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A Multicomponent Route to Functionalized Amides and Oxazolidinones

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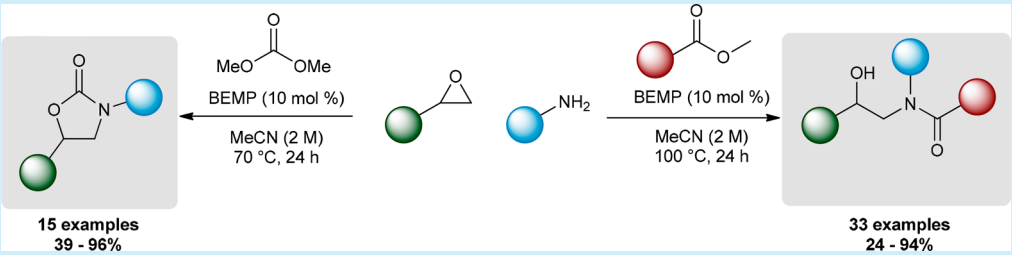
Supporting Information



ABSTRACT: An organobase-mediated multicomponent reaction of unactivated esters, epoxides, and amines is reported, furnishing functionalized amide derivatives. A wide range of substrates are tolerated under the reaction conditions, including chiral epoxides, which react with no erosion of enantiopurity. Facile modification of the method through replacing the ester derivative with dimethyl carbonate enables access to the corresponding oxazolidinone derivatives.

The amide functional group is ubiquitous within nature and medicinal chemistry, where it is commonly encountered within peptide bonds in proteins and small-molecule drugs, respectively.[1,2] With approximately 25% of all registered drugs containing an amide bond,[3] formation of this motif is therefore one of the most widely performed reactions within the pharmaceutical industry.[4,5] As widely established methods for the synthesis of amides from carboxylic acids have significant drawbacks, particularly with regard to atom economy and sustainability, the development of mild and efficient approaches to synthesize amide bonds is therefore a key objective in organic chemistry.[6] In recent years, several catalytic approaches have been reported seeking to address these issues, thereby minimizing the environmental impact of the process.[7−13]

Stoichiometric approaches allowing the direct conversion of esters to amides have also been developed, overcoming the use of protracted reaction times and elevated temperatures related to aminolysis.[14,15] In recent years, catalytic approaches enabling the aminolysis of esters have been reported, but drawbacks such as limited scope of the acylating species and the use of finite and toxic transition or rare-earth metals have hindered their application.[16−22]

The use of multicomponent reactions (MCRs) is an attractive approach to synthesize complex and structurally diverse products rapidly from simple starting materials, with most, if not all, of the atoms retained in the final product.[23] When applied to amide bond formation, multicomponent reactions would offer an efficient and atom-economical approach, mitigating the requirement for stoichiometric coupling reagents and hence the formation of associated byproducts.

Within our own laboratories a program focused on catalytic amidation has been developed, with the aim of addressing some of the outstanding issues still encountered with this important transformation.[24−29] During these studies we recently reported an organobase-mediated process for the catalytic formation of amides from esters and amino alcohols (Scheme 1).[24,26]

This approach represented a mild, efficient, and unprotracted synthesis of amides, utilizing a catalytic quantity (10 mol %) of *tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, **1**)[30] as a base. The reaction was proposed to proceed through an initial transesterification event mediated by BEMP, followed by a rearrangement to the thermodynamically more stable amide product.

Having successfully developed this original process, we envisaged that the utility of the reaction could be significantly extended to enable base-mediated amidation from epoxide, ester, and amine inputs, thereby representing a multicomponent process. Following on from our progenitor process, an amino alcohol, in this instance formed as an intermediate via the reaction of the epoxide and amine, would undergo a transesterification/rearrangement process to furnish the desired amide product (Scheme 1).

In the first instance, we commenced our investigation by applying the conditions used in our original process to a model reaction between glycidyl phenyl ether (**2**), benzylamine (**3**), and methyl benzoate (**4**) (Table 1, entry 1). Unfortunately, this led to no observed formation of the desired amide product **5**. However, increasing the reaction temperature resulted in a

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Scheme 1. Relevant Antecedent and Proposed Method

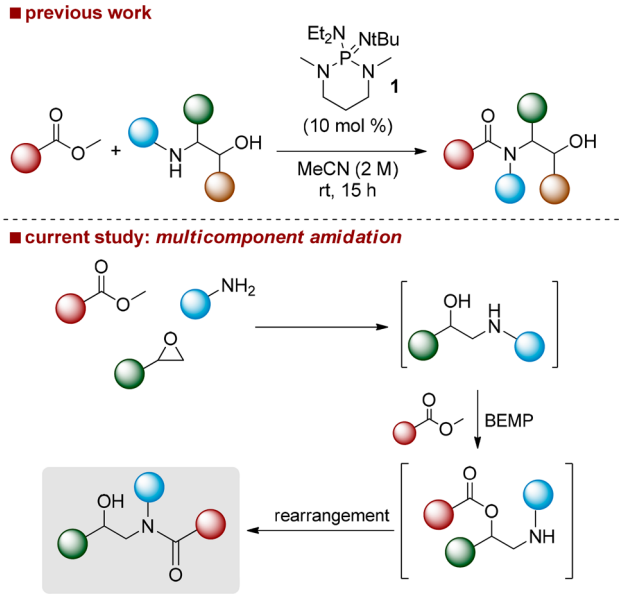
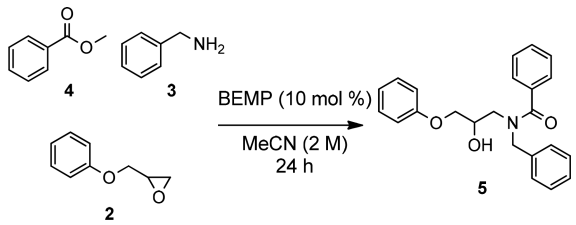


Table 1. Reaction Optimization



entry	reaction temperature (°C)	conversion (%)[a]
1	20	0
2	40	17
3	60	30
4	70	52
5	100	71[b]
6[c]	100	17

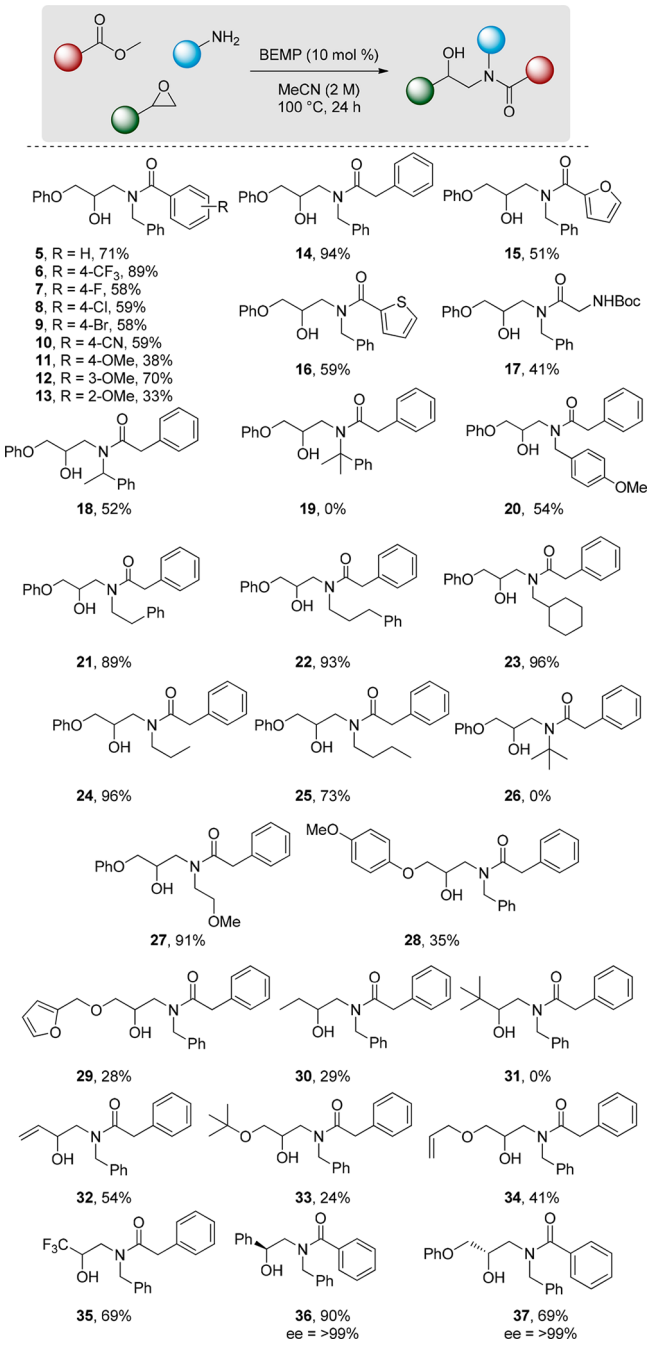
[a]Determined by HPLC using an internal calibrant. [b]Isolated yield. [c]Reaction performed with 5 mol % BEMP.

consistent increase in conversion to the desired product, with 71% isolated yield achieved at 100 °C (Table 1, entries 2−5). Decreasing the quantity of BEMP to 5 mol % had a deleterious effect on conversion, with only a 17% yield of the desired amide observed (Table 1, entry 6). Further studies on altering the solvent and base used in the reaction were also performed, with a positive effect on the reaction conversion noted.[31] Microwave heating was also examined but did not offer an advantage over thermal methods.

Following on from this short optimization campaign, the scope of the ester, amine, and epoxide components were then investigated (Scheme 2), with each reaction carried out on a 1 mmol scale. In general, the products were formed as single regioisomers from opening of the epoxide, although in some cases they existed as rotamers.

The incorporation of both electron-withdrawing and electron-donating substituents onto the aryl ring of the benzoate moiety is well-tolerated, with the corresponding amides **6**−**13** formed in moderate to excellent yields. Homologation of the ester, affording compound **14**, leads to

Scheme 2. Scope of the Amidation Method



an improvement in yield to 94%, as expected on the basis of the increased electrophilicity of the carbonyl center. Heteroaryl esters, specifically furan **15** and thiophene **16,** were also tolerated within the reaction, furnishing the corresponding amides in moderate yields. Amino acid esters such as **17** were also compatible with the reaction manifold.

Examination of the amine component initially focused on increasing substitution at the α-position of the amine. It was found that increasing substitution at this position leads to a significant decrease in reaction efficiency, with the methyl-substituted amine furnishing the corresponding amide **18** in 52% yield. Increasing the substitution further to the *gem*-dimethyl amine led to no formation of the desired amide **19**, implying that only limited substitution at this position is

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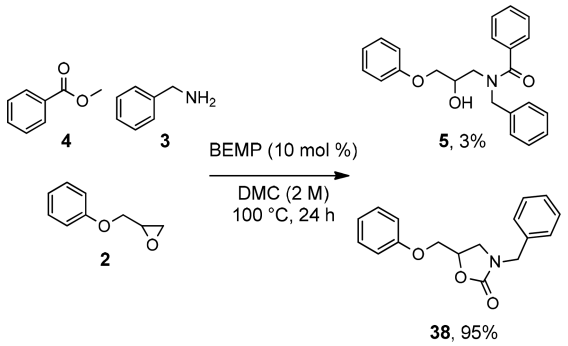
tolerated before the reaction is impeded as a result of increasing steric encumbrance. Substitution of the aromatic ring is also tolerated in moderate yields, furnishing amide **20**. Homologation of the amine to afford amides **21** and **22** leads to excellent yields of 89 and 93%, respectively. Alkyl amines were also examined in the reaction manifold, with aminomethylcyclohexane, propylamine, butylamine, and 2-methoxyethylamine found to afford the corresponding amides **23**–**25** and **27** in good to excellent yields. However, *tert*-butylamine derivative **26** was not formed, which is likely attributable to the increased steric bulk associated with the alkyl substituent.

In the last aspect of this phase of the study, the scope of the epoxide component was examined. Further examples of epoxides with aromatic components, **28** and **29**, were less efficient substrates when subjected to the optimum conditions, furnishing the corresponding amides in yields of 35 and 28%, respectively. Although these yields are comparatively lower than those reported above, it should be noted that the average yield per step (ring opening, transesterification, and amidation) is still around 65%, with the reaction still maintaining the operational efficiencies associated with a multicomponent process. A range of aliphatic epoxides were then probed. Ethyl and *tert*-butyl substituents on the epoxide ring were first examined, with the ethyl substituted amide **30** formed in a moderate yield of 29%. Vinyl epoxide was found to be a competent substrate, with the resulting amide **32** formed in 54% yield. *tert*-Butyl glycidyl ether led to the formation of amide **33** in 24% yield. Compared with compound **31**, the *tert*-butyl group is more remote from the oxygen and nitrogen centers involved in the transesterification/rearrangement events, potentially accounting for the enhancement in yield. Allyl glycidyl ether was an acceptable substrate, furnishing the corresponding amide **34** in 41% yield. Incorporation of a trifluoromethyl substituent directly on the epoxide ring resulted in the synthesis of corresponding amide **35** in a good yield of 69%. Two chiral epoxides, (*S*)-styrene oxide and (*S*)-glycidyl phenyl ether, were also subjected to the optimized conditions, giving **36** and **37** in excellent and good yields, respectively, without any degradation in enantiopurity.

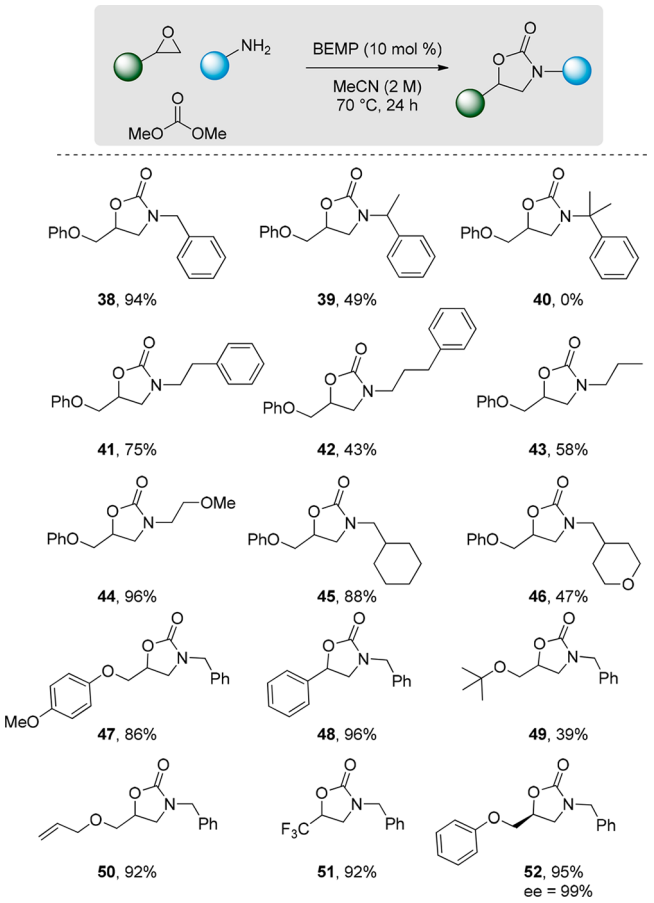
During optimization of the amidation process, it was noted that the use of dimethyl carbonate (DMC) as a solvent in lieu of acetonitrile led to only 3% conversion to amide **5**.[32] However, HPLC analysis showed that full consumption of the amine, epoxide, and corresponding amino alcohol had occurred, forming a previously unobserved product, with little consumption of methyl benzoate detected. Upon isolation it was determined that the use of DMC in fact led to the preferential formation of oxazolidinone moiety **38** in 95% yield (Scheme 3). As this represents a second MCR utilizing a similar transesterification-type/rearrangement process and oxazoldinone scaffolds are an important class of antibiotic drug compounds,[33,34] a focused optimization was undertaken to further adapt the method toward the synthesis of oxazolidinones. This effort resulted in the rapid identification of a set of generally applicable reaction conditions.[35] The current approach is therefore complementary to a very recent report on organocatalyzed oxazolidinone formation,[36] but it avoids the use of isocyanates, which are potential respiratory sensitizers.[37]

With optimum conditions toward the synthesis of oxazolidinones successfully developed, the scope of this novel MCR was then examined (Scheme 4), again using a 1 mmol scale. As noted in the amide substrate scope, increasing substitution at the α-position of the amine leads to a significant

Scheme 3. Preferential Formation of Oxazolidinone 38



Scheme 4. Oxazolidinone Substrate Scope[a]



[a]The reactions were performed in neat dimethyl carbonate (2 M).

decrease in the yield of the corresponding oxazolidinone products (**39** and **40**). Homologation of the amine from benzylamine to 2-phenethylamine results in a decrease in yield (**38**, 94%; **41**, 75%), and a further reduction is observed when 3-phenylpropylamine **42** is subjected to the reaction conditions (**42**, 43%). Linear alkyl amines such as propylamine are compatible with the reaction (**43**, 58%), while 2-methoxyethylamine undergoes near-complete conversion to the desired oxazolidinone **44**. Cyclic aliphatic amines are tolerated in moderate to excellent yields, with cyclohexylamine furnishing the desired oxazolidinone **45** in 88% yield and the tetrahydropyran derivative affording a 47% yield of oxazolidinone **46**.

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Considering the epoxide substrate scope, substitution of the phenyl group (**47**) results in a yield comparable to that for the original substrate (**38**). Shortening the epoxide component by applying styrene oxide to the optimized conditions affords oxazolidinone **48** in an excellent yield of 96%. Ether-containing epoxides are also tolerated, with *tert*-butyl glycidyl ether proving to be a competent substrate (**49**), and allyl glycidyl ether performs well to furnish compound **50** in excellent yield. Again, as for the amide protocol, the presence of a trifluoromethyl group directly on the epoxide ring is tolerated in the reaction, with product **51** formed in an excellent yield of 92%. Lastly, use of the chiral epoxide (*S*)-glycidyl phenyl ether afforded oxazolidinone **52** in a yield comparable to that for the racemate, with no erosion in enantiopurity observed.

In summary, through further development of our previously reported amidation method,[24−26] we have successfully crafted a multicomponent approach to amide bond formation in a highly atom-economical manner. Additionally, as only catalytic quantities of base are required for the reaction to proceed, this is a distinct advantage over widely employed amide-bond-forming conditions where stoichiometric coupling reagents are employed. Adaptation of the optimized reaction conditions also extends the application of the method to allow the synthesis of oxazolidinone moieties, which are important scaffolds in small-molecule drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03470.

Experimental procedures and spectroscopic data for all products (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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