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Direct Synthesis of Amides from Carboxylic Acids and Amines Using $B(OCH_2CF_3)_3$

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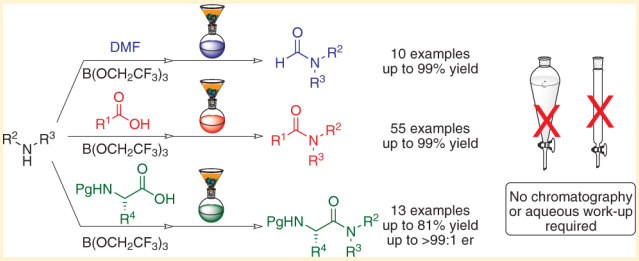
Supporting Information

ABSTRACT: $B(OCH_2CF_3)_3$, prepared from readily available B_2O_3 and 2,2,2-trifluoroethanol, is as an effective reagent for the direct amidation of a variety of carboxylic acids with a broad range of amines. In most cases, the amide products can be purified by a simple filtration procedure using commercially available resins, with no need for aqueous workup or chromatography. The amidation of *N*-protected amino acids with both primary and secondary amines proceeds effectively, with very low levels of racemization. $B(OCH_2CF_3)_3$ can also be used for the formylation of a range of amines in good to excellent yield, via transamidation of dimethylformamide.



INTRODUCTION

The amide bond is widely prevalent in both naturally occurring and synthetic compounds. It is increasingly important in pharmaceutical chemistry, being present in 25% of available drugs, with amidation reactions being among the most commonly used reactions in medicinal chemistry. There is considerable interest in the development of new approaches to direct amidation,[1,2] and organizations such as the ACS Green Chemistry Institute Pharmaceutical Roundtable have indicated that amide bond formation is one of the most important reactions used in industry for which better reagents are required.[3] Although there are a large range of reagents and strategies for amide bond formation available,[4] few can really be considered ideal. Currently there is a focus on the development of novel, atom-economical, benign methods for amidation, and there have been many recent developments in this field. An important consideration here is the ease with which the reagent or catalyst can be separated from the resulting product. Direct thermal amide formation from amines and carboxylic acids has been reported using toluene as the reaction solvent[5] or using radiofrequency heating under neat conditions,[6] and this reagent-free approach is practical in many cases, but the substrate scope is quite limited. Alternatively, a number of metal-based catalytic systems have also been reported, with recent examples including the use of $Ti(O^iPr)_4$,[7] Cp_2ZrCl_2,[5] and $ZrCl_4$[5,8] under strictly anhydrous dehydrating conditions. Boron mediated amidation reactions have attracted considerable attention,[9−12] and boronic acids have been shown to be effective catalysts for direct amide formation from carboxylic acids and amines.[9] In general, boronic acid catalyzed amidation reactions require the removal of water from the reaction either by a dehydrating agent such as molecular sieves or by azeotropic reflux. The reactions also typically require relatively dilute reaction conditions. Stoichiometric boron reagents for amidation often require anhydrous conditions and/or an excess of either the acid or the amine, however.[10−12] While many of these boron-mediated processes are promising, to date the substrate scope is limited to relatively activated systems.

We have recently reported that simple borate esters are effective reagents for the direct synthesis of amides from carboxylic acids or primary amides.[13] Although commercially available $B(OMe)_3$ was useful for amidation in some cases, the 2,2,2-trifluoroethanol-derived ester $B(OCH_2CF_3)_3$ gave consistently higher conversions and was applicable to a much wider range of substrates. The use of $B(OCH_2CF_3)_3$ as an amidation reagent is operationally simple, as the reaction can be carried out open to the air with equimolar quantities of acid and amine in a solvent in which most amines and acids are readily soluble (MeCN). In all of the examples examined, the thermal background yield of amide was found to be low in comparison to that obtained in the presence of the borate ester.

Herein, we report a method for the large-scale preparation of $B(OCH_2CF_3)_3$ from readily available B_2O_3 and a full study of the scope and limitations of $B(OCH_2CF_3)_3$ as a direct amidation reagent. We also describe its application to the formylation of amines by transamidation of DMF. Importantly, a solid phase purification procedure has been developed that enables the amide products to be obtained without aqueous workup or chromatography.

RESULTS AND DISCUSSION

Preparation of the $B(OCH_2CF_3)_3$ Reagent. In our initial work, we prepared $B(OCH_2CF_3)_3$ by reaction of 2,2,2-trifluoroethanol with BBr_3 at low temperature (Scheme 1). This gave $B(OCH_2CF_3)_3$ in excellent yield after purification by

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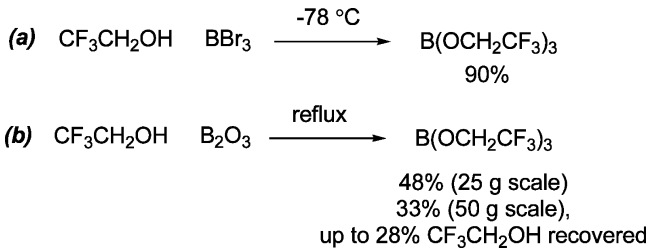
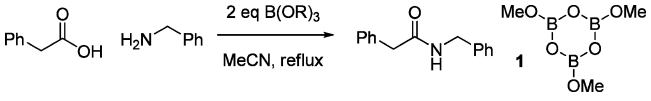
Scheme 1. Synthesis of $B(OCH_2CF_3)_3$ from (a) BBr_3 and (b) B_2O_3



distillation. However, BBr_3 is somewhat expensive and can be difficult to handle because of the fact that it readily hydrolyzes on contact with moisture. We therefore sought an alternative method for preparing the amidation reagent. The synthesis of $B(OCH_2CF_3)_3$ has been previously reported from boric acid[14] and from B_2O_3.[15] We found the latter procedure to be particularly straightforward on multigram scale. Simply heating a suspension of B_2O_3 in 2,2,2-trifluoroethanol for 24 h, followed by distillation, gave the borate ester in 33−48% yield on 25−50 g scale, and up to 28% of the trifluoroethanol could be recovered and recycled. Although this procedure is lower yielding in comparison to our original approach, B_2O_3 is considerably cheaper than BBr_3 and the reaction is not particularly moisture-sensitive. The $B(OCH_2CF_3)_3$ reagent can be stored at room temperature under inert atmosphere for at least four months without any observable deterioration.

Development of a Solid Phase Workup Procedure and Evaluation of Other Borates. In order to explore different workup procedures and reagents, the amidation of phenylacetic acid with benzylamine was selected as a test reaction (Table 1). After the amidation reaction, the reaction

Table 1. Comparison of Boron Reagents and Workup Procedures



entry	reagent	time [h]	yield [%][a]
1	$B(OCH_2CF_3)_3$	15	91[b]
2	$B(OCH_2CF_3)_3$	5	88[b]
3	$B(OCH_2CF_3)_3$	5	87[c]
4	$B(OMe)_3$	5	69[c]
5	$B(OMe)_3$	15	92[b]
6	B_2O_3	5	15[b]
7	**1**	5	72[c]
8	**1**	15	81[c]
9	none	15	18[b]

[a]Isolated yield. [b]Aqueous workup procedure. [c]Solid phase workup procedure.

mixture contains the amide product, borate-ester derived byproducts, and potentially some unreacted amine and/or carboxylic acid. In our preliminary report, the amidation reactions were purified by acid and base washes to remove these impurities.[13] Under our original conditions (2 equiv of borate, 15 h, 80 °C), the amide was obtained in 91% yield (entry 1). The reaction time could be reduced from 15 to 5 h with only a small decrease in yield (entry 2). We explored an alternative solid phase workup for the amidation reactions involving treatment of the crude reaction mixture with three commercially available resins (Amberlyst acidic, basic and Amberlite boron scavenger resins), followed by $MgSO_4$, and then filtration/evaporation (Figure 1). This provided the amide

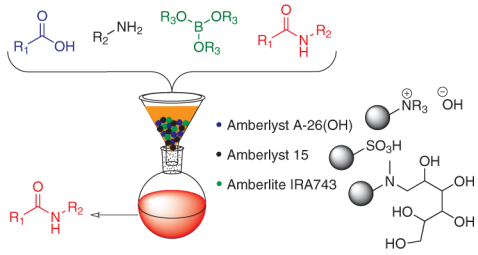


Figure 1. Solid phase workup of amidation reactions.

product in a comparable yield and purity to the aqueous workup (entry 3). This procedure is more convenient for general use and could potentially be used to enable automation of the reaction.

We subsequently compared different boron reagents under these conditions. Trimethyl borate was effective for amidation (entries 4 and 5), but a longer reaction time was required in order to obtain a good yield. B_2O_3 itself showed low reactivity in the amidation reaction with only 15% yield after a 5 h reaction time (entry 6). Commercially available trimethoxyboroxine **1** is reported to be a stronger Lewis acid than both $B(OMe)_3$ and $B(OCH_2CF_3)_3$ but did not offer any significant advantage in the amidation reaction (entry 7).[14] Interestingly, the reaction with **1** did not lead to comparable conversions even after a 15 h reaction time (entry 8). This may be due to the fact that **1** can more readily form oligomeric species such as B_2O_3 upon heating, and such species are much less active in the amidation reaction. It should be noted that the thermal reaction in the absence of any reagent gave only an 18% yield of the amide. In our preliminary communicaton[13] we determined the thermal reaction yield for the 15 other amidation reactions studied to be <9%. This clearly demonstrates the importance of the borate ester in mediating the amidation reaction.

Scope of the Amidation Reactions. The full scope of the amidation reactions was explored with a wide range of amines and carboxylic acids. To evaluate the amine scope, the preparation of phenylactetamides (Figure 2, **2a−2x**) from phenylacetic acid was explored using our standard reaction conditions (2 equiv of $B(OCH_2CF_3)_3$, MeCN, 80 °C). Primary amines including benzylamines (**2a−2d**), simple aliphatic amines (**2e**) and even functionalized examples (**2f−2h**) could be coupled in good yield. A range of cyclic secondary amines also underwent amidation efficiently, including several medicinally relevant examples (**2i−2m**). The hydrochloride salt of dimethylamine underwent amidation in good yield when two or more equivalents of the hydrochloride salt were employed (**2n**) in combination with 2 equiv of Hünig's base. The acyclic secondary amine dibenzylamine showed poor reactivity, however (**2o**), and a significant quantity of the secondary *N*-benzyl amide **2a** was obtained, indicating that partial cleavage of one of the benzyl units had occurred. Less nucleophilic systems such as anilines (**2p−2u**) and *tert*-butylamine (**2v**) could also be coupled, but higher reaction temperatures were needed in some cases in order to obtain reasonable yields. Extremely unreactive systems such as 2-pyridylamine (**2u**) gave only very low yields of the coupling product and adamantylamine (**2w**) and 2-mercaptoaniline (**2x**) did not undergo amidation at all.

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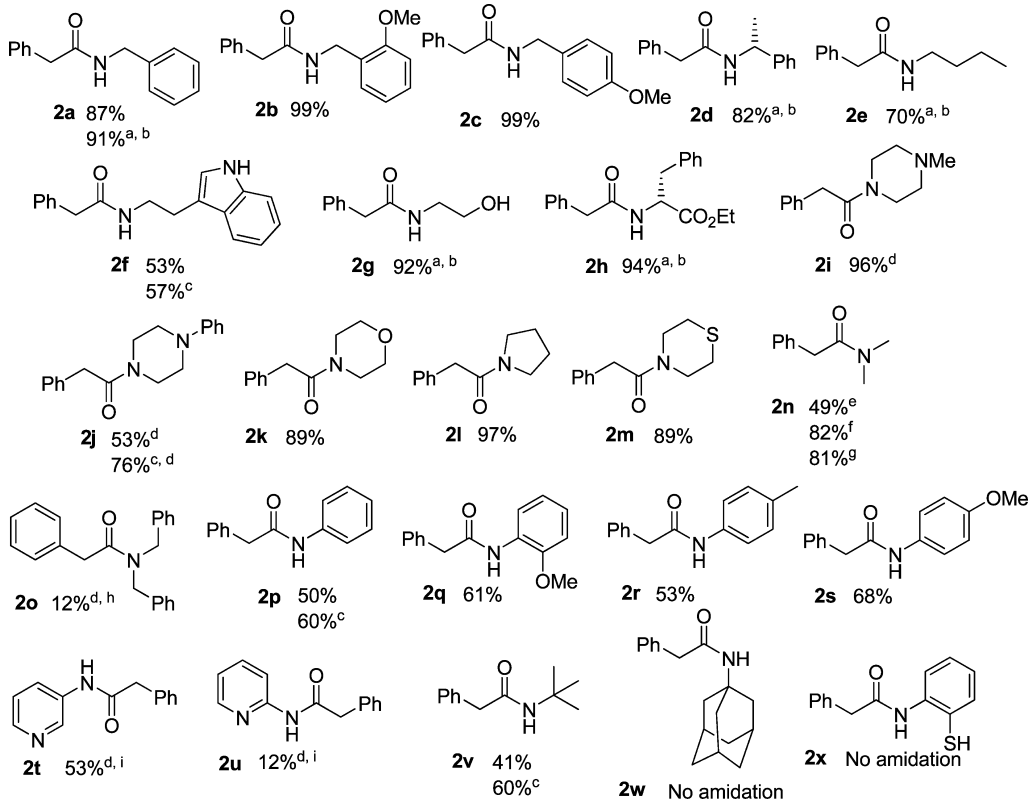

Figure 2. Scope of phenylacetamide synthesis with different amines. All reactions were carried out at 80 °C for 5 h, and the solid phase workup procedure was used unless otherwise stated. (a) Aqueous workup procedure; (b) 80 °C for 15 h; (c) 100 °C for 15 h in a sealed tube; (d) purified by column chromatography; (e) from 1 equiv of $Me_2NH{\cdot}HCl$, 1 equiv of DIPEA; (f) from 2 equiv of $Me_2NH{\cdot}HCl$, 2 equiv of DIPEA; (g) from 3 equiv of $Me_2NH{\cdot}HCl$, 3 equiv of DIPEA; (h) 6% of **2a** was also isolated; (i) 100 °C for 24 h in a sealed tube.

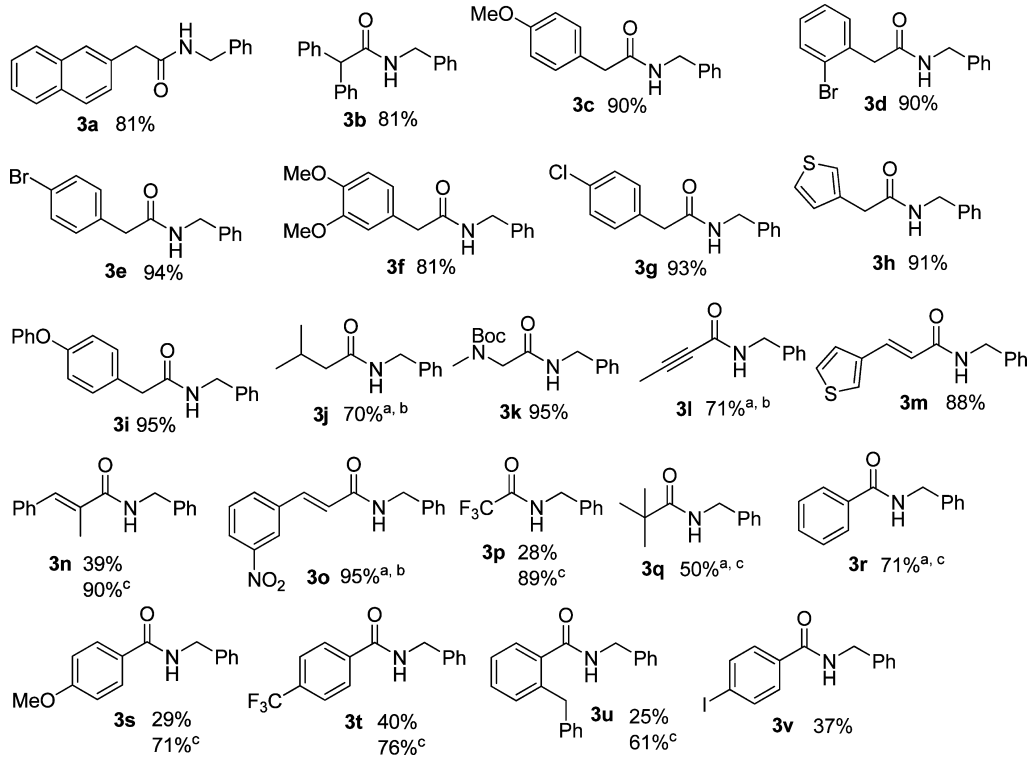

Figure 3. Scope of *N*-benzylamide synthesis using different carboxylic acids. All reactions were carried out at 80 °C for 5 h, and the solid phase workup procedure was used unless otherwise stated. (a) Aqueous workup procedure; (b) 80 °C for 15 h; (c) 100 °C for 15 h in a sealed tube.

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The preparation of *N*-benzylamides (Figure 3, **3a**–**3v**) was explored using our standard conditions in order to evaluate the carboxylic acid scope. A range of *N*-benzyl-2-arylacetamides (**2a**, **3a**–**3i**) were obtained in very good yield including α-substituted (**3b**) and heteroaromatic acids (**3h**). A simple aliphatic acid (**3j**) and *N*-Boc sarcosine (**3k**) also underwent amidation effectively. Carboxylic acids with conjugated alkyne (**3l**) and alkene groups (**3m**–**3o**) could be coupled efficiently, but more hindered examples required a higher reaction temperature (**3n**). More hindered aliphatic systems including trifluoroacetic acid (**3p**) and pivalic acid (**3q**) could also be coupled effectively by using a higher reaction temperature. Benzoic acids (**3r**–**3v**) were also relatively unreactive and required higher reaction temperatures in order for reasonable conversions to be obtained.

The coupling of a selection of other combinations of acids and amines (Figure 4, **4a**–**4g**) was explored, and yields were

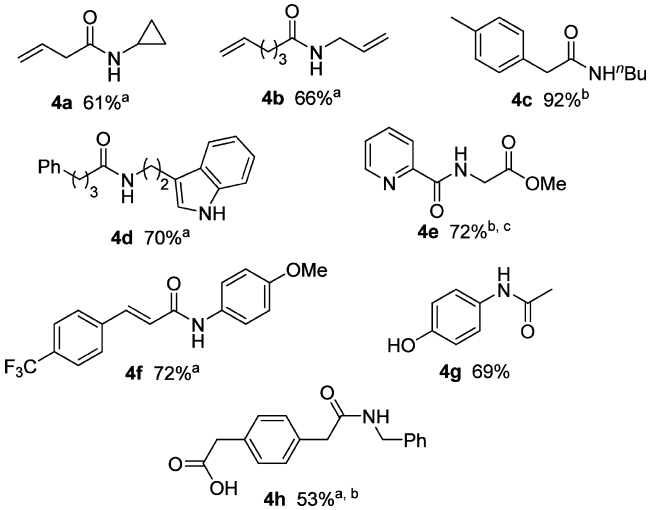


Figure 4. Further scope of the amidation reaction. All reactions were carried out at 80 °C for 15 h and purified by solid phase workup unless otherwise stated. (a) Aqueous workup procedure; (b) 80 °C for 5 h; (c) purified by column chromatography.

generally consistent with our observations of the relative reactivity of amines/acids outlined above. Thus, aliphatic amine/acid combinations (**4a**–**4d**) generally gave reasonable yields of the amide, even with fairly volatile components (**4a**, **4b**). Less reactive picolinic acid underwent amidation in relatively good yield with glycine methyl ester (**4e**). The reaction of a fairly nucleophilic aniline with an unsaturated acid also proceeded in good yield (**4f**). Pleasingly, we were also able to prepare paracetamol (**4g**) in moderate yield by coupling acetic acid with 4-hydroxyaniline. Interestingly, monoamidation of a dicarboxylic acid could also be achieved in 53% yield (**4h**). In the majority of cases, the amides **2**–**4** could be purified by the solid phase workup procedure, with the exception of amides containing strongly basic (**2i**, **2j**, **2t**, **2u**, **4e**) or acidic (**4h**) groups, which generally required chromatographic purification.

Lactam formation could also be achieved effectively (Figure 5, **5a**–**5c**). The background reaction for formation of six- (**5a**) and seven-membered (**5b**) lactams from simple thermal condensation was low in comparison to that observed in the presence of $B(OCH_2CF_3)_3$. Lactamization of Boc-L-ornithine (**5c**) proceeded in 84% yield.

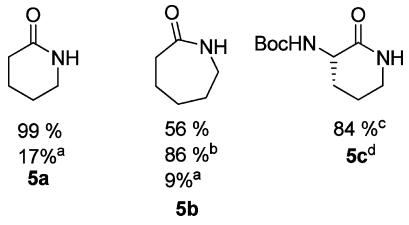
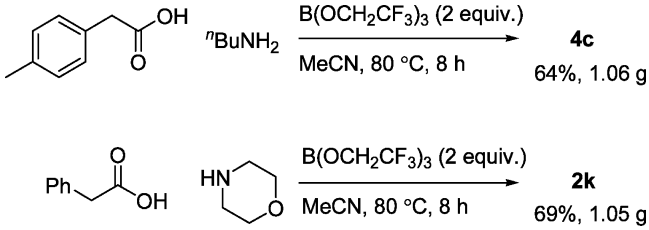


Figure 5. Lactamization reactions. All reactions were carried out at 80 °C for 5 h unless otherwise stated and purified by solid phase workup. (a) Yield without $B(OCH_2CF_3)_3$; (b) 100 °C for 5 h in a sealed tube; (c) 80 °C for 15 h; (d) $[\alpha]_D^{25}$ −9.5 (*c* 1.22, MeOH) [lit.[16] $[\alpha]_D^{20}$ −10.6 (*c* 1.22, MeOH)].

To evaluate the amidation reaction on larger scales, both a secondary (**4c**) and a tertiary amide (**2k**) were prepared using gram quantities of material (Scheme 2). Although in both cases

Scheme 2. Gram Scale Amidation Reactions



a slight reduction in yield was observed, more than 1 g of each amide could be synthesized in less than 15 mL of MeCN. In each case, the product was purified using the solid phase workup, without the need for aqueous workup or column chromatography. For comparison, the same reaction to give 1 g of **4c** using a boronic acid catalyst would require ca. 70 mL of solvent.[9i]

Coupling of Acids with an Adjacent Chiral Center. The amidation of carboxylic acids bearing a chiral center at the α-position is of high importance, and the coupling of α-amino acids is of particular significance. While there are many methods for achieving such couplings, the fact that $B(OCH_2CF_3)_3$-mediated amidation reactions can be easily purified by a solid phase workup might offer greater convenience. The successful amidation of amino acids using boronic acid catalysts or other boron-based amidation reagents has not been reported to date. We therefore wished to explore the application of $B(OCH_2CF_3)_3$ to the coupling of a selection of amino acids bearing commonly used nitrogen protecting groups to determine whether the corresponding amides could be obtained without racemization (Figure 6).

The coupling of a range of protected amino acids with benzylamine proceeded in good yield (**6a**–**6e**) including both Boc (**6a**–**6d**) and Cbz (**6e**) protected examples. In most cases no significant racemization was observed (**6a**, **6b**, **6d**). Where small levels of racemization were observed, this could be reduced significantly by decreasing the reaction time, albeit at the expense of product yield (**6b**, **6c**). The synthesis of prolinamide **6d** is notable, as derivatives of this compound have been used as organocatalysts in a variety of reactions.[17] Dipeptides (**6f**, **6g**) could also be obtained in moderate yield, by coupling of two suitably protected amino acids with no observable formation of diastereomeric products. Dipeptides **6f** and **6g** have previously been synthesized via carbodiimide

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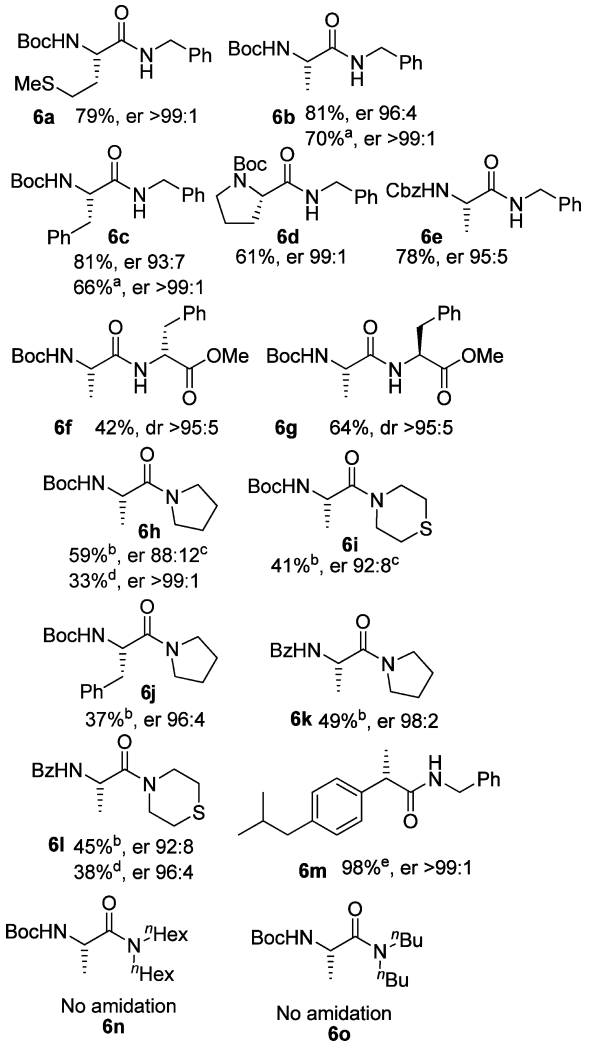


Figure 6. Coupling of acids containing adjacent chiral centers. All reactions were carried out at 80 °C for 15 h unless otherwise stated and purified by solid phase workup. (a) 80 °C for 8 h; (b) 100 °C for 24 h in a sealed tube; (c) er measured after conversion to the *N*-benzoyl amide derivative; (d) 100 °C for 8 h in a sealed tube; (e) 80 °C for 5 h.

coupling,[18−21] but purification by aqueous workup, recrystallization or chromatography was required.

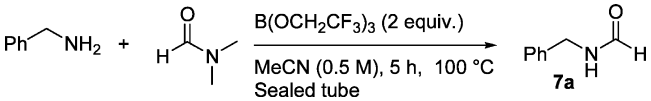
Pleasingly, amino acids could also be coupled with cyclic secondary amines (**6h−6l**) in reasonable yield, and these couplings also proceeded with relatively low levels of racemization. The synthesis of amides **6h−6j** has been reported using a range of different coupling reagents,[22−30] but the enantiomeric purity of the products was not directly determined in any of these cases. The preparation of benzamides **6k** and **6l** has never been previously reported. The preparation of *N*-benzylamide **6m** was achieved in excellent yield with negligible racemization. The coupling of amino acids with acyclic secondary amines was unsuccessful (**6n**, **6o**).

The above reactions serve to illustrate the scope of the $B(OCH_2CF_3)_3$ reagent for the coupling of acids bearing adjacent chiral centers. Commonly used nitrogen protecting groups (Boc, Cbz) are tolerated under the reaction conditions, and very little racemization is observed in many cases despite the high temperatures employed. Where racemization does occur, it can be reduced significantly by shortening the reaction time. Notably, the coupling of amino acids with secondary amines using conventional coupling reagents is often a considerable challenge, and an aqueous work up and/or chromatographic purification is generally required. Our method therefore offers a potentially valuable approach to tertiary amino acid amides, as it furnishes pure products in reasonable yield with high enantiopurity, following a simple solid phase workup.

Transamidation of DMF using $B(OCH_2CF_3)_3$. In our preliminary communication, we reported the transamidation of a limited selection of primary amides using $B(OCH_2CF_3)_3$. Since this report, a number of alternative catalysts and reagents for transamidation reactions have been reported including hydroxylamine hydrochloride,[31] Cp_2ZrCl_2,[32] $Cu(OAc)_2$,[33] $PhI(OAc)_2$,[34] boric acid,[35] CeO_2[36] and L-proline.[37] In many cases these reagents are cheap and readily available, and the reactions have a wide substrate scope. On this basis, it therefore seemed that the potential application of $B(OCH_2CF_3)_3$ as a reagent for transamidation of primary amides is somewhat limited. However, during our initial solvent screen for the direct amidation of carboxylic acids, we observed that $B(OCH_2CF_3)_3$ was highly effective for the transamidation of DMF. With this in mind, we opted to investigate the scope of this reaction. Recent literature methods for the *N*-formylation of amines include $HCONH_2$/NaOMe,[38] $HCONH_2/NH_2OH{\cdot}HCl$,[31] $HCONH_2/Cp_2ZrCl_2$,[32] HCO_2H in the presence of protic ionic liquids,[39] and HCO_2H/HCO_2Na.[40] All of these methods require high temperatures, anhydrous conditions and purification by column chromatography. The direct transamidation of DMF has recently been achieved with boric acid,[35] $PhI(OAc)_2$,[34] L-proline,[37] and imidazole,[41] but at high temperatures,[34,35] with extended reaction times,[34,35,41] and/or with purification by column chromatography.[41] We therefore anticipated that $B(OCH_2CF_3)_3$-mediated transamidation of DMF may provide a useful formylation method, especially if the products could be readily purified by solid phase workup.

The formylation of benzylamine was used as a model for optimization (Table 2). First, we confirmed that the background reaction, observed when the amine was heated in DMF

Table 2. Formylation Optimization[a]



entry	DMF [equiv]	yield [%][b]
1	neat[c]	11
2	neat[d]	41
3	1	60
4	2	62
5	3	66
6	4	72
7	5	74
8	10	98
9	15	92
10[e]	10	95

[a]Product isolated by solid phase workup followed by column chromatography unless otherwise stated. [b]Isolated yield. [c]DMF (0.5 M) as solvent, no $B(OCH_2CF_3)_3$. [d]DMF (0.5 M) as solvent. [e]80 °C, solid phase workup followed by evaporation of DMF, no column chromatography required.

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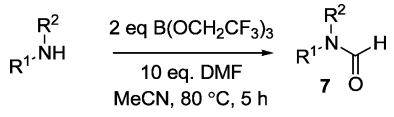
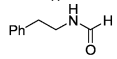
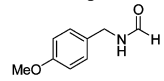
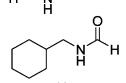
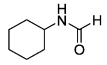
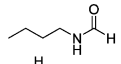
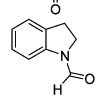
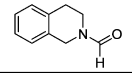
at 100 °C in the absence of $B(OCH_2CF_3)_3$, was negligible (entry 1). In neat DMF with 2 equiv of $B(OCH_2CF_3)_3$, a 41% yield of formamide was obtained (entry 2). Surprisingly, the reaction was more effective with small quantities of DMF in acetonitrile as solvent (entries 3–9). Although reasonable yields were obtained with as little as 1 equiv of DMF (entry 3), the use of 10 equiv was found to be optimal (entry 8). The reaction temperature could be lowered to 80 °C without a detrimental effect on yield, and the pure formamide could be obtained in good yield after solid phase workup and evaporation (entry 10). Formylation of benzylamine could also be achieved with similar efficiency using formamide (88% yield) and *N*-methylformamide (94%). However, DMF is considerably cheaper and easier to separate from the formamide product than these alternative formyl donors.

The scope of this reaction was evaluated on a range of amines (Table 3). Aromatic and aliphatic amines underwent formylation in moderate to excellent yield (**7a**–**7f**). Amines with α-substituents such as α-methylbenzylamine gave the corresponding formamide in excellent yield (**7d**). The volatile *N*-butylformamide (**7g**) could be obtained in good yield as calculated by ^{1}H NMR, but a significant loss of the product was observed during isolation. Less nucleophilic systems such as aniline and related derivatives (**7h**, **7i**) were formylated in relatively low yield. Secondary amines (**7i**, **7j**) could also be formylated, although higher temperatures were required to obtain better yields.

Table 3. Formylation of Amines with DMF



entry		product	yield [%][a]
1	**7a**		95
2	**7b**		99
3	**7c**		61
4	**7d**		85
5	**7e**		96
6	**7f**		78
7	**7g**		30 (63[b])
8	**7h**		21
9	**7i**		31 (38[c])
10	**7j**		36 (71[c])

[a]Isolated yield. [b]Yield measured using mesitylene as an internal standard. [c]100 °C for 5 h in a sealed tube.

CONCLUSION

A convenient synthesis of $B(OCH_2CF_3)_3$ from readily available bulk chemicals has been reported, and the full scope of its application in direct amidation reactions has been explored. A wide range of acids and amines containing varying functionalities can be successfully used in $B(OCH_2CF_3)_3$-mediated amidation reactions, and the pure amide products can be isolated following an operationally simple solid phase workup procedure using commercially available resins, avoiding the need for aqueous workup or chromatographic purification. The amidation of a series of *N*-protected amino acids with both primary and secondary amines has been successfully demonstrated, and the products were obtained with high enantiopurity. The formylation of a series of primary and secondary amines via transamidation of DMF was also successfully achieved.

EXPERIMENTAL SECTION

General Methods. All solvents and chemicals were used as supplied unless otherwise indicated. Reactions in MeCN at 100 °C were performed in a sealed (screw cap) carousel tube. All resins were washed with CH_2Cl_2 and dried under a vacuum prior to use. Column chromatography was carried out using silica gel, and analytical thin layer chromatography was carried out using aluminum-backed silica plates. Components were visualized using combinations of UV (254 nm) and potassium permanganate. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (c) in g per 100 mL. ^{1}H NMR spectra were recorded at 300, 400, 500, or 600 MHz in the stated solvent using residual protic solvent $CDCl_3$ (δ = 7.26 ppm, s), DMSO (δ = 2.56 ppm, qn) or MeOD (δ = 4.87, s and 3.31, quintet) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (J) are measured in Hertz. ^{13}C NMR spectra were recorded at 75, 100, 125, or 150 MHz in the stated solvent using the central reference of $CDCl_3$ (δ = 77.0 ppm, t), DMSO (δ = 39.52 ppm, septet) or MeOD (δ = 49.15 ppm, septet) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. Mass spectrometry data were collected on either TOF or magnetic sector analyzers. The ionization method is reported in the experimental data. The data for amides **2a**, **2d**, **2e**, **2g**, **2h**, **3j**, **3l**, **3o**, **3q**, **3r**, **4a**, **4b**, **4d**, **4f** and **6b** was reported in our preliminary communication.[13]

Tris-(2,2,2-trifluoroethyl) borate.[13] *25 g Scale.* A suspension of B_2O_3 (25.6 g, 0.37 mol) in 2,2,2-trifluoroethanol (53 mL, 0.73 mol) was stirred at 80 °C for 8 h. The reaction mixture was then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (36.0 g, 117 mmol, 48%).

50 g Scale (With CF_3CH_2OH Recovery). A suspension of B_2O_3 (48.1 g, 0.69 mol) in 2,2,2-trifluoroethanol (100 mL, 1.37 mol) was stirred at 80 °C for 24 h. The reaction mixture was then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (46.3 g, 150 mmol, 33%). 2,2,2-Trifluoroethanol (38.4 g, 28%) was recovered during the distillation: bp 122–125 °C (760 Torr) [lit.[13] 120–123 °C (760 Torr)]; ν_{max} (film/cm^{-1}) 3165 (C–H), 1441 (C–F), 1376 (B–O), 1156 (C–O); δ_H (300 MHz, $CDCl_3$) 4.24 (q, J 8.3 6H); δ_C (75 MHz, $CDCl_3$) 61.8 (q, J 36.5), 123.2 (q, J 276); δ_F (282 MHz, $CDCl_3$) −77.06; Found (CI) $[M + H]^+$ 309.0334 $C_6H_7O_3F_9B$, requires 309.0344.

General Procedure for Amidation of Carboxylic acids. All reactions were performed on a 1 mmol scale. $B(OCH_2CF_3)_3$ (2.0 mmol, 2 equiv) was added to a solution of acid (1.0 mmol, 1 equiv) and amine (1.0 mmol, 1 equiv) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at the indicated temperature (80 °C, or 100 °C in a sealed tube) for the indicated time (5–24 h).

Solid Phase Workup. After the indicated time, the reaction mixture was diluted with CH_2Cl_2 or EtOAc (3 mL) and water (0.5 mL). Amberlyst A-26(OH) (150 mg), Amberlyst 15 (150 mg) and

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Amberlite IRA743 (150 mg) were added to the reaction mixture, and it was stirred for 30 min. $MgSO_4$ was added to the reaction mixture, which was then filtered, the solids were washed three times with CH_2Cl_2 or EtOAc, and the filtrate was concentrated in vacuo to yield the amide product.

For amides **2i**, **2j**, **2t**, **2u** and **4e**, Amberlyst 15 was not used. In these cases, the product was separated from any excess amine by column chromatography.

Aqueous Workup Procedure. After the reaction was complete, the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (15 mL) and washed with aqueous solutions of $NaHCO_3$ (15 mL, 1 M) and HCl (15 mL, 1 M), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the amide product.

General Procedure for the Formylation of Amines with DMF. All reactions were performed on a 1 mmol scale. $B(OCH_2CF_3)_3$ (2.0 mmol, 2 equiv) was added to a solution of amine (1.0 mmol, 1 equiv) and DMF (10.0 mmol, 10 equiv) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at 80 °C for 5 h. After 5 h, the reaction mixture was diluted with CH_2Cl_2 or EtOAc (3 mL) and water (0.5 mL). Amberlyst 15 (150 mg) and Amberlite IRA743 (150 mg) were added to the reaction mixture, and it was stirred for 30 min. The reaction mixture was dried over $MgSO_4$ and then filtered, the solids were washed three times with CH_2Cl_2 or EtOAc, and the filtrate was diluted with toluene (10 mL) and then concentrated in vacuo repeatedly (5 times) to yield the clean product.

*N-(2-Methoxybenzyl)-2-phenylacetamide (**2b**).* Yellow solid (256 mg, 99%): mp 94−95 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3284 (N−H), 3066, 3030, 2939, 2837 (C−H), 1646 (C═O); δ_H (600 MHz, $CDCl_3$) 3.58 (s, 2H), 3.66 (s, 3H), 4.39 (d, *J* 5.8, 2H), 6.01 (br s, 1H), 6.80 (d, *J* 8.1, 1H), 6.87 (td, *J* 7.4, 0.9, 1H), 7.17 (dd, *J* 7.4, 1.6, 1H), 7.22−7.25 (m, 3H), 7.27−7.30 (m, 1H), 7.33−7.36 (m, 2H); δ_C (150 MHz, $CDCl_3$) 40.0, 44.0, 55.1, 110.2, 120.7, 126.1, 127.4, 128.9, 129.0, 129.6, 129.7, 135.1, 157.6, 170.7; Found (EI) $[M]^+$ 255.1251 $C_{16}H_{17}O_2N$, requires 255.1254.

*N-(4-Methoxybenzyl)-2-phenylacetamide (**2c**).*[42] Yellow solid (252 mg, 99%): mp 139−141 °C (CH_2Cl_2) [lit.[42] 138−139 °C]; ν_{max} (solid/cm^{-1}) 3235 (N−H), 3063, 3032, 2969, 2936 (C−H), 1623 (C═O); δ_H (600 MHz, $CDCl_3$) 3.62 (s, 2H), 3.78 (s, 3H), 4.34 (d, *J* 5.8, 2H), 5.60 (br s, 1H), 6.81−6.83 (m, 2H), 7.09−7.12 (m, 2H), 7.25−7.26 (m, 1H), 7.26−7.30 (m, 2H), 7.32−7.36 (m, 2H); δ_C (150 MHz, $CDCl_3$) 43.2, 44.0, 55.4, 114.1, 127.5, 129.0, 129.2, 129.6, 130.3, 134.9, 159.1, 170.9; Found (EI) $[M]^+$ 255.1257 $C_{16}H_{17}O_2N$, requires 255.1254.

*N-(2-(1H-Indol-3-yl)ethyl)-2-phenylacetamide (**2f**).*[43] Yellow solid (158 mg, 57%): mp 145−146 °C (CH_2Cl_2) [lit.[43] 151−153 °C]; ν_{max} (solid/cm^{-1}) 3391 (N−H), 3249 (N−H), 3062, 3033, 2920, 2850 (C−H), 1634 (C═O); δ_H (500 MHz, $CDCl_3$) 2.90 (t, *J* 6.7, 2H), 3.50−3.56 (m, 4H), 5.44 (br s, 1H), 6.77 (s, 1H), 7.08−7.15 (m, 3H), 7.18−7.22 (m, 1H), 7.23−7.28 (m, 1H), 7.26−7.30 (m, 2H), 7.35 (d, *J* 8.1, 1H), 7.54 (d, *J* 7.8, 1H), 8.00 (br s, 1H); δ_C (125 MHz, $CDCl_3$) 25.1, 39.8, 44.0, 111.3, 112.8, 118.7, 119.6, 122.0, 122.3, 127.3, 129.0 (2C), 129.5, 135.0, 136.4, 171.0; Found (ES) $[M + Na]^+$ 301.1305 $C_{18}H_{18}ON_2Na$, requires 301.1317.

*N-Methyl-N′-phenylacetylpiperazine (**2i**).*[44] Purified by column chromatography (Et_2O:MeOH:NEt_3 89:10:1). Yellow oil (170 mg, 96%): ν_{max} (film/cm^{-1}) 3029, 2940, 2853, 2795 (C−H), 1627 (C═O); δ_H (500 MHz, $CDCl_3$) 2.20 (t, *J* 5.1, 2H), 2.25 (s, 3H), 2.34 (t, *J* 5.1, 2H), 3.45 (t, *J* 5.1, 2H), 3.66 (t, *J* 5.1, 2H), 3.72 (s, 2H), 7.21−7.25 (m, 3H), 7.29−7.33 (m, 2H); δ_C (125 MHz, $CDCl_3$) 41.0, 41.7, 46.0 (2C), 54.7, 55.0, 126.9, 128.7, 128.8, 135.1, 169.5.

*N-Phenyl-N′-phenylacetylpiperazine (**2j**).* Purified by column chromatography (Et_2O). Brown solid (209 mg, 76%): mp 91−93 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 2919, 2827 (C−H), 1632 (C═O); δ_H (600 MHz, $CDCl_3$) 2.95−2.98 (m, 2H), 3.10−3.13 (m, 2H), 3.56−3.59 (m, 2H), 3.78−3.82 (m, 4H), 6.87−6.93 (m, 3H), 7.25−7.31 (m, 5H), 7.33−7.37 (m, 2H); δ_C (150 MHz, $CDCl_3$) 41.2, 41.8, 46.1, 49.3, 49.6, 116.7, 120.6, 127.1, 128.8, 129.0, 129.4, 135.2, 151.0, 169.6; Found (ES) $[M + H]^+$ 281.1656 $C_{18}H_{21}ON_2$, requires 281.1654.

*N-Phenylacetylmorpholine (**2k**).*[45] White solid (182 mg, 89%): mp 65−67 °C (CH_2Cl_2) [lit.[45] 62−64 °C]; ν_{max} (solid/cm^{-1}) 3064, 3033, 2961, 2917, 2893, 2851 (C−H), 1640 (C═O); δ_H (400 MHz, $CDCl_3$) 3.40−3.44 (m, 2H), 3.44−3.48 (m, 2H), 3.63 (s, 4H), 3.72 (s, 2H), 7.21−7.27 (m, 3H), 7.29−7.34 (m, 2H); δ_C (100 MHz, $CDCl_3$) 40.8, 42.1, 46.5, 66.4, 66.8, 126.9, 128.5, 128.8, 134.8, 169.6.

*2-Phenyl-1-(pyrrolidin-1-yl)ethanone (**2l**).* Clear oil (185 mg, 97%): ν_{max} (film/cm^{-1}) 3061, 3030, 2971, 2874 (C−H), 1623 (C═O); δ_H (500 MHz, $CDCl_3$) 1.80 (quintet, *J* 6.7, 2H), 1.88 (quintet, *J* 6.7, 2H), 3.39 (t, *J* 6.7, 2H), 3.46 (t, *J* 6.7, 2H), 3.63 (s, 2H), 7.19−7.23 (m, 1H), 7.24−7.31 (m, 4H); δ_C (125 MHz, $CDCl_3$) 24.4, 26.2, 42.3, 46.0, 47.0, 126.7, 128.6, 129.0, 135.0, 169.6; Found (ES+) $[M + H]^+$ 190.1226 $C_{12}H_{16}ON$, requires 190.1232.

*N-Phenylacetylthiomorpholine (**2m**).*[46] Yellow solid (194 mg, 89%): mp 73−74 °C (CH_2Cl_2) [lit.[46] 73−75 °C]; ν_{max} (solid/cm^{-1}) 3024, 2960, 2911 (C−H), 1639 (C═O); δ_H (400 MHz, $CDCl_3$) 2.26−2.30 (m, 2H), 2.52−2.59 (m, 2H), 3.65−3.70 (m, 2H), 3.72 (s, 2H), 3.85−3.90 (m, 2H), 7.20−7.26 (m, 3H), 7.29−7.34 (m, 2H); δ_C (100 MHz, $CDCl_3$) 27.2, 27.4, 41.3, 44.4, 48.8, 126.9, 128.5, 128.9, 134.8, 169.4.

*N,N-Dimethyl-2-phenylacetamide (**2n**).*[47] White solid (134 mg, 82 mg): mp 37−39 °C (CH_2Cl_2) [lit.[47] 38−40 °C]; ν_{max} (solid/cm^{-1}) 3062, 3029, 2931 (C−H), 1634 (C═O); δ_H (600 MHz, $CDCl_3$) 2.91 (s, 3H), 2.93 (s, 3H), 3.66 (s, 2H), 7.17−7.23 (m, 3H), 7.25−7.28 (m, 2H); δ_C (150 MHz, $CDCl_3$) 35.7, 37.8, 41.1, 126.8, 128.7, 128.9, 135.2, 171.1.

*N,N-Dibenzyl-2-phenylacetamide (**2o**).*[48] Purified by column chromatography (Et_2O:PE 3:1). Colorless oil (37 mg, 12%): ν_{max} (film/cm^{-1}) 3062, 3029, 2925 (C−H), 1639 (C═O); δ_H (500 MHz, $CDCl_3$, 35 °C) 3.83 (s, 2H), 4.47 (s, 2H), 4.66 (s, 2H), 7.11−7.17 (m, 2H), 7.19−7.25 (m, 2H), 7.25−7.42 (m, 12H); δ_C (125 MHz, $CDCl_3$, 35 °C) 41.0, 48.3, 50.3, 126.5, 126.9, 127.4, 127.6, 128.3, 128.5, 128.7, 128.8, 128.9, 135.0, 136.5, 137.3, 171.6.

*N,2-Diphenylacetamide (**2p**).*[49] Off white solid (125 mg, 60%): mp 116−118 °C (CH_2Cl_2) [lit.[49] 116−117 °C]; ν_{max} (solid/cm^{-1}) 3254 (N−H), 3135, 3061, 3025 (C−H), 1655 (C═O); δ_H (600 MHz, $CDCl_3$) 3.69 (s, 2H), 7.09 (t, *J* 7.4, 1H), 7.27 (t, *J* 7.8, 2H), 7.33−7.34 (m, 3H), 7.36−7.39 (m, 2H), 7.45 (d, *J* 8.0, 2H), 7.61 (br s, 1H); δ_C (150 MHz, $CDCl_3$) 44.8, 120.1, 124.6, 127.7, 129.1, 129.3, 129.6, 134.7, 137.9, 169.6.

*N-(2-Methoxyphenyl)-2-phenylacetamide (**2q**).*[50] Yellow solid (143 mg, 61%): mp 82−83 °C (CH_2Cl_2) [lit.[50] 80−81 °C]; ν_{max} (solid/cm^{-1}) 3284 (N−H), 3028, 3011, 2959, 2939, 2918, 2837 (C−H), 1648 (C═O), δ_H (500 MHz, $CDCl_3$) 3.72 (s, 3H), 3.76 (s, 2H), 6.80 (dd, *J* 8.1, 1.1, 1H), 6.93 (td, *J* 7.8, 1.1, 1H), 7.01 (td, *J* 7.8, 1.5, 1H), 7.31−7.37 (m, 3H), 7.37−7.42 (m, 2H), 7.79 (br s, 1H), 8.35 (dd, *J* 8.0, 1.4, 1H); δ_C (125 MHz, $CDCl_3$) 45.3, 55.7, 110.0, 119.6, 121.2, 123.8, 127.5, 127.7, 129.1, 129.7, 134.7, 147.9, 168.9.

*2-Phenyl-N-p-tolylacetamide (**2r**).*[49] White solid (105 mg, 53%): mp 132−133 °C (CH_2Cl_2) [lit.[49] 131−132 °C]; ν_{max} (solid/cm^{-1}) 3289 (N−H), 3063, 3031, 2922 (C−H), 1650 (C═O); δ_H (500 MHz, $CDCl_3$) 2.29 (s, 3H), 3.73 (s, 2H), 7.01 (br s, 1H), 7.08 (d, *J* 8.4, 2H), 7.28 (d, *J* 8.4, 2H), 7.31−7.36 (m, 3H), 7.38−7.42 (m, 2H); δ_C (125 MHz, $CDCl_3$) 23.6, 47.4, 122.9, 130.2, 131.8, 132.2, 133.3, 136.8, 137.5, 138.0, 172.1.

*N-(4-Methoxyphenyl)-2-phenylacetamide (**2s**).*[49] White solid (164 mg, 68%): mp 122−123 °C (CH_2Cl_2) [lit.[49] 124−125 °C]; ν_{max} (solid/cm^{-1}) 3315 (N−H), 3084, 3026, 3009, 2943 (C−H), 1650 (C═O); δ_H (500 MHz, $CDCl_3$) 3.73 (s, 2H), 3.77 (s, 3H), 6.80−6.83 (m, 2H), 6.97 (br s, 1H), 7.29−7.36 (m, 5H), 7.38−7.42 (m, 2H); δ_C (125 MHz, $CDCl_3$) 44.8, 55.5, 114.1, 121.9, 127.7, 129.3, 129.6, 130.7, 134.6, 156.6, 169.0.

*N-(Pyridin-3-yl)-2-phenylacetamide (**2t**).* Purified by column chromatography (4% MeOH in EtOAc). White solid (114 mg, 53%): mp 107−108 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3170 (N−H), 3032, 2971 (C−H), 1686 (C═O); δ_H (500 MHz, $CDCl_3$) 3.68 (s, 2H), 7.20 (dd, *J* 8.3, 4.7, 1H), 7.23−7.33 (m, 5H), 8.06−8.10 (m, 1H), 8.27 (dd, *J* 4.7, 1.2, 1H), 8.57 (d, *J* 2.4, 1H), 9.05 (br s, 1H); δ_C (125 MHz, $CDCl_3$) 44.3, 123.9, 127.5, 127.6, 129.0, 129.3, 134.4, 135.4,

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141.3, 144.9, 170.4; Found (EI) $[M]^+$ 212.0947 $C_{13}H_{12}ON_2$, requires 212.0944.

*N-(Pyridin-2-yl)-2-phenylacetamide (**2u**).*[49] Purified by column chromatography (EtOAc:PE 3:1, 10% NEt_3). White solid (25 mg, 12%): mp 121−122 °C (CH_2Cl_2) [lit.[49] 122−124 °C]; ν_{max} (solid/cm^{-1}) 3230 (N−H), 3046, 2959, 2921 (C−H), 1656 (C═O); δ_H (500 MHz, $CDCl_3$) 3.74 (s, 2H), 6.98−7.03 (m, 1H), 7.27−7.33 (m, 3H), 7.33−7.38 (m, 2H), 7.66−7.71 (m, 1H), 8.19−8.27 (m, 2H), 8.52 (br s, 1H); δ_C (125 MHz, $CDCl_3$) 45.1, 114.1, 120.0, 127.8, 129.3, 129.6, 134.0, 138.5, 147.7, 151.3, 169.6; Found (ES) $[M + H]^+$ 213.1035 $C_{13}H_{13}ON_2$, requires 213.1028.

*N-tert-Butyl-2-phenylacetamide (**2v**).*[51] White solid (116 mg, 60%): mp 104−106 °C (CH_2Cl_2) [lit.[51] 103 °C]; ν_{max} (solid/cm^{-1}) 3303 (N−H), 3063, 2962, 2872 (C−H), 1638 (C═O); δ_H (600 MHz, $CDCl_3$) 1.28 (s, 9H), 3.48 (s, 2H), 5.17 (br s, 1H), 7.24 (d, *J* 7.2, 2H), 7.26−7.30 (m, 1H), 7.35 (t, *J* 7.4, 2H); δ_C (150 MHz, $CDCl_3$) 28.8, 45.0, 51.4, 127.3, 129.1, 129.4, 135.6, 170.4.

*N-Benzyl-2-(naphthalen-2-yl)acetamide (**3a**).*[52] Yellow solid (225 mg, 81%): mp 168−169 °C (CH_2Cl_2) [lit.[52] 170−174 °C]; ν_{max} (solid/cm^{-1}) 3225 (N−H), 3053, 3030, 2976, 2936 (C−H), 1628 (C═O); δ_H (500 MHz, $CDCl_3$) 3.79 (s, 2H), 4.41 (d, *J* 5.8, 2H), 5.81 (br s, 1H), 7.18 (d, *J* 7.0, 2H), 7.21−7.30 (m, 3H), 7.39 (dd, *J* 8.3, 1.7, 1H), 7.46−7.52 (m, 2H), 7.72 (br s, 1H), 7.78−7.82 (m, 1H), 7.82−7.85 (m, 2H); δ_C (125 MHz, $CDCl_3$) 43.7, 44.1, 126.2, 126.5, 127.4, 127.5, 127.6, 127.7, 127.8, 128.4, 128.7, 129.0, 132.3, 132.6, 133.6, 138.2, 170.8.

*N-Benzyl-2,2-diphenylacetamide (**3b**).*[53] Yellow solid (247 mg, 81%): mp 127−128 °C (CH_2Cl_2) [lit.[53] 126−128 °C]; ν_{max} (solid/cm^{-1}) 3311 (N−H), 3060, 3030, 2930 (C−H), 1634 (C═O); δ_H (500 MHz, $CDCl_3$) 4.48 (d, *J* 5.7, 2H), 4.96 (s, 1H), 5.94 (br s, 1H), 7.19−7.22 (m, 2H), 7.24−7.30 (m, 8H), 7.30−7.35 (m, 5H); δ_C (125 MHz, $CDCl_3$) 43.9, 59.3, 127.4, 127.6, 127.7, 128.8, 128.9, 129.0, 138.2, 139.4, 171.8.

*N-Benzyl-2-(4-methoxyphenyl)acetamide (**3c**).*[54] Yellow solid (232 mg, 90%): mp 134−135 °C (CH_2Cl_2) [lit.[54] 136 °C]; ν_{max} (solid/cm^{-1}) 3286 (N−H), 3082, 3063, 3033, 2968, 2838 (C−H), 1635 (C═O); δ_H (600 MHz, $CDCl_3$) 3.57 (s, 2H), 3.79 (s, 3H), 4.40 (d, *J* 5.8, 2H), 5.75 (br s, 1H), 6.86−6.89 (m, 2H), 7.16−7.19 (m, 4H), 7.23−7.26 (m, 1H), 7.28−7.31 (m, 2H); δ_C (150 MHz, $CDCl_3$) 43.0, 43.7, 55.4, 114.6, 126.8, 127.5, 127.6, 128.8, 130.7, 138.3, 159.0, 171.5.

*N-Benzyl-2-(2-bromophenyl)acetamide (**3d**).*[55] Yellow solid (276 mg, 90%): mp 143−144 °C (CH_2Cl_2) [lit.[55] 144−145 °C]; ν_{max} (solid/cm^{-1}) 3272 (N−H), 3055, 3030, 2920, 2871 (C−H), 1642 (C═O); δ_H (600 MHz, $CDCl_3$) 3.77 (s, 2H), 4.44 (d, *J* 5.7, 2H), 5.75 (br s, 1H), 7.16 (td, *J* 7.7, 1.7, 1H), 7.21−7.27 (m, 3H), 7.30 (app t, *J* 7.6, 3H), 7.37 (dd, *J* 7.5, 1.6, 1H), 7.58 (dd, *J* 8.0, 1.0, 1H); δ_C (150 MHz, $CDCl_3$) 43.8, 44.2, 125.0, 127.6, 127.7, 128.2, 128.8, 129.4, 131.9, 133.3, 134.8, 138.1, 169.5.

*N-Benzyl-2-(4-bromophenyl)acetamide (**3e**).* Yellow solid (289 mg, 94%): mp 165−166 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3280 (N−H), 3056, 3026, 2917, 2872 (C−H), 1642 (C═O); δ_H (600 MHz, $CDCl_3$) 3.55 (s, 2H), 4.41 (d, *J* 5.6, 2H), 5.72 (br s, 1H), 7.15 (d, *J* 8.4, 2H), 7.19 (d, *J* 7.0, 2H), 7.25−7.28 (m, 1H), 7.29−7.33 (m, 2H), 7.45−7.48 (m, 2H); δ_C (150 MHz, $CDCl_3$) 43.2, 43.8, 121.6, 127.7, 127.8, 128.9, 131.2, 132.2, 133.8, 138.0, 170.2; Found (EI) $[M]^+$ 303.0256 $C_{15}H_{14}ONBr$, requires 303.0253.

*N-Benzyl-2-(3,4-dimethoxyphenyl)acetamide (**3f**).* Brown solid (235 mg, 81%): mp 100−101 °C (CH_2Cl_2) [lit.[56] 98−100 °C]; ν_{max} (solid/cm^{-1}) 3297 (N−H), 3065, 3033, 3000, 2936, 2835 (C−H), 1634 (C═O); δ_H (600 MHz, $CDCl_3$) 3.58 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.41 (d, *J* 5.6, 2H), 5.74 (br s, 1H), 6.76−6.80 (m, 2H), 6.83 (d, *J* 8.0, 1H), 7.18 (d, *J* 7.0, 2H), 7.23−7.26 (m, 1H), 7.28−7.31 (m, 2H); δ_C (150 MHz, $CDCl_3$) 43.6, 43.7, 55.98, 56.02, 111.6, 112.4, 121.8, 127.2, 127.58, 127.61, 128.8, 138.3, 148.4, 149.4, 171.3; Found (EI) $[M]^+$ 285.1353 $C_{17}H_{19}O_3N$, requires 285.1359.

*N-Benzyl-2-(4-chlorophenyl)acetamide (**3g**).*[57] Yellow solid (244 mg, 93%): mp 157−158 °C (CH_2Cl_2) [lit.[57] 151−153 °C]; ν_{max} (solid/cm^{-1}) 3277 (N−H), 3056, 3027, 2918, 2874 (C−H), 1642 (C═O), 690 (C−Cl); δ_H (600 MHz, $CDCl_3$) 3.56 (s, 2H), 4.41 (d, *J* 5.8, 2H), 5.76 (br s, 1H), 7.18−7.22 (m, 4H), 7.24−7.28 (m, 1H), 7.29−7.32 (m, 4H); δ_C (150 MHz, $CDCl_3$) 43.1, 43.8, 127.69, 127.74, 128.9, 129.2, 130.9, 133.3, 133.5, 138.1, 170.4.

*N-Benzyl-2-(thiophen-3-yl)acetamide (**3h**).* Yellow solid (212 mg, 91%): mp 96−98 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3279 (N−H), 3086, 3062, 3032, 2925 (C−H), 1635 (C═O); δ_H (600 MHz, $CDCl_3$) 3.65 (s, 2H), 4.42 (d, *J* 5.8, 2H), 5.85 (br s, 1H), 7.01 (d, *J* 4.8, 1H), 7.14−7.15 (m, 1H), 7.19 (d, *J* 7.5, 2H), 7.23−7.34 (m, 4H); δ_C (150 MHz, $CDCl_3$) 38.3, 43.7, 123.7, 127.0, 127.61, 127.62, 128.6, 128.8, 134.8, 138.2, 170.5; Found (ES) $[M + H]^+$ 232.0789 $C_{13}H_{14}ONS$, requires 232.0796.

*N-Benzyl-2-(4-phenoxyphenyl)acetamide (**3i**).* Yellow solid (298 mg, 95%): mp 125−126 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3285 (N−H), 3085, 3064, 3033, 2921 (C−H), 1636 (C═O); δ_H (600 MHz, $CDCl_3$) 3.60 (s, 2H), 4.43 (d, *J* 5.9, 2H), 5.71 (br s, 1H), 6.96−7.01 (m, 4H), 7.10−7.13 (m, 1H), 7.18−7.21 (m, 2H), 7.21−7.24 (m, 2H), 7.25−7.28 (m, 1H), 7.29−7.36 (m, 4H); δ_C (150 MHz, $CDCl_3$) 43.2, 43.8, 119.2, 119.3, 123.6, 127.6, 127.7, 128.8, 129.5, 129.9, 130.9, 138.2, 156.8, 157.0, 171.0; Found (EI) $[M]^+$ 317.1416 $C_{21}H_{19}O_2N$, requires 317.1410.

*Boc-Sarcosine-benzamide (**3k**).*[58] Yellow solid (265 mg, 95%): mp 82−84 °C (CH_2Cl_2) [lit.[58] 83−85 °C]; ν_{max} (solid/cm^{-1}) 3310 (N−H), 3067, 2978, 2931 (C−H), 1664 (C═O), 1685 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.40 (s, 9H), 2.90 (s, 3H), 3.83 (s, 2H), 4.41 (d, *J* 5.9, 2H), 6.52 (br s, 1H), 7.19−7.24 (m, 3H), 7.25−7.31 (m, 2H); δ_C (100 MHz, $CDCl_3$, 58 °C) 28.2, 35.7, 43.3, 53.4, 80.6, 127.3, 127.5, 128.6, 138.2, 155.9, 169.1; Found (EI) $[M]^+$ 278.1629 $C_{15}H_{22}O_3N_2$, requires 278.1625.

*(E)-N-Benzyl-3-(thiophen-3-yl)acrylamide (**3m**).* Yellow solid (217 mg, 88%): mp 107−110 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3275 (N−H), 3029, 2971 (C−H), 1739 (C═O); δ_H (600 MHz, $CDCl_3$) 4.55 (d, *J* 5.7, 2H), 6.05 (br s, 1H), 6.26 (d, *J* 15.5, 1H), 7.22−7.24 (m, 1H), 7.26−7.36 (m, 6H), 7.42 (d, *J* 2.1, 1H), 7.65 (d, *J* 15.5, 1H); δ_C (150 MHz, $CDCl_3$) 44.0, 120.2, 125.1, 126.9, 127.4, 127.7, 128.0, 128.9, 135.2, 137.8, 138.3, 166.1; Found (ES+) $[M + H]^+$ 244.0800 $C_{14}H_{14}NOS$, requires 244.0796.

*(E)-N-Benzyl-2-methyl-3-phenylacrylamide (**3n**).* White solid (229 mg, 90%): mp 120−121 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3332 (N−H), 3079, 3059, 2921, 2852 (C−H), 1531 (C═O); δ_H (600 MHz, $CDCl_3$) 2.11 (s, 3H), 4.56 (d, *J* 5.7, 2H), 6.69 (br s, 1H), 7.27−7.40 (m, 11H); δ_C (150 MHz, $CDCl_3$) 14.5, 44.2, 127.7, 127.98, 128.04, 128.5, 128.9, 129.5, 131.9, 134.3, 136.2, 138.5, 169.6; Found (ES) $[M + H]^+$ 252.1394 $C_{17}H_{18}ON$, requires 252.1388.

*N-Benzyl-2,2,2-trifluoroacetamide (**3p**).*[59] Yellow solid (183 mg, 89%): mp 72−74 °C (CH_2Cl_2) [lit.[59] 70−71 °C]; ν_{max} (solid/cm^{-1}) 3300 (N−H), 3110, 3035, 2923 (C−H), 1702 (C═O); δ_H (500 MHz, $CDCl_3$) 4.54 (d, *J* 5.8, 2H), 6.52 (br s, 1H), 7.28−7.32 (m, 2H), 7.32−7.41 (m, 3H); δ_C (125 MHz, $CDCl_3$) 43.9, 116.0 (q, *J* 285.4), 128.0, 128.2, 129.0, 136.1, 157.5 (q, *J* 36.9); δ_F (282 MHz, $CDCl_3$) −76.2.

*N-Benzyl-4-methoxybenzamide (**3s**).*[60] Yellow solid (172 mg, 71%): mp 129−130 °C (CH_2Cl_2) [lit.[60] 129−130 °C]; ν_{max} (solid/cm^{-1}) 3256 (N−H), 3058, 2957, 2930, 2834 (C−H), 1631 (C═O); δ_H (500 MHz, $CDCl_3$) 3.85 (s, 3H), 4.64 (d, *J* 5.7, 2H), 6.28 (br s, 1H), 6.90−6.94 (m, 2H), 7.28−7.32 (m, 1H), 7.36 (m, 4H), 7.74−7.77 (m, 2H); δ_C (125 MHz, $CDCl_3$) 44.1, 55.5, 113.8, 126.7, 127.6, 128.0, 128.8, 128.9, 138.5, 162.3, 167.0.

*N-Benzyl-4-(trifluoromethyl)benzamide (**3t**).*[61] Yellow solid (212 mg, 76%): mp 168−170 °C (CH_2Cl_2) [lit.[61] 149−151 °C]; ν_{max} (solid/cm^{-1}) 3326 (N−H), 3091, 3071, 3036 (C−H), 1643 (C═O); δ_H (600 MHz, $CDCl_3$) 4.65 (d, *J* 5.6, 2H), 6.53 (br s, 1H), 7.29−7.33 (m, 1H), 7.33−7.38 (m, 4H), 7.68 (d, *J* 8.2, 2H), 7.89 (d, *J* 8.2, 2H); δ_C (150 MHz, $CDCl_3$) 44.5, 123.7 (q, *J* 272.5), 125.8 (q, *J* 3.8), 127.6, 128.0, 128.1, 129.0, 133.4 (q, *J* 32.7), 137.7, 137.8, 166.2; δ_F (282 MHz, $CDCl_3$) −63.4.

*N,2-Dibenzylbenzamide (**3u**).* Yellow solid (184 mg, 61%): mp 119−120 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3296 (N−H), 3057, 3025, 3008, 2921, 2873 (C−H), 1633 (C═O), δ_H (600 MHz, $CDCl_3$) 4.22 (s, 2H), 4.49 (d, *J* 5.6, 2H), 5.86 (br s, 1H), 7.13 (d, *J* 7.1, 2H), 7.16−7.19 (m, 3H), 7.21−7.25 (m, 4H), 7.26−7.32 (m, 3H), 7.33−7.37 (m,

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1H), 7.39−7.42 (m, 1H); δ_C (150 MHz, $CDCl_3$) 39.0, 44.1, 126.2, 126.5, 127.3, 127.7, 128.0, 128.6, 128.9, 129.0, 130.3, 131.3, 136.5, 137.9, 139.0, 140.9, 169.9; Found (ES) $[M + H]^+$ 302.1532 $C_{21}H_{20}ON$, requires 302.1545.

*N-Benzyl-4-iodobenzamide (**3v**).*[62] White solid (124 mg, 37%): mp 167−168 °C (CH_2Cl_2) [lit.[62] 166−167 °C]; ν_{max} (solid/cm^{-1}) 3311 (N−H), 3083, 3060, 3028 (C−H), 1640 (C═O); δ_H (600 MHz, DMSO) 4.47 (d, *J* 6.0, 2H), 7.22−7.26 (m, 1H), 7.29−7.35 (m, 4H), 7.66−7.69 (m, 2H), 7.84−7.88 (m, 2H), 9.10 (br t, *J* 6.0, 1H); δ_C (150 MHz, DMSO) 42.7, 98.9, 126.8, 127.3, 128.3, 129.3, 133.8, 137.2, 139.5, 165.6; Found (EI) $[M + H]^+$ 337.9962 $C_{14}H_{13}ONI$, requires 337.9958.

*N-Butyl-2-p-tolylacetamide (**4c**).*[63] White solid (188 mg, 92%): mp 82−83 °C (CH_2Cl_2) [lit.[63] 73−74 °C]; ν_{max} (solid/cm^{-1}) 3301 (N−H), 2959, 2931, 2866 (C−H), 1649 (C═O); δ_H (500 MHz, $CDCl_3$) 0.86 (t, *J* 7.3, 3H), 1.24 (sextet, *J* 7.3, 2H), 1.39 (quintet, *J* 7.3, 2H), 2.34 (s, 3H), 3.18 (dt, *J* 7.3, 6.0, 2H), 3.52 (s, 2H), 5.43 (br s, 1H), 7.11−7.17 (m, 4H); δ_C (125 MHz, $CDCl_3$) 13.8, 20.0, 21.2, 31.6, 39.5, 43.6, 129.5, 129.8, 132.0, 137.1, 171.2; Found (EI) $[M]^+$ 205.1464 $C_{13}H_{19}ON$, requires 205.1461.

*Methyl 2-(picolinamido)acetate (**4e**).*[64] Purified by column chromatography (PE:EtOAc 1:1). White solid (132 mg, 72%): mp 82−84 °C (CH_2Cl_2) [lit.[64] 81−82 °C]; ν_{max} (film/cm^{-1}) 3375 (N−H), 3059, 2954, 2852 (C−H), 1746 (C═O), 1668 (C═O); δ_H (600 MHz, $CDCl_3$) 3.74 (s, 3H), 4.23 (d, *J* 5.7, 2H), 7.38−7.42 (m, 1H), 7.80 (t, *J* 7.6, 1H), 8.13 (d, *J* 7.6, 1H), 8.49 (br s, 1H), 8.53 (br d, *J* 4.5); δ_C (150 MHz, $CDCl_3$) 41.3, 52.5, 122.4, 126.6, 137.4, 148.4, 149.3, 164.7, 170.3.

*N-(4-Hydroxyphenyl)acetamide (**4g**).*[65] White solid (97 mg, 69%): mp 169−170 °C (CH_2Cl_2) [lit.[65] 167−168 °C]; ν_{max} (solid/cm^{-1}) 3242 (N−H/O−H), 1632 (C═O); δ_H (600 MHz, MeOD) 2.07 (s, 3H), 6.71−6.74 (m, 2H), 7.28−7.32 (m, 2H); δ_C (150 MHz, MeOD) 23.5, 116.2, 123.4, 131.7, 155.4, 171.4.

*2-(4-(2-(Benzylamino)-2-oxoethyl)phenyl)acetic acid (**4h**).* B-$(OCH_2CF_3)_3$ (621.8 mg, 2.02 mmol, 2 equiv) was added to a solution of phenylene diacetic acid (192 mg, 0.99 mmol, 1 equiv) and benzylamine (0.11 mL, 1.01 mmol, 1 equiv) in MeCN (2 mL, 0.5 M). The reaction mixture was stirred at 80 °C for 5 h. After 5 h the solvent was removed in vacuo, and the residue was diluted in Et_2O (20 mL), washed with $NaHCO_3$ (20 mL, 1 M), and extracted with Et_2O (3 × 20 mL). The aqueous layer was acidifed with HCl (1 M) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield the product as a white solid (146 mg, 0.52 mmol, 52%): mp 163−166 °C (CH_2Cl_2); ν_{max} (solid/cm^{-1}) 3284 (N−H/O−H), 3030, 3060 (C−H), 1699 (C═O), 1632 (C═O); δ_H (600 MHz, DMSO-d_6) 3.45 (s, 2H), 3.53 (s, 2H), 4.26 (d, *J* 6.0, 2H), 7.16−7.19 (m, 2H), 7.20−7.25 (m, 5H), 7.29−7.32 (m, 2H), 8.55 (br t, *J* 5.6, 1H), 12.31 (br s, 1H); δ_C (150 MHz, DMSO-d_6) 40.3, 42.0, 42,2, 126.8, 127.3, 128.3, 128.9, 129.3, 133.1, 134.7, 139.5, 170.2, 172.8; Found (EI) $[M + H]^+$ 284.1279 $C_{17}H_{18}O_3N$, requires 284.1287.

*Piperidin-2-one (**5a**).*[66] Colorless oil (95 mg, 99%): ν_{max} (film/cm^{-1}) 3245 (N−H), 2945, 2870 (C−H), 1637 (C═O); δ_H (500 MHz, $CDCl_3$) 1.69−1.82 (m, 4H), 2.30 (t, *J* 6.5, 2H), 3.26−3.32 (m, 2H), 7.03 (br s, 1H); δ_C (125 MHz, $CDCl_3$) 20.8, 22.2, 31.5, 42.1, 172.9.

*Azepan-2-one (**5b**).*[57] White solid (100 mg, 86%): mp 67−68 °C (CH_2Cl_2) [lit.[57] 66−68 °C]; ν_{max} (solid/cm^{-1}) 3202 (N−H), 2927, 2855 (C−H), 1648 (C═O); δ_H (500 MHz, $CDCl_3$) 1.60−1.71 (m, 4H), 1.72−1.78 (m, 2H), 2.42−2.47 (m, 2H), 3.17−3.22 (m, 2H), 6.42 (br s, 1H); δ_C (125 MHz, $CDCl_3$) 23.3, 29.8, 30.6, 36.8, 42.8, 179.5; Found (EI) $[M]^+$ 113.0828 $C_6H_{11}ON$, requires 113.0835.

*(S)-tert-Butyl 2-oxopiperidin-3-ylcarbamate (**5c**).*[16] White solid (180 mg, 84%): mp 100−101 °C (CH_2Cl_2) [lit.[16] 101−103 °C]; $[\alpha]_D^{25}$ −9.5 (*c* 1.22, MeOH) [lit.[16] $[\alpha]_D^{20}$ −10.6 (*c* 1.22, MeOH)]; ν_{max} (solid/cm^{-1}) 3264 (N−H), 2968 (C−H), 1715 (C═O), 1652 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.45 (s, 9H), 1.54−1.67 (m, 1H), 1.82−1.93 (m, 2H), 2.41−2.50 (m, 1H), 3.27−3.33 (m, 2H), 4.01 (dt, *J* 11.3, 5.6, 1H), 5.45 (br s, 1H), 6.33 (br s, 1H); δ_C (100 MHz, $CDCl_3$, 58 °C) 21.1, 27.9, 28.3, 41.7, 51.6, 79.5, 155.8, 171.6.

*Boc-L-Methionine-benzamide (**6a**).*[67] Yellow solid (266 mg, 79%): mp 98−100 °C (CH_2Cl_2); $[\alpha]_D^{25}$−9.1 (*c* 1.1, CH_2Cl_2) [lit.[67] $[\alpha]_D^{24}$ −9.2 (*c* 1.1, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3335 (N−H), 3314 (N−H), 3061, 3027, 2968, 2936 (C−H), 1679 (C═O), 1655 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.41 (s, 9H), 1.88−1.97 (m, 1H), 2.05 (s, 3H), 2.06−2.15 (m, 1H), 2.46−2.59 (m, 2H), 4.28 (app q, *J* 7.1, 1H), 4.36 (dd, *J* 14.8, 5.8, 1H), 4.43 (dd, *J* 14.8, 5.9, 1H), 5.42 (br d, *J* 8.1, 1H), 7.19−7.25 (m, 3H), 7.26−7.30 (m, 2H), 6.86 (br s, 1H); δ_C (100 MHz, $CDCl_3$, 58 °C) 15.2, 28.3, 30.4, 32.0, 43.4, 54.1, 80.1, 127.3, 127.5, 128.5, 138.2, 155.7, 171.6; Found (ES) $[M + Na]^+$ 361.1567 $C_{17}H_{26}O_3N_2SNa$, requires 361.1562; HPLC (hexane/*i*-PrOH 92:8, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 9.28 min (<1%), t_R (L) = 12.48 min (>99%).

*Boc-L-Phenylalanine-benzamide (**6c**).*[68] Yellow solid (287 mg, 81%): mp 128−129 °C (CH_2Cl_2) [lit.[68] 128 °C]; $[\alpha]_D^{25}$ +5.2 (*c* 1.1, CH_2Cl_2) [lit.[67] $[\alpha]_D^{22}$ +4.9 (*c* 0.20, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3343 (N−H), 3312 (N−H), 3024, 2927 (C−H), 1678 (C═O), 1659 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.43 (s, 9H), 3.09 (dd, *J* 13.8, 7.2, 1H), 3.13 (dd, *J* 13.8, 6.7, 1H), 4.32−4.40 (m, 3H), 5.00 (br s, 1H), 6.03 (br s, 1H), 7.12−7.16 (m, 2H), 7.20−7.25 (m, 3H), 7.25−7.32 (m, 5H); δ_C (100 MHz, $CDCl_3$, 58 °C) 28.2, 38.6, 43.5, 56.4, 80.2, 126.8, 127.4, 127.6, 128.5, 128.6, 129.3, 136.8, 137.8, 155.3, 171.0; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 10.62 min (<1%), t_R (L) = 13.24 min (>99%).

*Boc-L-Proline-benzamide (**6d**).*[69] Yellow solid (186 mg, 61%): mp 124−125 °C (CH_2Cl_2) [lit.[69] 125−126 °C]; $[\alpha]_D^{25}$ −77.0 (*c* 1.0, CH_2Cl_2) [lit.[66] $[\alpha]_D^{24}$ −76.2 (*c* 1.0, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3303 (N−H), 2978, 2933, 2909, 2874 (C−H), 1682 (C═O), 1653 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.40 (s, 9H), 1.78−2.07 (m, 3H), 2.25 (br s, 1H), 3.37−3.42 (m, 2H), 4.24−4.30 (m, 1H), 4.37 (dd, *J* 14.8, 5.6, 1H), 4.46 (dd, *J* 14.8, 5.7, 1H), 6.82 (br s, 1H), 7.18−7.30 (m, 5H); δ_C (100 MHz, $CDCl_3$, 58 °C) 24.1, 28.3 (2C), 43.3, 47.0, 60.6, 80.3, 127.2, 127.5, 128.5, 138.5, 155.2, 172.1; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 13.08 min (1%), t_R (L) = 15.79 min (99%).

*Cbz-L-Alanine-benzamide (**6e**).*[22] Yellow solid (245 mg, 78%): mp 138−139 °C (CH_2Cl_2) [lit.[22] 140−141 °C]; $[\alpha]_D^{25}$ −8.0 (*c* 1.02, $CHCl_3$) [lit.[22] $[\alpha]_D^{22}$−8.1 (*c* 1.3, $CHCl_3$)]; ν_{max} (solid/cm^{-1}) 3286 (N−H), 3059, 3035, 2975, 2930 (C−H), 1682 (C═O), 1641 (C═O); δ_H (500 MHz, $CDCl_3$) 1.37 (d, *J* 6.9, 3H), 4.28−4.32 (m, 1H), 4.34 (dd, *J* 15.0, 5.7, 1H), 4.41 (dd, *J* 15.0, 5.6, 1H), 4.98 (d, *J* 12.1, 1H), 5.01 (d, *J* 12.1, 1H), 5.68 (br d, *J* 6.5, 1H), 6.88 (br s, 1H), 7.18−7.35 (m, 10H); δ_C (125 MHz, $CDCl_3$) 18.9, 43.5, 50.7, 67.0, 127.5, 127.7, 128.1, 128.3, 128.6, 128.7, 136.2, 138.1, 156.1, 172.5; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel AD) t_R (L) = 5.13 min (95%), t_R (D) = 7.88 min (5%).

*Boc-L-Ala-D-Phe-OMe (**6f**).* Yellow solid (136 mg, 42%): mp 93−95 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −58.9 (*c* 0.99, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3283 (N−H), 3254 (N−H), 3134, 3060, 3024 (C−H), 1655 (C═O), 1599 (C═O), 1544 (C═O); δ_H (600 MHz, $CDCl_3$) 1.27 (d, *J* 7.1, 3H), 1.42 (s, 9H), 3.06 (dd, *J* 13.8, 6.3, 1H), 3.13 (dd, *J* 13.8, 5.7, 1H), 3.70 (s, 3H), 4.18 (br t, *J* 7.1, 1H), 4.85 (m, 1H), 5.04 (br d, *J* 5.5, 1H), 6.70 (br s, 1H), 7.10 (d, *J* 7.1, 2H), 7.20−7.24 (m, 1H), 7.25−7.29 (m, 2H); δ_C (150 MHz, $CDCl_3$) 18.6, 28.4, 38.0, 50.0, 52.5, 53.2, 80.2, 127.2, 128.7, 129.4, 135.9, 155.5, 171.9, 172.4; Found (ES) $[M + Na]^+$ 373.1720 $C_{18}H_{26}O_5N_2Na$, requires 373.1739.

*Boc-L-Ala-L-Phe-OMe (**6g**).*[70] Yellow solid (208 mg, 64%): mp 82−84 °C (CH_2Cl_2) [lit.[70] 85−86 °C]; $[\alpha]_D^{25}$ +23.2 (*c* 1.01, $CHCl_3$) [lit.[71] $[\alpha]_D$ +23.0 (*c* 0.61, $CHCl_3$)]; ν_{max} (solid/cm^{-1}) 3285 (N−H), 3061, 3030, 2926 (C−H), 1636 (C═O), 1547 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 1.27 (d, *J* 7.0, 3H), 1.41 (s, 9H), 3.04 (dd, *J* 13.9, 6.6, 1H), 3.12 (dd, *J* 13.9, 6.1, 1H), 3.64 (s, 3H), 4.13 (quintet, *J* 7.0, 1H), 4.81 (dt, *J* 7.6, 6.3, 1H), 5.16 (br d, *J* 7.6, 1H), 6.71 (br d, *J* 7.3, 1H), 7.08−7.12 (m, 2H), 7.15−7.26 (m, 3H); δ_C (100 MHz, $CDCl_3$, 58 °C) 18.1, 28.2, 38.0, 50.4, 51.9, 53.3, 79.9, 126.9, 128.4, 129.2, 136.0, 155.3, 171.7, 172.4.

*Boc-L-Alanine pyrrolidine amide (**6h**).*[22] Colorless oil (135 mg, 59%): $[\alpha]_D^{25}$−6.4 (*c* 1.1, $CHCl_3$) [lit.[22] $[\alpha]_D^{24}$ −6.8 (*c* 1.1, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3300 (N−H), 2976, 2936, 2879 (C−H), 1705 (C═O), 1636 (C═O); δ_H (400 MHz, $CDCl_3$) 1.24 (d, *J* 6.8, 3H), 1.36 (s,

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9H), 1.76−1.84 (m, 2H), 1.91 (app qn, *J* 6.8, 2H), 3.31−3.39 (m, 2H), 3.41−3.49 (m, 1H), 3.51−3.58 (m, 1H), 4.37 (app qn, *J* 6.8, 1H), 5.50 (br d, *J* 7.8, 1H); δ_C (100 MHz, $CDCl_3$) 18.6, 24.1, 26.0, 28.3, 45.9, 46.2, 47.8, 79.3, 155.1, 171.2; Found (EI) $[M + H]^+$ 243.1713 $C_{12}H_{23}O_3N_2$, requires 243.1709; HPLC measured after conversion to the benzoyl derivative **6k** (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 15.79 min (<1%), t_R (L) = 23.58 min (>99%).

*Boc-L-Alanine thiomorpholine amide (**6i**).* Yellow solid (113 mg, 41%): mp 65−68 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −3.8 (*c* 1.03, $CHCl_3$); ν_{max} (solid/cm^{-1}) 3317 (N−H), 2980, 2927 (C−H), 1699 (C═O), 1638 (C═O); δ_H (400 MHz, $CDCl_3$) 1.29 (d, *J* 6.8, 3H), 1.43 (s, 9H), 2.53−2.61 (m, 2H), 2.63−2.76 (m, 2H), 3.65−3.75 (m, 2H), 3.80−3.89 (m, 1H), 3.99−4.08 (m, 1H), 4.59 (app qn, *J* 7.2, 1H), 5.52 (br d, *J* 8.0, 1H); δ_C (100 MHz, $CDCl_3$) 19.3, 27.3, 27.9, 28.4, 44.8, 46.1, 48.1, 79.6, 155.0, 171.3; Found (EI) $[M]^+$ 274.1352 $C_{12}H_{22}O_3N_2S$, requires 274.1346; HPLC measured after conversion to the benzoyl derivative **6l** (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 22.20 min (8%), t_R (L) = 31.86 min (92%).

*Boc-L-Phenylalanine pyrrolidine amide (**6j**).*[22] Colorless oil (115 mg, 37%): $[\alpha]_D^{25}$ +37.2 (*c* 1.0, $CHCl_3$) [lit.[22] $[\alpha]_D^{20}$ +37.5 (*c* 1.0, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3432 (N−H), 2979, 2880 (C−H), 1702 (C═O), 1631 (C═O); δ_H (400 MHz, $CDCl_3$) 1.40 (s, 9H), 1.47−1.77 (m, 4H), 2.52−2.59 (m, 1H), 2.90−3.01 (m, 2H), 3.25−3.46 (m, 3H), 4.53−4.61 (m, 1H), 5.49 (br d, *J* 8.6, 1H), 7.16−7.28 (m, 5H); δ_C (100 MHz, $CDCl_3$) 24.0, 25.7, 28.3, 40.2, 45.7, 46.2, 53.6, 79.5, 126.8, 128.3, 129.4, 136.6, 155.1, 170.0; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 10.09 min (4%), t_R (L) = 13.21 (96%).

*Benz-L-Alanine-pyrrolidine amide (**6k**).* White solid (118 mg, 49%): mp 89−91 °C (PE/EtOAc); ν_{max} (solid/cm^{-1}) 3301 (N−H), 3061, 2975, 2877 (C−H), 1724 (C═O), 1629 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42(d, *J* 6.8, 3H), 1.81−1.89 (m, 2H), 1.96 (quintet, *J* 6.7, 2H), 3.39−3.54 (m, 3H), 3.65 (dt, *J* 10.1, 6.7, 1H), 4.90 (quintet, *J* 7.0, 1H), 7.34−7.40 (m, 2H), 7.41−7.47 (m, 2H), 7.77−7.81 (m, 2H); δ_C (100 MHz, $CDCl_3$) 18.3, 24.1, 26.0, 46.1, 46.4, 47.3, 127.1, 128.4, 131.5, 134.1, 166.4, 171.0; Found (ES) $[M - H]^+$ 245.1290 $C_{14}H_{17}N_2O_2$, requires 245.1291; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 17.08 min (2%), t_R (L) = 28.56 min (98%).

*Benz-L-Alanine-thiomorpholine amide (**6l**).* White solid (120 mg, 45%): mp 137−138 °C (PE/EtOAc); ν_{max} (solid/cm^{-1}) 3310 (N−H), 3059, 2981, 2918 (C−H), 1631 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42 (d, *J* 6.8, 3H), 2.52−2.77 (m, 4H), 3.69−3.80 (m, 2H), 3.89 (ddd, *J* 2.8, 6.6, 14.0, 1H), 4.04 (ddd, *J* 2.8, 6.6, 13.3, 1H), 5.07 (quintet, *J* 7.0, 1H), 7.37−7.51 (m, 4H), 7.78−7.83 (m, 2H); δ_C (100 MHz, $CDCl_3$)19.1, 27.4, 27.9, 44.9, 45.6, 48.2, 127.1, 128.5, 131.6, 134.0, 166.4, 171.1; Found (ES) $[M - H]^+$ 277.1011 $C_{14}H_{17}N_2O_2S$, requires 277.1011; HPLC (hexane/*i*-PrOH 90:10, 0.5 mL/min, Chiralcel Daicel OD) t_R (D) = 24.26 min (4%), t_R (L) = 34.28 min (96%).

*(S)-N-Benzyl-2-(4-isobutylphenyl)propanamide (**6m**).*[9i] Yellow solid (294 mg, 98%): mp 77−78 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +7.2 (*c* 0.88, CH_2Cl_2) [lit.[9i] $[\alpha]_D^{20}$ +7.1 (*c* 0.88, CH_2Cl_2)]; ν_{max} (solid/cm^{-1}) 3304 (N−H), 2949, 2866 (C−H), 1638 (C═O); δ_H (600 MHz, $CDCl_3$) 0.90 (d, *J* 6.6, 6H), 1.55 (d, *J* 7.2, 3H), 1.85 (app nonet, *J* 6.8, 1H), 2.45 (d, *J* 7.0, 2H), 3.58 (q, *J* 7.2, 1H), 4.37 (dd, *J* 15.1, 5.7, 1H), 4.41 (dd, *J* 15.1, 5.8, 1H), 5.66 (br s, 1H), 7.10−7.14 (m, 4H), 7.19−7.29 (m, 5H); δ_C (150 MHz, $CDCl_3$) 18.6, 22.5, 30.3, 43.5, 45.1, 46.6, 127.3, 127.41, 127.43, 128.6, 129.6, 138.7, 138.8, 140.6, 174.7; HPLC (hexane/*i*-PrOH 100:0, 0.5 mL/min, Chiralcel Daicel AD) t_R (S) = 5.01 min (>99%), t_R (R) = 7.41 min (<1%).

*N-Benzylformamide (**7a**).*[72] Mixture of rotamers (1:0.16). Data for major rotamer reported. White solid (139 mg, 98%): mp 63−64 °C (CH_2Cl_2) [lit.[72] 60−62 °C]; ν_{max} (solid/cm^{-1}) 3269 (N−H), 3089, 3056, 2925, 2886 (C−H), 1637 (C═O); δ_H (500 MHz, $CDCl_3$) 4.41 (d, *J* 6.0, 2H), 6.41 (br s, 1H), 7.20−7.28 (m, 3H) 7.29−7.37 (m, 2H), 8.17 (s, 1H); δ_C (125 MHz, $CDCl_3$) 42.3, 127.8, 127.9, 128.9, 137.6, 161.1.

*N-Phenethylformamide (**7b**).*[35] Mixture of rotamers (1:0.22). Data for major rotamer reported. Colorless oil (152 mg, 99%): ν_{max} (film/cm^{-1}) 3273 (N−H), 3061, 3028, 2934, 2866 (C−H), 1656 (C═O); δ_H (400 MHz, $CDCl_3$, 58 °C) 2.84 (t, *J* 7.1, 2H), 3.55 (app q, *J* 6.7, 2H), 5.96 (br s, 1H), 7.14−7.26 (m, 3H), 7.27−7.34 (m, 2H), 8.09 (s, 1H); δ_C (100 MHz, $CDCl_3$, 58 °C) 35.5, 39.2, 126.5, 128.59, 128.63, 138.6, 161.1.

*N-(4-Methoxybenzyl)formamide (**7c**).*[73] Mixture of rotamers (1:0.17). Data for major rotamer reported. Yellow solid (101 mg, 61%): mp 81−83 °C (CH_2Cl_2) [lit.[73] 79−80 °C]; ν_{max} (solid/cm^{-1}) 3283 (N−H), 3010, 2933, 2891 (C−H), 1642 (C═O); δ_H (600 MHz, $CDCl_3$) 3.77 (s, 3H), 4.37 (d, *J* 5.9, 2H), 6.11 (br s, 1H), 6.83−6.86 (m, 2H), 7.17−7.20 (m, 2H), 8.18 (s, 1H); δ_C (150 MHz, $CDCl_3$) 41.7, 55.4, 114.2, 129.2, 129.9, 159.1, 161.3.

*(R)-N-(1-Phenylethyl)formamide (**7d**).*[74] Mixture of rotamers (1:0.19). Data for major rotamer reported. Pale yellow oil (129 mg, 85%): $[\alpha]_D^{25}$ +160.9 (*c* 0.52, $CHCl_3$) [lit.[74] $[\alpha]_D^{20}$ +161.4 (*c* 0.50, $CHCl_3$)]; ν_{max} (film/cm^{-1}) 3270 (N−H), 3032, 2977, 2931, 2829 (C−H), 1653 (C═O); δ_H (500 MHz, $CDCl_3$) 1.45 (d, *J* 6.9, 3H), 5.13 (app quintet, *J* 7.2, 1H), 6.71 (br s, 1H), 7.21−7.35 (m, 5H), 8.04 (s, 1H); δ_C (125 MHz, $CDCl_3$) 22.0, 47.7, 126.2, 127.4, 128.7, 143.0, 160.7; Found (EI) $[M]^+$ 149.0833 $C_9H_{11}ON$, requires 149.0835.

*N-(Cyclohexylmethyl)formamide (**7e**).* Mixture of rotamers (1:0.25). Data for major rotamer reported. Colorless oil (135 mg, 96%): ν_{max} (film/cm^{-1}) 3280 (N−H), 3060, 2922, 2851 (C−H), 1657 (C═O); δ_H (600 MHz, $CDCl_3$) 0.77−0.88 (m, 2H), 1.00−1.18 (m, 3H), 1.34−1.42 (m, 1H), 1.53−1.68 (m, 5H) 3.01 (t, *J* 6.6, 2H), 6.71 (br s, 1H), 8.06 (s, 1H); δ_C (150 MHz, $CDCl_3$) 25.8, 26.4, 30.8, 37.8, 44.4, 161.8; Found (EI) $[M + H]^+$ 142.1227 $C_8H_{16}NO$, requires 142.1226.

*N-Cyclohexylformamide (**7f**).*[35] Mixture of rotamers (1:0.30). Data for major rotamer reported. Brown oil (95 mg, 78%): ν_{max} (film/cm^{-1}) 3268 (N−H), 3050, 2929, 2854 (C−H), 1652 (C═O); δ_H (500 MHz, $CDCl_3$) 1.09−1.39 (m, 5H), 1.53−1.63 (m, 1H), 1.64−1.76 (m, 2H), 1.82−1.95 (m, 2H), 3.78−3.86 (m, 1H), 5.78 (br s, 1H), 8.07 (s, 1H); δ_C (125 MHz, $CDCl_3$) 24.8, 25.5, 33.1, 47.1, 160.5.

*N-Butylformamide (**7g**).* Mixture of rotamers (1:0.23). Data for major rotamer reported. Yellow oil (31 mg, 30%): ν_{max} (film/cm^{-1}) 3280 (N−H), 3058, 2959, 2933, 2868 (C−H), 1655 (C═O); δ_H (500 MHz, $CDCl_3$) 0.90 (t, *J* 7.2, 3H), 1.33 (sext, *J* 7.2, 2H), 1.48 (quintet, *J* 7.2, 2H), 3.26 (q, *J* 6.7, 2H), 5.95 (br s, 1H), 8.12 (s, 1H); δ_C (125 MHz, $CDCl_3$) 13.7, 20.0, 31.5, 37.9, 161.5; Found (EI) $[M]^+$ 101.0827 $C_5H_{11}ON$, requires 101.0835.

*N-Phenylformamide (**7h**).*[75] Mixture of rotamers (1:0.93). Data for major rotamer reported. Yellow oil (25 mg, 21%): ν_{max} (film/cm^{-1}) 3273 (N−H), 3066, 2923, 2854 (C−H), 1682 (C═O); δ_H (600 MHz, $CDCl_3$) 7.08−7.11 (m, 1H), 7.19 (t, *J* 7.5, 1H), 7.31−7.38 (m, 2H), 7.53−7.56 (m, 1H), 8.41 (br s, 1H), 8.71 (d, *J* 11.3, 1H); δ_C (150 MHz, $CDCl_3$) 118.9, 125.4, 129.9, 136.8, 162.8.

*1-Indolinecarbaldehyde (**7i**).*[76] Mixture of rotamers (1:0.22). Data for major rotamer reported. Brown solid (55 mg, 38%): mp 56−58 °C (CH_2Cl_2) [lit.[76] 58−61 °C]; ν_{max} (solid/cm^{-1}) 3053, 2960, 2921, 2854 (C−H), 1656 (C═O); δ_H (600 MHz, $CDCl_3$) 3.14 (2H, t, *J* 8.6), 4.05 (2H, app td, *J* 8.5, 0.9), 7.04 (1H, td, *J* 7.2, 1.5), 7.14−7.22 (2H, m), 7.24 (1H, d, *J* 7.2) 8.92 (1H, s); δ_C (150 MHz, $CDCl_3$) 27.3, 44.8, 109.5, 124.4, 126.2, 127.7, 132.1, 141.2, 157.7.

*3,4-Dihydro-2(1H)-isoquinolinecarbaldehyde (**7j**).*[77] Mixture of rotamers (1:0.60). Data for major rotamer reported. Pale yellow oil (119 mg, 71%): ν_{max} (film/cm^{-1}) 3056, 3026, 2929, 2886 (C−H), 1646 (C═O); δ_H (500 MHz, $CDCl_3$) 2.87 (t, *J* 5.9, 2H), 3.60 (t, *J* 5.9, 2H), 4.65 (s, 2H), 7.05−7.19 (m, 4H), 8.16 (s, 1H); δ_C (125 MHz, $CDCl_3$) 29.8, 42.4, 43.3, 126.70, 126.71, 126.8, 129.0, 131.8, 133.7, 161.8.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C NMR and HPLC spectra are provided. 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.

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