

Amidation of Esters with Amino Alcohols using Organobase Catalysis

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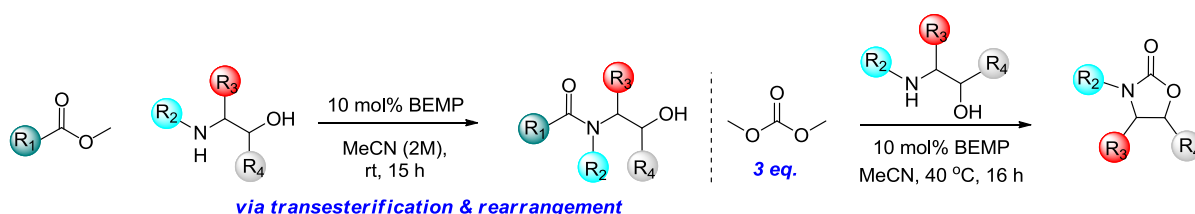
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Abstract

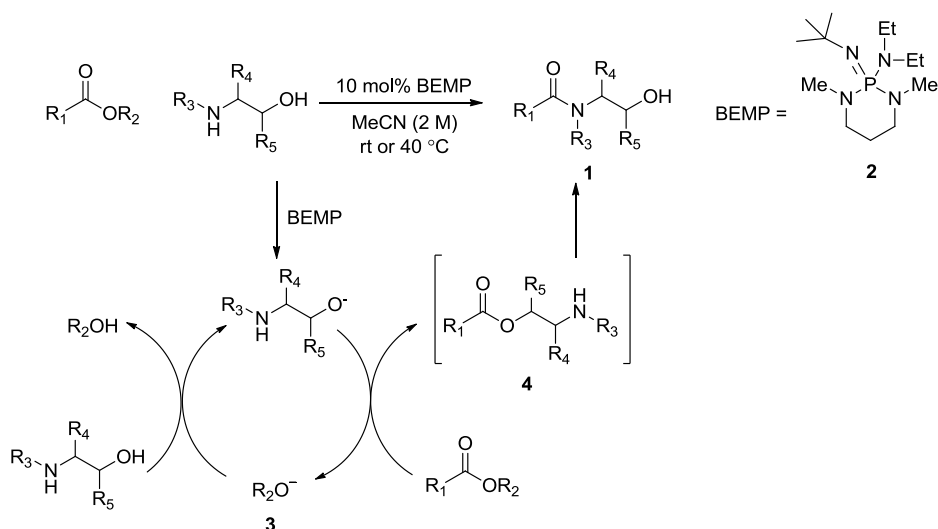
A catalytic protocol for the base-mediated amidation of unactivated esters with amino alcohol derivatives is reported. Investigations into mechanistic aspects of the process indicate the reaction involves an initial transesterification, followed by an intramolecular rearrangement. The reaction is highly general in nature, and can be extended to include the synthesis of oxazolidinone systems through use of dimethyl carbonate.

Introduction

The amide bond is a pivotal functional group from consideration of both chemistry and biology.^{1,2} In an industrial context, formation of the amide bond represents the single largest subset of all reactions conducted in medicinal chemistry laboratories,^{3,4} which further underlines the importance of this ubiquitous functionality. Accordingly, considerable investment has been made in the development of synthetic methodology which enables this transformation in a mild and efficient

manner, and a broad palette of reagents has now emerged from these efforts.⁵ Having stated this, the majority of reagents currently available to facilitate amide bond formation are stoichiometric in nature, and the poor atom economy associated with their use has prompted calls for their replacement by more efficient and sustainable alternatives.⁶ Given the urgent requirement to address this important issue, a number of catalytic approaches to amide bond formation have emerged in recent years.⁷ For example, these methods include the use of transition metal catalysts,^{8,9,10} boron-derived species,^{11,12,13} or enzymes.¹⁴ Although many of these catalytic processes have wide utility, they are often associated with some limitations, including use of high temperatures, unsustainable rare earth metals, or extended reaction times.

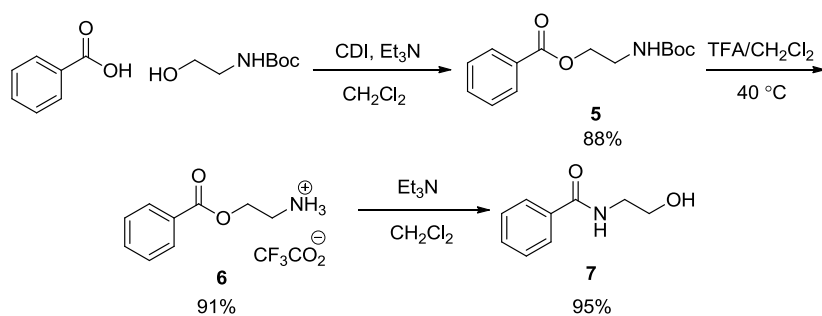
We recently reported a base-mediated process for the catalytic preparation of amides from esters and amino alcohol derivatives.¹⁵ Through a combination of reaction screening where we explored a range of organic and inorganic bases and application of Design of Experiments optimization methods,¹⁶ it was possible to develop a mild, efficient, and unprotracted procedure for the synthesis of amides from unactivated ester derivatives and amino alcohols using a catalytic (10 mol%) quantity of *tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, **2**)¹⁷ as a base (Scheme 1). The reaction was posited to proceed through an initial transesterification event mediated by BEMP which liberates an equivalent of alkoxide base capable of catalyzing a further reaction cycle. Rearrangement of the intermediate ester is then thought to lead to the thermodynamically more stable amide product (**1**). In this study, we present our work in relation to the mechanistic aspects of this base-catalyzed process, as well as a complete report on the scope and limitations of the reaction. Additionally, we demonstrate the applicability of the process to a new reaction manifold enabling the synthesis of oxazolidinone derivatives.



Scheme 1. Organobase-mediated amidation of esters with amino alcohols.

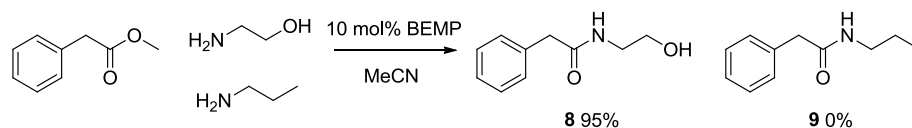
Results and Discussion

Investigation into reaction mechanism. As intimated in Scheme 1, we reasoned that the reaction proceeds *via* an initial transesterification process, to yield an intermediate ester represented by **4**. Based on this, we aimed to independently prepare a compound of this type and determine if it was capable of undergoing the requisite rearrangement to the observed amide product. Scheme 2 depicts the preparation of an appropriate test substrate, using a 1,1'-carbonyldiimidazole (CDI) mediated esterification,¹⁸ followed by acidolysis of the Boc protecting group to yield the salt **6**. We initially attempted to isolate intermediate ester **6** using the conditions established in Scheme 1 (10 mol% BEMP in MeCN), however, this was not successful as presumably the esterification is reversible if rearrangement to the amide cannot take place. Treatment of **6** with an organic base then enabled smooth conversion to the desired amide product **7** in high yield (95%). This result indicated that the intermediate esters represented by **4** (Scheme 1) were competent in rearranging to the amide product.



Scheme 2. Preparation of an ester intermediate to probe mechanism.

Previously, we had considered this process to be intramolecular in nature. Accordingly, we designed a series of probe molecules to confirm this proposal, and exclude any potential intermolecular amidation pathways. In the first instance, we conducted a competition experiment, condensing ethanolamine and propylamine with methyl phenylacetate (Scheme 3). In this case, the exclusive product obtained was ethanolamine-derived amide **8** in high yield, supporting the view that a more favourable transesterification and subsequent intramolecular rearrangement was operative.



Scheme 3. Competition experiment.

With this information in hand, we then designed a series of probe molecules which could offer additional support to the notion of an intramolecular rearrangement. Accordingly, we examined the effect of homologation of the amino alcohol partner on reaction yield (Figure 1). Increasing the chain length would be anticipated to have a deleterious effect on conversion due to the increased flexibility of the system, which then disfavours the required rearrangement of the proposed intermediate ester to the target amide. Additionally, when increasing the chain length of the amino alcohols, the cyclic transition states arising from the proposed intramolecular rearrangement increase from a five membered ring with ethanolamine, through to an eight membered ring with pentanolamine. The strain associated with the differing cycle sizes are calculated as follows: five

membered, 6 kcal/mol; six membered, 0.1 kcal/mol; seven membered, 6.2 kcal/mol; eight membered, 9.7 kcal/mol.¹⁹ From consideration of this aspect of the reaction, it can again be reasoned that longer chain amino alcohols should be less competent substrates. If an intermolecular process leading to a direct amidation was applicable, then it could be anticipated that the reaction yield would not be significantly affected by homologation over the range examined in the current study. Consideration of a range of products with increasing chain length (**8**, **10a-c**, Figure 1) under the standard conditions outlined in Scheme 1 confirms this to be the case; extending the chain length to the butanolamine analogue **10b** results in a significant erosion in yield compared to **10a**, with the pentanolamine system **10c** completely failing to form. The effect of the acidic pKa of the alcohol moiety is not believed to influence the observed yield; if an increase in acidic pKa was noted then it would disfavour initial deprotonation and retard the overall process. Consideration of the relevant pKa values for propanolamine, butanolamine and pentanolamine are all around 15,²⁰ indicating the differences in reactivity observed in homologating the amino alcohol species are unlikely to be attributable to changes in pKa. These results lend further credence to the initial hypothesis of an intramolecular rearrangement following transesterification.

We next examined a further set of substrates (**10d-f**, Figure 1) which could provide additional evidence in support of our proposed mechanism. The 4-hydroxypiperidine amide **10d** is a conformationally locked analogue of the propanolamine derivative **10a** and was thus anticipated to be too constrained to undergo rearrangement to the amide following transesterification, which is consistent with the conversion observed in this case. Additionally, the benzylamine-derived product **10e** is not an effective substrate from both enthalpic and entropic considerations. An analogous amide product **10f** was successfully isolated, albeit in reduced yield in comparison to aliphatic-based progenitors, indicating the tolerance of phenols as substrates. By contrast, however, the isomeric amide system **10g** did not form under the standard conditions developed, presumably due to the lower nucleophilicity of the aniline in the context of the ester rearrangement, which indicates a potential limitation of the current approach with this class of substrate.

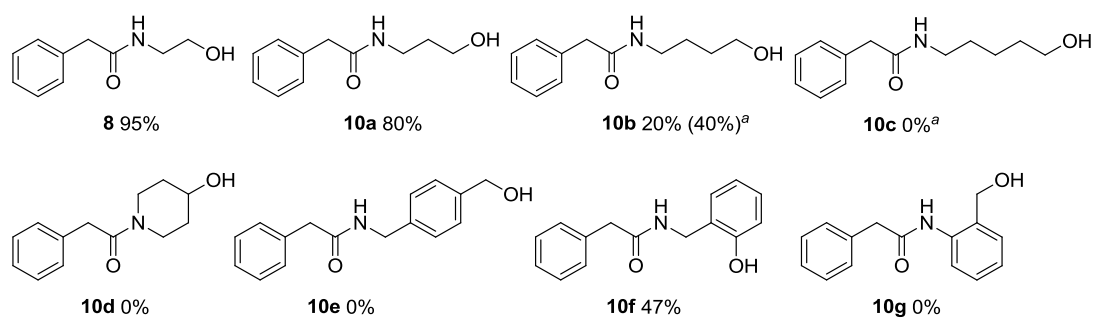
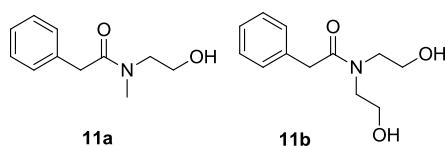


Figure 1. Mechanistic probes evaluated. (a) Reaction performed at 40 °C.

In the last part of this aspect of the study, we sought to establish relative rates of conversion between a secondary amine in comparison with a primary amine, and upon comparing an amino diol with an amino alcohol. Compounds **11a** and **11b** (Figure 2) could be isolated in excellent yields (91 and 88%, respectively) using the existing protocol and these were used together with compound **8** to assess conversion to each product as a function of time. The data which emerged from this experiment indicated rapid conversion to product in each case and in a relatively short timeframe (less than one hour). There was little difference between any of the substrates in terms of their rates of conversion, with the amino diol **11b** exhibiting a marginally faster temporal profile. No evidence for the corresponding ester intermediates could be detected in the HPLC assay, suggesting this is potentially the rate determining step and rearrangement to amide product is extremely rapid in each case.



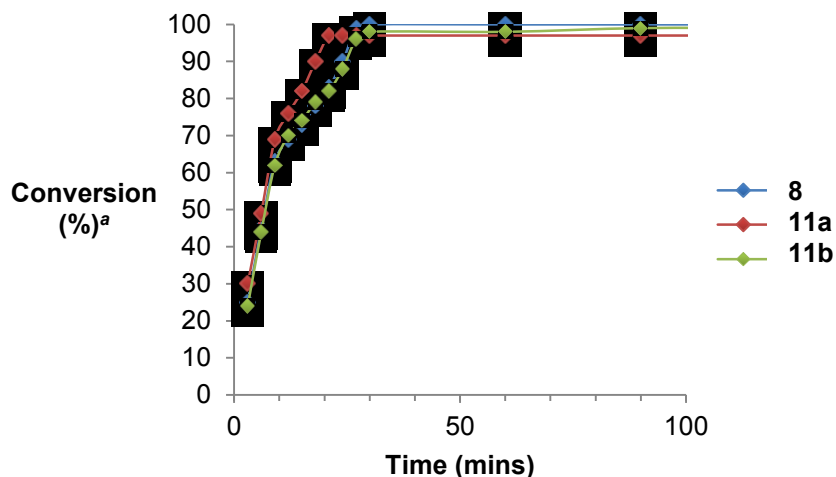


Figure 2. Assessment of conversion as a function of time. (a) Determined by HPLC using an internal standard.

Scope of the amidation process. In the second part of this study, we aimed to more fully delineate the scope of the reaction. In order to evaluate this, a broad range of ester derivatives and amino alcohols were examined using the established reaction conditions (10 mol% BEMP, MeCN, room temperature or 40 °C, 15 h), and the results of this survey are presented in Figure 3. Various substituted benzamide systems (**12a-e**) can be readily accessed and in good to excellent yield. Again, where yields are lower at room temperature, application of modest heating (**12b**) is effective in furnishing high yields. Aliphatic ester derivatives (**12f-h**) also perform well in the reaction which is useful for the synthesis of lead-like compounds²¹ in a discovery chemistry setting exemplified by **12g** and **12h**. In relation to this, the synthesis of heterocyclic amide derivatives is an important objective in a medicinal chemistry effort,²² therefore evaluation of the current methodology using such substrates is warranted. Accordingly, a raft of different heterocyclic motifs exemplified by compounds **12i-t** were examined. Pyridine (**12i**, **12l**), pyrimidine (**12k**, **12p**), pyrazine (**12j**), pyrrole (**12o**), thiophene (**12q**) and furan (**12r**) all perform well along with saturated heterocyclic motifs such as **12s** and lead-like architectures such as **12t**. Focusing on the triazole-derived motifs, compound **12m** was isolated in a low yield of 28%. However, we attribute this to the poor solubility of both the ester starting material and product itself in the reaction solvent. By contrast, the corresponding methylated analogue

12n is completely soluble in the reaction milieu, which is reflected in the excellent yield (94%) obtained with this compound.

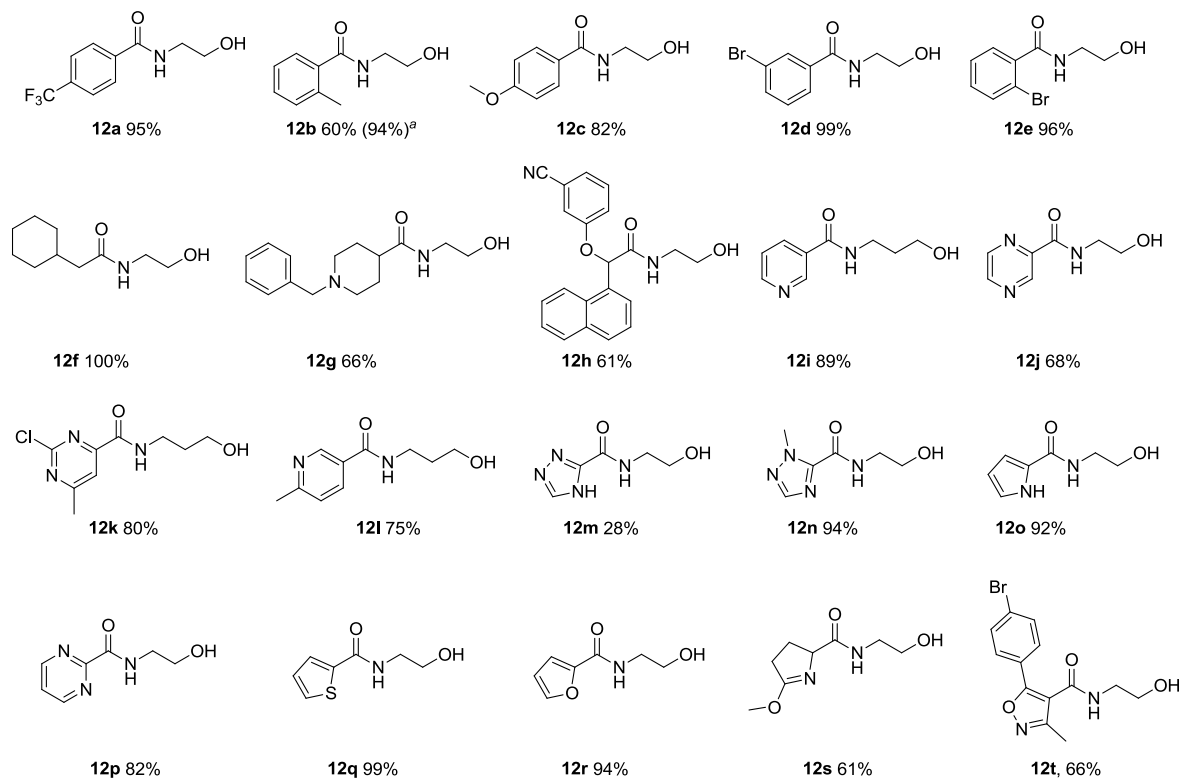
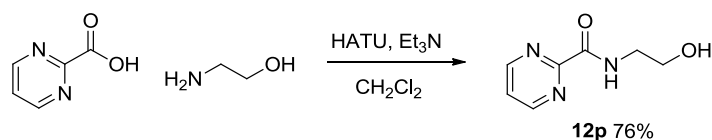


Figure 3. Scope of amide synthesis with straight chain amino alcohols.

Additionally, to enable a direct comparison between the current catalytic approach and existing stoichiometric methods, we independently prepared the pyrimidine derivative **12p** using *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uroniumhexafluorophosphate (HATU)²³ as a coupling agent with the corresponding carboxylic acid (Scheme 4). Pleasingly, the catalytic approach described here performs well in comparison to a standard coupling reagent, furnishing **12p** in a slightly improved yield over the existing method, with the clear advantage of obviating the need for stoichiometric reagents and generation of associated by-products



Scheme 4. Comparative synthesis of **12b** with stoichiometric reagents.

In addition to the straight-chain amino alcohol systems discussed above, we also examined further range of substrates as outlined in Figure 4. (*S*)-Prolinol proved to be an effective nucleophile with benzoate esters (**13a**), cinnamate derivatives (**13b**), heterocyclic systems (**13c**, **13d**) as well as alkyl esters (**13e**). Amide **13a** was also prepared from methyl 4-bromo-2-chlorobenzoate and (*S*)-prolinol on a 2.5 g scale in excellent yield, which serves to demonstrate the utility of the method for larger scale synthesis. Other amino alcohols derived from proteinogenic amino acids such as phenylalaninol were also competent substrates in the reaction (**13f**) allowing access to peptidic structures. Further evaluation of secondary amine derivatives as nucleophiles showed that these to be robust substrates as exemplified by compounds **13g** and **13h**. As discussed above, amino diols performed well in the reaction and amide **13i** is a further example of this substrate class. Secondary and tertiary alcohols represent a more significant challenge which can be ascribed to a more demanding initial transesterification reaction. Having stated this, application of modest heating enabled the isolation of **13j** in good yield using our catalytic process. In the case of tertiary alcohols, we could not prepare amides from electron-neutral substrates such as methyl phenylacetate (leading to **13k**), suggesting a possible limitation of the methodology. However, when more electron withdrawing esters are employed, the corresponding products such as **13l** can be isolated in preparatively useful yield. It was not possible to identify any ester intermediate in the reaction to form **13l** indicating rapid rearrangement to the thermodynamically favourable amide, as noted previously.

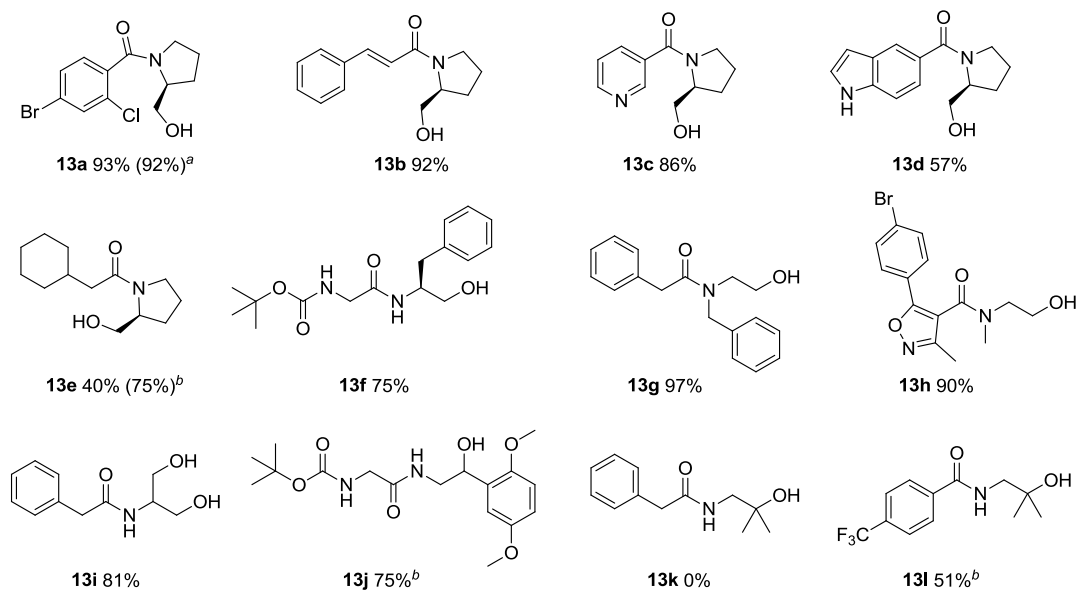
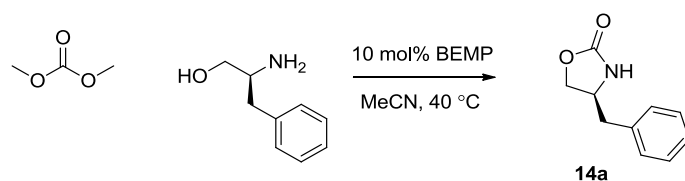


Figure 4. Scope of amino alcohol component. (a) 2.5g scale input; (b) performed at 40 °C.

In the concluding part of our study, we turned our attention to application of the methodology to the synthesis of oxazolidinone derivatives. These important heterocyclic motifs are used widely in both asymmetric synthesis²⁴ and medicinal chemistry,²⁵ therefore a mild and efficient approach to their synthesis would be attractive. Typically, oxazolidinones are synthesized by the reaction of a suitable amino alcohol and diethyl carbonate in the presence of excess base (*e.g.* K₂CO₃, NaOMe) whilst heating, usually to temperatures in excess of 100 °C.²⁶ Given that we had established that formation of an intermediate ester followed by cyclisation to an amide was taking place in the amidation reaction, it was reasoned that this could be exploited in the synthesis of oxazolidinones. Adapting the reaction conditions outlined above could potentially offer a favourable alternative to the typical synthesis of such compounds, having the advantage of being performed at significantly lower temperatures and through the use of catalytic amounts of base. A brief survey of stoichiometry of the dimethylcarbonate (DMC) starting material was carried out in a model reaction with phenylalaninol (Table 1). Given the low cost and abundance of DMC in relation to the amino alcohol precursors, we elected to use an excess of this reagent. To afford the highest probability of success, we also examined the use of slightly elevated temperatures from the outset.



Entry	Dimethyl carbonate (equiv.)	Conversion (%) ^a
1	1	68
2	3	72
3	5	69
4	6 (neat)	61

Table 1. Survey of conditions for oxazolidinone synthesis. (a) Determined by HPLC using an internal standard.

Pleasingly, we observed good levels of conversion to the desired product in each of the reactions attempted. From this short screening exercise, we confirmed that 3 equivalents of the carbonate component was optimal, which provided encouragement to explore the synthesis of a small range of oxazolidinone derivatives using this approach (Figure 5).

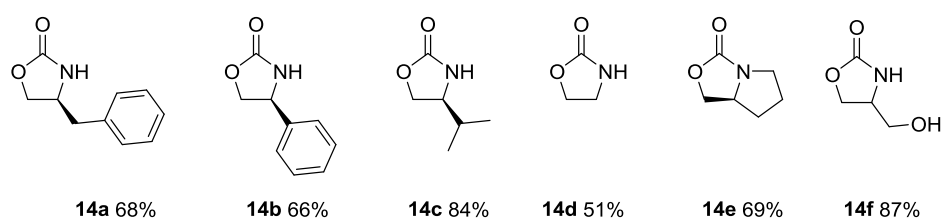


Figure 5. Application to the synthesis of oxazolidinone systems.

Considering the focused sub-set outlined in Figure 5, a range of oxazolidinone derivatives could be prepared using an appropriate amino alcohol and dimethyl carbonate under relatively mild conditions using catalytic BEMP, and in generally good yield. Amino alcohols derived from proteinogenic amino acids were very effective in the reaction (**14a-c**, **14e**), while ethanolamine gave acceptable yields of oxazolidin-2-one (**14d**). Aminodiols were also tolerated in this process, leading to products such as **14f** in excellent isolated yield.

Conclusion

A mild and efficient synthesis of amide derivatives from esters and amino alcohols has been reported using an organic base as a catalyst. The full scope of the reaction has been evaluated including application towards amide products of potential pharmaceutical relevance and extension of the methodology towards the preparation of the versatile oxazolidinone motif. Additionally, through design and study of appropriate probe molecules, the mechanism of the reaction has been delineated, indicating an initial transesterification is taking place, followed by rapid and facile rearrangement to the corresponding amide products.

Experimental Section

General Methods. All reagents and solvents were used as obtained unless otherwise stated. Purification was carried out according to standard laboratory methods.²⁷ BEMP was purified by vacuum distillation from CaH₂ and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen. Reactions were carried out under Schlenk conditions using oven-dried glassware, which was evacuated and purged with N₂ before use. Thin layer chromatography was carried out using aluminium-backed silica plates which were analysed under 254 nm UV light or developed using potassium permanganate solution. Flash chromatography was carried out using prepacked silica cartridges. ¹H NMR spectra were recorded at 400 or 500 MHz and ¹³C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz with CDCl₃ referenced at 7.27 (¹H) and 77.23 ppm (¹³C), and DMSO referenced at 2.50 (¹H) and 39.51 ppm (¹³C). Mass spectrometry data was generated using a TOF analyser. Optical rotations were measured at 589 nm, with concentrations reported in g per 100 mL. Conversions were determined by HPLC using iodobenzene as an internal standard. The data for products **8**, **12a**, **12b**, **12c**, **12f**, **12i**, **12q**, **12r**, **13c**, **13e**, **13f** and **13j** were reported in our earlier communication.¹⁵

2-((tert-Butoxycarbonyl)amino)ethyl benzoate (5).²⁸ To a solution of benzoic acid (341 mg, 2.8 mmol) in CH₂Cl₂ (2 mL) was added CDI (456 mg, 3 mmol) and Et₃N (418 μL, 3 mmol). The

reaction mixture was stirred at room temperature for 16 h, then washed with water, dried (MgSO₄), filtered, and concentrated to a residue that was purified by flash column chromatography (25% ethyl acetate/petroleum ether) to afford the title compound as a white solid (653 mg, 88%): ν_{\max} (neat) 3375, 1701, 1530 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ_{H} 8.07 – 8.04 (m, 2H), 7.58 (tt, $J = 7.5, 1.5$ Hz, 1H), 7.47 – 7.43 (m, 2H), 4.87 (br. s, 1H), 4.39 (t, $J = 5.5$ Hz, 2H); 3.54 (d, $J = 4.5$ Hz, 2H), 1.45 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ_{C} 166.7, 156.0, 133.3, 130.1, 130.0, 128.6, 79.8, 64.5, 40.0, 28.6; HRMS (ESI) m/z : [M+Na]⁺ Calcd for C₁₄H₁₉NO₄Na 288.1204, Found 288.1204.

2-(Benzoyloxy)ethanaminium 2,2,2-trifluoroacetate (6) To a solution of 2-((tert-butoxycarbonyl)amino)ethyl benzoate (**5**, 398 mg, 1.5 mmol) in CH₂Cl₂ (1 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 16 h, heated at 40 °C for 24 h then concentrated under vacuum to afford the title compound as a white solid (381 mg, 91%): ν_{\max} (neat) 3330, 3107, 2967, 1725, 1544 cm⁻¹; ¹H NMR (500 MHz, DMSO) δ_{H} 8.09 (dd, $J = 8.2, 1.3$ Hz, 2H), 8.03 (br. s, 2H), 7.69 (tt, $J = 7.3, 1.3$ Hz, 1H), 7.57 – 7.54 (m, 2H), 4.44 (t, $J = 5.8$ Hz, 2H), 3.25 (q, $J = 4.7$ Hz, 2H), 1H missing (exchangeable); ¹³C NMR (126 MHz, DMSO) δ_{C} 165.6, 133.6, 129.6, 129.3, 128.6, 61.5, 38.0; HRMS (ESI) m/z : [M]⁺ Calcd for C₉H₁₂NO₂ 166.0863, Found 166.0858.

N-(2-Hydroxyethyl)benzamide (7).¹⁵ To a solution of 2-aminoethyl benzoate (**6**, 381 mg, 1.37 mmol) in CH₂Cl₂ (3 mL) was added Et₃N (226 μ L, 1.64 mmol). The reaction mixture was stirred at room temperature for 16 hours then concentrated to a residue that was purified by flash column chromatography (5% methanol/CH₂Cl₂) to afford the title compound as a white solid (306 mg, 95%): ν_{\max} (neat) 3296, 2937, 2876, 1634, 1537 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_{H} 7.80 – 7.78 (m, 2H), 7.51 (tt, $J = 7.3, 1.6$ Hz, 1H), 7.45 – 7.41 (m, 2H), 6.75 (br. s, 1H), 3.83 (t, $J = 5.0$ Hz, 2H), 3.63 (q, $J = 5.2$ Hz, 2H), 2.16 (br. s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ_{C} 168.9, 134.3, 131.9, 128.8, 127.2, 62.6, 43.1; HRMS (ESI) m/z : [M+H]⁺ Calcd for C₉H₁₂NO₂ 166.0863, Found 166.0860.

General Procedure for Base-Catalysed Amide Bond Formation To an oven-dried Schlenk tube containing BEMP (41 μ L, 0.14 mmol) and acetonitrile (700 μ L) was added ester (1.42 mmol) and amino alcohol (1.42 mmol). The reaction mixture was stirred at room temperature or 40 $^{\circ}$ C for 15 h then concentrated to a residue that was purified by flash column chromatography (methanol/ CH_2Cl_2). For oxazolidinone synthesis, the ester was replaced with dimethyl carbonate (350 μ L, 4.26 mmol).

N-(3-Hydroxypropyl)-2-phenylacetamide (**10a**).²⁹ White solid (220 mg, 80%): ν_{max} (neat) 3310, 3242, 3067, 2945, 2882, 1655, 1564 cm^{-1} ; ^1H NMR (400 MHz, DMSO) δ_{H} 8.01 (t, $J = 4.4$ Hz, 1H), 7.31 – 7.19 (m, 5H), 4.42 (t, $J = 4.8$ Hz, 1H), 3.40 – 3.38 (m, 4H), 3.09 (q, $J = 6.5$ Hz, 2H), 1.54 (app. quin, $J = 6.7$ Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ_{C} 170.0, 136.6, 128.9, 128.2, 126.3, 58.4, 42.4, 35.8, 32.4; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{Na}$ 216.0995, Found 216.0991.

N-(4-Hydroxybutyl)-2-phenylacetamide (**10b**).³⁰ White solid (118 mg, 40%): ν_{max} (neat) 3358, 3291, 2951, 1636, 1541 cm^{-1} ; ^1H NMR (400 MHz, DMSO) δ_{H} 8.01 (t, $J = 5.0$ Hz 1H), 7.31 – 7.18 (m, 5H), 4.38 (t, $J = 5.2$ Hz, 1H), 3.39 – 3.35 (m, 4H), 3.05 – 3.00 (m, 2H), 1.43 – 1.37 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ_{C} 169.8, 136.6, 128.9, 128.1, 126.2, 60.4, 42.4, 38.5, 29.8, 25.8; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{Na}$ 230.1152, Found 230.1146.

N-(2-Hydroxybenzyl)-2-phenylacetamide (**10f**). White solid (161 mg, 47%): ν_{max} (neat) 3279, 3102, 2569, 1626, 1568 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.47 (br. s, 1H), 7.41 – 7.35 (m, 3H), 7.29 – 7.25 (m, 3H), 7.10 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.00 (dd, $J = 8.1, 1.0$ Hz, 1H), 6.91 – 6.86 (m, 2H), 4.35 (d, $J = 6.5$ Hz, 2H), 3.60 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 174.0, 156.0, 134.0, 130.9, 130.2, 129.7, 129.3, 127.9, 124.2, 120.0, 118.0, 43.1, 40.9; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_2$ 242.1176, Found 242.1177.

N-(2-Hydroxyethyl)-*N*-methyl-2-phenylacetamide (**11a**).³¹ Yellow oil (249 mg, 91%): ν_{max} (neat) 3339, 3129, 2900, 1641, 1500 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.36 – 7.30 (m, 2H), 7.28 – 7.25 (m, 3H), 3.82 (s, 0.73H, minor rotamer), 3.76 – 3.73 (m, 2.47H, major + minor rotamers), 3.65 (t, $J = 5.4$ Hz, 0.75H, minor rotamer), 3.55 (t, 1.28H, $J = 5.4$ Hz, major rotamer), 3.43 (t, $J = 5.4$ Hz, 0.84H, minor rotamer), 3.32 (br. s, 1H), 3.06 (s, 1.85H, major rotamer), 2.96 (s, 1.10H, minor

rotamer); ^{13}C NMR (101 MHz, CDCl_3 , major rotamer) δ_{C} 172.9, 134.7, 128.9, 128.8, 126.9, 60.8, 51.3, 41.1, 37.2; ^{13}C NMR (101 MHz, CDCl_3 , minor rotamer) δ_{C} 172.3, 135.5, 129.0, 128.6, 126.8, 59.5, 52.4, 40.6, 33.9; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_2$ 194.1176, Found 194.1173.

N,N-Bis(2-hydroxyethyl)-2-phenylacetamide (**11b**). White solid (279 mg, 88%): ν_{max} (neat) 3329, 3204, 2903, 1601, 1479 cm^{-1} ; ^1H NMR (500 MHz, DMSO): δ_{H} 7.31 – 7.28 (m, 2H), 7.22 – 7.20 (m, 3H), 4.86 (t, $J = 5.3$ Hz, 1H), 4.65 (t, $J = 5.3$ Hz, 1H), 3.73 (s, 2H), 3.52 (q, $J = 5.7$ Hz, 2H), 3.48 (q, $J = 5.9$ Hz, 2H), 3.43 (t, $J = 5.8$ Hz, 2H), 3.36 (t, $J = 6.2$ Hz, 2H); ^{13}C NMR (126 MHz, DMSO) δ_{C} 170.6, 136.3, 129.0, 128.2, 126.2, 59.2, 58.8, 50.8, 48.4, 1C missing (coincident); HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_3\text{Na}$ 246.1101, Found 246.1099.

3-Bromo-*N*-(2-hydroxyethyl)benzamide (**12d**). White solid (343 mg, 99%): ν_{max} (neat) 3360, 3291, 3065, 2951, 1636, 1541 cm^{-1} ; ^1H NMR (500 MHz, DMSO) δ_{H} 8.55 (t, $J = 5.2$ Hz, 1H), 8.04 (t, $J = 1.8$ Hz, 1H), 7.86 – 7.84 (m, 1H), 7.72 (ddd, $J = 8.0, 2.0, 1.0$ Hz, 1H), 7.43 (t, $J = 7.9$ Hz, 1H), 3.51 (t, $J = 6.2$ Hz, 2H), 3.32 (q, $J = 6.1$ Hz, 2H), 1H missing (exchangeable); ^{13}C NMR (126 MHz, DMSO) δ_{C} 164.8, 136.7, 133.8, 130.5, 129.9, 126.3, 121.6, 59.6, 42.3; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_9\text{H}_{10}\text{BrNO}_2\text{Na}$ 265.9784, Found 265.9785.

2-Bromo-*N*-(2-hydroxyethyl)benzamide (**12e**). White solid (332 mg, 96%): ν_{max} (neat) 3412, 3220, 3066, 2928, 1623, 1558 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.57 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.50 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.34 (td, $J = 7.5, 1.2$ Hz, 1H), 7.28 – 7.24 (m, 1H), 6.58 (br. s, 1H), 3.82 (t, $J = 4.8$ Hz, 2H), 3.60 (q, $J = 5.2$ Hz, 2H), 2.70 (br. s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 168.8, 137.7, 133.5, 131.6, 129.6, 127.8, 119.5, 62.0, 42.9; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_9\text{H}_{10}\text{BrNO}_2\text{Na}$ 265.9784, Found 265.9784.

1-Benzyl-*N*-(2-hydroxyethyl)piperidine-4-carboxamide (**12g**). Yellow oil (245 mg, 66%): ν_{max} (neat) 3437, 3233, 2922, 1651, 1599, 1537 cm^{-1} ; ^1H NMR (400 MHz, DMSO) δ_{H} 7.71 (t, $J = 5.5$ Hz, 1H), 7.33 – 7.26 (m, 4H), 7.25 – 7.21 (m, 1H), 4.62 (t, $J = 5.5$ Hz, 1H), 3.42 (s, 2H), 3.38 – 3.33 (m, 2H), 3.08 (q, $J = 6.1$ Hz, 2H), 2.79 (d, $J = 11.5$ Hz, 2H), 2.10 – 2.03 (m, 1H), 1.87 (td, $J = 11.4, 3.0$ Hz, 2H), 1.63 – 1.49 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 176.5, 138.3, 129.3, 128.4, 127.3,

63.4, 62.4, 53.2, 43.5, 42.5, 29.1; HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{15}H_{23}N_2O_2$ 263.1754, Found 263.1752.

2-(3-Cyanophenoxy)-N-(2-hydroxyethyl)-2-(naphthalen-1-yl)acetamide (12h). Colourless oil (298 mg, 61%): ν_{\max} (neat) 3350, 3098, 2958, 2232, 1661, 1530, 1248 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (d, $J = 8.4$ Hz, 1H), 7.90 (dd, $J = 12.5, 8.1$ Hz, 2H), 7.66 – 7.56 (m, 3H), 7.52 – 7.43 (m, 2H), 7.34 – 7.23 (m, 2H), 7.22 – 7.10 (m, 1H), 7.01 – 6.91 (m, 1H), 6.28 (s, 1H), 3.70 (t, $J = 5.1$ Hz, 2H), 3.58 (s, 1H), 3.50 (q, $J = 5.2$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.0, 156.9, 134.3, 131.4, 131.2, 130.9, 130.3, 129.3, 127.4, 126.5, 126.2, 125.5, 123.9, 123.6, 120.9, 120.0, 118.4, 113.7, 78.7, 66.5, 38.3; HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{21}H_{19}N_2O_3$ 347.1390, Found 347.1392.

N-(2-Hydroxyethyl)pyrazine-2-carboxamide (12j). White solid (161 mg, 68%): ν_{\max} (neat) 3410, 3261, 2940, 1666, 1564 cm^{-1} ; 1H NMR (400 MHz, DMSO) δ_H 9.18 (d, $J = 1.5$ Hz, 1H), 8.87 (d, $J = 2.5$ Hz, 1H), 8.78 (t, $J = 5.2$ Hz, 1H), 8.73 – 8.72 (m, 1H), 4.81 (t, $J = 5.6$ Hz, 1H), 3.53 (q, $J = 6.0$ Hz, 2H), 3.39 (q, $J = 6.1$ Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C 162.8, 147.5, 144.7, 143.5, 143.3, 59.5, 41.6; HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_7H_{10}N_3O_2$ 168.0768, Found 168.0765.

2-Chloro-N-(3-hydroxypropyl)-6-methylpyrimidine-4-carboxamide (12k). Yellow oil (261 mg, 80%): ν_{\max} (neat) 3365, 3101, 1671, cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ_H 8.12 (br. s, 1H), 7.91 (s, 1H), 3.70 (t, $J = 5.4$ Hz, 2H), 3.64 (q, $J = 6.4$ Hz, 2H), 2.87 (br. s, 1H), 2.64 (s, 3H), 1.87 – 1.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.7, 162.8, 160.3, 158.8, 117.0, 59.6, 36.7, 32.3, 24.6; HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_9H_{13}N_3O_2Cl$ 230.0961, Found 230.0960.

N-(3-Hydroxypropyl)-6-methylnicotinamide (12l). White solid (207 mg, 75%): ν_{\max} (neat) 3444, 3237, 2926, 2895, 1651, 1539 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ_H 8.85 (d, $J = 2.1$ Hz, 1H), 8.03 (dd, $J = 8.1, 2.3$ Hz, 1H), 7.44 (br. s, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 3.76 (t, $J = 5.5$ Hz, 2H), 3.62 (q, $J = 5.9$ Hz, 2H), 2.58 (s, 3H), 1.85 – 1.80 (m, 2H), 1H missing (exchangeable); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 166.5, 161.7, 147.4, 135.9, 127.6, 123.4, 60.6, 38.2, 31.8, 24.6; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{10}H_{14}N_2O_2Na$ 217.0941, Found 217.0945.

N-(2-Hydroxyethyl)-4H-1,2,4-triazole-3-carboxamide (12m). White solid (62 mg, 28%): ν_{\max} (neat) 3406, 3273, 3102, 2982, 1644, 1563 cm^{-1} ; 1H NMR (400 MHz, DMSO) δ_H 8.43 (s, 1H), 4.78

(br. s, 1H), 3.49 (t, $J = 6.2$ Hz, 2H), 3.34 – 3.30 (m, 3H), 1H missing (exchangeable); ^{13}C NMR (101 MHz, DMSO) δ_{C} 158.2, 147.0, 59.5, 41.4, 1C missing (coincident); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_9\text{N}_4\text{O}_2$ 157.0720, Found 157.0718.

N-(2-Hydroxyethyl)-1-methyl-1H-1,2,4-triazole-5-carboxamide (**12n**). White solid (227 mg, 94%): ν_{max} (neat) 3237, 3101, 1671, 1580 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.87 (br. s, 1H), 7.82 (s, 1H), 4.25 (s, 3H), 3.83 (t, $J = 5.2$ Hz, 2H), 3.60 (q, $J = 5.5$ Hz, 2H), 3.01 (br. s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 157.9, 149.5, 146.3, 61.6, 42.2, 38.5; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_6\text{H}_{10}\text{N}_4\text{O}_2\text{Na}$ 193.0691, Found 193.0693.

N-(2-Hydroxyethyl)-1H-pyrrole-2-carboxamide (**12o**). Yellow oil (201 mg, 92%): ν_{max} (neat) 3277, 2940, 2878, 1607, 1560 cm^{-1} ; ^1H NMR (400 MHz, DMSO) δ_{H} 11.41 (br. s, 1H), 7.96 (t, $J = 5.6$ Hz, 1H), 6.83 (td, $J = 2.7, 1.5$ Hz, 1H), 6.76 – 6.74 (m, 1H), 6.06 (dt, $J = 3.6, 2.4$ Hz, 1H), 4.72 (br. s, 1H), 3.47 (t, $J = 6.3$ Hz, 2H), 3.27 (q, $J = 6.1$ Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ_{C} 160.9, 126.4, 121.2, 109.9, 108.5, 60.1, 41.4; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2\text{Na}$ 177.0632, Found 177.0631.

N-(2-Hydroxyethyl)pyrimidine-2-carboxamide (**12p**). White solid (195 mg, 82%); Also prepared as follows: To a solution of pyrimidine-2-carboxylic acid (176 mg, 1.42 mmol) and Et_3N (395 μL , 2.84 mmol) in CH_2Cl_2 (1 mL) was added HATU (648 mg, 1.7 mmol) and ethanolamine (86 μL , 1.42 mmol). The reaction mixture was stirred at room temperature for 16 h, then washed with water and 2M HCl, dried (MgSO_4), filtered, and concentrated to a residue that was purified by flash column chromatography (4% methanol/ CH_2Cl_2) to afford the title compound as a white solid (180 mg, 76%). ν_{max} (neat) 3403, 3310, 2919, 1651, 1538 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.85 (d, $J = 4.8$ Hz, 2H), 8.48 (br. s, 1 H), 7.42 (t, $J = 4.9$ Hz, 1H), 3.87 – 3.85 (m, 2H), 3.68 (q, $J = 5.8$ Hz, 2H), 3.36 (br. s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 163.3, 157.7, 157.6, 122.8, 62.0, 42.8, 1C missing (coincident); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_7\text{H}_{10}\text{N}_3\text{O}_2$ 168.0768, Found 168.0765.

N-(2-Hydroxyethyl)-5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxamide (**12s**). White solid (136 mg, 61%): ν_{max} (neat) 3410, 3277, 3090, 2931, 1663, 1647, 1559 cm^{-1} ; ^1H NMR (500 MHz, DMSO) δ_{H} 8.20 (t, $J = 4.8$ Hz, 1H), 4.73 (br. s, 1H), 4.02 – 4.00 (m, 1H), 3.42 (t, $J = 6.0$ Hz, 2H),

3.15 (q, $J = 5.8$ Hz, 2H), 2.60 (s, 3H), 2.26 – 2.15 (m, 3H), 1.81 – 1.76 (m, 1H); ^{13}C NMR (126 MHz, DMSO): δ_{C} 174.5, 171.1, 61.8, 59.7, 41.5, 29.3, 27.9, 22.5; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_8\text{H}_{15}\text{N}_2\text{O}_3$ 187.1077, Found 187.1075.

5-(4-Bromophenyl)-N-(2-hydroxyethyl)-3-methylisoxazole-4-carboxamide (12t). White solid (305 mg, 66%): ν_{max} (neat) 3271, 3112, 2955, 1643, 1545 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.70 – 7.67 (m, 2H), 7.65 – 7.63 (m, 2H), 6.13 (br. s, 1H), 3.78 (t, $J = 5.0$ Hz, 2H), 3.56 (q, $J = 5.2$ Hz, 2H), 2.46 (s, 3H), 1.96 (br. s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 167.1, 162.9, 160.0, 132.6, 129.6, 126.0, 125.7, 112.3, 61.9, 42.4, 11.2; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{14}\text{BrN}_2\text{O}_3$ 325.0182, Found 325.0184.

(S)-(4-bromo-2-chlorophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone (13a).¹⁵ 2.5 g scale. To an oven-dried Schlenk tube containing BEMP (290 μL , 1 mmol) and acetonitrile (5 mL) was added methyl 4-bromo-2-chlorobenzoate (12.5 g, 10 mmol) and *(S)*-(+)-2-(hydroxymethyl)pyrrolidine (987 μL , 10 mmol). The reaction mixture was stirred at room temperature for 15 h then concentrated to a residue that was purified by flash column chromatography (4% methanol/ CH_2Cl_2) to afford the title compound as a colourless oil (2.92 g, 92%): ν_{max} (neat) 3389, 2949, 2876, 1612, 1581, 1425 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.60 (d, $J = 1.5$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 4.36 (qd, $J = 7.3, 3.6$ Hz, 1H), 3.82 (dd, $J = 11.5, 3.0$ Hz, 1H), 3.76 (dd, $J = 11.8, 7.3$ Hz, 1H), 3.27 – 3.26 (m, 2H), 2.20 – 2.15 (m, 1H), 1.92 – 1.87 (m, 1H), 1.86 – 1.77 (m, 1H), 1.74 – 1.67 (m, 1H), 1H missing (exchangeable); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 168.3, 136.0, 132.7, 130.9, 128.8, 123.7, 66.8, 61.8, 49.6, 28.8, 24.7, 1C missing (coincident); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{BrClNO}_2$ 317.9891, Found 317.9896; $[\alpha]_{\text{D}}^{20} -50$ (c 2.0, CHCl_3).

(S,E)-1-(2-(Hydroxymethyl)pyrrolidin-1-yl)-3-phenylprop-2-en-1-one (13b).³² Yellow oil (302 mg, 92%): ν_{max} (neat) 3350, 2949, 2876, 1645, 1582, 1422 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.63 – 7.56 (m, 1H), 7.45 – 7.42 (m, 2H), 7.31 – 7.20 (m, 3H), 6.90 (d, $J = 15.2$ Hz, 0.23H, minor rotamer), 6.66 (d, $J = 15.2$ Hz, 0.73H, major rotamer), 5.30 (br. s, 1H), 4.23 (app. quin, $J = 5.7$ Hz, 0.75H major rotamer), 4.15 – 4.10 (m, 0.27H, minor rotamer), 3.61 – 3.47 (m, 4H, major + minor rotamers), 1.98 – 1.86 (m, 2H, major + minor rotamers), 1.84 – 1.76 (m, 1.2H, major rotamer), 1.69 –

1.62 (m, 0.78H, minor rotamer); ^{13}C NMR (101 MHz, CDCl_3 , major rotamer) δ_{C} 166.6, 142.6, 134.8, 129.7, 128.7, 127.8, 118.3, 65.9, 60.8, 47.8, 27.8, 24.1; ^{13}C NMR (101 MHz, CDCl_3 , minor rotamer) δ_{C} 165.3, 141.4, 135.1, 129.2, 128.5, 127.7, 119.1, 64.1, 58.9, 46.1, 28.2, 21.7; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ 232.1332, Found 232.1331; $[\alpha]_{\text{D}}^{20}$ -39 (c 2.1, MeOH).

(S)-(2-(Hydroxymethyl)pyrrolidin-1-yl)(1H-indol-5-yl)methanone (**13d**). Colourless oil (197 mg, 57%): ν_{max} (neat) 3318, 3211, 2963, 2891, 2846, 1629, 1554 cm^{-1} ; ^1H NMR (400 MHz, DMSO) δ_{H} 11.25 (s, 1H), 7.72 (br. s, 1H), 7.41 – 7.40 (m, 2H), 7.25 – 7.24 (m, 1H), 6.49 (t, J = 2.0 Hz, 1H), 4.81 (s, 1H), 4.18 – 4.08 (m, 1H), 3.68 – 3.59 (m, 1H), 3.52 – 3.49 (m, 2H), 3.42 – 3.38 (m, 1H), 1.98 – 1.87 (m, 3H), 1.66 (br. s, 1H); ^{13}C NMR (126 MHz, DMSO) δ_{C} 170.3, 136.3, 128.1, 126.7, 126.4, 120.7, 119.8, 110.8, 101.8, 61.8, 58.7, 50.5, 27.2, 24.7; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2$ 245.1285, Found 245.1284; $[\alpha]_{\text{D}}^{20}$ -139 (c 1.0, MeOH).

N-Benzyl-*N*-(2-hydroxyethyl)-2-phenylacetamide (**13g**). White solid (371 mg, 97%): ν_{max} (neat) 3399, 3333, 3063, 2934, 1624, 1489 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.35 – 7.19 (m, 8H), 7.17 – 7.15 (m, 1H), 7.09 (d, J = 6.8 Hz, 1H), 4.62 (s, 0.73H, minor rotamer), 4.58 (s, 1.27H, major rotamer), 3.86 (s, 0.77H, minor rotamer), 3.72 – 3.67 (m, 2.41H, major rotamer), 3.59 (t, J = 5.4 Hz, 0.76H, minor rotamer), 3.53 (t, J = 5.0 Hz, 1.30H, major rotamer), 3.34 (t, J = 5.6 Hz, 0.71H, minor rotamer), 2.43 (br. s, 1H); ^{13}C NMR (101 MHz, CDCl_3 , major rotamer) δ_{C} 174.0, 136.4, 134.8, 129.2, 129.0, 128.8, 128.1, 127.2, 126.6, 62.3, 53.1, 49.4, 41.4; ^{13}C NMR (101 MHz, CDCl_3 , minor rotamer) δ_{C} 174.0, 137.9, 135.5, 129.1, 128.9, 128.7, 128.2, 127.6, 127.0, 60.3, 50.3, 48.8, 41.0; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_2$ 270.1489, Found 270.1489.

5-(4-Bromophenyl)-*N*-(2-hydroxyethyl)-*N*,3-dimethylisoxazole-4-carboxamide (**13h**). Colourless oil (433 mg, 90%): ν_{max} (neat) 3399, 2934, 1612, 1398 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , major rotamer): δ_{H} 7.64 – 7.55 (m, 4H), 3.85 (t, J = 5.4 Hz, 1.30H, major rotamer), 3.70 (s, 1.13H, major rotamer), 3.49 (t, J = 4.8 Hz, 0.64H minor rotamer), 3.10 (s, 1.03H, minor rotamer), 2.85 (s, 3H), 2.30 (s, 2H, major rotamer), 2.27 (s, 0.98H, minor rotamer), 1H missing (exchangeable); ^{13}C NMR (101 MHz, CDCl_3 , major rotamer) δ_{C} 164.9, 164.5, 159.1, 132.6, 128.0, 125.7, 125.5, 111.4, 60.2, 50.1, 37.2, 10.4; ^{13}C NMR (101 MHz, CDCl_3 , minor rotamer) δ_{C} 164.4, 164.1, 159.5, 132.5,

127.9, 125.8, 125.3, 111.8, 58.8, 52.8, 33.0, 10.3, 1C missing (overlapping peaks); HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{14}H_{16}BrN_2O_3$ 339.0339, Found 339.0336.

N,N-Bis(2-hydroxyethyl)-2-phenylacetamide (**13i**).³³ White solid (279 mg, 81%): ν_{\max} (neat) 3329, 3204, 2903, 1601, 1479 cm^{-1} ; 1H NMR (500 MHz, DMSO) δ_H 7.74 (d, $J = 8.0$ Hz, 1H), 7.30 – 7.24 (m, 4H), 7.22 – 7.19 (m, 1H), 4.60 (t, $J = 5.3$ Hz, 2H), 3.72 – 3.66 (m, 1H), 3.43 (s, 2H), 3.40 (t, $J = 5.3$ Hz, 4H); ^{13}C NMR (126 MHz, DMSO) δ_C 170.0, 136.6, 129.0, 128.1, 126.2, 60.1 52.9, 42.3; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{11}H_{15}NO_3Na$ 232.0944, Found 232.0941.

N-(2-Hydroxy-2-methylpropyl)-4-(trifluoromethyl)benzamide (**13l**). White solid (189 mg, 51%): ν_{\max} (neat) 3447, 3312, 2980, 1639, 1547 cm^{-1} ; 1H NMR (500 MHz, DMSO) δ_H 8.47 (t, $J = 6.0$ Hz, 1H), 8.05 (d, $J = 8.1$ Hz, 2H), 7.84 (d, $J = 8.3$ Hz, 2H), 4.54 (s, 1H), 3.27 (d, $J = 6.2$ Hz, 2H), 1.11 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ_C 165.6, 138.6, 131.0 (q, $^2J_{CF} = 32.2$ Hz), 128.2, 125.2 (q, $^3J_{CF} = 3.2$ Hz), 124.0 (q, $^1J_{CF} = 272.2$ Hz), 69.8, 50.3, 27.4; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_{12}H_{14}NO_2F_3Na$ 284.0869, Found 284.0867.

(*S*)-4-Benzylloxazolidin-2-one (**14a**).²⁵ White solid (171 mg, 68%): ν_{\max} (neat) 3263, 2921, 1707 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ_H 7.35 (tt, $J = 8.1, 1.8$ Hz, 2H), 7.30 (dt, $J = 5.1, 2.1$ Hz, 1H), 7.20 – 7.17 (m, 2H), 5.19 (br. s, 1H), 4.50 – 4.46 (m, 1H), 4.17 (dd, $J = 8.5, 5.6$ Hz, 1H), 4.13 – 4.06 (m, 1H), 2.93 – 2.84 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 159.4, 136.2, 129.2, 129.1, 127.5, 69.9, 54.0, 41.7; HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{10}H_{12}NO_2$ 178.0863, Found 178.0858; $[\alpha]_D^{20} -60$ (c 1.0, $CHCl_3$), lit³⁴ $[\alpha]_D^{20} -62$ (c 1.0, $CHCl_3$).

(*S*)-4-Phenylloxazolidin-2-one (**14b**).³⁵ White solid (153 mg, 66%): ν_{\max} (neat) 3237, 3142, 1705 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.33 (m, 5H), 6.12 (br. s, 1H), 4.97 (t, $J = 7.8$ Hz, 1H), 4.74 (t, $J = 8.7$ Hz, 1H), 4.19 (dd, $J = 8.6, 6.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 160.0, 139.7, 129.4, 129.0, 126.2, 72.7, 56.6; HRMS (ESI) m/z : $[M+Na]^+$ Calcd for $C_9H_9NO_2Na$ 186.0521, Found 186.0523; $[\alpha]_D^{20} +53$ (c 2.0, $CHCl_3$), lit³⁶ $[\alpha]_D^{20} +48$ (c 2.0, $CHCl_3$).

(*S*)-4-Isopropylloxazolidin-2-one (**14c**).³⁴ White solid (154 mg, 84%): ν_{\max} (neat) 3253, 3153, 2958, 1721, 1472 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ_H 6.23 (br. s, 1H), 4.45 (t, $J = 8.6$ Hz, 1H), 4.11 (dd, $J = 8.7, 6.3$ Hz, 1H), 3.64 – 3.59 (m, 1H), 1.74 (dq, $J = 13.5, 6.8$ Hz, 1H), 0.97 (d, $J = 6.7$ Hz,

3H), 0.91 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 160.7, 68.8, 58.6, 32.9, 18.2, 17.8; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_{12}\text{NO}_2$ 130.0863, Found 130.0862; $[\alpha]_{\text{D}}^{20} +6$ (c 1.0, CHCl_3), lit³⁷ $[\alpha]_{\text{D}}^{20} +8$ (c 1.0, CHCl_3).

Oxazolidin-2-one (14d).³³ White solid (73 mg, 51%): ν_{max} (neat) 3248, 2989, 2919, 1712, 1485 cm^{-1} ; ^1H NMR (500 MHz, DMSO) δ_{H} 7.45 (br. s, 1H), 4.30 – 4.27 (m, 2H), 3.46 – 3.42 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 161.2, 65.2, 40.8; HRMS (EI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_3\text{H}_5\text{NO}_2$ 87.0315, Found 87.0316.

*(S)-Tetrahydropyrrolo[1,2-*c*]oxazol-3(1H)-one (14e)*.³⁸ Yellow oil (125 mg, 69%): ν_{max} (neat): 2974, 2911, 1738, 1481 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.45 (dd, $J = 8.9, 7.9$ Hz, 1H), 4.10 (dd, $J = 8.9, 3.6$ Hz, 1H), 3.88 – 3.81 (m, 1H), 3.60 – 3.53 (m, 1H), 3.13 – 3.08 (m, 1H), 2.07 – 1.97 (m, 2H), 1.93 – 1.83 (m, 1H), 1.46 – 1.36 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 161.8, 67.8, 59.5, 45.8, 30.7, 25.7; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_{10}\text{NO}_2$ 128.0706, Found 128.0704; $[\alpha]_{\text{D}}^{20} -68$ (c 2.3, MeOH).

4-(Hydroxymethyl)oxazolidin-2-one (14f).³⁹ Yellow oil (144 mg, 87%): ν_{max} (neat): 3331, 3242, 2933, 2878, 1722, 1418 cm^{-1} ; ^1H NMR (500 MHz, DMSO) δ 7.57 (s, 1H), 4.94 (t, $J = 5.4$ Hz, 1H), 4.30 (t, $J = 8.6$ Hz, 1H), 4.05 (dd, $J = 8.5, 5.0$ Hz, 1H), 3.78 – 3.71 (m, 1H), 3.37 – 3.35 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 159.1, 64.4, 62.7, 53.2; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_4\text{H}_8\text{NO}_3$ 118.0499, Found 118.0496.

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Supporting Information

Copies of spectroscopic data (^1H and ^{13}C NMR) for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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