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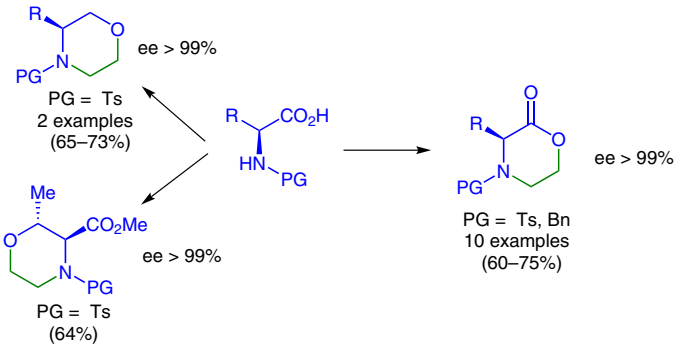
Racemization-Free Synthesis of Morpholinone Derivatives from α-Amino Acids

Sauvik Samanta
Abhijit Mal
Sandipan Halder
Manas K. Ghorai*

Department of Chemistry, Indian Institute of Technology, Kanpur-208016, India
mkghorai@iitk.ac.in



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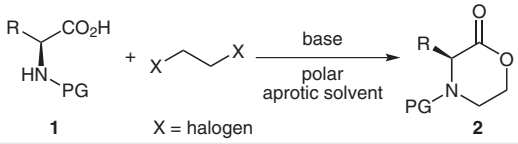
Abstract A simple strategy is reported for the synthesis of chiral N-protected morpholinone derivatives by a base (potassium carbonate)-mediated cyclization reaction of N-protected α-amino acids with 1,2-dibromoethane. The morpholinone derivatives are obtained in good yields and in enantiomerically pure forms.

Key words morpholines, asymmetric synthesis, amino acids, cyclizations

Morpholines and morpholinones are important classes of heterocyclic compounds that form structural units of many natural products and synthetic compounds of biological and pharmaceutical relevance.[1] In particular, N- and/or 2-substituted morpholines[2] and morpholinones[3] exhibit a wide spectrum of biological activities. Chiral morpholine derivatives have been synthesized from naturally occurring amino acids,[4] amino alcohols,[5] epoxides,[6] small-ring azaheterocycles,[7] olefins,[8] carbohydrates,[9] or vinylsulfonium salts.[2d,10] Asymmetric hydrogen-transfer reactions[11] and metal-catalyzed cyclization reactions[12] are also important routes to chiral morpholines. There are only a few reports on syntheses of chiral morpholinone derivatives. Syntheses of optically active morpholinones from amino alcohols, α-bromo esters, and α-amino acids by various base-catalyzed cyclization reactions have been reported.[13] Another novel strategy for the synthesis of 4-aminomorpholinone derivatives from (*S*)-malic acid has also been reported.[3a] Enantioselective syntheses of morpholinone derivatives have also been accomplished by using chiral auxiliary approaches.[14] Morpholinone derivatives have also been synthesized from α-bromo esters by L-malate-mediated dynamic kinetic resolution.[15] Very recently, the synthesis of *trans*-selective oxomorpholinecarboxylic acid derivatives from dioxanedione and aromatic imines has been reported.[16] We surmised that enantiopure morpholin-2-one derivatives might be readily synthesized from N-protected chiral α-amino acids by a base-mediated cyclization reaction with a 1,2-dihaloethane (Scheme 1).

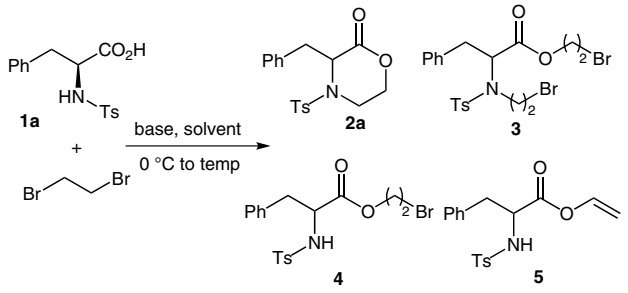


Scheme 1 Racemization-free synthesis of morpholin-2-ones

In continuation of our research activities on the synthesis of six-membered carbacycles[17] and heterocycles,[7a,b,18] we have developed a simple strategy for the synthesis of chiral N-protected morpholinone derivatives **2** from N-protected chiral α-amino acids. Here, we report our results in detail.

To test the viability of our approach, we first treated *N*-tosylphenylalanine (**1a**) with 1,2-dibromoethane in the presence of 2.5 equivalents of sodium hydroxide in dimethyl sulfoxide. Addition of the reagents at 0 °C, followed by stirring at room temperature for 24 hours led to the formation of the acyclic dialkylated product **3**, along with the O-alkylated ester **4** (Table 1, entry 1). When potassium carbonate (2.5 equiv.) was used as the base at room temperature, the ester **4** was isolated as the sole product after 24 hours (entry 2). To effect cyclization, another 2.5 equivalents of potassium carbonate were added to the reaction mixture, which was stirred at room temperature for a further 24 hours. The *N*-tosylmorpholinone derivative **2a** was obtained in only 18% yield (entry 3). When the reaction mixture was heated at 100 °C, the acyclic dialkylated product **3** along with the allyl ester **5** were formed instead of the cyclic product **2a** (entry 4).

Table 1 Optimization Study



Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]			
					2a	**3**	**4**	**5**
1	NaOH (2.5)	DMSO	r.t.	24	–	12	28	–
2	K_2CO_3 (2.5)	DMSO	r.t.	24	–	–	40	–
3	K_2CO_3 (2.5, 2.5)	DMSO	r.t.	24 + 24[b]	18	–	15	–
4	K_2CO_3 (2.5)	DMSO	100	24	–	15	–	32
5	K_2CO_3 (5.0)	DMSO	r.t.	16	42	–	10	–
6	K_2CO_3 (5.0)	DMF	r.t.	16	72	–	-	–
7	K_2CO_3 (5.0)	MeCN	r.t.	16	20	–	16	–
8	K_2CO_3 (5.0)	acetone	r.t.	16	-	–	30	–

[a] Yield of the isolated product.
[b] After 24 h reaction with 2.5 equiv of base, the reaction was continued for another 24 h with excess (2.5 equiv) base.

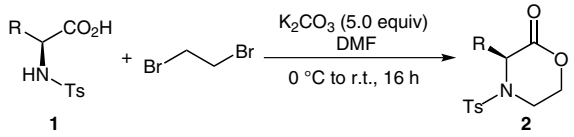
With excess base (5.0 equiv) and a longer reaction time (16 h) at room temperature, the morpholinone derivative **2a** was obtained in moderate yield (Table 1, entry 5). The base-catalyzed cyclization step was also studied in other polar aprotic solvents (entries 6–8). The best result was obtained in *N*,*N*-dimethylformamide, where **2a** was obtained as the only product in 72% yield (entry 6).

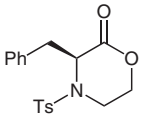
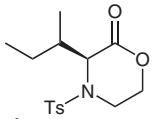
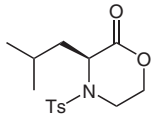
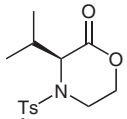
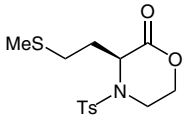
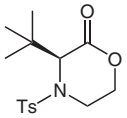
The strategy was generalized with various *N*-tosyl α-amino acids **1b**–**e** and 1,2-dibromoethane to give the corresponding morpholinones **2b**–**e** in 62–75% yields (Table 2) in enantiomerically pure forms.[19,20] Our strategy worked well with other unnatural α-amino acids; for example, the *tert*-leucine derivative **1f** afforded the corresponding morpholinone **2f** (Table 2, entry 6) in good yield.

The structures of the morpholinone derivatives **2a** and **2b** were unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[21]

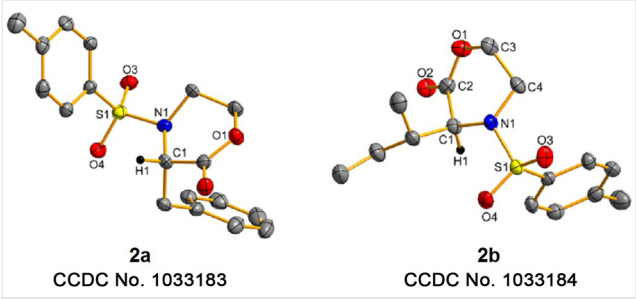
Next, we extended our strategy to the synthesis of the chiral morpholinecarboxylate derivative **7**. When we subjected the methyl ester of *N*-tosylthreonine (**6**) to our cyclization protocol, we obtained the corresponding *N*-tosylmorpholinecarboxylate derivative **7** in good yield (Scheme 2) as a single stereoisomer (de, ee > 99%).

Table 2 Synthesis of Chiral *N*-Tosylmorpholin-2-one Derivatives



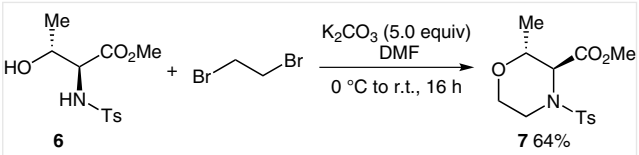
Entry	Substrate	R	Product	Yield[a] (%)
1	**1a**	Bn	 **2a**	72
2	**1b**	*s*-Bu	 **2b**	75[b]
3	**1c**	*i*-Bu	 **2c**	68
4	**1d**	*i*-Pr	 **2d**	70
5	**1e**	$(CH_2)_2SMe$	 **2e**	65
6	**1f**	*t*-Bu	 **2f**	62

[a] Yield of the isolated product.
[b] > 99% ee, as determined by chiral HPLC analysis.



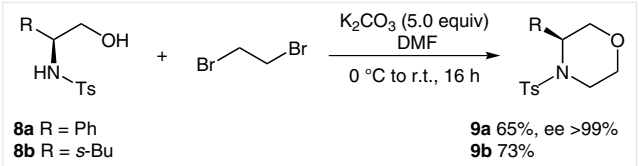
2a CCDC No. 1033183 **2b** CCDC No. 1033184

Figure 1 X-ray crystal structure of **2a** and **2b**



Scheme 2 Synthesis of chiral morpholinecarboxylate

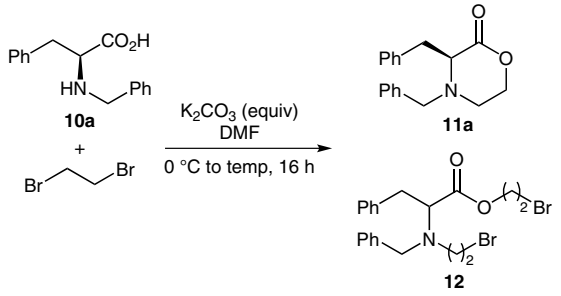
The cyclization reaction of *N*-tosyl α-amino alcohols **8a** and **8b** with 1,2-dibromoethane under the same reaction condition gave the nonracemic[20,22] morpholine derivatives **9a** and **9b**, respectively, in good yields as single enantiomers (Scheme 3).



Scheme 3 Synthesis of chiral morpholines

Next, we extended our protocol to the synthesis of nonracemic *N*-benzylmorpholinone derivatives. Surprisingly, the expected morpholine product could not be obtained from the reaction of *N*-benzylphenylalanine (**10a**) with 1,2-dibromoethane under the reaction conditions mentioned in Table 2 (Table 3, entry 1). When the amount of potassium carbonate was decreased to 3.0 equivalents and the mixture was heated to 100 °C after addition of all the reagents at 0 °C, the *N*-benzylmorpholinone **11a** was obtained in high yield, albeit with a reduced enantiomeric excess (entry 2). Interestingly, when the reaction temperature was lowered to 65 °C, the morpholinone product **11a** was obtained in enantiopure form, but with a slightly reduced yield (entry 3). Note that *N*-tosylmorpholinones **2a**–**f** and morpholines **9a**–**b** were obtained in enantiopure form when the reactions were performed at room temperature.

Table 3 Optimization of the Synthesis of 3,4-Dibenzylmorpholin-2-one (**11a**)

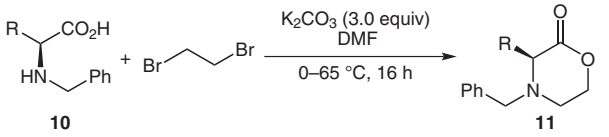


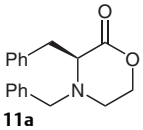
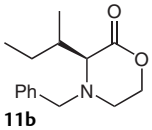
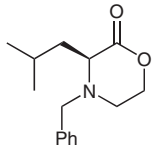
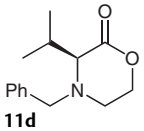
Entry	K_2CO_3 (equiv)	Temp (°C)	Yield (%)[a]		ee[b] (%) of **11a**
			11a	**12**	
1	5.0	r.t.	–	30	–
2	3.0	100	78	–	72
3	3.0	65	65	–	>99

[a] Yield of the isolated product.
[b] Racemic morpholinone **11a** was synthesized from the racemic α-amino acid.

A number of *N*-benzyl-protected morpholinone derivatives **11a**–**d** in enantiomerically pure forms[20,23] were synthesized in good yields starting from various *N*-benzyl α-amino acids **10a**–**d** (Table 4).

Table 4 Synthesis of Chiral *N*-Benzylmorpholinone Derivatives



Entry	Substrate	R	Product	Yield[a] (%)
1	**10a**	Bn	 **11a**	65[b]
2	**10b**	*s*-Bu	 **11b**	66
3	**10c**	*i*-Bu	 **11c**	60
4	**10d**	*i*-Pr	 **11d**	62

[a] Yield of the isolated product.
[b] ee > 99%; racemic morpholinone was synthesized starting from racemic α-amino acid.

Earlier, **11d** and another example of an *N*-benzyl-protected morpholinone were reported by Kashima and Harada, who used similar reaction condition (K_2CO_3, DMF, 80 °C, 12 h).[13] However, we found that 65 °C is the optimal temperature for obtaining enantiopure compounds. At higher temperatures, the products were obtained with reduced enantiomeric excesses, albeit in higher yields.

In conclusion, we have developed a simple and efficient strategy for the synthesis of chiral *N*-tosylmorpholinones, morpholinecarboxylates, and other morpholine derivatives from *N*-tosyl α-amino acids under mild reaction conditions. *N*-Benzylmorpholinones were also synthesized in enantio-

pure forms by using our strategy. Our method will be very useful for the syntheses of various morpholine derivatives in enantiopure forms.

All commercial reagents were purchased from Sigma-Aldrich, Spectrochem Pvt. Ltd. and Avra Laboratories Pvt. Ltd. and used directly. 1,2-Dibromoethane was purified by distillation under reduced pressure. Solvents were dried by using standard procedures and preserved under 4 Å molecular sieves. Melting points were determined on a MEL-TEMP® capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol JNM-LA 400 FT-NMR or Jeol JNM-LA 500 FT-NMR spectrometers. Chemical shifts (δ) are referenced to TMS as an internal standard. Mass spectra were recorded on a Jeol SX 102/DA-6000 spectrometer operated in the ESI mode. Optical rotations were measured on a Rudolph Autopol IV polarimeter. Enantiomeric excess (ee) values were determined on a Perkin-Elmer Flexer HPLC. X-ray crystal diffraction data were collected on a Bruker AXS smart APEX CCD diffractometer.

4-Tosylmorpholin-2-ones 2a–f; General Procedure

Anhyd DMF (10 mL) was added to dried K_2CO_3 (5.0 equiv), and the mixture was cooled to 0 °C. Solid *N*-tosyl amino acid **1** (1.0 equiv) was added under an inert gas (argon or N_2), and the mixture was stirred for 30 min at 0 °C. 1,2-Dibromoethane (1.3 equiv) was then added at 0 °C, and the mixture was warmed to r.t. and stirred for 16 h. The reaction was quenched with ice-cold water, the organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10.0 mL). The organic extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography [silica gel (230–400 mesh), 10% EtOAc–PE].

3-Benzyl-4-tosylmorpholin-2-one (2a)

Prepared from *N*-tosylphenylalanine (**1a**, 100 mg, 0.31 mmol) and $Br(CH_2)_2Br$ (0.03 mL, 0.4 mmol) as a white solid; yield: 78 mg (72%); mp 104–108 °C; R_f = 0.40 (30% EtOAc–PE); $[\alpha]_D^{25}$ −12.62 (*c* 0.21, CH_2Cl_2).

IR (neat): 3058, 3024, 2971, 2948, 2926, 2900, 2851, 2588, 1940, 1741, 1597, 1494, 1455, 1402, 1351, 1289, 1243, 1195, 1163, 1100, 1022, 1001, 932, 906, 853, 821, 756, 704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.13–3.27 (m, 2 H), 3.35–3.46 (m, 3 H), 3.90–3.94 (m, 1 H), 4.62 (t, *J* = 4.3 Hz, 1 H), 7.23–7.25 (m, 3 H), 7.27–7.30 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 40.7, 41.6, 58.8, 65.8, 127.5, 128.6, 130.2, 133.7, 135.3, 144.7, 167.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{19}NaNO_4S$: 368.0933; found: 368.0931.

3-*sec*-Butyl-4-tosylmorpholin-2-one (2b)

Prepared from *N*-tosylisoleucine (**1b**, 100 mg, 0.35 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.46 mmol) as a white solid; yield: 82 mg (75%); mp 114–116 °C; R_f = 0.32 (30% EtOAc–PE); $[\alpha]_D^{25}$ +37.6 (*c* 0.28, $CHCl_3$) (>99% ee sample).

IR (neat): 2962, 2929, 2873, 2852, 1735, 1596, 1453, 1405, 1351, 1302, 1252, 1212, 1165, 1097, 1017, 978, 939, 841, 819, 782, 711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 10.4 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.29–1.35 (m, 1 H), 1.80–1.85 (m, 1 H), 1.97–2.02 (m, 1 H), 2.43 (s, 3 H), 3.34–3.39 (m, 1 H), 3.62–3.67 (m, 1 H), 4.11–4.15 (m, 1 H), 4.22 (d, *J* = 7.3 Hz, 1 H), 4.31–4.36 (m, 1 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 7.68 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 15.4, 21.7, 26.3, 39.5, 41.7, 62.4, 64.8, 127.6, 130.3, 134.1, 144.7, 167.0.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_4S$: 312.1270; found: 312.1270.

The enantiomeric excess was determined by chiral HPLC analysis [column: Chiralpak Cellulose 2; hexane–*i*-PrOH (90:10), flow rate = 1.0 mL/min; t_R (1) = 25.21 min (major)].

3-Isobutyl-4-tosylmorpholin-2-one (2c)

Prepared from *N*-tosylleucine (**1c**, 100 mg, 0.35 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.46 mmol) as a yellowish gummy liquid; yield: 74 mg (68%); R_f = 0.37 (30% EtOAc–PE); $[\alpha]_D^{25}$ −1.88 (*c* 0.29, CH_2Cl_2).

IR (neat): 2960, 2872, 1748, 1598, 1495, 1470, 1403, 1358, 1307, 1280, 1262, 1215, 1165, 1122, 1090, 1028, 967, 868, 816, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.0 Hz, 3 H), 0.98 (d, *J* = 6.0 Hz, 3 H), 1.65–1.72 (m, 1 H), 1.78–1.83 (m, 2 H), 2.42 (s, 3 H), 3.49–3.54 (m, 1 H), 3.57–3.62 (m, 1 H), 4.12–4.16 (m, 1 H), 4.26–4.31 (m, 1 H), 4.46 (t, *J* = 7.2 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 22.0, 22.5, 24.4, 40.0, 43.0, 55.9, 65.9, 127.4, 130.4, 135.1, 144.8, 167.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{21}NNaO_4S$: 334.1089; found: 334.1088.

3-Isopropyl-4-tosylmorpholin-2-one (2d)

Prepared from *N*-tosylvaline (**1d**, 100 mg, 0.37 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.48 mmol) as yellowish gummy liquid; yield: 77 mg (70%); R_f = 0.35 (30% EtOAc–PE); $[\alpha]_D^{25}$ +63.85 (*c* 0.26, CH_2Cl_2).

IR (neat): 2963, 2925, 2871, 1749, 1596, 1495, 1467, 1409, 1364, 1350, 1308, 1286, 1163, 1116, 1070, 1021, 997, 919, 846, 766, 709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.55 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 2.16–2.24 (m, 1 H), 2.42 (s, 3 H), 3.35–3.41 (m, 1 H), 3.60–3.65 (m, 1 H), 4.09–4.14 (m, 2 H), 4.30–4.34 (m, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1, 20.1, 21.7, 33.0, 41.5, 63.6, 64.9, 127.6, 130.3, 134.3, 144.7, 167.0.

HRMS (ESI): *m/z* [M + NH_4]$^+$ calcd for $C_{14}H_{23}N_2O_4S$: 315.1375; found: 315.1379.

3-[2-(Methylsulfanyl)ethyl]-4-tosylmorpholin-2-one (2e)

Prepared from *N*-tosylmethionine (**1e**, 100 mg, 0.33 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.43 mmol) as a yellowish gummy liquid; yield: 71 mg (65%); R_f = 0.23 (30% EtOAc–PE); $[\alpha]_D^{25}$ +63.5 (*c* 0.27, CH_2Cl_2).

IR (neat): 2921, 2856, 1747, 1597, 1494, 1441, 1403, 1346, 1306, 1282, 1226, 1165, 1113, 1089, 1019, 984, 896, 816, 740, 721, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.23–2.27 (m, 2 H), 2.44 (s, 3 H), 2.60–2.67 (m, 2 H), 3.50–3.54 (m, 1 H), 3.61–3.66 (m, 1 H), 4.14–4.22 (m, 1 H), 4.31–4.35 (m, 1 H), 4.51 (t, *J* = 6.4 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.70 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.3, 21.7, 29.9, 33.4, 41.2, 56.3, 66.3, 127.5, 130.4, 134.5, 145.0, 167.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{19}NNaO_4S_2$: 352.0653; found: 352.0651.

3-*tert*-Butyl-4-tosylmorpholin-2-one (2f)

Prepared from *N*-tosyl-*tert*-leucine (**1f**, 100 mg, 0.35 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.46 mmol) as a yellowish gummy liquid; yield: 68 mg (62%); R_f = 0.36 (30% EtOAc–PE).

IR (neat): 2968, 2926, 2874, 1741, 1598, 1476, 1402, 1358, 1296, 1253, 1226, 1201, 1119, 1088, 1019, 983, 933, 887, 818, 769, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (s, 9 H), 2.43 (s, 3 H), 3.64–3.73 (m, 2 H), 3.79–3.84 (m, 1 H), 4.15–4.19 (m, 1 H), 4.38 (s, 1 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 7.69 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 28.9, 37.4, 39.7, 64.9, 66.0, 127.2, 130.4, 136.3, 144.7, 166.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{21}NNaO_4S$: 334.1089; found: 334.1082.

Methyl 2-Methyl-4-tosylmorpholine-3-carboxylate (7)

Anhyd DMF (5 mL) was added to dried K_2CO_3 (242 mg, 1.75 mmol), and the mixture was cooled to 0 °C. A soln of methyl *N*-tosylthreoninate (**6**, 100 mg, 0.35 mmol) in DMF (5 mL) was added, and the mixture was stirred for 30 min at 0 °C. $Br(CH_2)_2Br$ (0.04 mL, 0.46 mmol) was added at 0 °C, and the mixture was heated to r.t. and stirred for 16 h. The reaction was quenched with ice-cold water, and the organic and the aqueous layers were separated. The aqueous layer was extracted with EtOAc (3 × 10.0 mL), and the organic extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography [silica gel (230–400 mesh), 10% EtOAc–PE] to give a yellowish gummy liquid; yield: 70 mg (64%); R_f = 0.42 (30% EtOAc–PE).

IR (neat): 2954, 2925, 2873, 1747, 1598, 1495, 1450, 1349, 1307, 1284, 1166, 1122, 1089, 1073, 1050, 1026, 933, 922, 904, 864, 845, 818, 805, 745, 708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.1 Hz, 3 H), 2.43 (s, 3 H), 2.94–2.99 (m, 1 H), 3.45–3.49 (m, 1 H), 3.62–3.66 (m, 2 H), 3.70 (s, 3 H), 3.87–3.91 (m, 1 H), 4.10–4.15 (m, 1 H), 7.33 (d, *J* = 8.3 Hz, 2 H), 7.68 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.9, 21.7, 29.8, 43.3, 52.6, 61.8, 71.9, 128.1, 129.7, 133.6, 144.1, 169.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_5S$: 314.1062; found: 314.1060.

N-Tosylmorpholines 9; General Procedure

Anhyd DMF (5 mL) was added to dried K_2CO_3 (5.0 equiv), and the mixture was cooled to 0 °C. A solution of the appropriate *N*-tosyl amino alcohol **8** (1.0 equiv) in DMF (5 mL) was added, and the mixture was stirred for 30 min at 0 °C. $Br(CH_2)_2Br$ (1.3 equiv) was added at 0 °C, and the mixture was warmed to r.t. and stirred for 16 h. The reaction was quenched with ice-cold water, and the organic and the aqueous layers were separated. The aqueous layer was extracted with EtOAc (3 × 10.0 mL), and the organic extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography [silica gel (230–400 mesh), 10% EtOAc–PE].

3-Phenyl-4-tosylmorpholine (9a)

Prepared from alcohol **8a** (100 mg, 0.34 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.45 mmol) as a white solid; yield: 71 mg (65%); mp 118–120 °C; R_f = 0.33 (15% EtOAc–PE); $[\alpha]_D^{25}$ +23.6 (*c* 0.42, $CHCl_3$) for a > 99% ee sample.

IR (neat): 3087, 3051, 3026, 2964, 2924, 2854, 1925, 1597, 1494, 1447, 1401, 1360, 1345, 1328, 1307, 1271, 1237, 1161, 1114, 1092, 1034, 1017, 1002, 986, 946, 922, 909. 839, 817, 762, 735, 706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.31–3.36 (m, 1 H), 3.45–3.55 (m, 2 H), 3.71 (dd, *J* = 3.8, 12.4 Hz, 1 H), 3.79 (dt, *J* = 2.9, 11.5 Hz, 1 H), 4.13 (dd, *J* = 2.4, 11.9 Hz, 1 H), 4.76 (br s, 1 H), 7.22 (d, *J* = 7.2 Hz, 2 H), 7.25–7.30 (m, 3 H), 7.43–7.45 (m, 2 H), 7.56 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 42.2, 56.2, 66.3, 69.4, 127.4, 127.8, 128.4, 128.5, 129.7, 137.0, 137.8, 143.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{20}NO_3S$: 318.1164; found: 318.1163.

The enantiomeric excess was determined by chiral HPLC analysis [column: Chiralpak Cellulose 2; hexane–*i*-PrOH (90:10), flow rate = 1.0 mL/min; t_R (1) = 26.23 min (major)].

3-*sec*-Butyl-4-tosylmorpholine (9b)

Prepared from alcohol **8b** (100 mg, 0.37 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.48 mmol) as a white solid; yield: 80 mg (73%); mp 108–111 °C; R_f = 0.33 (15% EtOAc–PE).

IR (neat): 3048, 2963, 2926, 2859, 1597, 1495, 1455, 1381, 1344, 1267, 1249, 1159, 1096, 1031, 981, 957, 915, 838, 818, 801, 773, 742, 720, 720, 709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.92 (m, 6 H), 1.03–1.10 (m, 1 H), 1.61–1.67 (m, 1 H), 2.00–2.06 (m, 1 H), 2.43 (s, 3 H), 3.11–3.21 (m, 2 H), 3.26–3.32 (m, 1 H), 3.39–3.41 (m, 1 H), 3.55–3.60 (m, 2 H), 3.80–3.83 (m, 1 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 7.71 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 16.0, 21.6, 25.4, 31.7, 41.4, 58.5, 65.5, 66.3, 127.2, 129.9, 138.9, 143.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{24}NO_3S$: 298.4130; found: 298.4134.

4-Benzylmorpholin-2-ones 11; General Procedure

Anhyd DMF (10 mL) was added to dried K_2CO_3 (3.0 equiv), and the mixture was cooled to 0 °C. Solid *N*-benzyl amino acid **10** (1.0 equiv) was added under an inert gas (Ar or N_2), and the mixture was stirred for 30 min at 0 °C. $Br(CH_2)_2Br$ (1.3 equiv) was added at 0 °C, and the mixture was heated to 65 °C and stirred for 16 h. The reaction was quenched with ice-cold water, and the organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3 × 10.0 mL), and the organic extracts were combined, washed successively with ice-cold water (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography [silica gel (230–400 mesh), 10% EtOAc–PE].

3,4-Dibenzylmorpholin-2-one (11a)

Prepared from *N*-benzylphenylalanine (**10a**, 100 mg, 0.39 mmol) and $Br(CH_2)_2Br$ (0.04 mL, 0.51 mmol) as a yellowish gummy liquid; yield: 71 mg (65%); R_f = 0.4 (30% EtOAc–PE); $[\alpha]_D^{25}$ +13.6 (*c* 0.36, $CHCl_3$) for a 99% ee sample.

IR (neat): 3062, 3029, 2954, 2816, 1737, 1603, 1495, 1454, 1407, 1365, 1331, 1287, 1221, 1195, 1161, 1129, 1101, 1075, 1060, 1028, 944, 813, 750, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43–2.50 (m, 1 H), 2.81 (dt, *J* = 4.6, 12.92 Hz, 1 H), 3.19 (dd, *J* = 4.7, 13.9 Hz, 1 H), 3.31 (dd, *J* = 4.6, 13.9 Hz, 1 H), 3.39, (d, *J* = 13.2 Hz, 1 H), 3.69 (t, *J* = 4.7 Hz, 1 H), 3.84 (td, *J* = 2.7, 10.0 Hz, 1 H), 4.05 (d, *J* = 13.2 Hz, 1 H), 4.10 (dt, *J* = 2.9, 11.0 Hz, 1 H), 7.23–7.34 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6, 46.6, 59.2, 66.2, 67.5, 126.9, 127.7, 128.3, 128.7, 128.8, 128.9, 130.2, 137.1, 137.5, 170.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$: 282.1494; found: 282.1498.

The enantiomeric excess was determined by chiral HPLC analysis [column: Chiralpak cellulose 2 column; hexane–*i*-PrOH = 90:10), flow rate = 1.0 mL/min; t_R (1) = 15.8 min (major)].

4-Benzyl-3-*sec*-butylmorpholin-2-one (11b)

Prepared from *N*-benzylisoleucine (**10b**, 100 mg, 0.45 mmol) and $Br(CH_2)_2Br$ (0.05 mL, 0.59 mmol) as a yellowish gummy liquid; yield: 74 mg (66%); R_f = 0.52 (30% EtOAc–PE); $[\alpha]_D^{25}$ +72 (*c* 0.2, CH_2Cl_2).

IR (neat): 3064, 3029, 2964, 2933, 2876, 1733, 1604, 1496, 1454, 1381, 1329, 1278, 1172, 1144, 1073, 1028, 996, 908, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.91 (m, 6 H), 1.18–1.27 (m, 1 H), 1.56–1.61 (m, 1 H), 1.72–1.76 (m, 1 H), 3.13 (d, *J* = 6.3 Hz, 1 H), 3.53 (t, *J* = 5.8 Hz, 2 H), 3.61 (d, *J* = 12.6 Hz, 1 H), 3.84 (d, *J* = 13.2, 1 H), 4.37–4.45 (m, 2 H), 7.23–7.35 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 15.8, 25.6, 28.8, 38.3, 52.6, 63.9, 65.5, 127.1, 128.4, 140.0, 174.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$: 248.1651; found: 248.1653.

4-Benzyl-3-isobutylmorpholin-2-one (11c):

Prepared from *N*-benzylleucine (**10c**, 100 mg, 0.45 mmol) and $Br(CH_2)_2Br$ (0.05 mL, 0.59 mmol) as colorless liquid; yield: 67 mg (60%); R_f = 0.46 (30% EtOAc–PE).

IR (neat): 3062, 2956, 2871, 1731, 1502, 1454, 1373, 1355, 1272, 1215, 1166, 1139, 1052, 1018, 1010, 936, 872, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 1.48–1.52 (m, 2 H), 1.76–1.80 (m, 1 H), 3.34 (t, *J* = 7.3 Hz, 1 H), 3.64 (d, *J* = 12.9 Hz, 1 H), 3.81–3.83 (m, 3 H), 4.21–4.29 (m, 2 H), 7.24–7.32 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 22.9, 25.0, 42.8, 52.2, 59.3, 61.3, 66.3, 127.2, 128.4, 128.5, 139.7, 176.3.

HRMS (ESI): *m/z* $[M + NH_4]^+$ calcd for $C_{15}H_{25}N_2O_2$: 265.1916; found: 265.1911.

4-Benzyl-3-isopropylmorpholin-2-one (11d)

Prepared from *N*-benzylvaline (**10d**, 100 mg, 0.48 mmol) and $Br(CH_2)_2Br$ (0.05 mL, 0.63 mmol) as a yellowish liquid; yield: 70 mg (62%); R_f = 0.42 (30% EtOAc–PE); $[\alpha]_D^{25}$ +67.67 (*c* 0.32, $CHCl_3$).

IR (neat): 2961, 2931, 2874, 1733, 1496, 1454, 1386, 1366, 1283, 1207, 1168, 1143, 1060, 1028, 1012, 941, 871, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.9 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 2.08–2.21 (m, 1 H), 2.50–2.56 (m, 1 H), 2.87 (dt, *J* = 2.3, 13.2 Hz, 1 H), 3.25 (d, *J* = 3.5 Hz, 1 H), 3.92 (d, *J* = 13.8 Hz, 1 H), 4.25–4.38 (m, 3 H), 7.23–7.35 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4, 19.9, 32.6, 47.1, 60.7, 67.6, 70.6, 127.6, 128.4, 128.7, 137.9, 170.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$: 234.1494, found: 234.1490.

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Supporting Information

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References

(1) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641; and references therein.

(2) (a) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8333. (b) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8337. (c) Clark, S. M.; Osborn, H. M. I. *Tetrahedron: Asymmetry* **2004**, *15*, 3643. (d) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257. (e) Hajós, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23. (f) Versiani, M.; Cassano, G.; Perugi, G.; Benedetti, A.; Mastalli, L.; Nardi, A.; Savino, M. *J. Clin. Psychiatry* **2002**, *63*, 31. (g) Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinholt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818. (h) Pendergrass, K.; Hargreaves, R.; Petty, K. J.; Carides, A. D.; Evans, J. K.; Horgan, K. J. *Drugs Today* **2004**, *40*, 853. (i) Hikichi, M.; Yokokura, T.; Furuta, T.; Yaegashi, T. JP 62135472, **1987**; *Chem. Abstr.* **1987**, *107*, 198358 (j) Gharpure, J. S.; Prasad, K. V. J. *J. Org. Chem.* **2011**, *76*, 10325.

(3) (a) Nilsson, J. W.; Kvarnström, I.; Musil, D.; Nilsson, I.; Samuelsson, B. *J. Med. Chem.* **2003**, *46*, 3985. (b) Gonzalez, A. Z.; Eksterowicz, J.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chow, D.; Duquette, J.; Fox, B. M.; Fu, J.; Huang, X.; Houze, J. B.; Jin, L.; Li, Y.; Li, Z.; Ling, Y.; Lo, M.-C.; Long, A. M.; McGee, L. R.; McIntosh, J.; McMinn, D. L.; Oliner, J. D.; Osgood, T.; Rew, Y.; Saiki, A. Y.; Shaffer, P.; Wortman, S.; Yakowec, P.; Yan, X.; Ye, Q.; Yu, D.; Zhao, X.; Zhou, J.; Olson, S. H.; Medina, J. C.; Sun, D. *J. Med. Chem.* **2014**, *57*, 2472.

(4) (a) Dave, R.; Sasaki, N. A. *Org. Lett.* **2004**, *6*, 15. (b) Dave, R.; Sasaki, N. A. *Tetrahedron: Asymmetry* **2006**, *17*, 388. (c) Bettoni, G.; Frachini, C.; Perrone, P.; Tortorella, V. *Tetrahedron* **1980**, *36*, 409. (d) Sladojevich, F.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2007**, *72*, 4254.

(5) (a) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100. (b) Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045. (c) Métro, T.-X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707. (d) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937. (e) Cupples, C. A.; Morton, H. N. WO 9638465, **1996**. (f) Fish, P. V.; Mackenny, M.; Bish, G.; Buxton, T.; Cave, R.; Drouard, D.; Hoople, D.; Jessiman, A.; Miller, D.; Pasquinet, C.; Patel, B.; Reeves, K.; Ryckmans, T.; Skerten, M.; Wakenhut, F. *Tetrahedron Lett.* **2009**, *50*, 389.

(6) (a) Albanese, D.; Salsa, M.; Landini, D.; Lupi, V.; Penso, M. *Eur. J. Org. Chem.* **2007**, 2107. (b) Abdel-Jalil, R. J.; Ali Shah, S. T.; Khan, K. M.; Voelter, W. *Lett. Org. Chem.* **2005**, *2*, 306. (c) Henegar, K. E. *J. Org. Chem.* **2008**, *73*, 3662. (d) Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. *Tetrahedron* **2004**, *60*, 11709.

(7) (a) Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740. (b) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013. (c) Wang, L.; Liu, Q.-B.; Wang, D.-S.; Li, X.; Han, X.-W.; Xiao, W.-J.; Zhou, Y.-G. *Org. Lett.* **2009**, *11*, 1119. (d) Bera, M.; Roy, S. *J. Org. Chem.* **2009**, *74*, 8814. (e) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678. (f) Taylor, A. M.; Schreiber, S. L. *Tetrahedron Lett.* **2009**, *50*, 3230. (g) Kogami, Y.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2963. (h) Mollet, K.; Goossens, H.; Piens, N.; Catak, S.; Waroquier, M.; Törnroos, K. W.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *Chem. Eur. J.* **2013**, *19*, 3383.

(8) (a) Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, 1771. (b) Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukuzawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3251. (c) Takemoto, T.; Iio, Y.; Nishi, T. *Tetrahedron Lett.* **2000**, *41*, 1785. (d) D'Arrigo, P.; Lattanzio, M.; Pedrocchi, G.; Servi, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4021. (e) Wilkinson, M. C. *Tetrahedron Lett.* **2005**, *46*, 4773.

(9) (a) Grotenberg, G. M.; Christina, A. E.; Buizert, A. E. M.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *J. Org. Chem.* **2004**, *69*, 8331. (b) Du, M.; Hindsgaul, O. *Synlett* **1997**, 395.

(10) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3784.

(11) Ritzen, B.; Hoekman, S.; Duràn Verdasco, E.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2010**, *75*, 3461.

(12) (a) Pedrosa, R.; Andrés, C.; Mendiguchia, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854. (b) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1021.

(13) Kasima, C.; Harada, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1521.

(14) (a) Devine, P. N.; Foster, B. S.; Grabowski, E. J. J.; Reider, P. J. *Heterocycles* **2002**, *58*, 119. (b) Park, Y. S.; Lee, Y. M.; Kang, K. H.; Min, H. M.; Lim, H. J.; Park, E. H. *ARKIVOC* **2010**, *(ii)*, 1.

(15) Baek, J.; Jang, J. I.; Park, Y. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 4067.

(16) Burdzhiev, N.; Stanoeva, E.; Shivachev, B.; Nikolova, R. *C. R. Chim.* **2014**, *17*, 420.

(17) (a) Samanta, S.; Bhattacharyya, A.; Das, S.; Ghorai, M. K. *Curr. Org. Chem.* **2014**, *18*, 2842. (b) Talukdar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954. (c) Ghorai, M. K.; Samanta, S.; Das, S. *Asian J. Org. Chem.* **2013**, *2*, 1026.

(18) (a) Ghorai, M. K.; Nanaji, Y.; Yadav, A. K. *Org. Lett.* **2011**, *13*, 4256. (b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373. (c) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191. (d) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105. (e) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103. (f) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (g) Ghorai, M. K.; Sahoo, A. K.; Kumar, S. *Org. Lett.* **2011**, *13*, 5972. (h) Ghorai, M. K.; Halder, S.; Samanta, S. *Aust. J. Chem.* **2012**, *65*, 1262. (i) Ghorai, M. K.; Halder, S.; Das, R. K. *J. Org. Chem.* **2010**, *75*, 7061.

(19) The ee of morpholinone **2b** (>99%), as a representative example of morpholinones **2a**–**f**, was determined by chiral HPLC analysis.

(20) See the Supporting Information for details.

(21) Crystallographic data for compounds **2a** and **2b** have been deposited with the accession numbers CCDC 1033183 and 1033184, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

(22) The ee of morpholine **9a** (>99%), as a representative example of morpholines **9a** and **9b**, was determined by chiral HPLC analysis.

(23) The ee of morpholine **11a** (>99%), as a representative example of morpholines **11a**–**d**, was determined by chiral HPLC analysis.