JOC The Journal of Organic Chemistry

Article

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Amidation of Esters with Amino Alcohols Using Organobase Catalysis

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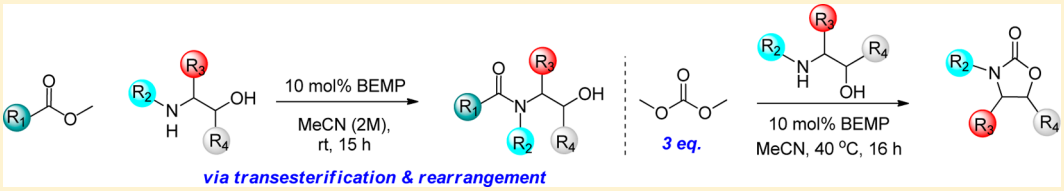
Supporting Information



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 that 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] However, 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,[8−10] boron-derived species,[11−13] 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 1 equiv 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.

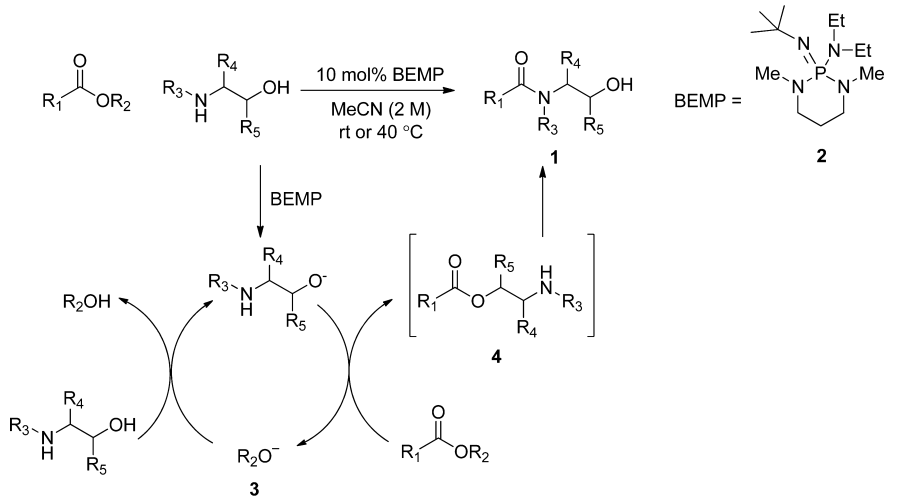
RESULTS AND DISCUSSION

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**. On the basis of 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

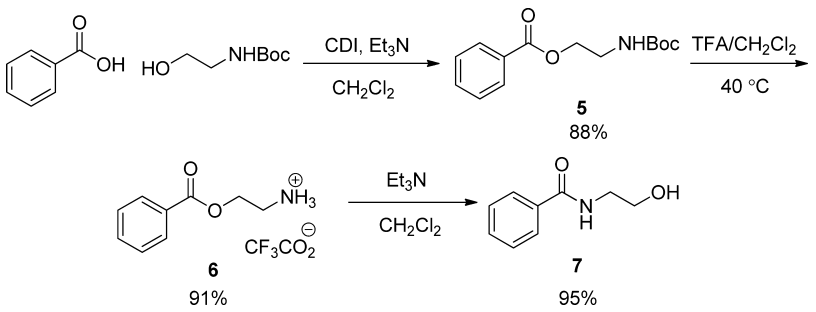
Received: August 20, 2014

   dx.doi.org/10.1021/jo501929c | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. Organobase-Mediated Amidation of Esters with Amino Alcohols



Scheme 2. Preparation of an Ester Intermediate To Probe Mechanism



Scheme 3. Competition Experiment

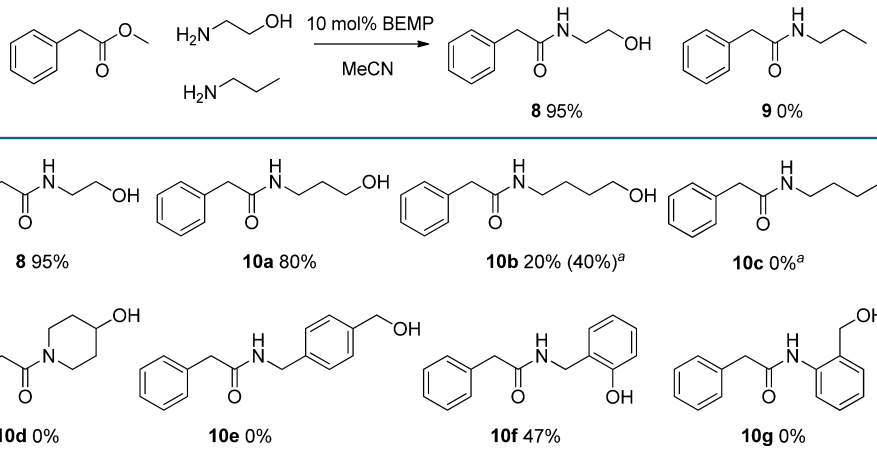


Figure 1. Mechanistic probes evaluated. (a) Reaction performed at 40 °C.

indicated that the intermediate esters represented by **4** (Scheme 1) were competent in rearranging to the amide product.

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 favorable transesterification and subsequent intramolecular rearrangement was operative.

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 disfavors the required rearrangement of the proposed intermediate ester to the target amide. Additionally, when

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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 pK_a of the alcohol moiety is not believed to influence the observed yield; if an increase in acidic pK_a was noted then it would disfavor initial deprotonation and retard the overall process. Consideration of the relevant pK_a values for propanolamine, butanolamine, and pentanolamine are all around 15,[20] indicating that the differences in reactivity observed in homologating the amino alcohol species are unlikely to be attributable to changes in pK_a. 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.

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 time frame (less than 1 h). 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 that rearrangement to amide product is extremely rapid in each case.

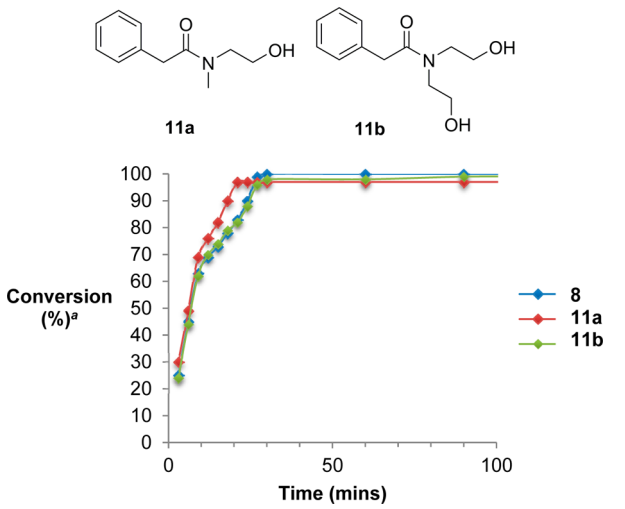

Figure 2. Assessment of conversion as a function of time. (a) Determined by HPLC using an internal standard.

Scope of the Amidation Process. In the second part of this study, we aimed to more fully delineate the scope of the reaction. 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 compounds[21] 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.

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 byproducts.

In addition to the straight-chain amino alcohol systems discussed above, we also examined further range of substrates as

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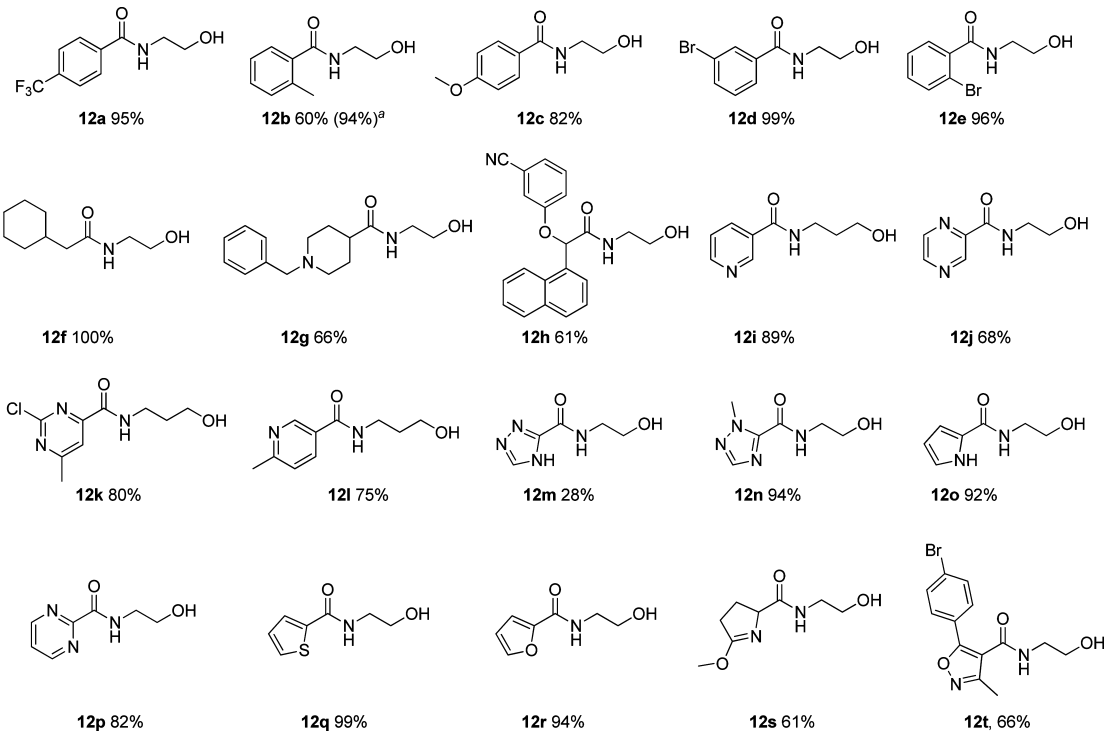
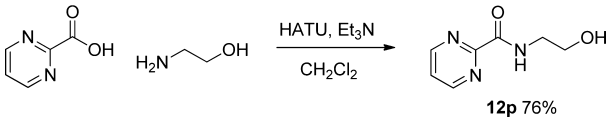


Figure 3. Scope of amide synthesis with straight chain amino alcohols. (a) Reaction performed at 40 °C.

Scheme 4. Comparative Synthesis of 12b with Stoichiometric Reagents



outlined in Figure 4. (*S*)-Prolinol proved to be an effective nucleophile with benzoate esters (**13a**), cinnamate derivatives (**13b**), and 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 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. However, application of modest heating enabled the isolation of **13j** in good yield using our catalytic process. In the case of

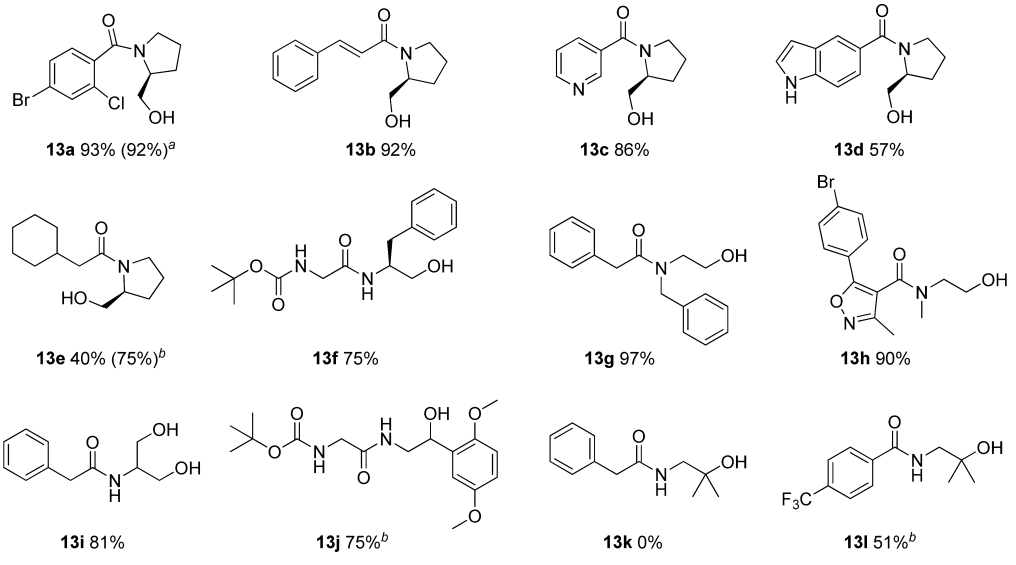


Figure 4. Scope of amino alcohol component: (a) 2.5 g scale input; (b) performed at 40 °C.

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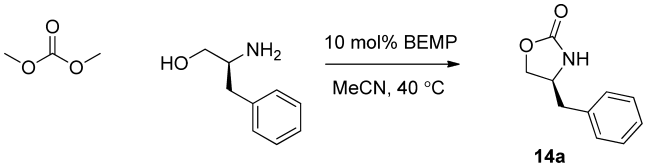
tertiary alcohols, we could not prepare amides from electron-neutral substrates such as methyl phenylacetate (leading to **13k**), suggesting a possible limitation of the methodology. However, when more electron-withdrawing esters are employed, the corresponding products such as **13l** can be isolated 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 favorable amide, as noted previously.

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 synthesis[24] 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., K_2CO_3, NaOMe) while heating, usually to temperatures in excess of 100 °C.[26] Given that we had established that formation of an intermediate ester followed by cyclization 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 favorable 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 dimethyl carbonate (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.

Table 1. Survey of Conditions for Oxazolidinone Synthesis



14a

entry	dimethyl carbonate (equiv)	conversion (%)[a]
1	1	68
2	3	72
3	5	69
4	6 (neat)	61

[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 equiv 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).

Considering the focused subset 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**). Amino diols were also tolerated in this process, leading to products such as **14f** in excellent isolated yield.

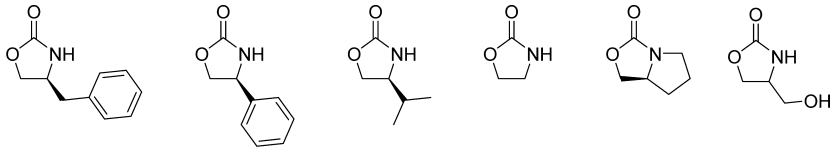
CONCLUSION

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 toward amide products of potential pharmaceutical relevance and extension of the methodology toward 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 that 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 CaH_2 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 N_2 before use. Thin layer chromatography was carried out using aluminum-backed silica plates which were analyzed under 254 nm UV light or developed using potassium permanganate solution. Flash chromatography was carried out using prepacked silica cartridges. ^{1}H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts are reported in ppm, and coupling constants are reported in hertz with $CDCl_3$ referenced at 7.27 (^{1}H) and 77.23 ppm (^{13}C), and DMSO referenced at 2.50 (^{1}H) and 39.51 ppm (^{13}C). Mass spectrometry data was generated using a TOF analyzer. Optical rotations were measured at 589 nm, with concentrations reported in grams 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 CH_2Cl_2 (2 mL) were added CDI (456 mg, 3 mmol) and Et_3N (418 μL, 3 mmol). The reaction mixture was stirred at room temperature for 16 h, washed with water, dried ($MgSO_4$), filtered, and then 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}; ^{1}H NMR (500 MHz, $CDCl_3$): 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



14a 68% **14b** 66% **14c** 84% **14d** 51% **14e** 69% **14f** 87%

Figure 5. Application to the synthesis of oxazolidinone systems.

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(br s, 1H), 4.39 (t, J = 5.5 Hz, 2H); 3.54 (d, J = 4.5 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{14}H_{19}NO_4Na$ 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 CH_2Cl_2 (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, and 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}; ^{1}H 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); ^{13}C 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 $C_9H_{12}NO_2$ 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 CH_2Cl_2 (3 mL) was added Et_3N (226 μL, 1.64 mmol). The reaction mixture was stirred at room temperature for 16 h and then concentrated to a residue that was purified by flash column chromatography (5% methanol/CH_2Cl_2) to afford the title compound as a white solid (306 mg, 95%): ν_{max} (neat) 3296, 2937, 2876, 1634, 1537 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 168.9, 134.3, 131.9, 128.8, 127.2, 62.6, 43.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{12}NO_2$ 166.0863, found 166.0860.

General Procedure for Base-Catalyzed Amide Bond Formation. To an oven-dried Schlenk tube containing BEMP (41 μL, 0.14 mmol) and acetonitrile (700 μL) were added ester (1.42 mmol) and amino alcohol (1.42 mmol). The reaction mixture was stirred at room temperature or 40 °C for 15 h and 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 μL, 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}; ^{1}H 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: $[M + Na]^+$ calcd for $C_{11}H_{15}NO_2Na$ 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}; ^{1}H 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: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_2Na$ 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}; ^{1}H 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: $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$ 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}; ^{1}H 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: $[M + H]^+$ calcd for $C_{11}H_{16}NO_2$ 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}; ^{1}H 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: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_3Na$ 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}; ^{1}H 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: $[M + Na]^+$ calcd for $C_9H_{10}BrNO_2Na$ 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}; ^{1}H 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: $[M + Na]^+$ calcd for $C_9H_{10}BrNO_2Na$ 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}; ^{1}H 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**).* Colorless oil (298 mg, 61%): ν_{max} (neat) 3350, 3098, 2958, 2232, 1661, 1530, 1248 cm^{-1}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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.

dx.doi.org/10.1021/jo501929c | J. Org. Chem. XXXX, XXX, XXX−XXX

*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: $[M + H]^+$ calcd for $C_5H_9N_4O_2$ 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: $[M + Na]^+$ calcd for $C_6H_{10}N_4O_2Na$ 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: $[M + Na]^+$ calcd for $C_7H_{10}N_2O_2Na$ 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) were 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, washed with water and 2 M HCl, dried ($MgSO_4$), filtered, and then 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: $[M + H]^+$ calcd for $C_7H_{10}N_3O_2$ 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: $[M + H]^+$ calcd for $C_8H_{15}N_2O_3$ 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: $[M + H]^+$ calcd for $C_{13}H_{14}BrN_2O_3$ 325.0182, found 325.0184.

*(S)-(4-Bromo-2-chlorophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)-methanone (**13a**).*[15] A 2.5 g scale: To an oven-dried Schlenk tube containing BEMP (290 μL, 1 mmol) and acetonitrile (5 mL) were 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 and then concentrated to a residue that was purified by flash column chromatography (4% methanol/CH_2Cl_2) to afford the title compound as a colorless 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: $[M + H]^+$ calcd for $C_{12}H_{14}BrClNO_2$ 317.9891, found 317.9896; $[\alpha]_D^{20}$ −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: $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$ 232.1332, found 232.1331; $[\alpha]_D^{20}$ −39 (*c* 2.1, MeOH).

*(S)-(2-(Hydroxymethyl)pyrrolidin-1-yl)(1H-indol-5-yl)methanone (**13d**).* Colorless 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: $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2$ 245.1285, found 245.1284; $[\alpha]_D^{20}$ −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: $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1489, found 270.1489.

*5-(4-Bromophenyl)-N-(2-hydroxyethyl)-N,3-dimethylisoxazole-4-carboxamide (**13h**).* Colorless 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-Benzyloxazolidin-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

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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, $CHCl_3$), lit.[34] $[\alpha]_D^{20}$ −62 (c 1.0, $CHCl_3$).

*(S)-4-Phenyloxazolidin-2-one (**14b**).*[35] White solid (153 mg, 66%): ν_{max} (neat) 3237, 3142, 1705 cm^{-1}; ^{1}H 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, $CHCl_3$), lit[36] $[\alpha]_D^{20}$ +48 (c 2.0, $CHCl_3$).

*(S)-4-Isopropyloxazolidin-2-one (**14c**).*[34] White solid (154 mg, 84%): ν_{max} (neat) 3253, 3153, 2958, 1721, 1472 cm^{-1}; ^{1}H 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: $[M + H]^+$ calcd for $C_6H_{12}NO_2$ 130.0863, found 130.0862; $[\alpha]_D^{20}$ +6 (c 1.0, $CHCl_3$), lit[37] $[\alpha]_D^{20}$ +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}; ^{1}H 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: $[M]^+$ calcd for $C_3H_5NO_2$ 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}; ^{1}H 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: $[M + H]^+$ calcd for $C_6H_{10}NO_2$ 128.0706, found 128.0704; $[\alpha]_D^{20}$ −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}; ^{1}H 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: $[M + H]^+$ calcd for $C_4H_8NO_3$ 118.0499, found 118.0496.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of spectroscopic data (^{1}H 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank AstraZeneca and the EPSRC for financial support of this work. HRMS data were generated by the EPSRC National Mass Spectrometry Service at the University of Swansea, UK.

■ REFERENCES

(1) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471−479.

(2) *Peptides, Synthesis, Structures and Applications*; Gutte, B., Ed.; Academic Press: San Diego, 1995.

(3) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451−3479.

(4) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 8082−8091.

(5) For a review, see: El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557−6602.

(6) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411−420.

(7) For a recent review, see: Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *42*, 2714−2742.

(8) Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666−668.

(9) Lundberg, H.; Tinnis, F.; Adolfsson, H. *Synlett* **2012**, *23*, 2201−2204.

(10) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018−2021.

(11) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876−2879.

(12) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196−4197.

(13) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124−134.

(14) Tuccio, B.; Ferre, E.; Comeau, L. *Tetrahedron Lett.* **1991**, *32*, 2763−2764.

(15) Caldwell, N.; Jamieson, C.; Simpson, I.; Tuttle, T. *Org. Lett.* **2013**, *15*, 2506−2509.

(16) Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992; Chapter 2.

(17) Schwesinger, R. *Chimia* **1985**, *39*, 269.

(18) Armstrong, A.; Li, W. N,N′-Carbonyldiimidazole. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Hoboken, 2007.

(19) Anslyn, E. V.; Dougherty, D. A. Strain and Stability. In *Modern Physical Organic Chemistry*; University Science: Sausalito, CA, 2006; Chapter 2, pp 100−109.

(20) pK_a values calculated by ACD

(21) Gleeson, M. P. *J. Med. Chem.* **2008**, *51*, 817−834.

(22) Mukherjee, S.; Pal, M. *Curr. Med. Chem.* **2013**, *20*, 4386−4410 and references cited therein..

(23) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(24) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(25) Mullen, G.; Napier, J.; Balestra, M.; DeCory, T.; Hale, G.; Macor, J.; Mack, R.; Loch, J.; Wu, E.; Kover, A.; Verhoest, P.; Sampognaro, A.; Phillips, E.; Zhu, Y.; Murray, R.; Griffith, R.; Blosser, J.; Gurley, D.; Machulskis, A.; Zongrone, J.; Rosen, A.; Gordon, J. *J. Med. Chem.* **2000**, *43*, 4045−4050.

(26) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−80.

(27) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th ed.; Elsevier Inc.: Oxford, UK, 2009.

(28) Heller, S. T.; Fu, T.; Sarpong, R. *Org. Lett.* **2012**, *14*, 1970−1973.

(29) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453−2456.

(30) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027−1033.

(31) Mahe, O.; Desroches, J.; Paquin, J.-F. *Eur. J. Org. Chem.* **2013**, 4325−4331.

(32) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190−1191.

(33) Gu, K.; Bi, L.; Zhao, M.; Wang, C.; Ju, J.; Peng, S. *Bioorg. Med. Chem.* **2007**, *15*, 4775−4799.

(34) Pridgen, L. N.; Prol, J., Jr. *J. Org. Chem.* **1989**, *54*, 3231−3233.

(35) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625−627.

(36) Xiong, H.; Grebe, T. M. R.; Mulder, J. A.; Hsung, R. P. *Org. Synth.* **2005**, *81*, 147−156.

(37) Adams, H.; Collins, R. C.; Jones, S.; Warner, C. J. A. *Org. Lett.* **2011**, *13*, 6576−6579.

(38) Imada, Y.; Mitsue, Y.; Ike, K.; Washizuka, K.-I.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2079−2090.

(39) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514−2515.