31] The B(OCH₂CF₃)₃ reagent is considerably more effective than B(OMe)₃ and can be used for amidation reactions with a wide range of amines and carboxylic acids including many functionalised examples, which show low or poor reactivity with other boron-based systems (Scheme 15). The products can be purified by aqueous workup or by a simple solid-phase workup with commercially available resins (Figure 2). The resins scavenge any unreacted amine and carboxylic acid, along with boron-containing byproducts, leaving the pure amide in solution.

A variety of Boc- and Cbz-protected amino acids can be converted into the corresponding amides in good yields and with very low levels of racemisation, despite the elevated reaction temperatures employed (Scheme 15).[31] Dipeptides can also be synthesised in good yield with excellent diastereoselectivity.

Each of the above boron-containing reagents can, in principle, generate an acyloxyboron species in situ; this is generally considered to be the active acylating reagent in the reaction medium (Scheme 16). By analogy with mechanistic studies on boronic acid catalysed amidation reactions (vide infra), the reactive acylating agent could contain either a trigonal or a tetrahedral boron atom.

The use of boronic acids (Figure 3) as catalysts for the amidation of carboxylic acids with amines was first reported by Yamamoto in 1996 with catalyst 5,[33] and this area of research has attracted considerable interest (Scheme 17). These reactions require heating at reflux in PhMe, xylene or mesitylene with molecular sieves as a drying agent. Although excellent yields were generally obtained, there was a limited substrate scope, and long reaction times (up to 29 h) were required in many cases. It should be noted that the thermal background amidation rates under these conditions are likely to be considerable for those cases involving relatively reactive combinations of acid and amine.[15] Subsequent reports included the use of recyclable boronic acid 6 (Figure 3) as an efficient amidation catalyst that can be fully recovered into a fluorous phase after completion of the reaction.[34] Pyridinium boronic acid 7 is also notable as a boronic acid catalyst that can be used in relatively polar organic solvents.[35] Chlorinated catechol derivatives 8 and 9 were developed as catalysts for the amidation of hindered carboxylic acids.[36] More recently, efforts have been directed towards reducing the reaction temperature needed for effective catalysis. Tertiary-amine-containing boronic acid 10 is able to mediate several amidation reactions in fluorobenzene at reflux (85 °C).[37] Remarkably, ortho-iodobenzeneboronic acid (11) is able to catalyse amide formation at room temperature in the presence of molecular sieves as a dehydrating agent.[38] The electron-rich variant 12 was recently reported to show even greater reactivity.[39]
Recent Developments in Amide Synthesis

Scheme 17. Boronic acid catalysed amidation reactions.

very attractive, due to the low cost of this compound, high reaction temperatures are required and the substrate scope is limited in comparison with that of the boronic acid catalysed processes. In general, the reactivities of substrates in these boron-mediated amidation processes follow a similar trend to their reactivities in thermal amidation reactions.\textsuperscript{[12,15]}

The exact mechanism of boronic acid catalysed amidation reactions is still a matter of debate. However, there is a general consensus in the literature that the active acylating agent is likely to be an acyloxyboron species generated by formation of a mixed anhydride between the carboxylic and the boronic acids (Scheme 18). In two recent computational studies it was proposed that the rate-determining step (rds) of the reaction is the collapse of the tetrahedral intermediate after attack of the amine.\textsuperscript{[42,43]} In the earlier report, the reaction pathway involves the amine attacking the tetravalent boron species \textsuperscript{13} to give \textsuperscript{14}, prior to dehydration and rate-determining expulsion of the boronic acid catalyst. In the more recent report, which sought to provide a more realistic model of the solvent role in the process, dehydration to give acyl boronate \textsuperscript{15} precedes attack of the amine to form tetrahedral zwitterion \textsuperscript{16}, which then undergoes rate-determining collapse to give the product and regenerate the catalyst.

For the most reactive boronic acid catalysts\textsuperscript{[38,39]} it is proposed that the adjacent iodine atom accelerates the collapse of the tetrahedral intermediates, through a favourable hydrogen-bonding interaction, an interaction with the vacant orbital on the boron atom or steric destabilisation of the tetrahedral intermediate.\textsuperscript{[42,43]}

Given the fact that boron compounds are potentially cheap, widely available and environmentally benign, further developments in this field could well lead to a widely adopted amidation method that offers considerable cost and environmental benefits over existing approaches. As yet the substrate scope of boronic acid catalysed amidation processes is still somewhat limited in comparison with better-established methods, however.

Transamidation Reactions

The direct interconversion of amides, known as transamidation (Scheme 19), is a fairly unusual reaction that is rapidly gaining prominence, because it offers an alternative strategy for preparing amides that avoids the use of carboxylic acids. Although amides themselves are generally poor electrophiles, in the presence of a suitable catalytic or stoichiometric activating agent, reaction with an amine can occur, leading to interconversion of amide derivatives. Many simple amides are readily available, so this process can provide a synthetically useful route to more complex derivatives.

Scheme 19. A general transamidation reaction.

The reactivities of primary, secondary and tertiary amides towards transamidation differ greatly, depending on the reaction conditions and activating agent employed, as well as on the structure of the amide itself (Scheme 19). In principle, the transamidation of primary amides (R2 = R3 = H) should be most synthetically useful because it can provide a route to higher amides through expulsion of a molecule of ammonia. Thanks to its low boiling point, this can readily be removed from the reaction, providing secondary or tertiary amides efficiently. Secondary or tertiary amides
are generally less reactive towards transamidation, although there are several activating agents capable of mediating transamidation of these compounds. Formamides ($R^1 = H$) are inherently more reactive towards transamidation and will readily undergo transamidation at high temperatures, in the absence of reagents or catalysts. Transamidation is in principle reversible, so care must be taken to select reaction conditions that enable the selective formation of the desired amide product. As with ammonia, if the expelled amine is volatile, it can be driven off by heating to provide high levels of conversion into the desired product. Alternatively, control can be achieved by exploitation of differences in the nucleophilicities of the two amines, or by addition of a large excess of the starting amine.

In a very early report, the boron trifluoride complex of acetamide was reported to react with a range of primary and secondary amines to yield secondary and tertiary amides, respectively.[44] Interestingly, in this case the reactions with aniline as the nucleophile were particularly efficient. Since this early publication, a variety of other Lewis acids have been reported to mediate transamidation reactions; they include salts of aluminium,[45,46] scandium,[45] hafnium,[47] zirconium[45] and titanium.[45,48]

We have reported that $\text{B(OCH}_2\text{CF}_3 \text{)}_3$ is an effective reagent for the transamidation of primary amides to secondary amides (Scheme 20).[30] Moderate to good yields of amides could be obtained by transamidation of propionamide or glycolamide. The reagent does not generally mediate the transamidation of secondary amides, so efficient conversion to the product can be achieved with only one equivalent of amine.

Although $\text{B(OCH}_2\text{CF}_3 \text{)}_3$ does not generally mediate the transamidation of secondary and tertiary amides, it is able to activate $\text{N}$-methylformamide and DMF towards transamidation.[31] The latter process is potentially useful for the formylation of amines because DMF is cheap and available as a reagent, and excess DMF can readily be separated from the product by evaporation (Scheme 21).

A further interesting application of this process was the conversion of phthalimide into $\text{N}$-substituted derivatives through expulsion of ammonia (Scheme 22). This offers a convenient approach to the synthesis of phthalimide-protected amines. Its extension to amino acid derivatives was not reported, however, so it is unclear whether such a transformation could be carried out without epimerisation of nearby chiral centres. This could be worth investigating as an economical route to phthalimide-protected derivatives.

The proposed mechanism involves coordination of the amide oxygen to the boron, followed by the formation of a hydrogen bond stabilised tetrahedral intermediate upon attack of the amine (Scheme 23).
Remarkably, readily available hydroxylamine hydrochloride was shown to act as an efficient catalyst for the transamidation of primary amides to secondary amides.\[50]\] The reactions were carried out in PhMe at 105 °C and good to excellent yields of a variety of secondary amides were obtained (Scheme 24). A tertiary amide could also be generated in good yield, and the catalyst could also be employed for the transamidation of a primary urea. Hydroxylamine hydrochloride was completely unreactive for transamidation of secondary amides.

The proposed mechanism involves formation of a hydrogen-bonded complex between hydroxylamine hydrochloride and the amide, followed by attack of the amine on this activated complex (Scheme 25). A second pathway discussed was initial attack of hydroxylamine on the complex to generate an intermediate hydroxamic acid. The pathway involving direct attack of the amine was preferred by the authors on the basis of some preliminary kinetic data.

Copper acetate is able to catalyse the transamidation of primary amides at high temperature (140 °C) in alcohol solvent (Scheme 26). Reactions with α-hydroxyamides were particularly efficient; this might be due to coordination of the proximal hydroxy group to the metal during activation. The transamidation of enantiopure mandelic acid proceeded without any observable epimerisation. Interestingly, with this catalyst the transamidation of primary ureas and N-aryl ureas was also possible (Scheme 27).

The proposed mechanism involves coordination of copper to the amide to form an imidate complex, which then undergoes nucleophilic attack (Scheme 28a). The relative ease with which ureas underwent transamidation might suggest that an alternative mechanism in which an isocyanate...
is generated by expulsion of one of the nitrogen atoms prior to attack of the incoming amine (Scheme 28b) could be operative.

Cp₂ZrCl₂ has been reported to catalyse the transamidation of primary amides at relatively moderate temperatures (30–80 °C) in cyclohexane (Scheme 29). A wide range of both amides and amines were examined, and in some activated examples such as formamides, the reactions proceeded to completion within 5 h at only 30 °C.

It was proposed on the basis of preliminary kinetic studies that the mechanism involves the interaction of the catalyst and the amide with two molecules of amine (Scheme 31).

Solid CeO₂ has been reported to act as a recoverable heterogeneous catalyst for transamidation of primary amides to secondary amides. This reaction requires high temperatures (160 °C) but works with a range of (largely unfunctionalised) amides and amines (Scheme 32). The absorption of the amides and amines onto the CeO₂ surface was studied by infrared spectroscopy; on the basis of these observations it was proposed that the mechanism proceeds through activation of both reaction partners on the surface of the catalyst.

PhI(OAc)₂ is able to catalyse the transamidation of primary amides under neat conditions (Scheme 33) at high temperatures (120–150 °C). The transamidation of phthalimide and of a secondary anilide was possible under these conditions, and activated systems such as formamide...
Recent Developments in Amide Synthesis

underwent transamidation at much lower temperature (60–100 °C). The thermal background yields were not determined but could well be significant for more reactive systems such as DMF.

In a very recent report, L-proline has been reported to catalyse transamidation of primary amides to give secondary and tertiary amides (Scheme 34). The reactions were carried out neat at 100–150 °C and were applicable to a range of primary amides and amines, although less reactive amines such as anilines gave considerably lower yields in most cases. As with many of the other systems, formylation reactions were considerably easier to achieve, and transamidation of formamide took place even at room temperature. The catalyst was also effective for transamidation of phthalimide to give phthalyl-protected amines in a similar manner to boric acid.

Interestingly, other amino acids were also reported to catalyse the transamidation of primary amides. Lysine and glycine gave very good levels of conversion, but the authors did not comment on whether competing acylation of the amino acid catalyst was observed in any of these cases. Although a mechanism based on formation of an iminium-like intermediate was proposed, it seems plausible that this transamidation protocol might well proceed through hydrogen-bonding interactions in an analogous fashion to the hydroxylamine-catalysed process described above (Figure 4).

There have been many developments in the past few years in the search for new and more effective amidation reagents. Several studies on both thermal and catalytic amidations of carboxylic acids have shed considerable light on the relative reactivities of different combinations of carboxylic acids and amines. For more reactive combinations, the thermal approach is extremely practical and efficient and ought to be considered a method of choice. It is clear, however, that catalysts and/or reagents are essential for mediating the amidation of less reactive substrates and of those containing more delicate functionality. As yet, none of the catalytic systems reported to date show the broad substrate scope of reagent-based systems, though further improvements in catalyst activity can be expected in the coming years. At present, most thermal and catalytic amidations proceed better in relatively nonpolar solvents, which are not always suitable for many substrates. This is certainly an issue that will need to be addressed before catalytic amidation reactions become widely adopted.

Transamidation has emerged as a useful alternative strategy for amide synthesis with the discovery of a variety of new reagents and catalysts that enable this process to take place under milder conditions, and with a range of substrates. This transformation could be especially valuable for multistep synthetic sequences in which an unfunctionalised (and unreactive) amide could be carried through multiple steps, before conversion into the desired functionalised product by transamidation at a later stage. Transamidation might also offer a useful approach to amide synthesis in cases in which the corresponding carboxylic acid is unstable (e.g., 1,3-ketoacids).

In both cases, little attention has been paid to the development of more efficient purification methods for isolating the amide product. It is clear, however, that heterogeneous catalysts and/or solid-phase workup procedures to enable amides to be isolated without the need for aqueous workup or chromatography offer considerable advantages. The application of scavenger resins, as used in the borate-mediated amidations developed in our laboratory, could readily be extended to other amidation methods to enable convenient purification of the products.

It is clear that a considerable amount of ongoing research effort is directed towards the improvement of amidation methods through the discovery of more efficient reagents, catalysts and protocols. The mechanistic understand-
ing of many of the reactions described above is still somewhat limited, but with further research it is likely that considerable improvements will result, either through the optimisation of existing catalytic systems, or through the evolution of new classes of catalyst from existing stoichiometric reagents. The degree to which there is widespread adoption of the above methods by synthetic chemists will serve to demonstrate whether or not they truly offer advantages over existing more established approaches. As efficiency and environmental considerations become ever more important, it is surely desirable that chemists consider these recent developments when planning the synthesis of molecules in the laboratory.

Acknowledgments

The authors would like to thank the UCL Chemistry Department for providing a UCL Impact Studentship (to R. M. L.).


Received: April 19, 2013
Published Online: August 6, 2013