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Efficient One-Pot Synthesis of Enantiomerically Pure 2-(Hydroxymethyl)-morpholines

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An efficient and convenient one-pot procedure for the synthesis of enantiomerically pure 2-(hydroxymethyl)morpholines with a widely variable substitution pattern was developed. Addition of chiral β-amino alcohols to (*S*)- or (*R*)-epichlorohydrin in the presence of $LiClO_4$ afforded the corresponding chloro alcohols, which were treated with NaOMe to give the epoxides and, by subsequent intramolecular cyclization, the target compounds in good yields (57–77 %).

Introduction

Mono- and disubstituted morpholines are the chiral cores of a wide variety of pharmacologically highly active substances.[1] A selection of such compounds, with the clinically used antidepressant reboxetine (**1**)[2] as the prime example, is shown in Figure 1.[3] Characteristic of these morpholines are side chains in the 2-position of various complexity, which are synthetically accessible from a functionalized C_1 unit. In particular, enantiomerically pure morpholines of type **6**, possessing a 2-(hydroxymethyl) substituent, provide excellent precursors for the stereoselective preparation of heterocycles, as already demonstrated in several syntheses.[4] Despite their importance, only a few stereoselective approaches have so far been developed,[5,6] which are based on the condensation of chiral β-amino alcohols with activated glycerols,[7] glycidols,[8] chloroacetyl chloride,[9] methyl 4-bromo-2-butenoate,[10] or 1,3-difunctionalized 2-butenes.[11] However, all of these procedures require two or more steps for the construction of the morpholine system.

Herein we present a straightforward one-pot procedure that allows fast and efficient access to enantiomerically pure 2-(hydroxymethyl)morpholines **6** with a widely variable substitution pattern. The key step is the Lewis acid assisted addition of chiral β-amino alcohols to (*S*)- and (*R*)-epichlorohydrin, followed by intramolecular cyclization in the presence of a base.

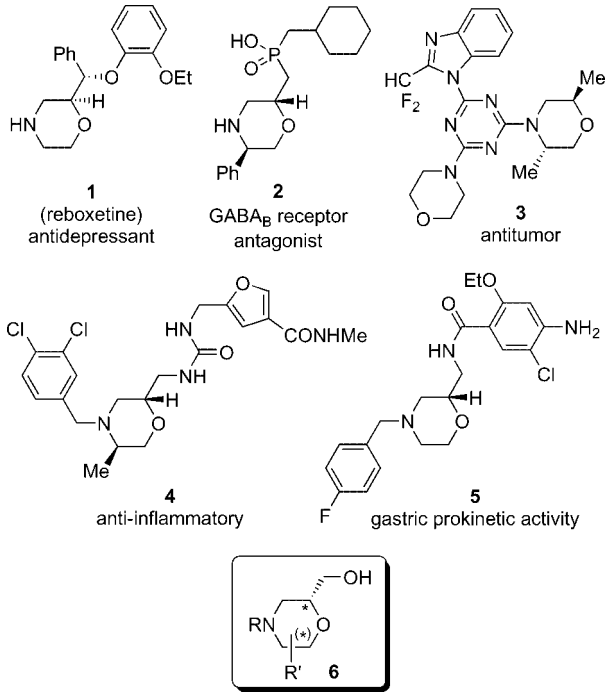

Figure 1. Pharmacologically active compounds possessing a chiral morpholine subunit and the target morpholines **6**.

Results and Discussion

The desired one-pot approach comprises three steps (Scheme 1): (1) the addition of an amino alcohol **7** to enantiomerically pure epichlorohydrin **8** [e.g. (*S*)-**8**] to give the chloro alcohol **9**, (2) its base-induced cyclization to the epoxide **10**, and (3) the final ring closure, delivering the desired morpholine **6**. In addition to the necessity to find reaction conditions compatible with all three steps, there are two major problems to be solved concerning the regioselectivity. Firstly, the initial addition of **7** to (*S*)-**8** has to proceed highly selectively at the epoxide group. Any competing attack of **7** at the chlorine-bearing terminal carbon atom of (*S*)-**8** would lead to the enantiomeric or, in the case of chiral

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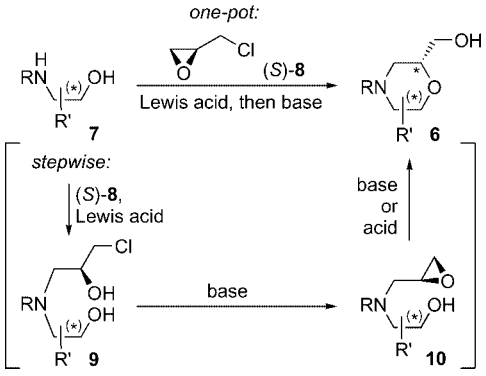
amino alcohols, to the diastereomeric epoxide and, thus, to a reduced optical purity in the product **6**. Secondly, the final ring closure of **10** has to occur in a 6-*exo-tet* fashion in order to give **6**, which requires an attack of the OH group at the inner position of the epoxide **10**. A competing reaction at the terminal site of the epoxide would deliver an oxazepane as a byproduct (7-*endo-tet* ring closure).



Scheme 1. Concept for the intended one-pot synthesis of enantiomerically pure 2-(hydroxymethyl)morpholines **6**.

Initial studies to establish the stepwise route and, subsequently, the one-pot procedure, were performed on the condensation of 2-(benzylamino)ethanol (**7a**) and racemic epichlorohydrin (*rac*-**8**) as the model reaction.

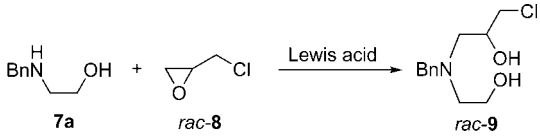
Optimization of the Stepwise Route

It is known that the ring opening of epichlorohydrin (**8**) with nucleophiles[12] proceeds smoothly and highly regioselectively at C-3 in the presence of many Lewis acids such as $MgSO_4$, $BF_3{\cdot}OEt_2$, or $LiClO_4$.[13] In our case, quantitative conversion of **7a** into the chloro alcohol *rac*-**9** only occurred with $LiClO_4$ in toluene or dichloroethane (Table 1); the intermediate *rac*-**9** was obtained in high isolated yield (84–89%) within 14 h at 20 °C or 4 h at 60 °C (Table 1, Entries 5–7). The Lewis acid $LiClO_4$ had to be applied in a slight excess, since the reaction rate in the presence of catalytic amounts was too low for the efficient formation of *rac*-**9** (ca. 70% conversion within 72 h, Table 1, Entries 9 and 10).

It is important to mention that, in the reactions with $LiClO_4$ as the Lewis acid, the epoxide *rac*-**10** was not detected in the ^1H NMR spectra of the crude reaction mixtures. Since *rac*-**10** would be the product of the unwanted S_N2 reaction at the terminal chlorine-bearing carbon atom of *rac*-**8**, this proves a highly regioselective attack of **7a** at the epoxide function of *rac*-**8** and also suggests that high regiocontrol (and, therefore, also potentially high stereocontrol) would be obtained in the intended morpholine syntheses with enantiomerically pure epichlorohydrin (vide infra).

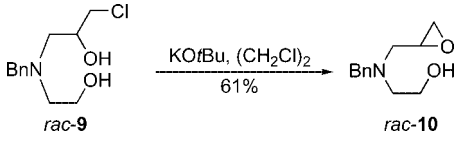
The second step, the cyclization of the chloro alcohol *rac*-**9** to the epoxide *rac*-**10**, proved to be difficult (Scheme 2). With most of the base/solvent systems screened, the reaction could not be stopped selectively at this stage but delivered instead mixtures of unreacted starting material *rac*-**9**, the desired product *rac*-**10**, and ring-closure products like *rac*-**6a**. Good yields of the epoxide *rac*-**10** (61%) were obtained with KO*t*Bu in dichloroethane. The direct preparation of *rac*-**10** from **7a** is also possible; the addition of **7a** to *rac*-**8** in dichloroethane (see Table 1, Entry 5) and subsequent treatment with KO*t*Bu afforded *rac*-**10** in 63% isolated yield.

Table 1. Lewis acid mediated addition of the amino alcohol **7a** to *rac*-**8**.



Entry	Lewis acid[a] (equiv.)	Solvent	*T* [°C]	*t* [h]	Conversion[b] (Yield[c]) [%]
1	–	$(CH_2Cl)_2$	20	72	trace
2	LiX[d] (1.3)	$(CH_2Cl)_2$	20	72	50
3	$CsClO_4$ (1.3)	$(CH_2Cl)_2$	20	72	50
4	$Mg(ClO_4)_2$ (1.3)	$(CH_2Cl)_2$	20	72	50
5	$LiClO_4$ (1.3)	$(CH_2Cl)_2$	20	14	100 (86)
6	$LiClO_4$ (1.3)	toluene	20	14	100 (89)
7	$LiClO_4$ (1.3)	toluene	60	4	100 (84)
8	$LiClO_4$ (1.3)	MeOH	20	14	50
9	$LiClO_4$ (0.1)	$(CH_2Cl)_2$	20	72	70
10	$LiClO_4$ (0.1)	toluene	20	72	70 (61)

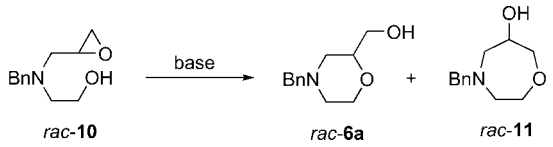
[a] Low conversion or decomposition with NaI, CsI, $ZnBr_2$, $BiBr_3$, $SnCl_4$, $ZrCl_4$, CuI, $MgSO_4$, and $BF_3{\cdot}OEt_2$ as the Lewis acids. [b] Judged by TLC. [c] Isolated yields. [d] LiCl, LiBr, or $LiI{\cdot}2H_2O$.



Scheme 2. Base-induced cyclization of the chloro alcohol *rac*-**9** to the epoxide *rac*-**10**.

The intramolecular cyclization of the epoxide *rac*-**10** to the morpholine *rac*-**6a**[14] requires a 6-*exo* ring closure (i.e. a reaction at the more highly substituted inner position of the epoxide, Table 2). Since this attack should be favored under protic or Lewis acidic conditions, camphorsulfonic acid in CH_2Cl_2[15] and $LiClO_4$ in toluene or dichloroethane were screened; however, only traces of *rac*-**6a** were detected. In contrast, basic conditions, which bear the risk of a competing 7-*endo* cyclization at the less-substituted terminal carbon atom of *rac*-**10** to afford the oxazepane *rac*-**11**, proved to be successful. With NaOMe in MeOH, KO*t*Bu in *t*BuOH, or LiOH in Et_2O (Table 2), the desired morpholine *rac*-**6a** was obtained in 42–50% yield, albeit accompanied by 10–22% of *rac*-**11**. Weaker bases like NaOH in H_2O/MeOH or DBU in EtOH[16] delivered inseparable mixtures of unidentified compounds.

Table 2. Cyclization of the epoxide *rac*-**10** to the morpholine *rac*-**6a** and the oxazepane *rac*-**11**.



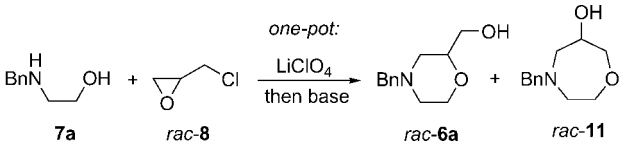
Entry	Base (equiv.)	Solvent	*T* [°C]	*t* [h]	*rac*-**6a**[a] Yield [%]	*rac*-**11**[a] Yield [%]
1	NaOMe (1.3)	MeOH	20	14	49	16
2	KO*t*Bu (1.4)	*t*BuOH	20	72	50	22
3	LiOH (3.2)	Et_2O	35	72	42	10

[a] Isolated yields.

Optimization of the One-Pot Procedure

With these results in hand we turned our attention to the one-pot procedure (Table 3). A mixture of **7a**, *rac*-**8**, and $LiClO_4$ was stirred in a given solvent until TLC indicated quantitative conversion into the intermediate *rac*-**9**. After the addition of base, continued stirring for 14–72 h, and workup, the products *rac*-**6a** and *rac*-**11** were separated by column chromatography, and their yields were determined. The best results were obtained at 20 and 60 °C in toluene with NaOMe as the base and MeOH as a cosolvent (Table 3, Entries 1 and 2). Under these conditions, the morpholine *rac*-**6a** was isolated in 55 and 62% yield, respectively, which is by far better than the overall yield of the single-step reactions (ca. 23%). Other base/solvent combinations afforded *rac*-**6a** in significantly lower yields, even at elevated temperatures or prolonged reaction times (Table 3, Entries 3–6). The oxazepane *rac*-**11** was formed as a minor side product in all reactions. Cyclizations with LiO*t*Bu or LiOH as the bases afforded complex product mixtures.

Table 3. Conditions for the one-pot synthesis of *rac*-**6a**.



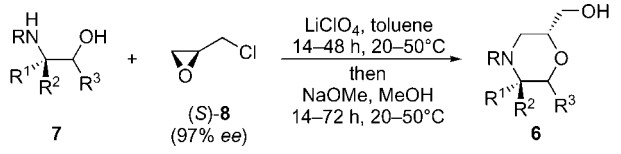
Entry	Base (equiv.)	Solvent[a]	*T* [°C]	*t*[a] [h]	*rac*-**6a**[b] Yield [%]	*rac*-**11**[b] Yield [%]
1	NaOMe (2.5)	toluene[c]	20	14/14	55	14
2	NaOMe (2.5)	toluene[c]	60	4/4	62	24
3	NaOH (1.4)	toluene	20	14/72	37	8
4	KO*t*Bu (2.0)	*t*BuOH	90	72/6	35	20
5	KO*t*Bu (2.0)	$(CH_2Cl)_2$	60	14/72	31[d]	8
6	KO*t*Bu (2.0)	toluene	60	14/72	45[e]	12

[a] Reaction time prior to/after the addition of base. [b] Isolated yields. [c] Methanol was added as a cosolvent prior to treatment with base. [d] 47% of the epoxide *rac*-**10** was isolated. [e] 14% of the epoxide *rac*-**10** was isolated.

Stereoselective One-Pot Synthesis of 2-(Hydroxymethyl)-morpholines

Finally, the scope of this one-pot procedure was evaluated in the stereoselective synthesis of several morpholines **6** (Table 4). Condensation of commercially available (*S*)-epichlorohydrin [(*S*)-**8**, 97% *ee*] with a selection of achiral and chiral β-amino alcohols **7** delivered the target molecules **6** in good yields of 57–77%. The structures of all products **6** were unambiguously proven by extensive two-dimensional NMR experiments.[17] Alkyl, dialkyl, and phenyl groups are tolerated in the α-position to the nitrogen atom of **7** (Table 4, Entries 2–6). The *N*-benzyl group, which will allow further manipulations at the nitrogen atom after hydrogenolytic deprotection,[18] is not essential; the *N*-methyl derivative **7f** also underwent the cyclization to give **6f** in 61% yield (Table 4, Entry 6). With the secondary *o*-hydroxyaniline **7g** as the substrate, the benzoxazine **6g** was formed in 67% yield (Table 4, Entry 7). Primary amines like 2-aminoethanol (**6h**), however, failed to give a defined product (Table 4, Entry 8). An *N*-Boc protecting group as in **7i**, which significantly reduces the nucleophilicity of the nitrogen atom, inhibits the reaction with (*S*)-**8**, even at elevated temperatures (Table 4, Entry 9). Finally, it is noteworthy to mention that a significant amount (18% yield) of an oxazepane byproduct of type **11** was found only in the cyclization of the unsubstituted amino alcohol **7a** with (*S*)-**8**, but not in the analogous reactions of the substituted amino alcohols **7b**–**g**.[19]

Table 4. Enantioselective preparation of the morpholines **6** from (*S*)-**8** and a selection of β-amino alcohols **7**.



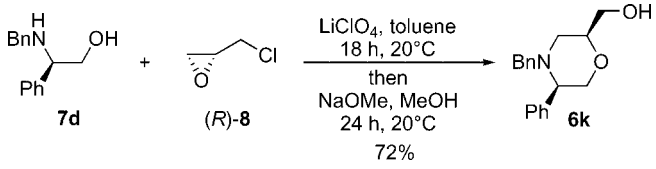
Entry	**6**, **7**	R	R^1	R^2	R^3	Yield of **6**[a] [%]	*eelde* [%]
1[b]	**a**	Bn	H	H	H	59[c]	94[d]
2[e]	**b**	Bn	*i*Pr	H	H	63	>97[f]
3[e]	**c**	Bn	*t*Bu	H	H	60	>97[f]
4[b]	**d**	Bn	H	Ph	H	77	>97[f]
5[b]	**e**	Bn	Me	Me	H	57	97[d]
6[b]	**f**	Me	H	Ph	H	61	>97[f]
7[e]	**g**	Bn	–	R^2–R^3 = benzo		67	97[d]
8[b]	**h**	H	H	H	H	–[g]	–
9[e]	**i**	Boc	H	Bn	H	–[h]	–

[a] Isolated yields. [b] 20 °C. [c] 14% of the oxazepane **11** was isolated. [d] Enantiomeric excess (*ee*) was determined by ^{19}F NMR spectroscopy of the corresponding Mosher esters. [e] 50 °C. [f] According to ^1H NMR spectroscopy, diastereomerically pure compounds after column chromatography.[20] [g] Complex product mixture. [h] No reaction.

The enantiomeric purities of **6a**, **6e**, and **6g** were analyzed by ^{19}F NMR spectroscopy of the corresponding Mosher esters. A slightly diminished *ee* of 94%, as compared to the 97% *ee* of the chiral reactant [(*S*)-**8**] used, was found for the

morpholine **6a**; thus, a slight erosion of the optical purity had occurred, probably a consequence of an interfering S_N2 reaction in the first step, which is the addition of **7a** to (*S*)-**8** (vide supra). However, no such erosions of the *ee* were observed for the dimethyl derivative **6e** (97% *ee*) and the oxazepane **6g** (97% *ee*). Furthermore, no diastereomeric products were detected in the reactions of the chiral amino alcohols **7b–d** and **7f** with (*S*)-**8**.[20] The morpholines **6b–d** and **6f** were obtained in enantio- and diastereomerically pure form after column chromatography.

With this one-pot procedure, both, *cis*- (**7b**,**c**) and *trans*-disubstituted morpholines (**7d**,**f**) are accessible in stereochemically homogeneous form and good yields. Therefore, the relative configuration of the two chiral reactants **7** and **8** to each other is not critical. All possible stereoisomers of a given disubstituted morpholine can be synthesized, as also shown in the condensation of **7d** with the enantiomeric epichlorohydrin (*R*)-**8** giving the morpholine **6k**, the *cis*-configured diastereomer of **6d**, in 72% yield (Scheme 3).



Scheme 3. Condensation of **7d** with (*R*)-**8** to give the morpholine **6k**.

Conclusions

An efficient and convenient one-pot procedure for the preparation of enantiomerically pure 2-(hydroxymethyl)-morpholines, which are versatile synthetic building blocks, was developed. Treatment of chiral β-amino alcohols with (*S*)-epichlorohydrin and $LiClO_4$ in toluene and, subsequently, with NaOMe in MeOH delivered the desired target molecules in 57–77% yield. The scope of this reaction was demonstrated in the stereoselective synthesis of seven 2-(hydroxymethyl)morpholines and of one benzoxazine. The epimeric products are likewise accessible from (*R*)-epichlorohydrin and the respective amino alcohols. Further investigations like the extension of this method to the stereoselective synthesis of chiral 3-(hydroxymethyl)morpholines, 2-(hydroxymethyl)piperazines, and -dioxanes are in progress.

Experimental Section

General: Optical rotations (25 °C, 10 cm cell) were measured with a Jasco P-1020 polarimeter. All NMR spectra were acquired at 20 °C with a Bruker AV 400 instrument with $CDCl_3$ as the internal reference. IR spectra were recorded with a Jasco FT-IR-410 spectrometer. High resolution mass spectra were measured with a Bruker Daltonics micrOTOF focus spectrometer. R_f values refer to TLC on aluminum foil backed silica gel plates. Column chromatography was performed on silica gel (63–200 mesh). For the detection of compounds, the extinction of fluorescence at 254 nm was used. All reactions were performed under argon in dry solvents. Compounds *rac*-, (*S*)- and (*R*)-epichlorohydrin [*rac*-**8**, (*S*)-**8** (97% *ee*), and (*R*)-**8** (97% *ee*)], and 2-(benzylamino)ethanol (**7a**) are commercially available and were used as received. The enantiomerically pure benzylamino alcohols **7b**,[21] **7d**,[22] **7e**,[23] and **7g**[24] are known compounds, which were prepared by reductive amination of benzaldehyde in analogy to **7c**; the methylamino alcohol **7f** was prepared according to a literature procedure.[25]

(*S*)-2-(Benzylamino)-3,3-dimethylbutan-1-ol (7c): A solution of (*S*)-2-amino-3,3-dimethylbutan-1-ol (318 mg, 2.71 mmol) and benzaldehyde (277 μL, 287 mg, 2.71 mmol) in absolute MeOH (5 mL) was stirred at 20 °C for 2 h. $NaBH_4$ (102 mg, 271 mmol) was added at 0 °C, and stirring was continued for 1 h. CH_2Cl_2 (50 mL) and saturated aq. NH_4Cl (30 mL) were added, and the layers were separated. After extraction of the aqueous layer with CH_2Cl_2 (20 mL), the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was chromatographed (silica gel; EtOAc) to afford **7c** (471 mg, 2.27 mmol, 84% yield) as a highly viscous colorless oil. R_f = 0.40 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{23}$ = +9.85 (*c* = 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 [s, 9 H, C(C*H*$_3$)$_3$], 1.50–3.00 (br. s, 2 H, NH, OH), 2.40 (dd, *J* = 6.4, 4.7 Hz, 1 H, C*H*N), 3.41 (dd, *J* = 10.6, 6.4 Hz, 1 H, C*H*HOH), 3.66 (dd, *J* = 10.6, 4.7 Hz, 1 H, CH*H*OH), 3.84 (d, *J* = 12.8 Hz, 1 H, C*H*HPh), 3.91 (d, *J* = 12.8 Hz, 1 H, CH*H*Ph), 7.24–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 [C(*C*H$_3$)$_3$], 34.6 [*C*(CH$_3$)$_3$], 54.5 (*C*H$_2$Ph), 60.2 (*C*H$_2$OH), 67.3 (*C*HN), 127.3 (Ph), 128.3 (Ph), 128.7 (Ph), 140.7 (Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3170, 2952, 2863, 1483, 1453, 1053, 748, 697 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for [$C_{13}H_{21}NO$ + H]$^+$ 208.1696; found 208.1696.

1-[Benzyl(2-hydroxyethyl)amino]-3-chloropropan-2-ol (*rac*-9): Racemic epichlorohydrin (*rac*-**8**, 2.15 g, 1.83 mL, 23.3 mmol) and $LiClO_4$ (2.49 g, 23.3 mmol) were added to a solution of **7a** (3.20 g, 21.2 mmol) in toluene (40 mL). After 14 h at 20 °C, EtOAc (100 mL) was added, and the reaction mixture was washed with water (2 × 50 mL). The combined aqueous layers were extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and the solvent was removed in vacuo. Purification by column chromatography (silica gel; EtOAc/Et_3N, 100:1) delivered *rac*-**9** (4.60 g, 18.9 mmol, 89% yield) as a slightly yellow oil. R_f = 0.25 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (br. s, 1 H, OH), 2.67 (dd, *J* = 13.4, 8.3 Hz, 1 H, 1-H), 2.70 (ddd, *J* = 13.4, 5.3, 4.4 Hz, 1 H, 1-H′), 2.74 (dd, *J* = 13.4, 4.2 Hz, 1 H, 1′-H), 2.79 (ddd, *J* = 13.4, 6.8, 4.8 Hz, 1 H, 1′-H′), 3.25 (br. s, 1 H, OH), 3.50 (dd, *J* = 11.1, 5.6 Hz, 1 H, 3-H), 3.54 (dd, *J* = 11.1, 4.8 Hz, 1 H, 3-H′), 3.64 (m, 2 H, 2′-H, 2′-H′), 3.67 (d, *J* = 13.9 Hz, 1 H, C*H*HPh), 3.79 (d, *J* = 13.6 Hz, 1 H, CH*H*Ph), 3.88 (m, 1 H, 2-H), 7.20–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.5 (C-3), 56.7 (C-1′), 57.7 (C-2′, *C*H$_2$Ph), 68.9 (C-2), 127.6 (Ph), 128.7 (Ph), 129.1 (Ph), 138.5 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3348, 2952, 2885, 2834, 1638, 1495, 1453, 1049, 738, 702 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for [$C_{12}H_{18}ClNO_2$ + H]$^+$ 244.1099; found 244.1097.

2-[Benzyl(oxiranylmethyl)amino]ethanol (*rac*-10) from *rac*-9: A solution of *rac*-**9** (800 mg, 3.28 mmol) in $(CH_2Cl)_2$ (15 mL) was treated with KO*t*Bu (438 mg, 3.92 mmol) and stirred at 20 °C for 8 h. CH_2Cl_2 (50 mL) was added, and the reaction mixture was washed with saturated aq. NH_4Cl (50 mL) and brine (50 mL), dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH, 95:5) to give *rac*-**10** (415 mg, 2.00 mmol, 61% yield) as a slightly yellow oil. R_f = 0.30 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (dd, *J* = 4.8, 2.7 Hz, 1 H, 3′-H), 2.51 (dd, *J* = 14.0, 6.3 Hz, 1 H, 1′-H),

2.55–2.80 (br. s, 1 H, OH), 2.72 (ddd, J = 13.1, 5.6, 4.4 Hz, 1 H, 2-H), 2.74 (dd, J = 4.8, 4.1 Hz, 1 H, 3′-H′), 2.85 (ddd, J = 13.1, 6.6, 4.8 Hz, 1 H, 2-H′), 2.89 (dd, J = 14.1, 3.3 Hz, 1 H, 1′-H′), 3.07 (m, 1 H, 2′-H), 3.62 (m, 2 H, 1-H, 1-H′), 3.68 (d, J = 13.6 Hz, 1 H, C*H*HPh), 3.83 (d, J = 13.5 Hz, 1 H, CH*H*Ph), 7.20–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.1 (C-3′), 50.9 (C-2′), 56.0 (C-1′), 56.1 (C-2), 59.0 (C-1), 59.4 (*C*H_2Ph), 127.5 (Ph), 128.6 (Ph), 129.1 (Ph), 138.7 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3409, 2943, 2833, 1602, 1453, 1051, 739 cm^{-1}. HRMS (ESI; MeOH): calcd. for $[C_{12}H_{17}NO_2 + H]^+$ 208.1332; found 208.1324.

2-[Benzyl(oxiranylmethyl)amino]ethanol (*rac*-10) from 7a and *rac*-8: To a solution of **7a** (1.00 g, 940 μL, 6.60 mmol) in $(CH_2Cl)_2$ (10 mL), *rac*-**8** (670 mg, 570 μL, 7.30 mmol) and $LiClO_4$ (800 mg, 7.50 mmol) were added. The reaction mixture was stirred at 20 °C for 14 h, cooled to 0 °C, treated with KO*t*Bu (2.96 g, 26.4 mmol), and stirred at 20 °C for a further 6 h. Workup and chromatography as described above afforded *rac*-**10** (862 mg, 4.16 mmol, 63% yield) as a slightly yellow oil.

***N*-Benzyl-2-(hydroxymethyl)morpholine (*rac*-6a) and *N*-Benzyl-1,4-oxazepan-6-ol (*rac*-11):** NaOMe (42.0 mg, 780 μmol) was added to a solution of *rac*-**10** (125 mg, 600 μmol) in MeOH (3 mL). The reaction mixture was stirred at 20 °C for 14 h, and the solvent was removed in vacuo. The residue was dissolved in Et_2O (5 mL) and washed with saturated aq. NH_4Cl (5 mL) and brine (5 mL). The organic layer was dried with $MgSO_4$, and the solvent removed in vacuo. Column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2) afforded, in the order of elution, *rac*-**11** (20.0 mg, 96.5 μmol, 16% yield) and *rac*-**6a**[26] (61 mg, 290 μmol, 49% yield) as slightly yellow oils. For the characterization, see the enantiomerically pure compounds below.

General Procedure for the One-Pot Synthesis of the 2-(Hydroxymethyl)morpholines 6: A solution of the amino alcohol **7** (1.00 mmol) in absolute toluene (5 mL) was treated with (*S*)-epichlorohydrin [(*S*)-**8**, 102 μL, 120 mg, 1.30 mmol] and $LiClO_4$ (138 mg, 1.30 mmol). After 14–48 h at 20 °C or 50 °C, MeOH (1.3 mL) and NaOMe (135 mg, 2.50 mmol) were added, and stirring was continued for 14–72 h. The reaction mixture was quenched with saturated aq. NH_4Cl (30 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were extracted with brine (20 mL), dried with $MgSO_4$, and the solvent was removed in vacuo. Chromatographic purification (silica gel; Et_2O/hexanes, 50:50 or CH_2Cl_2/MeOH, 98:2 → 90:10) delivered the desired 2-(hydroxymethyl)morpholine **6**. In the case of **7a**, the oxazepane **11** was formed as a byproduct.

(*R*)-*N*-Benzyl-2-(hydroxymethyl)morpholine (6a): 123 mg, 593 μmol, 59% yield; 94% *ee*; R_f = 0.19 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{22}$ = –23.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (br. s, 1 H, OH), 2.01 (dd, J = 12.4, 9.9 Hz, 1 H, 3-H), 2.19 (td, J = 11.4, 3.3 Hz, 1 H, 5-H), 2.67 (m, 2 H, 3-H′, 5-H′), 3.48 (d, J = 12.7 Hz, 1 H, C*H*HPh), 3.53 (d, J = 12.6 Hz, 1 H, CH*H*Ph), 3.56 (dd, J = 11.4, 6.4 Hz, 1 H, C*H*HOH), 3.62 (dd, J = 11.4, 3.5 Hz, 1 H, CH*H*OH), 3.66 (m, 1 H, 2-H), 3.71 (td, J = 11.3, 2.5 Hz, 1 H, 6-H), 3.90 (ddd, J = 11.4, 3.3, 1.9 Hz, 1 H, 6-H′), 7.20–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 (C-5), 54.7 (C-3), 63.5 (*C*H_2Ph), 64.5 (*C*H_2OH), 66.8 (C-6), 76.1 (C-2), 127.4 (Ph), 128.5 (Ph), 129.3 (Ph), 137.7 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3408, 2927, 2868, 2815, 1454, 1117, 1052, 748, 700 cm^{-1}. HRMS (ESI; MeCN): calcd. for $[C_{12}H_{17}NO_2 + H]^+$ 208.1332; found 208.1329. The *ee* of **6a** was determined by ^{19}F NMR spectroscopy of the corresponding (*R*)-Mosher ester, as shown below.

(*S*)-*N*-Benzyl-1,4-oxazepan-6-ol (11): 37.1 mg, 179 μmol, 18% yield; R_f = 0.30 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{22}$ = +12.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (ddd, J = 12.4, 7.3, 5.1 Hz, 1 H, 3-H), 2.83 (m, 2 H, 3-H′, 5-H), 2.97 (ddd, J = 12.6, 5.8, 1.5 Hz, 1 H, 5-H′), 3.73 (m, 4 H, 2-H, 2-H′, CH_2Ph), 3.79 (m, 2 H, 7-H, 7-H′), 3.83 (m, 1 H, 6-H), 3.96 (m, 1 H, OH), 7.20–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.2 (C-5), 57.8 (C-3), 63.5 (*C*H_2Ph), 69.1 (C-6), 70.2 (C-2), 76.4 (C-7), 127.6 (Ph), 128.6 (Ph), 129.1 (Ph), 138.6 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3408, 2937, 2861, 1455, 1103, 1058, 742, 700 cm^{-1}. HRMS (ESI; MeOH): calcd. for $[C_{12}H_{17}NO_2 + H]^+$ 208.1332; found 208.1335.

(2*R*,5*S*)-*N*-Benzyl-2-(hydroxymethyl)-5-isopropylmorpholine (6b): 157 mg, 631 μmol, 63% yield; R_f = 0.60 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{23}$ = +19.2 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 0.99 [d, J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 2.15 (m, 1 H, 5-H), 2.30 [oct, J = 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.37 (dd, J = 13.1, 3.2 Hz, 1 H, 3-H), 2.45 (br. s, 1 H, OH), 2.82 (dd, J = 13.1, 7.8 Hz, 1 H, 3-H′), 3.57 (dd, J = 11.5, 3.3 Hz, 1 H, C*H*HOH), 3.59 (d, J = 13.5 Hz, 1 H, C*H*HPh), 3.67 (dd, J = 11.5, 6.6 Hz, 1 H, CH*H*OH), 3.76 (m, 1 H, 2-H), 3.82 (dd, J = 11.8, 3.3 Hz, 1 H, 6-H), 3.90 (dd, J = 11.8, 4.4 Hz, 1 H, 6-H′), 4.02 (d, J = 13.5 Hz, 1 H, CH*H*Ph), 7.20–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 [CH(*C*H$_3$)$_2$], 20.4 [CH(*C*H$_3$)$_2$], 26.1 [*C*H(CH$_3$)$_2$], 48.7 (C-3), 58.2 (*C*H_2Ph), 62.3 (C-6), 63.9 (C-5), 64.7 (*C*H_2OH), 71.6 (C-2), 127.2 (Ph), 128.5 (Ph), 128.8 (Ph), 139.4 (Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3423, 2958, 2869, 1452, 1093, 1072, 1045, 742, 698 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for $[C_{15}H_{23}NO_2 + H]^+$ 250.1802; found 250.1806.

(2*R*,5*S*)-*N*-Benzyl-5-*tert*-butyl-2-(hydroxymethyl)morpholine (6c): Colorless solid, 158 mg, 599 μmol, 60% yield; R_f = 0.60 (CH_2Cl_2/MeOH, 95:5); m.p. 92–93 °C. $[\alpha]_D^{23}$ = –6.79 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 [s, 9 H, C(CH_3)$_3$], 1.89 (dd, J = 7.1, 5.0 Hz, 1 H, OH), 2.34 (t, J = 5.6 Hz, 1 H, 5-H), 2.46 (dd, J = 14.6, 3.9 Hz, 1 H, 3-H), 2.87 (dd, J = 14.6, 11.5 Hz, 1 H, 3-H′), 3.45 (m, 2 H, CH_2OH), 3.83 (dd, J = 12.2, 5.6 Hz, 1 H, 6-H), 3.85 (d, J = 13.7 Hz, 1 H, C*H*HPh), 3.88 (dd, J = 12.1, 5.8 Hz, 1 H, 6-H′), 3.94 (m, 1 H, 2-H), 4.05 (d, J = 13.7 Hz, 1 H, CH*H*Ph), 7.25 (m, 1 H, Ph), 7.31 (m, 2 H, Ph), 7.36 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [C(*C*H$_3$)$_3$], 36.1 [*C*(CH$_3$)$_3$], 45.2 (C-3), 60.6 (C-6), 61.2 (*C*H_2Ph), 64.1 (*C*H_2OH), 66.7 (C-5), 69.7 (C-2), 127.2 (Ph), 128.4 (Ph), 128.8 (Ph), 140.2 (Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3474, 2955, 2926, 2862, 2808, 1351, 1260, 1112, 1021, 805, 738 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for $[C_{16}H_{25}NO_2 + H]^+$ 264.1958; found 264.1958.

(2*R*,5*R*)-*N*-Benzyl-2-(hydroxymethyl)-5-phenylmorpholine (6d): 218 mg, 770 μmol, 77% yield; R_f = 0.65 (*n*-pentane/Et_2O, 25:75). $[\alpha]_D^{23}$ = –69.7 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (dd, J = 7.1, 5.4 Hz, 1 H, OH), 2.06 (dd, J = 11.5, 10.7 Hz, 1 H, 3-H), 2.78 (dd, J = 11.5, 2.3 Hz, 1 H, 3-H′), 2.88 (d, J = 13.3 Hz, 1 H, C*H*HPh), 3.38 (dd, J = 10.4, 3.4 Hz, 1 H, 5-H), 3.54 (ddd, J = 11.5, 6.3, 5.3 Hz, 1 H, C*H*HOH), 3.56 (dd, J = 11.4, 10.5 Hz, 1 H, 6-H), 3.62 (ddd, J = 11.6, 7.1, 3.4 Hz, 1 H, CH*H*OH), 3.75 (m, 1 H, 2-H), 3.84 (d, J = 13.4 Hz, 1 H, CH*H*Ph), 3.86 (dd, J = 11.4, 3.5 Hz, 1 H, 6-H′), 7.20–7.32 (m, 6 H, Ph), 7.37 (t, J = 8.0 Hz, 2 H, Ph), 7.49 (d, 7.2 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 (C-3), 59.4 (*C*H_2Ph), 64.3 (*C*H_2OH), 67.3 (C-5), 73.5 (C-6), 76.8 (C-2), 127.1 (Ph), 128.1 (Ph), 128.4 (Ph), 128.87 (Ph), 128.94 (Ph), 138.5 (Ph), 139.5 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3440, 2953, 2854, 2808, 1738, 1494, 1452, 1266, 1119, 1045, 738, 702 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for $[C_{18}H_{21}NO_2 + H]^+$ 284.1645; found 284.1642.

(*R*)-*N*-Benzyl-2-(hydroxymethyl)-5,5-dimethylmorpholine (6e): 135 mg, 574 μmol, 57% yield; 97% ee; R_f = 0.65 (*n*-pentane/Et_2O, 25:75). $[\alpha]_D^{23}$ = –68.5 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 1.05 (s, 6 H, 2 × 5-CH_3), 1.88 (br. s, 1 H, OH), 2.26 (dd, J = 11.8, 9.9 Hz, 1 H, 3-H), 2.34 (dd, J = 11.8, 2.9 Hz, 1 H, 3-H′), 3.02 (d, J = 13.8 Hz, 1 H, CHHPh), 3.45 (dd, J = 10.9, 0.6 Hz, 1 H, 6-H), 3.52 (d, J = 10.9 Hz, 1 H, 6-H′), 3.57 (m, 3 H, CH_2OH, 2-H), 4.01 (d, J = 13.8 Hz, 1 H, CHHPh), 7.20–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (5-CH$_3$), 24.4 (5-CH$_3$), 47.5 (C-3), 52.9 (C-5), 53.8 (CH$_2$Ph), 64.3 (CH$_2$OH), 77.3 (C-2), 77.7 (C-6), 126.9 (Ph), 128.4 (Ph), 128.7 (Ph), 140.1 (Ph) ppm. IR (film): $\tilde{\nu}$ = 3432, 2964, 2852, 1454, 1362, 1070, 1055, 731, 698 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for [$C_{14}H_{21}NO_2$ + H]$^+$ 236.1645; found 236.1639. The *ee* of **6e** was determined by ^{19}F NMR spectroscopy of the corresponding (*S*)- and (*R*)-Mosher esters, as shown below.

(2*R*,5*R*)-2-(Hydroxymethyl)-*N*-methyl-5-phenylmorpholine (6f): 127 mg, 612 μmol, 61% yield; R_f = 0.20 (*n*-pentane/Et_2O, 50:50). $[\alpha]_D^{23}$ = –129.5 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (br. s, 1 H, OH), 2.07 (s, 3 H, NCH_3), 2.21 (dd, J = 11.4, 10.9 Hz, 1 H, 3-H), 2.87 (dd, J = 11.5, 2.3 Hz, 1 H, 3-H′), 3.04 (dd, J = 10.4, 3.4 Hz, 1 H, 5-H), 3.51 (dd, J = 11.5, 10.4 Hz, 1 H, 6-H), 3.63 (br. dd, J = 11.4, 6.5 Hz, 1 H, CHHOH), 3.72 (br. d, J = 11.4 Hz, 1 H, CHHOH), 3.80 (dd, J = 11.5, 3.5 Hz, 1 H, 6-H′), 3.86 (m, 1 H, 2-H), 7.25–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.8 (NCH$_3$), 56.9 (C-3), 64.3 (CH$_2$OH), 69.0 (C-5), 73.1 (C-6), 76.6 (C-2), 128.0 (Ph), 128.6 (Ph), 128.7 (Ph), 139.0 (Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3404, 2949, 2850, 2792, 1451, 1121, 1056, 759, 702 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for [$C_{12}H_{17}NO_2$ + H]$^+$ 208.1332; found 208.1336.

(*R*)-*N*-Benzyl-2-(hydroxymethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (6g): 178 mg, 697 μmol, 70% yield; 97% *ee*; R_f = 0.20 (*n*-pentane/Et_2O, 75:25). $[\alpha]_D^{23}$ = –14.3 (c = 0.10 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (t, J = 6.4 Hz, 1 H, OH), 3.28 (m, 2 H, 3-H, 3-H′), 3.82 (m, 2 H, CH_2OH), 4.29 (m, 1 H, 2-H), 4.44 (s, 2 H, CH_2Ph), 6.66 (m, 1 H, H-7), 6.71 (dd, J = 8.1, 1.5 Hz, 1 H, H-8), 6.81 (m, 1 H, 6-H), 6.87 (dd, J = 7.9, 1.5 Hz, 1 H, 5-H), 7.23–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.4 (C-3), 55.1 (CH$_2$Ph), 63.6 (CH$_2$OH), 73.9 (C-2), 112.7 (C-8), 118.2 (C-7), 116.6 (C-5), 121.9 (C-6), 127.3 (Ph), 127.4 (Ph), 128.9 (Ph), 135.3 (C-4a), 138.0 (Ph), 143.6 (C-8a) ppm. IR (KBr): $\tilde{\nu}$ = 3393, 3031, 2923, 2852, 1605, 1504, 1245, 1221, 1049, 741 cm^{-1}. HRMS (ESI; MeCN/$CHCl_3$, 1:1): calcd. for [$C_{16}H_{17}NO_2$ + H]$^+$ 256.1332; found 256.1332. The *ee* of **6g** was determined by ^{19}F NMR spectroscopy of the corresponding (*S*)- and (*R*)-Mosher esters, as shown below.

(2*S*,5*R*)-*N*-Benzyl-2-(hydroxymethyl)-5-phenylmorpholine (6k): Colorless solid, 205 mg, 723 μmol, 72% yield; R_f = 0.45 (*n*-pentane/Et_2O, 25:75); m.p. 104–105 °C. $[\alpha]_D^{23}$ = –30.8 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (dd, J = 12.1, 4.0 Hz, 1 H, 3-H), 2.83 (dd, J = 12.1, 2.7 Hz, 1 H, 3-H′), 2.91 (d, J = 13.4 Hz, 1 H, CHHPh), 2.99 (br. s, 1 H, OH), 3.51 (dd, J = 9.3, 3.8 Hz, 1 H, 5-H), 3.73 (m, 2 H, 6-H, CHHOH), 3.75 (d, J = 13.4 Hz, 1 H, CHHPh), 3.87 (m, 1 H, 2-H), 4.02 (dd, J = 11.6, 7.4 Hz, 1 H, 6-H′), 4.20 (dd, J = 11.6, 7.4 Hz, 1 H, CHHOH), 7.20–7.40 (m, 8 H, Ph), 7.46 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.7 (C-3), 59.3 (CH$_2$Ph), 63.7 (CH$_2$OH), 66.8 (C-5), 68.3 (C-6), 73.4 (C-2), 127.3 (Ph), 128.1 (Ph), 128.52 (Ph), 128.54 (Ph), 128.76 (Ph), 128.81 (Ph), 138.1 (Ph), 139.0 (Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3487, 2987, 2939, 2919, 2887, 2827, 1738, 1493, 1454, 1280, 1121, 1057, 1008, 7.64, 701 cm^{-1}. HRMS (ESI; MeOH): calcd. for [$C_{18}H_{21}NO_2$ + Na]$^+$ 306.1465; found 306.1468.

General Procedure for the Preparation of the Mosher Esters: All reactions were performed on a 30–50 μmol scale. A solution of the Mosher chloride [(*R*)- or (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride, 99% *ee*, 2.0 equiv.] in CH_2Cl_2 (20 mL/mmol **6**) was added to a solution of the morpholine **6** (1.0 equiv.), Et_3N (2.0 equiv.), and a catalytic amount of DMAP in CH_2Cl_2 (20 mL/mmol **6**). After 2 h at 25 °C, water (200 mL/mmol **6**) was added, and the reaction mixture was extracted with Et_2O (3 × 300 mL/mmol **6**). The combined organic layers were washed with brine (300 mL/mmol **6**), dried with $MgSO_4$, and the solvent was removed in vacuo. Purification by column chromatography (silica gel; *n*-pentane/Et_2O, 1:1) gave the Mosher esters as slightly yellow oils.

(*R*)-Mosher Ester of *rac*-6a: 16.0 mg, 37.8 μmol, 71% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.70 (s, CF_3), –71.73 (s, CF_3) ppm.

(*R*)-Mosher Ester of 6a: 17.2 mg, 40.6 μmol, 76% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.73 (s, CF_3) ppm. Calculated diastereomeric excess: 94%.

Mosher Esters of 6e: (*S*)-Mosher ester: 12.6 mg, 27.9 μmol, 57% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.78 (s, CF_3) ppm. (*R*)-Mosher ester: 17.9 mg, 38.0 μmol, 96% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.80 (s, CF_3) ppm. Calculated diastereomeric excess: 97%.

Mosher Esters of 6g: (*S*)-Mosher ester: 16.3 mg, 34.5 μmol, 87% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.65 (s, CF_3) ppm. (*R*)-Mosher ester: 16.1 mg, 34.1 μmol, 86% yield. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.69 (s, CF_3) ppm. Calculated diastereomeric excess: 97%.

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