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Catalyst-Free, Metal-Free, and Chemoselective Transamidation of Activated Secondary Amides

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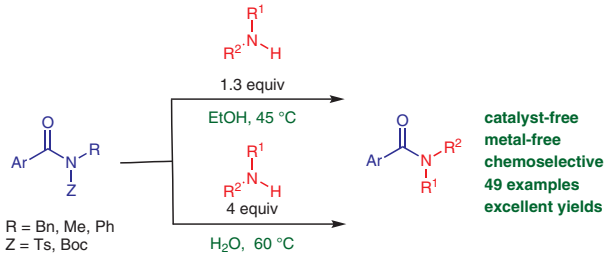

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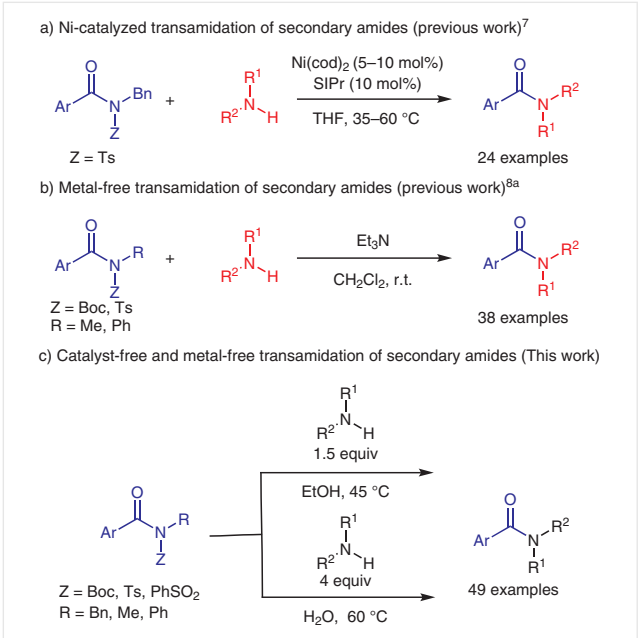
Abstract A simple protocol, which is catalyst-free, metal-free, and chemoselective, for transamidation of activated secondary amides in ethanol as solvent under mild conditions is reported. A wide range of amines, amino acids, amino alcohols, and the substituents, which are problematic in catalyzed transamidation, are tolerated in this methodology. The transamidation reaction was successfully extended to water as the medium as well. The present methodology appears to be better than the other catalyzed transamidations reported recently.

Keywords amino acid, catalyst-free, metal-free, chemoselective, secondary amide, transamidation

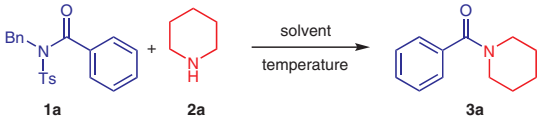
The interconversion of one amide to another amide is known as the transamidation reaction. The transamidation reactions are one of the most fundamental transformations in synthetic organic chemistry because amides are ubiquitous in nature and are most important functional molecules in industry.[1] However, the notorious stability[2] of the amide group is a major challenge arising out of the high kinetic barrier, the thermodynamic factor to break the C–N bond, and the resonance stabilization of the amide group.[3] In spite of this, notable headway has been made with transamidation of primary amides.[4] Recently several successful attempts have been reported for transamidation reactions of secondary amides.[5] The Lewis acid catalyzed transamidation reaction of secondary amide is accomplished by the activation of the amide carbonyl group.[6] Gellman and co-workers reported the use of dimeric aluminum complex[6a] and Bertrand reported the use of excess $AlCl_3$ for simple substrates.[6b] Garg and co-workers achieved transamidation of Boc-activated aliphatic and aryl substituted secondary amides in a two-step process using nickel catalysis (Scheme 1a).[7] More recently, a metal-free transamidation involving triethylamine[8a,b] and a Pd-NHC complex-mediated[8c] transamidation of secondary amides were reported by Szostak (Scheme 1b).[8] Despite these reports, a more general approach to the problem of transamidation has remained a challenge and a more sustainable green methodology is warranted. Herein, we describe the results of a successful approach and report a highly selective methodology for transamidation of secondary amides under catalyst-free conditions in ethanol or water as solvent (Scheme 1c). The N-functionalized substrates with appropriate activating groups such as Boc or Ts or aryl sulfonyl groups generally undergo an efficient transamidation reaction smoothly (Scheme 1c).[9]



Scheme 1 Transamidation of secondary amides

Initially, when the transamidation was performed with activated secondary benzamide **1a** (1 equiv) and piperidine (**2a**; 1.3 equiv) at room temperature there was no reaction in ethanol or dichloromethane (Table 1, entries a, b) even after 24 hours. The above reaction performed at 45 °C in dichloromethane gave the transamidation product **3a** in 68% yield after 12 hours (entry c). Encouraged by this initial result, the reaction was tested in other solvents like toluene and THF at higher temperatures (45–80 °C) and the product **3a** was obtained in moderate yields (entries d, e). Interestingly, the transamidation reaction was found to occur when performed in water at 60 °C, affording the secondary amide **3a** in 58% yield (entry f). Finally, when the transamidation reaction was performed in ethanol at 45 °C it gave an excellent yield (99%) of **3a** in 1.5 hours (entry g). It is pertinent to point out that the reaction of unactivated amides like *N*-benzyl-*N*-methylbenzamide with piperidine under the same reaction conditions does not provide any transamidation product.

Table 1 Optimization of Reaction Conditions[a]

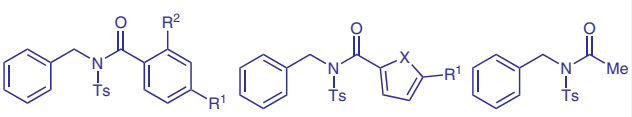


1a **2a** **3a**

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
a	EtOH	r.t.	24	0
b	CH_2Cl_2	r.t.	24	0
c	CH_2Cl_2	45	12	68
d	toluene	45	12	61
e	THF	80	24	59
f	H_2O	60	12	58[c]
g	**EtOH**	**45**	**1.5**	**99**

[a] Reaction conditions: activated secondary amide substrate **1a** (1 equiv), amine (1.3 equiv), EtOH (1 mL).
[b] Isolated yields.
[c] Reaction was performed with activated secondary amide substrate **1a** (1 equiv) and amine (1.3 equiv) in H_2O (1 mL).

With optimized conditions in hand, the scope and generality of the transamidation protocol were explored with a variety of primary and secondary amine partners with different activated amides **1** (Figure 1, Scheme 2). The cyclic secondary amines such as pyrrolidine and morpholine could be utilized for the transamidation reaction with **1a** to furnish the corresponding products **3b** and **3c**, respectively, in excellent yields (97% and 99%). Substrates with electron-donating substituents on the aryl ring of activated secondary amides **1b**,**c** readily undergo transamidation to give products **3d**,**e** in excellent yields. Interestingly, this green protocol tolerates several functional groups such as bromo and iodo that would be problematic substrates in the metal-catalyzed transamidation to form **3f–i**.[8,10] Further, the N-activated heterocyclic secondary amides **1f–h** also furnished the corresponding transamidation products **3j–l** in excellent yields. The reaction of secondary amide with *N*-methylaniline also gave the transamidation product **3m** in 95% yield.



1a, R^1 = H, R^2 = H
1b, R^1 = Me, R^2 = H
1c, R^1 = OMe, R^2 = H
1d, R^1 = Br, R^2 = H
1e, R^1 = H, R^2 = I

1f, R^1 = H, X = O
1g, R^1 = H, X = S
1h, R^1 = Br, R^2 = S

1i

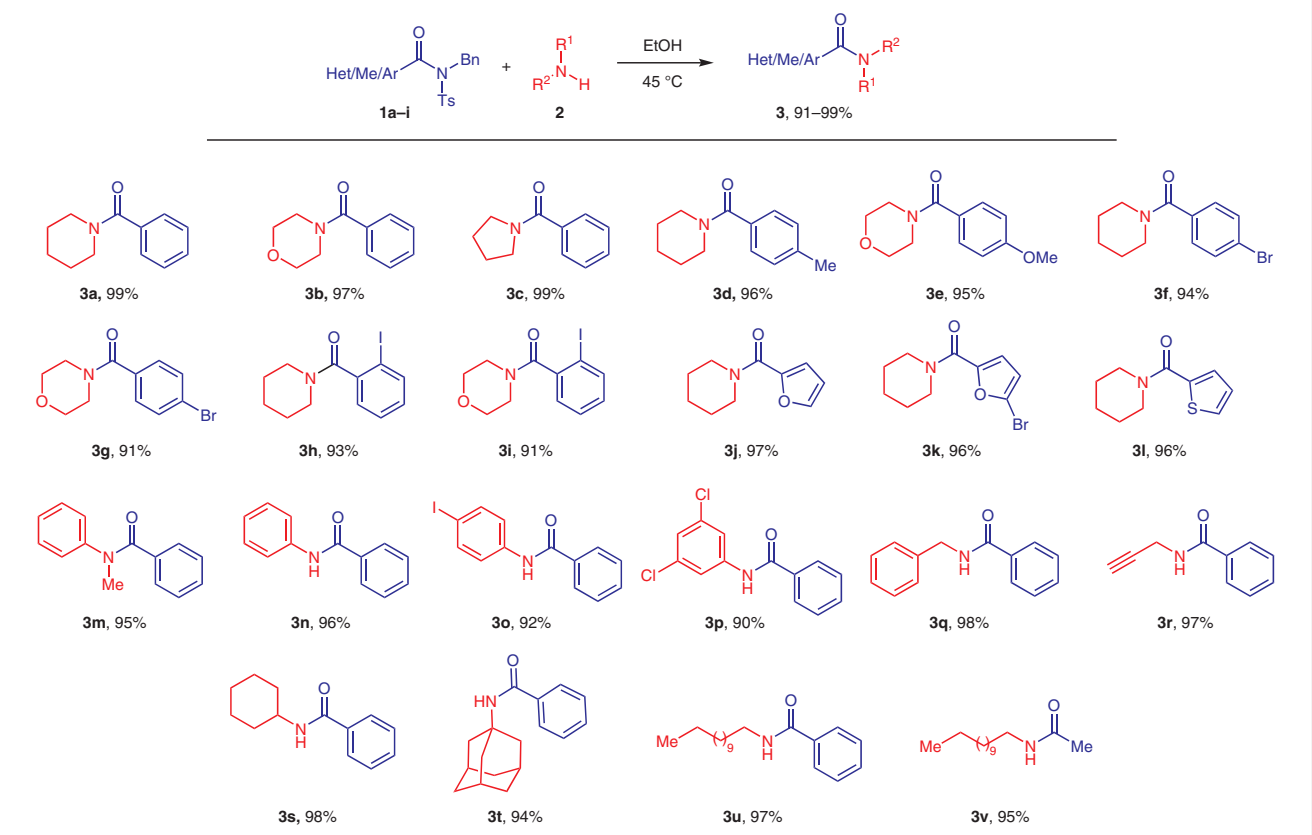
Figure 1 Activated amides used in this work

Further, we examined the scope of reaction with different anilines as shown by the formation of secondary amides **3n–p**. In all the cases, the reactions occur very smoothly without affecting the yield.[8] Reaction of benzylamine with activated amide **1a** also furnished the secondary amide **3q** in high yield. Additionally, propargylamine could also be used to form the secondary amide **3r** in 97% yield. Cyclohexylamine or hindered 1-adamantylamine also undergo smooth transamidation with **1a** to furnish the corresponding secondary amides **3s**,**t** in 98% and 94% yield, respectively. The results of this study are summarized in Scheme 2.

The scope of this methodology was then extended to tosyl-activated *N*-methylamide derivatives **4** with piperidine and α-branched amines. The amide substrates **4a**,**b** containing either electron-donating substituents or electron-withdrawing substituents on the aryl ring furnish the corresponding amides **5a**,**b** in excellent yields. α-Branched amine such as isopropylamine and primary amine like *n*-butylamine also react with amide **4c** leading to the formation of the desired secondary amides **5c**,**d** in high yields (Scheme 3).

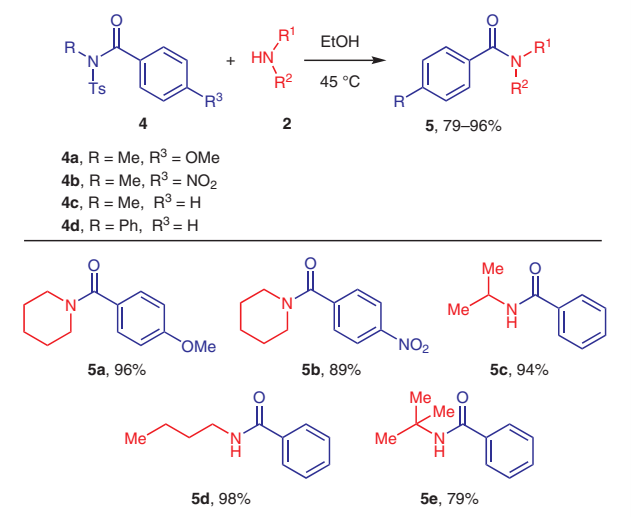
It was of interest to study the reaction of amides activated with N-Boc group in the transamidation reaction. Reaction of N-Boc-activated amides **6a**,**b** with secondary or primary amines was explored in ethanol at 45 °C and the results are presented in the Scheme 4. The reactions generally yielded the expected products **7a–f** in almost quantitative yield.

To evaluate the efficiency of this protocol, the transamidation of activated secondary amide substrate **1a** was performed with amino acid and amino alcohol derived nucleophiles. All the nucleophiles derived from amino acids, phenylalanine, alanine, and methionine, and the amino alcohols could be utilized for the reaction, leading to the corresponding secondary amides **8a–d**, respectively in high yields (Scheme 5). It is of interest to note that the reaction is chemoselective in that only N-nucleophiles react in the

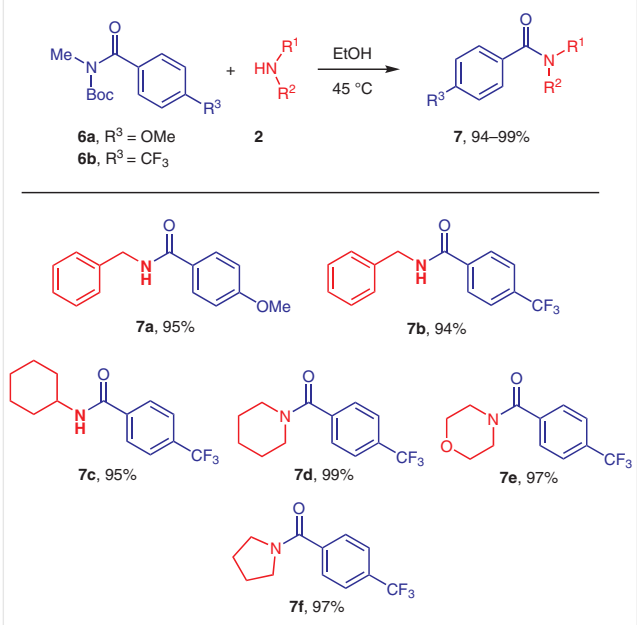


Scheme 2 Transamidation of tosyl-activated *N*-benzylamide **1** with various amines **2**. *Reagents and conditions*: activated secondary amide substrate **1a** (1 equiv), amine (1.3 equiv), EtOH (1 mL). Isolated yields are shown.

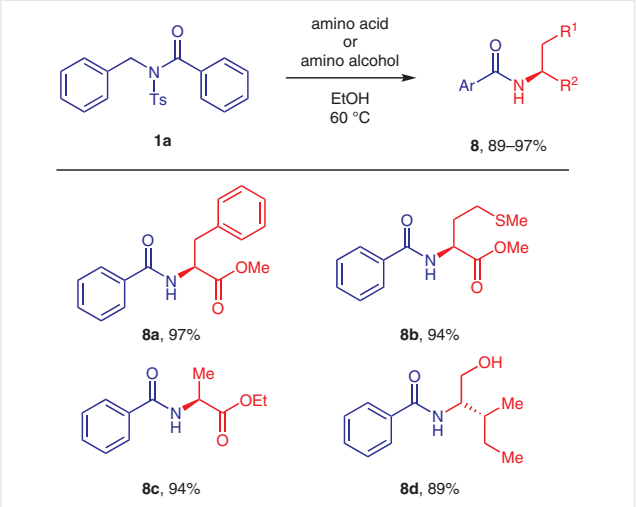
presence of O-nucleophiles in amino alcohols. This selectivity is not known with nickel-catalyzed[7] transamidation reactions.



Scheme 3 Transamidation of tosyl-activated *N*-methylamide **4** with amines **2**. *Reagents and conditions*: activated secondary amide substrate **5** (1 equiv), amine (1.3 equiv), EtOH (1 mL). Isolated yields are shown.

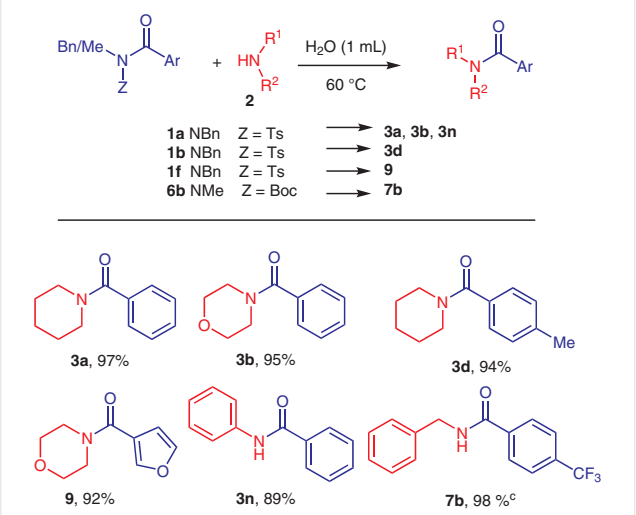


Scheme 4 Transamidation of Boc-activated *N*-methylamide **6** with amines **2**. *Reagents and conditions*: Boc-activated secondary amide **7** (1 equiv), amine (1.3 equiv), EtOH (1 mL). Isolated yields are shown.



Scheme 5 Transamidation of Ts-activated *N*-benzylamide **1a** with amino acids and amino alcohols. *Reagents and conditions*: amide **1a** (1 equiv), amino acid, or amino alcohol (1.5 equiv), EtOH (1 mL) at 60 °C. Isolated yields are shown.

At this stage, we decided to test the feasibility of this transamidation in water. Our initial studies with **1a** and piperidine (1.5 equiv) in water gave only 58% the product **3a**. When the stoichiometry of the amine was increased to 4 equivalents at 60 °C, the yield of the product **3a** went up to to 97%. Some of the successful experiments in water are presented in Scheme 6.



Scheme 6 Transamidation of activated secondary amides in water. *Reagents and conditions*: Amide **1a–b,f** (1 equiv), amine **2** (4 equiv), H_2O (1 mL) at 60 °C; amide **6b** (1 equiv), amine **2** (4 equiv), H_2O (1 mL) at 60 °C. Isolated yields are shown.

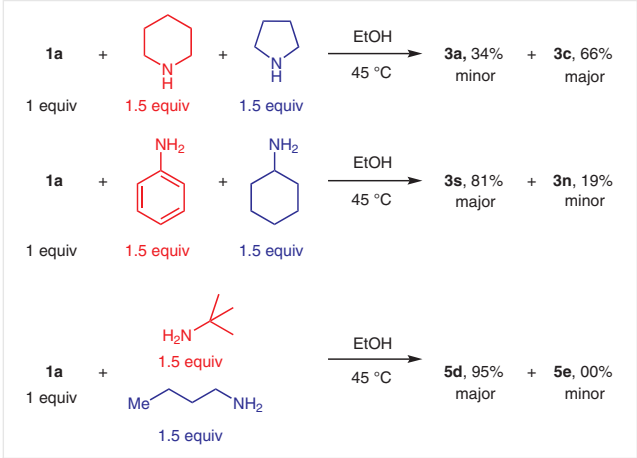
Having successfully carried out many transamidation reactions under catalyst-free, metal-free conditions, we decided to compare our results with similar transamidation reaction reported in the literature recently under nickel-catalyzed[7] condition as well the reaction performed in the presence of triethylamine.[8]

The Boc-activated amide **11a** on transamidation with sterically hindered 1-adamantylamine and 2,6-dimethylaniline in Et_3N is reported to give no product while under Ni-catalyzed condition[7] gave 58% and 49% of corresponding amides (**3t** and **12a**). Under our reaction condition both the amines reacted with **11a** to give 73% and 69% yield of products (Table 2, entries 1, 2). While the reaction of benzylamine and morpholine with **11b** has not been reported under nickel catalysis,[7] under Et_3N catalysis benzylamine afforded excellent yield of the product **12b** (Table 2, entries 3,4).[8] In the present protocol, both the amines react with **11b** to give higher yield of the transamidation products **3g** and **12b**.

Verho reported[11] a protocol where they find that the reaction of **10** with (*R*)-1-methylbenzylamine (5 equiv) gave the corresponding amide in 52% yield after 24 hours. However, using our methodology the same reaction of **10** with chiral amine (*R*)-1-methylbenzylamine (1.5 equiv) gave the product **12c** without loss of optical purity in 88% yield in 6 hours (Table 2, entry 5). Thus our methodology appears to be as good as the other reported transamidations in the literature and in some cases better.

Mechanistic Studies

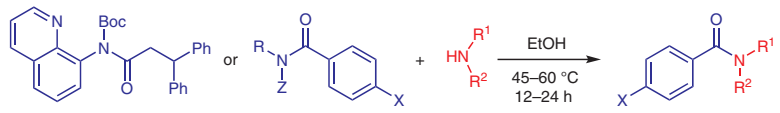
A series of competitive experiments were performed using N-activated amide **1a** with various amine nucleophiles to identify the selectivity patterns of the transamidation (Scheme 7). To study the effect of ring size, we compared the reaction of cyclic amines piperidine and pyrrolidine with **1a**. The major product obtained was **3c** (reaction with pyrrolidine) in 66% yield while **3a** was found to be the minor product.



Scheme 7 Competitive reactivity of various amines

The reaction of aryl- versus alkylamine was tested by the reaction of aniline and cyclohexylamine with **1a**. The product **3s** derived from cyclohexylamine was found to be

Table 2 Comparison Table of Transamidation of *N*-Activated 2° Amides Using [Ni] Catalysis, Metal-Free Conditions and Our Protocol[a]



10 **11** **2** **3g,t** and **12a–c**

11a: R = Bn; Z = Boc; X = H
11b: R = Bn; Z = Boc; X = Br

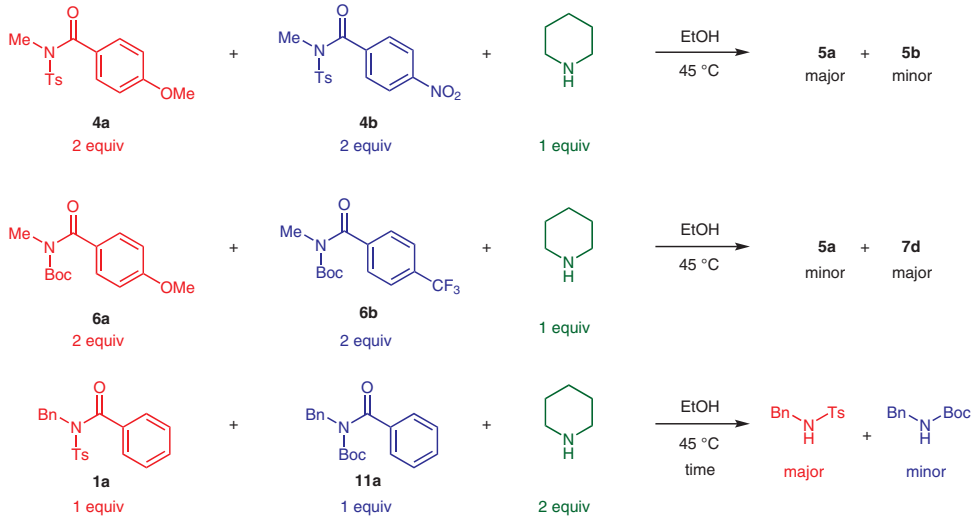
Entry	Amide	Amine	Product	Ni catalyst[7]	Et_3N[8]	Metal-free[11]	Our work[b]
1	**11a**	1-adamantylamine	**3t**	58	no reaction	not reported	**73**
2	**11a**	2,6-dimethylaniline	**12a**	49	no reaction	not reported	**69**
3	**11b**	benzylamine	**12b**	not reported	98	not reported	96
4	**11b**	morpholine	**3g**	not reported	not reported	not reported	78
5	**10**	(*R*)-1-methylbenzylamine[c]	**12c**	not reported	not reported	52	**88**

[a] Reaction conditions: Amide **11** (1 equiv), amine **2** (1.3 equiv), EtOH (1 mL) at 45–60 °C.
[b] Isolated yields.
[c] Amide **10** (1 equiv), amine **2** (1.5 equiv), EtOH (1 mL) at 60 °C, 6 h.

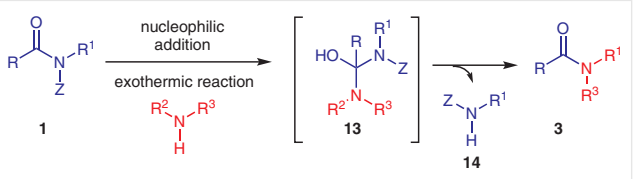
the major product (81%). The involvement of the steric factors in the reaction was tested using *n*-butylamine and *tert*-butylamine as partners for transamidation. The only product obtained in this case was the amide **5d** resulting from the reaction of *n*-butylamine.

The study of selectivity and reactivity of Ts- and Boc-activated amides containing electron-donating or electron-withdrawing substituents with piperidine was carried out (Scheme 8). When a 1:1 mixture of Ts-activated amides **4a** and **4b** was treated with piperidine (EtOH, 45 °C, 1.5 h) the major product was found to be **5a**. Similarly, the reaction of a 1:1 mixture of Boc-activated amides **6a** and **6b** with piperidine gave **7d** as the major product. Additionally we tested the competitive reactivity of Ts-activated amide **1a** and Boc-activated amide **11a** with piperidine at different time intervals. The amide **11a** started to react with piperidine only after 1 hour but **1a** was already fully consumed. It shows that N-Ts-activated amide **1a** reacts faster than Boc-activated amide **11a**.

Based on the above observations we propose a reaction mechanism, which is similar to the one proposed by Szostak.[8a,b] The transamidation of secondary amides is achieved by exothermic nucleophilic addition of amine to form intermediate **13**. Subsequent release of the N-functionalized amine **14**, which is less nucleophilic than the amine involved in the transamidation reaction leads to the formation of product **3** (Scheme 9).



Scheme 8 Competition studies with N-Ts- and N-Boc-activated amides



Scheme 9 Proposed Mechanism

Conclusion

In summary, we have developed a simple protocol for the transamidation of a number of activated secondary amides using a broad range of amines in ethanol as solvent under catalyst-free and metal-free conditions. We have also extended the scope of the transamidation to water medium. This effective procedure is highly chemoselective as shown in the reaction of amino acid and amino alcohols. The stereochemical integrity of the amino acid and amino alcohol derivatives is preserved in the reaction. The present methodology appears to be better than other catalyzed transamidations reported in the literature recently.

Melting points were determined using a capillary melting point apparatus and are uncorrected. All the transamidation reactions were performed using sealed vial under air atmosphere, unless stated otherwise. The starting materials were prepared based on the previously reported literature method. The solvents purchased were of the laboratory grade (LR) and used as received or purified by distillation following standard procedure. All other chemicals were purchased from Sigma-Aldrich, Alfa Acer, and TCI. ^{1}HNMR spectra were recorded on a Bruker Avance at 400 MHz using $CDCl_3$ or DMSO-d_6 in ppm (δ) related to TMS (δ = 0.00) as an internal standard and are reported as follows; chemical shift (ppm), multiplicity (standard abbreviations), coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.7 ppm for $CDCl_3$ or 39.5 ppm for DMSO-d_6. Carbon types were determined from ^{13}C NMR and DEPT experiments. Mass spectra were measured with Micromass Q-Tof (ESI-HRMS). Optical rotations were measured on JASCO P-2000 polarimeter at r.t. using 50 mm cell of 1 mL capacity. TLC was performed on silica gel GF-254 and components visualized by observation under I_2/UV light at 254 nm. Column chromatography was performed on silica gel (230–400 mesh).

N-Ts-Activated Secondary Amides; General Procedure

An oven-dried 100 mL round-bottomed flask was charged with *N*-benzyl-4-methylbenzenesulfonamide (1.0 mmol, 1.0 equiv), and NaH (1.5 mmol, 1.5 equiv) in anhyd THF (20 mL). A solution of the respective acyl chloride (1.0 mmol, 1.0 equiv) in anhyd THF (10 mL) was added at 0 °C. The reaction mixture was stirred at r.t. (25 °C) for 3 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was quenched with H_2O and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4), and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/PE) to afford the desired *N*-tosyl-activated secondary amide.

N-Benzyl-*N*-tosylbenzamide (1a)[12]

Eluent: PE/EtOAc (90:10); white solid; yield: 1.29 g (92%); mp 95–97 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H, CH_3), 5.01 (s, 2 H, CH_2), 7.21–7.26 (m, 7 H, ArH), 7.34 (t, *J* = 7.2 Hz, 2 H, ArH), 7.46 (t, *J* = 7.6 Hz, 3 H, ArH), 7.63 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.61, 51.25, 127.75, 127.91, 128.18, 128.50, 128.55, 129.37, 130.14, 131.70, 133.72, 134.90, 135.85, 136.21, 144.70, 171.56.

N-Benzyl-4-methyl-*N*-tosylbenzamide (1b)[12]

Eluent: PE/EtOAc (90:10); colorless oil; yield: 256 mg (88%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 4.94 (s, 2 H, CH_2), 7.14 (d, *J* = 8.0 Hz, 2 H, ArH), 7.19–7.25 (m, 7 H, ArH), 7.41 (d, *J* = 7.6 Hz, 2 H, ArH), 7.60 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.56, 21.59, 51.32, 127.68, 127.93, 128.47, 128.50, 128.60, 128.86, 129.33, 132.05, 135.89, 136.18, 142.61, 144.54, 171.65.

N-Benzyl-4-methoxy-*N*-tosylbenzamide (1c)

Eluent: PE/EtOAc (85:15); white solid; yield: 269 mg (89%); mp 121–123 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.40 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 4.88 (s, 2 H, CH_2), 6.84 (d, *J* = 8.8 Hz, 2 H, ArH), 7.21–7.24 (m, 7 H, ArH), 7.56 (d, *J* = 8.8 Hz, 2 H, ArH), 7.61 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.58, 51.33, 55.40, 113.47, 127.12, 127.68, 128.02, 128.32, 128.49, 129.41, 131.26, 135.82, 136.12, 144.48, 162.89, 171.26.

HRMS: *m*/*z* calcd for $C_{22}H_{21}NO_4SNa$ [M + Na]$^+$: 418.1089; found: 418.1089.

N-Benzyl-4-bromo-*N*-tosylbenzamide (1d)

Eluent: PE/EtOAc (90:10); white solid; yield: 292 mg (86%); mp 131–133 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H, CH_3), 4.92 (s, 2 H, CH_2), 7.20–7.26 (m, 7 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH), 7.46 (d, *J* = 8.4 Hz, 2 H, ArH), 7.56 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.62, 50.98, 126.57, 127.86, 127.95, 128.33, 128.60, 129.51, 129.89, 131.37, 133.90, 135.60, 135.92, 144.91, 170.68.

HRMS: *m*/*z* calcd for $C_{21}H_{18}BrNO_3SNa$ [M + Na]$^+$: 466.0088; found: 466.0094.

N-Benzyl-2-iodo-*N*-tosylbenzamide (1e)

Eluent: PE/EtOAc (88:12); white solid; yield: 320 g (85%); mp 146–148 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (s, 3 H, CH_3), 4.93 (s, 2 H, CH_2), 7.23–7.33 (m, 9 H, ArH), 7.47 (d, *J* = 7.6 Hz, 2 H, ArH), 7.57 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.63, 51.01, 126.56, 127.27, 127.86, 127.96, 128.34, 128.39, 128.61, 129.53, 129.89, 129.99, 131.38, 133.91, 135.61, 135.95, 144.92, 170.67.

HRMS: *m*/*z* calcd for $C_{21}H_{18}INO_3SNa$ [M + Na]$^+$: 513.9950; found: 513.9947.

N-Benzyl-*N*-tosylfuran-2-carboxamide (1f)[12]

Eluent: PE/EtOAc (85:15); light yellow solid; yield: 242 mg (89%); mp 113–115 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.45 (s, 3 H, CH_3), 5.27 (s, 2 H, CH_2), 6.48 (d, *J* = 2.0 Hz, 1 H, ArH), 7.15 (d, *J* = 3.2 Hz, 1 H, ArH), 7.25–7.30 (m, 7 H, ArH), 7.52 (s, 1 H, ArH), 7.80 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.61, 50.49, 112.17, 120.42, 127.16, 127.58, 128.57, 128.80, 129.30, 135.86, 136.48, 144.73, 146.01, 146.53, 159.48.

N-Benzyl-*N*-tosylthiophene-2-carboxamide (1g)

Eluent: PE/EtOAc (85:15); white solid; yield: 259 mg 91%); mp 86–88 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H, CH_3), 5.06 (s, 2 H, CH_2), 6.98 (t, *J* = 4.4 Hz, 1 H, ArH), 7.25–7.29 (m, 7 H, ArH), 7.53 (d, *J* = 4.4 Hz, 2 H, ArH), 7.73 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.62, 51.66, 127.46, 127.48, 127.74, 128.65, 128.66, 129.44, 133.19, 133.33, 135.60, 136.14, 137.29, 144.73, 164.66.

HRMS: *m*/*z* calcd for $C_{19}H_{17}NO_3S_2Na$ [M + Na]$^+$: 394.0548; found: 394.0548.

N-Benzyl-5-bromo-*N*-tosylfuran-2-carboxamide (1h)

Eluent: PE/EtOAc (80:20); white solid; yield: 283 mg (85%); mp 119–121 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H, CH_3), 5.17 (s, 2 H, CH_2), 6.36 (d, *J* = 3.6 Hz, 1 H, ArH), 7.02 (d, *J* = 3.6 Hz, 1 H, ArH), 7.20–7.29 (m, 7 H, ArH), 7.78 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.64, 50.51, 114.23, 122.46, 127.24, 127.52, 127.64, 128.60, 128.74, 129.43, 135.66, 136.18, 144.89, 148.10, 158.30.

HRMS: *m*/*z* calcd for $C_{19}H_{16}BrNO_4SNa$ [M + Na]$^+$: 455.9881; found: 455.9881.

N-Benzyl-*N*-tosylacetamide (1i)[13]

Eluent: PE/EtOAc (90:10); colorless oil; yield: 195 mg (84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 5.11 (s, 2 H, CH_2) 7.29–7.36 (m, 6 H, ArH), 7.39 (t, *J* = 7.6 Hz, 2 H, ArH), 7.64 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.56, 24.86, 49.48, 127.71, 127.83, 127.93, 128.57, 128.66, 129.71, 136.49, 136.63, 144.88, 170.33.

4-Methoxy-*N*-methyl-*N*-tosylbenzamide (4a)[14]

Eluent: PE/EtOAc (90:10); white solid; yield: 785 mg (91%); mp 46–48 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (s, 3 H, CH_3), 3.24 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 7.89 (d, *J* = 7.6 Hz, 2 H, ArH), 7.32 (d, *J* = 7.6 Hz, 2 H, ArH), 7.61 (d, *J* = 7.6 Hz, 2 H, ArH), 7.84 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.61, 35.90, 55.44, 113.55, 126.24, 128.35, 129.57, 131.30, 134.97, 144.74, 162.91, 171.20.

N-Methyl-4-nitro-*N*-tosylbenzamide (4b)[14]

Eluent: PE/EtOAc (85:15); light yellow solid; yield: 794 mg (88%); mp 114–116 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.47 (s, 3 H, CH_3), 3.27 (s, 3 H, NCH_3), 7.36 (d, *J* = 8.4 Hz, 2 H, ArH), 7.69 (t, *J* = 9.6 Hz, 4 H, ArH), 8.26 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.67, 34.62, 123.32, 128.01, 129.16, 129.95, 134.55, 140.88, 145.59, 149.28, 169.55.

N-Methyl-*N*-tosylbenzamide (4c)[14]

Eluent: PE/EtOAc (85:15); white solid; yield: 672 mg (86%); mp 65–67 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (s, 3 H, CH_3), 3.27 (s, 3 H, NCH_3), 7.32 (d, 2 H, *J* = 8.0 Hz, ArH), 7.39 (t, 2 H, *J* = 7.6 Hz, ArH), 7.49 (dd, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1 H, ArH), 7.53 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2 H, ArH), 7.83 (d, *J* = 7.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.63, 35.61, 128.28, 128.38, 128.43, 129.61, 130.09, 131.94, 134.47, 135.18, 144.93, 171.45.

N-Phenyl-*N*-tosylbenzamide (4d)[8d]

Eluent: PE/EtOAc (85:15); white solid; yield: 2.44 g (86%); mp 151–153 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.43 (s, 3 H, CH_3), 7.14–7.15 (m, 3 H, ArH), 7.26–7.30 (m, 5 H, ArH), 7.42 (d, *J* = 7.2 Hz, 2 H, ArH), 7.82 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.67, 127.95, 129.01, 129.07, 129.22, 129.42, 130.35, 131.71, 133.60, 135.17, 137.36, 144.81, 169.87.

N-Boc-Activated Secondary Amides; General Procedure

To an oven-dried 100 mL round-bottomed flask containing a secondary amide substrate (1.0 mmol, 1.0 equiv) and DMAP (0.1 mmol, 0.1 equiv) in CH_2Cl_2 (20 mL) was added Boc_2O (1.3 mmol, 1.3 equiv) in one portion and the reaction mixture was allowed to stir at r.t. After the indicated time, the mixture was quenched with aq $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 20 mL). the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried (anhyd Na_2SO_4), and concentrated. The crude product was purified by column chromatography (EtOAc/PE) to afford the pure product.

tert-Butyl (4-Methoxybenzoyl)(methyl)carbamate (6a)[8d]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 715 mg (89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (s, 9 H, 3 × CH_3), 3.24 (s, 3 H, NCH_3), 3.81 (s, 3 H, OCH_3), 6.85 (d, *J* = 8.8 Hz, 2 H, ArH), 7.49 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.46, 32.75, 55.36, 82.58, 133.14, 129.69, 129.90, 153.77, 162.06, 173.13.

tert-Butyl Methyl[4-(trifluoromethyl)benzoyl]carbamate (6b)[8d]

Eluent: PE/EtOAc (90:10); white solid; yield: 627 mg (84%); mp 147–149 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 9 H, 3 × CH_3), 3.31 (s, 3 H, NCH_3), 7.57 (d, *J* = 8.0 Hz, 2 H, ArH), 7.64 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.33, 32.37, 83.63, 124.98, 127.40, 141.29, 152.92, 172.04.

tert-Butyl Benzoyl(benzyl)carbamate (11a)[8d]

Eluent: PE/EtOAc (90:10); colorless oil; yield: 1.31 g (89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.11 (s, 9 H, 3 × CH_3), 4.99 (s, 2 H, CH_2), 7.24 (t, *J* = 6.4 Hz, 1 H, ArH), 7.29–7.37 (m, 4 H, ArH), 7.42 (t, *J* = 6.0 Hz, 3 H, ArH), 7.50 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.31, 48.84, 83.10, 127.38, 127.44, 128.04, 128.14, 128.43, 131.02, 137.71, 137.86, 153.42, 173.03.

tert-Butyl Benzyl(4-bromobenzoyl)carbamate (11b)

Eluent: PE/EtOAc (90:10); colorless oil; yield: 504 mg (75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 9 H, 3 × CH_3), 4.95 (s, 2 H, CH_2), 7.25–7.27 (m, 2 H, ArH), 7.32 (t, *J* = 7.6 Hz, 2 H, ArH), 7.38 (t, *J* = 6.4 Hz, 3 H, ArH), 7.52 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.39, 48.88, 83.53, 125.51, 127.46, 128.06, 128.45, 129.02, 131.26, 136.40, 137.60, 153.16, 172.07.

HRMS: *m*/*z* calcd for $C_{19}H_{20}BrNO_3Na$ [M + Na]$^+$: 412.0524; found: 412.0527.

Transamidation of Activated Amides; General Procedure

The amide substrate **1**, **4**, **6**, **10**, or **11** (1.0 mmol, 1.0 equiv) and the respective amine **2** (1.3 mmol, 1.3 equiv) in EtOH (1 mL) were taken in a vial and the reaction mixture was stirred at 45 °C. The reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated in vacuo and the residue was purified by column chromatography using silica gel (EtOAc/PE) to give the corresponding transamidation product.

Phenyl(piperidin-1-yl)methanone (3a)[8d]

Eluent: PE/EtOAc (75:25); colorless oil; yield: 51.3 mg (99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.47 (s, 2 H, CH_2), 1.63 (s, 4 H, CH_2), 3.29 (s, 2 H, CH_2), 3.67 (s, 2 H, CH_2), 7.35 (d, *J* = 4.0 Hz, 5 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.51, 25.57, 26.46, 29.62, 43.03, 48.69, 126.70, 128.32, 129.27, 136.43, 170.22.

Morpholino(phenyl)methanone (3b)[8d]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 50.7 mg (97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.28–3.59 (m, 8 H, CH_2), 7.26 (d, *J* = 7.6 Hz, 5 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 42.45, 48.04, 66.66, 126.98, 128.12, 128.41, 129.75, 132.64, 135.12, 170.26.

Phenyl(pyrrolidin-1-yl)methanone (3c)[8d]

Eluent: PE/EtOAc (75:25); colorless oil; yield: 47.5 mg (99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.68–1.73 (m, 2 H, CH_2), 1.76–1.81 (m, 2 H, CH_2), 3.26 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.50 (t, *J* = 6.8 Hz, 2 H, CH_2), 7.23–7.25 (m, 3 H, ArH), 7.37–7.39 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.29, 26.22, 46.08, 49.49, 126.95, 128.03, 128.09, 129.67, 130.81, 132.43, 136.95, 169.60.

Piperidin-1-yl(*p*-tolyl)methanone (3d)[15]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 53.4 mg (96%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 2 H, CH_2), 1.59 (s, 4 H, CH_2), 2.29 (s, 3 H, CH_3), 3.29 (s, 2 H, CH_2), 3.63 (s, 2 H, CH_2), 7.12 (d, *J* = 6.8 Hz, 2 H, ArH), 7.22 (dd, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.29, 24.53, 25.59, 26.43, 43.11, 48.75, 126.83, 128.90, 133.40, 139.33, 170.44.

(4-Methoxyphenyl)(morpholino)methanone (3e)[16]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 53.1 mg (95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.66 (m, 8 H, CH_2), 3.79 (s, 3 H, OCH_3), 6.87–6.89 (m, 2 H, ArH), 7.34–7.36 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.31, 66.87, 113.72, 127.25, 129.15, 160.83, 170.35.

(4-Bromophenyl)(piperidin-1-yl)methanone (3f)[17]

Eluent: PE/EtOAc (85:15); white solid; yield: 56.5 mg (94%); mp 93–95 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.47 (s, 2 H, CH_2), 1.63 (s, 4 H, CH_2), 3.28 (s, 2 H, CH_2), 3.65 (s, 2 H, CH_2), 7.23 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2 H, ArH), 7.49 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.46, 25.55, 43.19, 48.72, 123.54, 128.52, 131.57, 135.25, 169.16

(4-Bromophenyl)(morpholino)methanone (3g)[16]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 55.3 mg (91%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.44–3.71 (m, 8 H, CH_2), 7.29 (d, *J* = 8.0 Hz, 2 H, ArH), 7.55 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 42.60, 48.09, 66.74, 124.14, 128.85, 131.75, 134.09, 169.25.

(2-Iodophenyl)(piperidin-1-yl)methanone (3h)[18]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 59.7 mg (93%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.41–1.71 (m, 6 H, CH_2), 3.08–3.21 (m, 2 H, CH_2), 3.65–3.79 (m, 2 H, CH_2), 7.03 (td, J_1 = 7.4 Hz, J_2 = 2.0 Hz, 1 H, ArH), 7.16 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1 H, ArH), 7.35 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H, ArH), 7.79 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.45, 25.36, 26.22, 42.46, 47.91, 92.47, 126.78, 128.27, 129.90, 139.13, 142.76, 169.14.

(2-Iodophenyl)(morpholino)methanone (3i)[19]

Eluent: PE/EtOAc (85:15); white solid; yield: 59.4 mg (91%); mp 82–84 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.15 (s, 1 H, CH_2), 3.22 (s, 1 H, CH_2), 3.55 (s, 1 H, CH_2), 3.72–3.79 (m, 5 H, CH_2), 7.04 (t, *J* = 7.6 Hz, 1 H, ArH), 7.16 (d, *J* = 7.2 Hz, 1 H, ArH), 7.35 (t, *J* = 7.2 Hz, 1 H, ArH), 7.89 (t, *J* = 7.6 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 41.95, 47.20, 66.52, 66.63, 92.38, 127.04, 128.45, 130.38, 139.20, 141.62, 169.38.

Furan-2-yl(piperidin-1-yl)methanone (3j)[20]

Eluent: PE/EtOAc (85:15); white solid; yield: 48.9 mg (97%); mp 46–48 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48–1.55 (m, 6 H, CH_2), 3.55 (s, 4 H, CH_2), 6.31–6.33 (m, 1 H, ArH), 6.79 (dd, J_1 = 3.4 Hz , J_2 = 0.8 Hz, 1 H, ArH), 7.34 (d, *J* = 0.8 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.51, 25.99, 29.52, 43.88, 47.57, 110.94, 115.38, 143.34, 147.94, 159.10.

(5-Bromofuran-2-yl)(piperidin-1-yl)methanone (3k)[21]

Eluent: PE/EtOAc (85:15); white solid; yield: 57.1 mg (96%); mp 53–55 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.61–1.69 (m, 6 H, CH_2), 3.65 (s, 4 H, CH_2), 6.37 (d, *J* = 3.6 Hz, 1 H, ArH), 6.88 (d, *J* = 3.6 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.57, 25.71, 29.65, 113.05, 118.03, 123.71, 149.85, 157.91.

Piperidin-1-yl(thiophen-2-yl)methanone (3l)[20]

Eluent: PE/EtOAc (85:15); white solid; yield: 50.9 mg (96%); mp 55–57 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.59–1.60 (m, 4 H, CH_2), 1.65–1.67 (m, 2 H, CH_2), 3.61–3.64 (m, 4 H, CH_2), 6.99 (td, J_1 = 4.0 Hz, J_2 = 0.8 Hz, 1 H, ArH), 7.22 (d, *J* = 3.2 Hz, 1 H, ArH), 7.38 (d, *J* = 5.2 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.56, 26.08, 26.29, 29.63, 126.49, 128.03, 128.20, 137.56, 163.41.

***N*-Methyl-*N*-phenylbenzamide (3m)**[15]

Eluent: PE/EtOAc (90:10); white solid; yield: 54.9 mg (95%); mp 61–63 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.46 (s, 3 H, CH_3), 6.99 (d, *J* = 7.6 Hz, 2 H, ArH), 7.11 (t, *J* = 8.0 Hz, 3 H, ArH), 7.16–7.17 (m, 3 H, ArH), 7.26 (d, *J* = 7.6 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 38.37, 126.47, 126.85, 127.68, 128.65, 129.10, 129.56, 135.82, 144.79, 170.68.

***N*-Phenylbenzamide (3n)**[7a]

Eluent: PE/EtOAc (70:30); brownish solid; yield: 51.8 mg (96%); mp 160–162 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (td, J_1 = 7.0 Hz, J_2 = 0.4 Hz, 1 H, ArH), 7.35 (t, *J* = 7.6 Hz, 2 H, ArH), 7.45 (t, *J* = 8.0 Hz, 2 H, ArH), 7.52 (td, J_1 = 7.4 Hz, J_2 = 0.4 Hz, 1 H, ArH), 7.63 (d, *J* = 8.0 Hz, 2 H, ArH), 7.85 (t, *J* = 7.6 Hz, 2 H, ArH), 7.98 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 120.26, 124.56, 127.02, 128.41, 128.73, 129.04, 130.12, 131.80, 134.91, 137.87, 165.87.

***N*-(4-Iodophenyl)benzamide (3o)**[22]

Eluent: PE/EtOAc (70:30); white solid; yield: 81.3 mg (92%); mp 214–216 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.46–7.41 (m, 2 H, ArH), 7.54–7.59 (m, 3 H, ArH), 7.65 (d, *J* = 8.8 Hz, 2 H, ArH), 7.89 (d, *J* = 7.2 Hz, 2 H, ArH), 10. 32 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 122.96, 128.05, 128.86, 128.99, 129.66, 132.17, 135.03, 137.69, 139.56, 166.15.

***N*-(3,5-Dichlorophenyl)benzamide (3p)**[23]

Eluent: PE/EtOAc (70:30); white solid; yield: 65.5 mg (90%); mp 148–150 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (td, J_1 = 7.4 Hz, J_2 = 0.4 Hz, 3 H, ArH), 7.61 (td, J_1 = 6.6 Hz, J_2 = 1.2 Hz, 2 H, ArH), 8.13 (dd, 3 H, J_1 = 7.8 Hz, J_2 = 1.2 Hz, ArH), 10.60 (br, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 128.46, 129.29, 130.18, 133.79, 172.42.

***N*-Benzylbenzamide (3q)**[8d]

Eluent: PE/EtOAc (75:25); white solid; yield: 56.6 mg (98%); mp 105–107 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.64 (d, *J* = 5.6 Hz, 2 H, ArH), 6.57 (s, 1 H, NH), 7.23–7.36 (m, 5 H, ArH), 7.42 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2 H, ArH), 7.50 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1 H, ArH), 7.80 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 44.08, 126.93, 127.58, 127.87, 128.55, 128.74, 131.52, 134.30, 138.14, 167.37.

***N*-(Prop-2-yn-1-yl)benzamide (3r)**[24]

Eluent: PE/EtOAc (85:15); colorless oil; yield: 42.7 mg (97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.22 (t, *J* = 2.4 Hz, 1 H, CH), 4.18 (dd, J_1 = 5.2 Hz, J_2 = 2.4 Hz, 2 H, CH_2), 7.01 (s, 1 H, NH), 7.35 (td, J_1 = 7.6 Hz, J_2 = 0.4 Hz, 2 H, ArH), 7.44 (td, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1 H, ArH), 7.78 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.66, 71.54, 79.66, 127.16, 128.48, 131.69, 133.67, 167.44

***N*-Cyclohexylbenzamide (3s)**[25]

Eluent: PE/EtOAc (80:20); white solid; yield: 54.2 mg (98%); mp 153–155 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13–1.26 (m, 3 H, CH_2), 1.34–1.44 (m, 2 H, CH_2), 1.63 (d, *J* = 12.8 Hz, 1 H, CH), 1.71–1.74 (m, 2 H, CH_2), 1.99 (d, *J* = 11.6 Hz, 2 H, CH_2), 3.91–3.98 (m, 1 H, CH), 6.06 (s, 1 H, NH), 7.36–7.74 (m, 2 H, ArH), 7.43–7.47 (m, 1 H, ArH), 7.73 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.91, 25.49, 33.10, 48.67, 126.85, 128.39, 131.12, 135.02, 166.65.

***N*-[(3s,5s,7s)-Adamantan-1-yl]benzamide (3t)**[7a]

Eluent: PE/EtOAc (80:20); white solid; yield: 65.7 mg (94%); mp 125–127 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.68 (s, 6 H), 2.09 (m, 9 H), 5.87 (s, 1 H, NH), 7.34 (t, *J* = 7.6 Hz, 2 H, ArH), 7.41 (t, *J* = 7.2 Hz, 1 H, ArH), 7.68 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.44, 36.32, 41.57, 52.20, 126.68, 128.35, 130.94, 135.95, 166.60.

***N*-Dodecylbenzamide (3u)**[8d]

Eluent: PE/EtOAc (90:10); white solid; yield: 73.4 mg (97%); mp 83–85 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.83 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.21–1.36 (m, 16 H, CH_2), 1.55–1.58 (m, 2 H, CH_2), 3.03 (q, *J* = 7.6; 7.2 Hz, 2 H, CH_2), 3.39 (q, *J* = 6.8; 6.4 Hz, 2 H, CH_2), 6.38 (s, 1 H, NH), 7.37 (t, *J* = 6.8 Hz, 2 H, ArH), 7.43 (d, *J* = 7.2 Hz, 1 H, ArH), 7.73 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): d = 08.55, 14.06, 22.62, 26.96, 29.28, 29.50, 29.53, 29.58, 31.85, 40.06, 45.74, 126.83, 128.42, 131.19, 134.80, 167.49.

***N*-Dodecylacetamide (3v)**[26]

Eluent: PE/EtOAc (90:10); white solid; yield: 71.2 mg (95%); mp 52–54 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84 (t, *J* = 6 Hz, 3 H, CH_3), 1.22–1.25 (m, 18 H, CH_2), 1.45 (t, *J* = 6.8 Hz, 2 H, CH_2), 1.94 (s, 3 H, CH_3), 3.19 (q, *J* = 6.8; 6.4 Hz, 2 H, CH_2), 5.64 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.06, 22.62, 23.27, 26.87, 29.25, 29.28, 29.49, 29.53, 29.56, 29.58, 31.85, 39.65, 170.03.

(4-Methoxyphenyl)(piperidin-1-yl)methanone (5a)[20]

Eluent: PE/EtOAc (80:20); white solid; yield: 66.9 mg (96%); mp 36–38 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.51–1.59 (m, 6 H, CH_2), 3.36–3.56 (m, 4 H, CH_2), 3.75 (s, 3 H, OCH_3), 6.82 (d, *J* = 8.4 Hz, 2 H, ArH), 7.29 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.59, 55.27, 113.55, 128.52, 128.80, 160.43, 170.25.

(4-Nitrophenyl)(piperidin-1-yl)methanone (5b)[20]

Eluent: PE/EtOAc (80:20); light yellow solid; yield: 62.4 mg (89%); mp 121–123 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (s, 2 H, CH_2), 1.60 (s, 4 H, CH_2), 3.19 (s, 2 H, CH_2), 3.63 (s, 2 H, CH_2), 7.46 (d, *J* = 6.8 Hz, 2 H, ArH), 8.15–8.18 (m, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.32, 25.43, 26.43, 43.11, 48.58, 123.78,127.74, 142.67, 148.07, 167.79.

***N*-Isopropylbenzamide (5c)**[8a]

Eluent: PE/EtOAc (85:15); white solid; yield: 53.0 mg (94%); mp 97–99 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 4.23–4.31 (m, 1 H, CH), 6.01 (s, 1 H, NH), 7.39 (t, *J* = 8.0 Hz, 2 H, ArH), 7.46 (t, *J* = 7.6 Hz, 1 H, ArH), 7.73 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.82, 41.84, 126.76, 128.45, 131.21, 134.92, 166.65.

***N*-Butylbenzamide (5d)**[8d]

Eluent: PE/EtOAc (90:10); colorless oil; yield: 60.1 mg (98%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (s, 3 H, CH_3), 1.31–1.42 (m, 2 H, CH_2), 1.53–1.60 (m, 2 H, CH_2), 3.39–3.44 (q, *J* = 7.2; 6.8 Hz, 2 H, CH_2), 6.32 (s, 1 H, NH), 7.38 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2 H, ArH), 7.45 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 1 H, ArH), 7.74 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.75, 20.11, 31.68, 39.77, 126.81, 128.46, 131.23, 134.79, 167.55.

***N*-(*tert*-Butyl)benzamide (5e)**[27]

Eluent: PE/EtOAc (90:10); white solid; yield: 48.4 mg (79%); mp 131–133 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (s, 9 H, 3 × CH_3), 5.96 (s, 1 H, NH), 7.31 (t, *J* = 7.6 Hz, 2 H, ArH), 7.38 (t, *J* = 7.2 Hz, 1 H, ArH), 7.64 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.82, 41.84, 126.76, 128.45, 131.21, 134.92, 166.65.

***N*-Benzyl-4-methoxybenzamide (7a)**[8d]

Eluent: PE/EtOAc (80:20); white solid; yield: 86.4 mg (95%); mp 122–124 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.80 (s, 3 H, OCH_3), 4.56 (d, *J* = 6 Hz, 2 H, CH_2), 6.75 (br, 1 H, NH), 6.84–6.87 (m, 2 H, ArH), 7.23–7.30 (m, 5 H, ArH), 7.75 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.91, 55.34, 113.65, 126.59, 127.38, 127.78, 128.64, 128.83, 138.49, 162.12, 166.96.

***N*-Benzyl-4-(trifluoromethyl)benzamide (7b)**[8d]

Eluent: PE/EtOAc (80:20); white solid; yield: 86.6 mg (94%); mp 149–151 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.64 (d, *J* = 5.6 Hz, 2 H, CH_2), 6.61 (br, 1 H, NH), 7.29–7.38 (m, 5 H, ArH), 7.67 (d, *J* = 8.4 Hz, 2 H, ArH), 7.88 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 44.77, 122.74, 125.45, 126.11 (*J* = 3.6 Hz), 128.29, 134.78 (*J* = 33.8 Hz), 138.09, 138.9, 138.19, 166.56.

***N*-Cyclohexyl-4-(trifluoromethyl)benzamide (7c)**[28]

Eluent: PE/EtOAc (75:25); white solid; 85.0 g (95%); mp 167–169 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16–1.28 (m, 3 H, CH_2), 1.36–1.46 (m, 2 H, CH_2), 1.63–1.67 (m, 1 H, CH), 1.75 (dt, J_1 = 13.6 Hz, J_2 = 3.6 Hz, 2 H, CH_2), 2.02 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 2 H, CH_2), 3.91–4.01 (m, 1 H, CH), 6.03 (br, 1 H, NH) 7.66 (d, *J* = 8.0 Hz, 2 H, ArH), 7.83 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.35, 25.97, 33.62, 49.47, 122.79, 125.51, 126.042 (*J* = 3.4 Hz), 127.79, 133.47 (*J* = 32.5 Hz), 138.84, 165.83.

Piperidin-1-yl[4-(trifluoromethyl)phenyl]methanone (7d)[20]

Eluent: PE/EtOAc (85:15); white solid; yield: 84.0 g (99%); mp 98–100 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.43 (s, 2 H, CH_2), 1.60 (s, 4 H, CH_2), 3.32 (s, 2 H, CH_2), 3.64 (s, 2 H, CH_2), 7.42 (d, *J* = 8.0 Hz, 2 H, ArH), 7.58 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.88, 25.97, 26.94, 43.56, 49.09, 122.88, 125.58, 125.95 (*J* = 3.7 Hz), 127.58, 13.72 (*J* = 32.6 Hz), 140.55, 169.20.

Morpholino[4-(trifluoromethyl)phenyl]methanone (7e)[7a]

Eluent: PE/EtOAc (80:20); white solid; yield: 81.2 mg (97%); mp 47–49 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.32 (s, 2 H, CH_2), 3.54 (s, 2 H, CH_2), 3.71 (s, 4 H, CH_2), 7.46 (d, *J* = 7.6 Hz, 2 H, ArH), 7.61 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 42.42, 47.99, 66.68, 119.53, 122.24, 124.95, 125.60 (*J* = 3.5 Hz), 127.40, 131.68 (*J* = 31.6 Hz), 138.82, 168.81.

Pyrrolidin-1-yl[4-(trifluoromethyl)phenyl]methanone (7f)[24]

Eluent: PE/EtOAc (85:15); white solid; yield: 77.8 mg (97%); mp 80–82 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.84 (pent, *J* = 6.5 Hz, 2 H, CH_2), 1.93 (pent, *J* = 6.7 Hz, 2 H, CH_2), 3.34 (t, *J* = 6.4.0 Hz, 2 H, CH_2), 3.61 (t, *J* = 6.8 Hz, 2 H, CH_2), 7.67–7.63 (m, 4 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.84, 26.81, 46.70, 49.93, 125.58, 125.81 (*J* = 3.6 Hz), 127.90, 132.08 (*J* = 32.7 Hz), 141.15, 168.68.

Transamidation of Activated Amide 1a with Amino Acids and Amino Alcohols

The amide substrate **1a** (0.273 mmol) and the respective amino acid or amino alcohol (0.356 mmol) in EtOH (1 mL) were taken in a vial and the reaction mixture was stirred at 60 °C (1–3 h). The mixture was concentrated in vacuo and the crude product was purified by column chromatography as described in the general procedure to give the corresponding transamidation product **8a–d**.

Methyl Benzoyl-L-phenylalaninate (8a)[29]

Eluent: PE/EtOAc (85:15); white solid; yield: 75.1 mg (97%); mp 84–86 °C; $[\alpha]_D^{20}$ +65.56 (*c* 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.19–3.31 (m, 2 H, CH_2), 3.75 (s, 3 H, OCH_3), 5.08 (q, *J* = 5.6 Hz, 1 H, CH), 6.57 (d, *J* = 5.6 Hz, 1 H, NH), 7.12 (d, *J* = 7.2 Hz, 2 H, ArH), 7.24–7.30 (m, 3 H, ArH), 7.41 (t, *J* = 7.2 Hz, 2 H, ArH), 7.49 (t, *J* = 7.2 Hz, 1 H, ArH), 7.71 (d, *J* = 7.6 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 37.80, 53.40, 53.56, 127.02, 127.15, 128.56, 128.59, 129.29, 131.76, 133.78, 135.88, 166.93, 172.10.

Methyl Benzoyl-L-methioninate (8b)[30]

Eluent: PE/EtOAc (85:15); white solid; yield: 68.8 mg (94%); mp 87–89 °C; $[\alpha]_D^{20}$ +19.5 (*c* 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.08 (s, 4 H, CH_2), 2.26 (s, 1 H, CH), 2.56 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 4.906 (s, 1 H, CH), 6.99 (s, 1 H, NH), 7.24–7.48 (m, 3 H, ArH), 7.79 (s, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.47, 30.03, 31.49, 52.01, 52.60, 127.05, 128.57, 131.81, 133.64, 167.05, 172.55.

Ethyl Benzoyl-L-alaninate (8c)[31]

Eluent: PE/EtOAc (85:15); white solid; yield: 53.3 mg (94%); mp 76–78 °C; $[\alpha]_D^{20}$ +30.14 (*c* 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_2), 1.50 (d, *J* = 7.2 Hz, 3 H, CH_3), 5.72 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.76 (pent, *J* = 7.2 Hz, 1 H, CH), 6.79 (s, 1 H, NH), 7.41 (t, *J* = 7.2 Hz, 2 H, ArH), 7.49 (d, *J* = 7.2 Hz, 1 H, ArH), 7.79 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.10, 18.66, 48.51, 61.62, 126.98, 128.53, 131.66, 133.91, 166.77, 173.25.

***N*-[(2*R*,3*R*)-1-Hydroxy-3-methylpentan-2-yl]benzamide (8d)**

Eluent: PE/EtOAc (80:20); white solid; yield: 53.9 mg (89%); mp 79–81 °C; $[\alpha]_D^{20}$ –8.28 (*c* 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.97 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.16–1.27 (m, 2 H, CH_2), 1.53–1.61 (m, 1 H, CH), 1.75–1.76 (m, 1 H, CH), 3.73–3.80 (m, 2 H, CH_2), 3.99 (t, *J* = 7.2 Hz, 1 H, OH), 6.48 (d, *J* = 7.2 Hz, 1 H, NH), 7.39 (t, *J* = 7.6 Hz, 2 H, ArH), 7.47 (t, *J* = 7.2 Hz, 1 H, ArH), 7.74 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.34, 15.60, 25.63, 35.73, 56.25, 63.53, 126.93, 128.54, 131.54, 134.41, 168.34.

HRMS: *m*/z calcd for $C_{13}H_{19}NO_2Na$ [M + Na]$^+$: 244.1313; found: 244.1318.

Transamidation of Activated Secondary Amides in Water; General Procedure

The amide substrate **1** or **6b** (1 equiv) and the respective amine (4 equiv) in H_2O (1 mL) were taken in a vial and the reaction mixture was stirred at 60 °C (1–2 h). After the reaction was complete, EtOAc (20 mL) was added. The organic layer was separated, dried (anhyd Na_2SO_4), and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel to afford the corresponding transamidation product.

Furan-2-yl(morpholino)methanone (9)[32]

According to the general procedure, the reaction of **1f** (0.28 mmol) and morpholine (1.13 mmol) in H_2O (1 mL) at 60 °C for 2 h, afforded the corresponding transamidation product **9** (46.9 mg, 92%) after column chromatography (PE/EtOAc, 85:15); white solid; mp 51–53 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.69–3.77 (m, 8 H, CH_2), 6.44–6.45 (m, 1 H, ArH), 6.98 (d, *J* = 3.6 Hz, 1 H, ArH), 7.43–7.44 (m, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 66.89, 111.32, 116.73, 143.73, 147.66, 159.04.

Comparative Studies

The amide substrate **10** or **11** (1.0 equiv) and the respective amine (1.3 equiv) in ethanol (1 mL) were taken in a vial and the reaction mixture was stirred at 45–60 °C (1–12 h). After completion of the reaction, the mixture was concentrated. The crude product was purified by column chromatography (PE/EtOAc) on SiO_2 to give the corresponding transamidation product.

***N*-(2,6-Dimethylphenyl)benzamide (12a)**[7a]

Eluent: PE/EtOAc (85:15); white solid; yield: 49.9 mg (69%); mp 155–157 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (s, 6 H, CH_3), 7.12 (m, 3 H, ArH), 7.38 (s, 1 H, ArH), 7.49 (t, *J* = 7.6 Hz, 1 H, ArH), 7.56 (t, *J* = 7.2 Hz, 1 H, ArH), 7.91 (d, *J* = 7.2 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.42, 127.21, 127.34, 128.21, 128.67, 131.69, 133.93, 134.43, 135.58, 165.91.

***N*-Benzyl-4-bromobenzamide (12b)**[8d]

Eluent: PE/EtOAc (80:20); white solid; yield: 71.4 mg (96%); mp 125–127 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.62 (d, *J* = 5.2 Hz, 2 H, CH_2), 6.62 (s, 1 H, NH), 7.28–7.35 (m, 5 H, ArH), 7.55 (d, *J* = 8.0 Hz, 2 H, ArH), 7.66 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 44.68,126.71, 128.19, 128.39, 129.08, 129.30, 132.28, 133.64, 138.38, 166.91.

(*S*)-3,3-Diphenyl-*N*-(1-phenylethyl)propanamide (12c)[11]

Eluent: PE/EtOAc (90:10); yellowish solid; yield: 64.2 mg (88%); mp 121–123 °C; $[\alpha]_D^{20}$ +46.18 (*c* 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.25 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.90 (d, *J* = 8.0 Hz, 2 H, CH_2), 4.56 (t, *J* = 7.6 Hz, 1 H, CH), 4.98 (pent, *J* = 7.2 Hz, 1 H, CH), 5.65 (s, 1 H, NH), 6.98 (d, *J* = 7.6 Hz, 2 H, ArH), 7.21–7.31 (m, 12 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.31, 43.51, 47.62, 48.37, 125.97, 126.52, 127.08, 127.77, 128.47, 128.60, 142.80, 143.48, 143.66, 170.14.

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Supporting Information

Supporting information (copies of ^{1}H and ^{13}NMR spectra of all compounds) for this article is available online at https://doi.org/10.1055/s-0037-1610664.

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