Organic Process Research & Development **2010**, *14*, 705–711

Concise Synthesis of C_2-Symmetrical 2,6-Disubstituted Morpholines by $N \rightarrow O$ Boc Migration under SL-PTC Conditions

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Abstract:

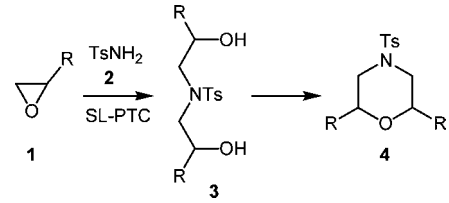
A novel, straightforward synthesis of enantiomerically pure 2,6-disubstituted morpholines has been developed. The ring-opening of epoxides with TsNHBoc under solid−liquid phase transfer catalysis conditions occurred with N → O migration of the Boc group, affording an intermediate carbonate that has been easily transformed to morpholines.

Introduction

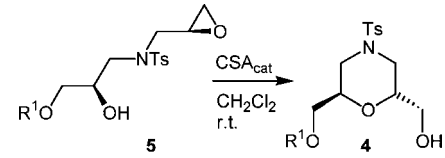
Substituted morpholines have received considerable attention due to their wide range of biological and therapeutic properties.[1] 2,6-Disubstituted morpholines are also used as active ingredients in agricultural formulations for the control of disease in cereal crops.[2] Enantiomerically enriched 2-vinyl morpholines have been generated in moderate to good ee through palladium-catalyzed tandem allylic substitution.[3] However, excellent stereoselectivity has only been obtained by using a xylofuranose-based phosphinooxazinane as ligand.[4] Moreover, C_2-symmetrical morpholines have been used as chiral auxiliaries.[5] Optically pure 2,6-disubstituted morpholines could also be prepared by diastereoselective alkylation of 6-substituted 3-oxo morpholines, followed by reduction of the carbonyl moiety and removal of the chiral auxiliary.[6]

In a previous paper we reported the concise synthesis of racemic 2,6-disubstituted morpholines **4** through the phase transfer catalyzed *bis*-alkylation of 4-methyl-benzenesulfonamide (**2**) by oxiranes **1**, followed by cyclization of hydroxysulfonamides **3** thus obtained (Scheme 1).[7]

Scheme 1



Scheme 2



R^1 = alkyl, aryl

Enantiomerically pure 2,6-disubstituted morpholines **4** have also been generated through acid-catalyzed cyclization of epoxy alcohols **5** derived from the ring-opening of enantiopure glycidols with a solketal-derived sulfonamide (Scheme 2).[8]

Chiral, 2,6-disubstituted morpholines were later prepared through the same procedure by using protecting group chemistry[9] or through regioselective functionalization of unsymmetrical diols **3** with 2,4,6-*tris*-isopropylbenzenesulfonyl chloride (Tris-Cl), followed by cyclization (Scheme 3).[10]

In the context of our recent interest in the synthesis of enantiomerically pure morpholines, we focused on the ring-opening of epoxides **1** with *N*-(*tert*-butoxycarbonyl)-4-methyl-benzenesulfonamide (**7**) (TsNHBoc) as nucleophile under SL-PTC conditions. The *tert*-butoxycarbonyl (Boc) substituent is one of the most widely used protecting groups in synthetic organic chemistry. However, under certain reaction conditions, migration of the Boc group has been observed, thus expanding its synthetic utility if controllable.[11]

Here we report a new pathway for the efficient synthesis of enantiomerically pure, 2,6-disubstituted C_2 symmetric morpholines.

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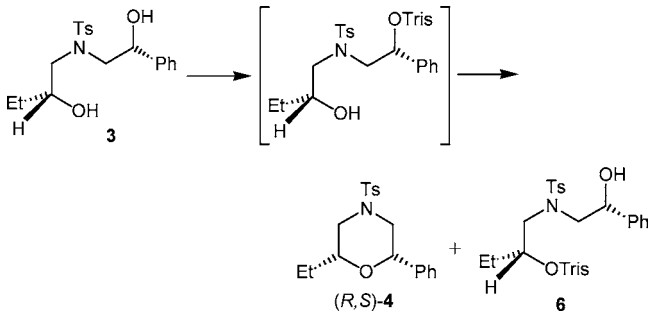
10.1021/op1000435
Published on Web 04/22/2010

Scheme 3



Results and Discussions

In order to study the reactivity of TsNHBoc **7** in the ring-opening of epoxides under SL-PTC conditions, a series of experiments were carried out by using 1,2-epoxy-3-phenoxypropane (**1a**) as a model compound under various reaction conditions (Scheme 4). In particular, the effect of the amount and nature of the base as well as the amount of TsNHBoc **7** has been investigated (Table 1).

When the reaction was carried out by stirring at 90 °C a heterogeneous mixture of **1a**, TsNHBoc (1.2 equiv), solid, anhydrous K_2CO_3 (0.1 equiv), and tetrabutylammonium hydrogensulfate (0.1 equiv) as a phase transfer catalyst, a 75% yield of carbonate **10a**, derived from the epoxide ring-opening followed by *N* → *O* migration of the Boc group, was obtained (entry 1). Lower yields were obtained by using *t*-BuOK or K_3PO_4 as base under the same reaction conditions (entries 2, 3). The reaction did not proceed without base, whereas it was unacceptably slow in the absence of the phase transfer catalyst. On the other hand, the use of 2 mol equiv of TsNHBoc led to 51% of compound **8a**, without migration of the Boc moiety (entry 4). Similar results were obtained with benzyltriethylammonium chloride (TEBA), that was preferred to $Bu_4N^+HSO_4^-$ in all subsequent experiments due to its lower atomic mass (ensuring higher atomic efficiency). Moreover, in reactions carried out with $Bu_4N^+HSO_4^-$ an additional amount of base was required to neutralize the acidic hydrogensulfate anion.

When the ring-opening was carried out in the presence of excess K_2CO_3, **9a** was generated as the main compound (entry 6). In order to confirm the structure of **9a**, the latter has been converted into diol **11a** by removal of the Boc moiety with K_2CO_3 in methanol at 25 °C.[12]

The nitrogen to oxygen (N → O) migration of the Boc group is likely to proceed through nucleophilic attack of the alkoxide anion **A**, generated from the ring-opening of epoxide, to the *N*-bonded carboxylic group, thus generating the aza anion **B** (Scheme 4). The latter can subsequently undergo protonation, leading to **10a**, or can act itself as a nucleophile in the ring-opening of a second epoxide molecule, in such case giving access to compound **9a**, formally deriving from the *bis*-alkylation of the nitrogen atom of TsNHBoc. Results show that pathway b is favored over pathway a in the presence of a greater quantity of base.

In accordance with the proposed mechanism, the yield of the *bis*-alkylation product **9a** could be increased by reducing the amount of TsNHBoc. Indeed, 71% of **9a** could be isolated by using 0.75 mol of TsNHBoc per mole of epoxide (entry 7). Although reactions carried out with excess K_2CO_3 proceeded in the absence of solvent, best results as regards to reaction time and reproducibility have been obtained by using small volumes of dioxane in order to maintain an efficient strirring of the heterogeneous reaction mixture (entries 6−13). Under these reaction conditions, diol **11a** was the main byproduct. The latter can be formed through the ring-opening of **1a** by $TsNH_2$, deriving from partial degradation of TsNHBoc, even though partial deprotection of carbamate **9a** can not be ruled out.

The substitution of K_2CO_3 for $KHCO_3$ or use of less polar solvents such as toluene instead of dioxane did not improve results. The use of minor amounts of base led to very low conversions.

It is worth noting that both mono-alkylated compounds **8a** and **10a** can be quickly converted to **9a** in quantitative yields by treating them with 1,2-epoxy-3-phenoxypropane (**1a**) (1 equiv) in the presence of a catalytic amount of K_2CO_3 and TEBA at 90 °C without solvent. A fast N → O migration of the Boc group occurred, followed by the ring-opening of the epoxide by the aza anion **B** (Scheme 4).

Benzyl glycidol (**1b**), 1,2-epoxyoctane (**1c**) and allyl glycidol (**1d**) have also been reacted with TsNHBoc (**7**), generating the corresponding carbonates **9b**−**d** in 72−75% yield (Table 1). On the other hand, styrene oxide afforded a complex reaction mixture since the nucleophilic attack can occur on both carbon atoms of the oxirane ring.

The 2,6-disubstituted morpholine synthesis could be easily completed by conversion of the hydroxy group of monoprotected diols **9** into a good leaving group through standard mesylation with methanesulfonyl chloride. After aqueous workup of the reaction mixture, crude methanesulfonates **12a**−**d** have been converted to morpholines **4a**−**d** in 80−88% overall yield by treating with K_2CO_3 in refluxing methanol (Scheme 5, Table 2). Cyclization occurred through nucleophilic displacement of the leaving group by the alkoxide generated from the removal of the Boc protecting group.

Although the ring-opening of (*S*)-1,2-epoxy-3-phenoxypropane (**1a)** afforded the enantiomerically pure monoprotected diol (*S*,*S*)-**9a** in 75% yield (Table 1, entry 9), the latter could only generate the achiral *meso*-morpholine (*S*,*R*)-**4a** since the cyclization proceeds through inversion of configuration of the stereocenter bearing the mesylate leaving group. However, the same pathway could be successfully adapted to generate the non-*meso* compound, an enantiomerically pure morpholine, through prior inversion of the stereocenter bearing the hydroxy group of (*S*,*S*)-**9a** by Mitsunobu conditions (Scheme 6).

Thus, (*S*,*S*)-**9a** was treated with PPh_3, diisopropyl azodicarboxylate (DIAD), and 4-nitrobenzoic acid in toluene at 25 °C. The reaction was completed after 2 h in toluene, whereas it reached 66% conversion only after 3 h in THF. After purification through column chromatography, the hydrolysis of the benzoate (*S*,*R*)-**14a** thus obtained was carried out in aq NaOH/THF/MeOH mixture affording the desired (*S*,*R*)-**9a** in a 86% overall yield from (*S*,*S*)-**9a**.

(12) ^{1}H NMR of **11a** proved to be identical to that previously published (ref 7).

Scheme 4. **Ring-opening of epoxide 1a with TsNHBoc (7)**

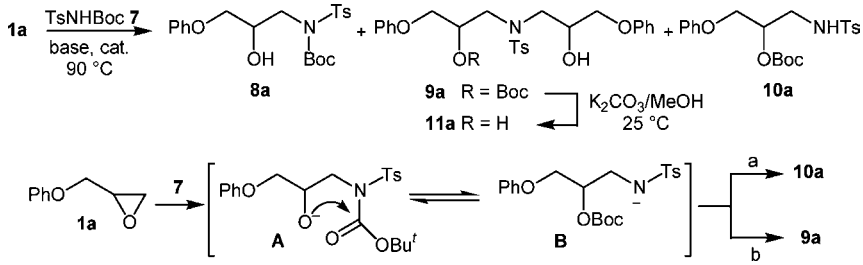


Table 1. **Ring-opening of epoxides 1a−d with TsNHBoc (7) under SL-PTC conditions at 90 °C**

	epoxide	**7** (equiv)	base (equiv)	cat.[a]	dioxane (M)	*t* (h)	**8**	**9**	**10**	**11**
1	**1a**	1.2	K_2CO_3 (0.2)	A	–	2	–	6	75	8
2	**1a**	1.2	*t*-BuOK (0.2)	A	–	7	–	–	53	–
3	**1a**	1.2	K_3PO_4 (0.2)	A	–	24	–	–	50	20
4	**1a**	2	K_2CO_3 (0.2)	A	–	2	51	–	–	–
5	**1a**	1.2	K_2CO_3 (0.1)	B	–	2	–	5	76	9
6	**1a**	1.2	K_2CO_3 (2)	B	5	24	–	50	28	20
7	**1a**	0.75	K_2CO_3 (2)	B	5	5	–	71	8	10
8	**1b**	0.75	K_2CO_3 (2)	B	5	5	–	72	8	10
9	(*S*)-**1a**	0.75	K_2CO_3 (2)	B	5	6	–	75	5	8
10	(*S*)-**1b**	0.75	K_2CO_3 (2)	B	5	6	–	75	–	–
11	**1c**	0.75	K_2CO_3 (2)	B	5	20	–	72	–	–
12	**1d**	0.75	K_2CO_3 (2)	B	5	14	–	64	–	–
13	(*R*)-**1d**	0.75	K_2CO_3 (2)	B	5	18	–	75	–	–

[a] A = $Bu_4N^+HSO_4^-$, B = TEBA (0.1 equiv).

Scheme 5. **Conversion of mono-protected diols into 2,6-disubstituted morpholines**

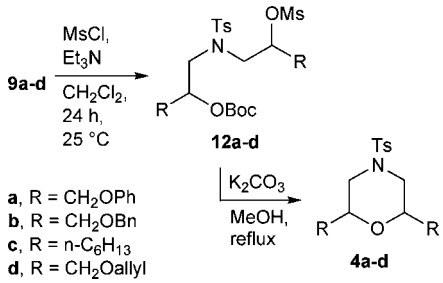


Table 2. **Synthesis of morpholines 4a−d from mono-protected diols 9a−d[a]**

	substrate	t_1[b] (h)	t_2[c] (h)	yield (%)	product
1	**9a**	22	6	88	**4a**
2	(*S*,*R*)-**9a**	24	7	85	(*S*,*S*)-**4a**
3	**9b**	18	6	82	**4b**
4	(*S*,*R*)-**9b**	10	5	85	(*S*,*S*)-**4b**
5	**9c**	24	9	81	**4c**
6	**9d**	15	5	85	**4d**
7	(*R*,*S*)-**9d**	18	4	80	(*R*,*R*)-**4d**

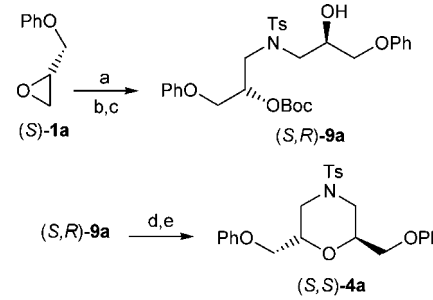
[a] Reaction conditions: (1) MsCl (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 25 °C; (2) K_2CO_3 (5 equiv), MeOH, reflux. [b] Time for the mesylation step. [c] Time for the cyclization step.

The monoprotected diols (*S*,*R*)-**9a,b** and (*R*,*S*)-**9d**, obtained by Mitsunobu inversion, have been converted to C_2-symmetric morpholines (*S*,*S*)-**4a,b** and (*R*,*R*)-**4d** in 80−85% overall yield (Table 2).[13]

A more efficient synthesis of these enantiopure morpholines **4** is possible through two sequential epoxide ring-opening steps,

(13) Morpholines have been shown to be enantiomerically pure by HPLC on chiral column. Racemic morpholines have been prepared as analytical standards from the ring opening of racemic epoxides.

Scheme 6. **Generation of (*S*,*S*)-9a by ring-opening, Mitsunobu inversion, and cyclization**



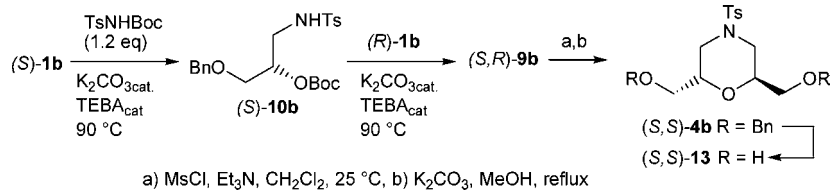
a) TsNHBoc (0.75 eq), K_2CO_3 (2 eq), TEBA (0.1 eq), dioxane, 6 h, 90°C, 75%. b) PPh_3, DIAD, 4-NO_2-C_6H_4-COOH, toluene, 2 h, 25 °C, 93%. c) NaOH, MeOH, H_2O, 10 min, 25 °C, 92%. d) MsCl, Et_3N,CH_2Cl_2, 24 h, 25 °C. e) K_2CO_3, MeOH, reflux.

but using the opposite epoxide enantiomer in the second step (Scheme 7). In this case the intermediate monoprotected diol (*S*,*R*)-**9b** has the correct absolute configuration to generate the desired C_2-symmetric morpholine (*S*,*S*)-**4b** through the cyclization protocol previously described. The benzyl groups could be removed by hydrogenolysis of morpholine (*S*,*S*)-**4b** thus generating C_2-symmetric 2,6-*bis*-hydroxymethylmorpholine (*S*,*S*)-**13**, a key intermediate for making a variety of C_2-symmetric morpholines through standard functional group chemistry.[8]

The enantiomeric morpholine (*R*,*R*)-**4b** can be obtained by simply reversing the charging order of two epoxide enantiomers.

The same procedure can also be exploited for the synthesis of a variety of chiral, nonsymmetric morpholines by using different chiral epoxides in the two ring-opening steps instead of the two opposite enantiomers of the same epoxide.

Scheme 7. **Alternative synthesis of (*S,S*)-2,6-disubstituted morpholines**



Conclusion

In summary, enantiopure 2,6-disubstituted morpholines **4** have been prepared in a straightforward manner through the ring-opening of epoxides with TsNHBoc under SL-PTC conditions.

The migration of the Boc group from the incoming nucleophile to the hydroxy group generated during the oxirane ring-opening enables the sequential double alkylation of TsNHBoc. Standard synthetic elaboration of the mono-protected diols **9** thus obtained generates C_2-symmetric morpholines **4** in high yields.

Since the Boc protecting group of carbonates **9** originates from the incoming nucleophile, this new procedure does not require additional steps of introduction and removal of external protecting groups in order to set the stage for the cyclization by differentiating two chemically equivalent hydroxy groups.

The crucial epoxide ring-opening step has been carried out under SL-PTC conditions in the presence of a small amount of solvent, and the following operations leading to the morpholine skeleton are high-yielding reactions and proceed under mild conditions.

Moreover, when two opposite enantiomers of the same epoxide are used in two sequential ring-opening steps under SL-PTC conditions without solvent (Scheme 7), C_2-symmetric morpholines **4** have been generated without the requirement of prior Mitsunobu inversion of one stereocenter. Also, nonsymmetrical, enantiopure 2,6-disubstituted morpholines can also be obtained by using two different epoxides in the alternative two steps protocol (Scheme 7).

Therefore, this new procedure enables the synthesis of a large number of chiral, symmetrical 2,6-disubstituted morpholines from a variety of readily available and inexpensive chiral epoxides by choosing the proper pathway.

Experimental Section

General. Anhydrous dioxane and chiral epoxides (ee 98%) were purchased from Fluka and used without further purification. NMR spectra were recorded on Bruker AC 300 or AC 200 spectrometers, operating at 300.13 or 200.13 MHz for ^{1}H NMR and 75.3 MHz for ^{13}C NMR. Optical rotations were measured with a Perkin-Elmer 241 polarimeter; the $[\alpha]_D$ values are reported in 10^{-1} deg cm^{-2} g^{-1}, concentration (*c*) is reported in g per 100 mL. Column chromatography on silica gel (230−400 mesh) was performed by the flash technique. Chiral HPLC separations were performed on a Agilent HP 1100 apparatus, equipped with a diode array detector, detection at 230 nm. The flux was set to 1 mL min^{-1}, and the volume of injection was 20 μL.

Carbamic Acid, [2-Hydroxy-3-phenoxypropane][(4-methylphenyl)sulfonyl]-1,1-dimethylethyl Ester (8a). 1,2-Epoxy-3-phenoxypropane (**1a**) (150 mg, 1 mmol) was added to a mixture of TsNHBoc (540 mg, 2 mmol), K_2CO_3 (28 mg, 0.2 mmol), and $Bu_4N^+HSO_4^-$ (34 mg, 0.1 mmol). After heating at 90 °C for 2 h, the reaction mixture was directly purified by column chromatography (AcOEt/PE, 1:6) to generate 215 mg of **8a**, 51% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.90 (m, 2 H), 7.39−7.30 (m, 5 H), 6.99−6.97 (m, 2 H), 4.40−4.36 (m, 1 H), 4.25−4.05 (m, 4 H), 2.49 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 158.4 (C), 151.5 (C), 149.3 (C), 144.4 (C), 144.2 (C), 137.0 (C), 136.1 (C), 129.3 (CH), 128.0 (CH), 121.1 (CH), 114.5 (CH), 83.6 + 84.8 (C), 69.6 (CH_2), 69.5 (CH), 49.3 (CH_2), 27.6 (CH_3), 21.4 (CH_3). ESI-MS: *m/z* = 440 [M + Na]$^+$.

Synthesis of *tert*-Butyl 1-(*N*-4-Methylphenylsulfonamido)-3-phenoxypropan-2-yl Carbonate (10a). 1,2-Epoxy-3-phenoxypropane (**1a**) (150 mg, 1 mmol) was added to a mixture of TsNHBoc (326 mg, 1.2 mmol), K_2CO_3 (28 mg, 0.2 mmol), and $Bu_4N^+HSO_4^-$ (34 mg, 0.1 mmol). After heating at 90 °C for 2 h the reaction mixture was directly purified through column chromatography (AcOEt/PE, 1:6) to generate 316 mg of **10a**, 75% yield, mp 94−95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.75 (d, 2 H, J = 8.3), 7.33−7.28 (m, 4 H), 7.03−6.98 (m, 1 H), 6.87−6.85 (d, 2 H, J = 8.1), 5.00−4.97 (m, 1 H), 4.83 (m, 1 H), 4.08 (ddd, 2 H, J = 5.1, 10.2 and 18.6), 3.47−3.35 (m, 2 H), 2.44 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 152.6 (C), 143.6 (C), 129.8 (CH), 129.5 (CH), 127.1 (CH), 121.4 (CH), 114.6 (CH), 83.2 (C), 73.2 (CH), 66.2 (CH_2), 43.5 (CH_2), 27.7 (CH_3), 21.5 (CH_3). ESI-MS: *m/z* = 440 [M + Na]$^+$.

General Method for the Synthesis of Carbonates 9a−d. A mixture of TsNHBoc **7** (4.07 g, 15 mmol), epoxide **1** (20 mmol), K_2CO_3 (0.55 g, 40 mmol), TEBA (0.46 g, 2 mmol), and dioxane (4 mL) was stirred at 90 °C for the time indicated in Table 1. Addition of water (2 mL), extraction with CH_2Cl_2 (2 × 20 mL), drying with $MgSO_4$, filtration, and solvent removal *in vacuo* gave a residue which was purified by flash column chromatography (eluting solvent mixture listed below) on silica gel to give carbonates **9a−d**.

***tert*-Butyl 1-(*N*-(2-hydroxy-3-phenoxypropyl)-4-methylphenylsulfonamido)-3-phenoxypropan-2-yl carbonate (*S,S*)-9a:** (AcOEt/PE, 1:4) 4.29 g, 75% yield, $[\alpha]^{23}_D$ +19.3 (*c* 0.85, $CHCl_3$), HPLC (CHIRALCEL OD, hexane/*i*-PrOH, 80:20) t_R (*S,S*) = 28.7 min, ee 98%.[14] (Anal. Calc for $C_{30}H_{37}NO_8S$: C, 63.03; H, 6.52; N, 2.45. Found: C, 63.11; H, 6.53; N, 2.46). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2 H, J = 8.3), 7.28−7.26 (m, 6 H), 6.95−6.88 (m, 6 H), 5.30 (m, 1 H), 4.31 (m, 1 H), 4.13 (m, 2 H), 3.98 (m, 2 H) 3.60−3.42 (m, 2 H), 2.41 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 158.3 (C), 158.10 (C), 152.8 (C), 143.7 (C), 135.1 (C), 129.7 (CH), 129.3 (CH), 127.4 (CH), 121.1 (CH), 121.0 (CH), 114.5 (CH), 82.9 (C) 73.4 (CH),

(14) Retention times for the racemic mixture: 20.6, 24.2, 28.8, 30.8 min.

69.4 (CH_2), 68.7 (CH), 66.7 (CH_2), 53.9 (CH_2), 50.8 (CH_2), 27.6 (CH_3), 21.3 (CH_3). ESI-MS: m/z = 594 $[M + Na]^+$.

***tert*-Butyl 1-(*N*-(2-hydroxy-3-benzyloxypropyl)-4-methylphenylsulfonamido)-3-benzyloxypropan-2-yl carbonate (*S,S*)-9b:** (AcOEt/PE, 1:4) 4.49 g, 75% yield, $[\alpha]^{23}_D$ - 8.5 (c 0.78, $CHCl_3$), HPLC (CHIRALPAK AD; hexane/*i*-PrOH, 80:20) t_R (*S,S*) = 21.0, ee 98%.[15] (Anal. Calc for $C_{32}H_{41}NO_8S$: C, 64.09; H, 6.89; N, 2.34. Found: C, 64.15; H, 6.93; N, 2.32); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.35−7.29 (m, 10 H), 5.12 (m, 1 H), 4.56 (m, 4 H), 4.11 (m, 1 H), 3.67−3.65 (m, 2 H), 3.53−3.20 (m, 6 H), 2.44 (s, 3 H), 1.49 (s, 9 H). ESI-MS: m/z = 622 $[M + Na]^+$.

***tert*-Butyl 1-(*N*-(2-hydroxy-3-hexyl)-4-methylphenylsulfonamido)-3-hexylpropan-2-yl carbonate 9c (diastereoisomeric mixture):** (AcOEt/ PE, 1:6) 3.80 g, 72% yield. ^1H NMR (300 MHz, $CDCl_3$) 7.71 (m, 2 H), 7.29 (m, 2 H), 4.90 (m, 1 H), 3.85 (m, 1 H), 3.47−2.96 (m, 4 H), 2.45 (s, 3 H), 1.58−1.29 (m, 29 H), 0.90 (m, 6 H). ^{13}C NMR ($CDCl_3$) 143.5 (C), 135.4 (C), 129.7 (CH), 127.4 (CH), 82.4 (C), 75.9 + 75.8 (CH), 70.1 + 69.6 (CH), 58.3 + 57.5 (CH), 54.7 + 53.5 (CH_2), 34.7 + 34.6 (CH_2), 32.0 + 31.7 (CH_2), 29.3 + 29.0 (CH_2), 27.7 (CH_3), 25.5 + 25.0 (CH_2), 22.4 (CH_2), 21.4 (CH_3), 13.9 (CH_3). ESI-MS: m/z = 550 $[M + Na]^+$.

***tert*-Butyl 1-(*N*-(2-hydroxy-3-allyloxypropyl)-4-methylphenylsulfonamido)-3-allyloxypropan-2-yl carbonate (*R,R*)-9d:** (AcOEt/PE, 1:5) 3.75 g, 75% yield, $[\alpha]^{23}_D$ +5.7 (*c* 1.03, $CHCl_3$), HPLC (CHIRALPAK AD; hexane/*i*-PrOH, 90:10) t_R (*R,R*) = 20.3, ee 98%. (Anal. Calc for $C_{24}H_{37}NO_8S$: C, 57.70; H, 7.46; N, 2.80. Found: C, 57.78; H, 7.47; N, 2.79); ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 2 H, *J* = 8.1), 7.33 (d, 2 H, *J* = 8.1), 5.92−5.85 (m, 2 H), 5.30−5.18 (m, 4 H,), 5.10 (m, 1 H), 4.04−4.02 (m, 5 H), 3.63 (d, 2 H, *J* = 4.6), 3.49−3.20 (m, 6 H), 2.44 (s, 3 H), 1.49 (s, 9 H);^{13}C NMR ($CDCl_3$) δ 152.8 (C), 143.6 (C), 135.3 (C), 134.4 (CH), 134.2 (CH), 129.6 (CH), 127.4 (CH), 117.1 (CH_2), 117.0 (CH_2), 82.6 (C), 74.0 (CH), 72.2 (CH_2), 71.7 (CH_2), 69.1 (CH), 68.8 (CH_2), 54.2 (CH_2), 50.9 (CH_2), 27.8 (CH_3), 21.4 (CH_3). ESI-MS: m/z = 522 $[M + Na]^+$.

General Procedure for the Mitsunobu Inversion of Stereocenter of Carbonates 9a,b,d. *tert*-Butyl 1-(*N*-(2-hydroxy-3-phenoxypropyl)-4-methylphenylsulfonamido)-3-phenoxypropan-2-yl carbonate (*S,R*)-9a. Carbonate (*S,S*)-**9a** (2.86 g, 5.0 mmol), PPh_3 (1.97 g, 7.5 mmol) and *p*-nitrobenzoic acid (1.25 g, 7.5 mmol) were dissolved in toluene (40 mL) and stirred at room temperature for 10 min. DIAD (1.62 g, 8 mmol) was added over 10 min and the reaction stirred until the starting material was no longer detectable (TLC analysis). After completion (2 h), the reaction mixture was evaporated to dryness and the *p*-nitrobenzoate (*S,R*)-**14a** isolated through column chromatography.

(*R*)-1-(*N*-((S)-2-(*tert*-Butoxycarbonyloxy)-3-phenoxypropyl)-4-methylphenylsulfonamido)-3-phenoxypropan-2-yl 4-nitrobenzoate (*S,R*)-14a: 5.03 g, 93% yield, $[\alpha]^{23}_D$ +3.2 (*c* 0.74, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 4 H), 7.68 (d, 2 H, J = 8.5 Hz), 7.25 (m, 6 H), 6.90 (m, 4 H), 6.69 (d, 2 H, J = 7.7 Hz), 5.77 (m, 1 H), 5.19 (m, 1 H), 4.25 (ddd, 2 H, J = 3.7, 10.7 and 18.4 Hz), 3.97 (ddd, 2 H, J = 4.4, 10.7, and 23.5 Hz), 3.75−3.67 (m, 3 H), 3.41 (dd, 1 H, J = 7.0 and 15.1 Hz), 2.36 (s, 3 H), 1.44 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 130.9 (CH), 129.9 (CH), 129.5 (CH), 129.3 (CH), 127.5 (CH), 123.4 (CH), 121.5 (CH), 121.2 (CH), 114.7 (CH), 114.3 (CH), 77.0 (CH), 72.1 (CH), 66.8 (CH_2), 66.5 (CH_2), 50.1 (CH_2), 49.8 (CH_2), 27.6 (CH_3), 2.5 (CH_3).

This was dissolved in 40 mL of a THF/H_2O/MeOH mixture (1:1:2) and solid NaOH (0.19 g, 4.74 mmol) was added. After 20 min (TLC), THF and MeOH were removed at reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was evaporated to dryness and the carbonate (*S,R*)-**9a** isolated by column chromatography.

(*S,R*)-**9a** (AcOEt/PE, 1:4) 3.67 g, 92% yield, $[\alpha]^{23}_D$: +53.0 (*c* 1, $CHCl_3$); HPLC (CHIRALCEL OD; hexane/*i*-PrOH, 80:20) t_R (*S,R*) = 20.1, ee 98%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 2 H), 7.32−7.23 (m, 6 H), 6.95−6.88 (m, 6 H), 5.32−5.28 (m, 1 H), 4.32 (m, 1 H), 4.16 (m, 2 H), 3.97 (m, 2 H), 3.6−3.2 (m, 4 H), 2.41 (s, 3 H), 1.47 (s, 9 H).

***tert*-Butyl 1-(*N*-(2-hydroxy-3-benzyloxypropyl)-4-methylphenylsulfonamido)-3-benzyloxypropan-2-yl carbonate (*S,R*)-9b.** Carbonate (*S,S*)-**9b** (3.00 g, 5 mmol), PPh_3 (1.97 g, 7.5 mmol) and *p*-nitrobenzoic acid (1.25 g, 7.5 mmol) were dissolved in toluene (40 mL) and stirred at room temperature for 10 min. DIAD (1.62 g, 8 mmol) was added over 10 min and the reaction stirred until the starting material was no longer detectable (TLC analysis). After completion (2 h), the reaction mixture was evaporated to dryness, and the *p*-nitrobenzoate (*S,R*)-**14b** was isolated through column chromatography.

(*R*)-1-(*N*-((*S*)-2-(*tert*-Butoxycarbonyloxy)-3-benzyloxypropyl)-4-methylphenylsulfonamido)-3-benzyloxypropan-2-yl 4-nitrobenzoate (*S,R*)-14b: (AcOEt/PE, 1:5) 5.28 g, 94% yield, $[\alpha]^{23}_D$ +8.4 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 4H), 7.65 (d, 2 H, *J* = 8.5), 7.30−7.20 (m, 12 H), 5.57 (m, 1 H), 5.01 (m, 1 H), 4.54 (s, 2 H), 4.39 (s, 2 H), 3.71−3.52 (m, 7 H), 3.28 (dd, 1 H, *J* = 6.6 and 14.7), 2.37 (s, 3 H), 1.53 (s, 9 H).

This was dissolved in 40 mL of a THF/H_2O/MeOH mixture (1:1:2), and solid NaOH (0.19 g, 4.79 mmol) was added. After stirring at room temperature for 20 min and following the general procedure, the carbonate (*S,R*)-**9b** was isolated through column chromatography.

***tert*-Butyl (*S*)-1-(*N*-((*R*)-2-hydroxy-3-benzyloxypropyl)-4-methylphenylsulfonamido)-3-benzyloxypropan-2-yl carbonate (*S,R*)-9b:** (AcOEt/ETP, 1:5) 3.68 g, 87% yield, $[\alpha]^{23}_D$ +11.8 (*c* 1, $CHCl_3$), HPLC (CHIRALCEL OD; hexane/*i*-PrOH, 80:20) t_R (*S,R*) = 25.2, ee 98%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.66 (d, 2 H, *J* = 8.3), 7.31−7.26 (m, 10 H), 5.13 (m, 1 H), 4.54 (s, 4 H), 4.10 (m, 1 H), 3.65 (d, 2 H, *J* = 7.1), 3.50−3.10 (m, 6 H), 2.41 (s, 3 H), 1.45 (s, 9 H).

***tert*-Butyl (*S*)-1-(*N*-((*R*)-2-hydroxy-3-allyloxypropyl)-4-methylphenylsulfonamido)-3-allyloxypropan-2-yl carbonate (*R,S*)-9d.** Carbonate (*R,R*)-**9d** (2.86 g, 5 mmol), PPh_3 (1.97 g, 7.5 mmol) and *p*-nitrobenzoic acid (1.25 g, 7.5 mmol) were dissolved in toluene (40 mL) and stirred at room temperature for 10 min. DIAD (1.62 g, 8 mmol) was added over 10 min and the reaction stirred until the starting material was no longer detectable (TLC analysis). After completion (2 h), the reaction

(15) Retention times for the racemic mixture: 18.6, 20.2, 22.5, 25.2 min.

mixture was evaporated to dryness, and the *p*-nitrobenzoate (*R*,*S*)-**14d** was isolated through column chromatography.

(*R*)-1-(*N*-((S)-2-(*tert*-Butoxycarbonyloxy)-3-allyloxypropyl)-4-methylphenylsulfonamido)-3-allyloxypropan-2-yl 4-nitrobenzoate (*R*,*S*)-14d: (AcOEt/PE, 1:8) 2.92 g (90% yield); $[\alpha]^{23}_D$: −9.7 (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, 4 H, J = 6.6 and 9.1), 7.70 (d, 2 H, J = 8.1), 7.25 (d, 2 H, J = 8.1), 5.94−5.73 (m, 2H), 5.55 (m, 1 H), 5.30−5.11 (m, 4 H), 4.98 (m, 1 H), 4.12 (d, 2 H, J = 7.0), 3.90 (d, 2 H, J = 5.5), 3.71−3.51 (m, 8 H), 3.34 (dd, 1 H, J = 7.0 and 15.0), 2.38 (s, 3H), 1.45 (s, 9 H).

This was dissolved in 40 mL of a THF/H_2O/MeOH mixture (1:1:2), and solid NaOH (0.18 g, 4.44 mmol) was added. After stirring at room temperature for 20 min and following the general procedure, the carbonate (*R*,*S*)-**9d** was isolated through column chromatography.

***tert*-Butyl (*S*)-1-(*N*-((*R*)-2-hydroxy-3-allyloxypropyl)-4-methylphenylsulfonamido)-3-allyloxypropan-2-yl carbonate (*R*,*S*)-9d:** (AcOEt/ETP, 1:5) 1.93 g, 86% yield, $[\alpha]^{23}_D$: −9.7 (*c* 1.28, $CHCl_3$); HPLC (CHIRALPAK AD; hexane/*i*-PrOH, 90:10) t_R (*R*,*S*) = 17.8, ee 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.72 (d, 2 H, J = 8.1), 7.33 (d, 2 H, J = 8.1), 5.94−5.89 (m, 2 H), 5.31−5.18 (m, 4 H), 5.12−5.08 (m, 1 H), 4.10−4.02 (m, 5 H), 3.66−3.64 (d, 2 H, J = 4.6), 3.56−3.15 (m, 6 H), 2.44 (s, 3 H), 1.49 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 152.8 (C), 143.5 (C), 135.4 (C), 134.4 (CH), 134.2 (CH), 129.7 (CH), 127.5 (CH), 117.2 (CH_2), 117.1 (CH_2), 82.5 (C), 73.9 (CH), 72.2 (CH_2), 71.7 (CH_2), 68.9 (CH_2), 53.8 (CH_2), 50.5 (CH_2), 27.7 (CH_3), 21.4 (CH_3).

General Method for the Cyclization of Carbonates 9a−d. Et_3N (0.9 mL, 6.4 mmol) was added to a stirred solution of carbamate (*S*,*R*)-**9a** (2.29 g, 4 mmol) in CH_2Cl_2 (20 mL). Methanesulfonyl chloride (0.46 mL, 6 mmol) was added over 3 min at 0 °C, and the temperature was allowed to reach room temperature. After 24 h, water (3 mL) was added, and the separated organic phase was washed with 0.5 M HCl (3 mL) and brine (2 × 5 mL). After drying over $MgSO_4$, the solvent was removed at reduced pressure to give crude methanesulfonate (*S*,*R*)-**12a** which was dissolved in methanol (20 mL) and treated with solid K_2CO_3 (2.76 g, 20 mmol). After heating at reflux for 7 h, methanol was removed at reduced pressure. The residue was dissolved in 50−50 AcOEt/H_2O mixture (15 mL). The separated aqueous phase was extracted with AcOEt (2 × 5 mL), and the combined organic phase was dried over $MgSO_4$, and the solvent was removed at reduced pressure to give morpholine (*S*,*S*)-**4a** which was purified by column chromatography.

(*S*,*S*)-2,6-Bis-(phenoxymethyl)-4-tosylmorpholine (4a). (AcOEt/ETP, 1:3) 1.54 g (85% yield), mp 142−143 °C; $[\alpha]^{23}_D$: −47.0 (*c* 0.6, $CHCl_3$); the optical purity of this compound has been determined after *N*-detosylation (see below).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 12.3), 7.34−7.24 (m, 6 H), 7.00−6.88 (m, 6 H), 4.29−4.01 (m, 6 H), 3.30−3.22 (dd, 2 H, J = 5.4 and 11.5), 3.09−3.00 (dd, 2 H, J = 2.8 and 11.3), 2.43 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 158.3 (C), 144.1 (C), 129.9 (CH), 129.5 (CH), 127.9 (CH), 121.3 (CH), 114.6 (CH), 69.3 (CH), 66.7 (CH_2), 46.9 (CH_2), 21.5 (CH_3).

(*S*,*S*)-2,6-Bis-(phenoxymethyl)morpholine (15a). (*S*,*S*)-**4a** (0.1 mmol, 45 mg) was dissolved in DME (5 mL), cooled to −70 °C and a freshly prepared 0.06 M sodium naphthalide DME solution (0.3 mmol, 5 mL) was added over 5 min. After 1 h (CH_2Cl_2/MeOH, 9:1) the reaction was quenched with sat. NH_4Cl and evaporated to dryness. The title compound (27 mg, 90% yield) was isolated in pure form by column chromatography (CH_2Cl_2/MeOH, 95:5).

(*S*,*S*)-**15a**: HPLC (CHIRALCEL OJ-H; hexane/*i*-PrOH, 50:50, 0.7 mL/min); t_R (*S*,*S*) = 27.3, t_R (*R*,*R*) = 39.6, ee 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.25 (m, 4 H), 6.95−6.92 (m, 6 H), 4.20−4.17 (m, 6 H), 3.12 (dd, 2 H, J = 2.7 and 12.1), 2.94 (dd, 2 H, J = 4.9 and 12.1), 2.25 (s, 1 H, NH).^{13}C NMR ($CDCl_3$) δ 158.7 (C), 129.4 (CH), 121.2 (CH), 114.7 (CH), 70.0 (CH), 67.9 (CH_2), 47.0 (CH_2). ESI-MS: m/z = 300 $[M + H]^+$.

(*S*,*S*)-2,6-Bis-(benzyloxymethyl)-4-tosylmorpholine (4b). Et_3N (0.9 mL, 6.4 mmol) was added to a stirred solution of carbamate (*S*,*R*)-**9b** (2.40 g, 4 mmol) in CH_2Cl_2 (20 mL). Methanesulfonyl chloride (0.46 mL, 6 mmol) was added over 3 min at 0 °C, and the temperature was allowed to reach room temperature. After 10 h, water (3 mL) was added, and the separated organic phase was washed with 0.5 M HCl (3 mL) and brine (2 × 5 mL). After drying over $MgSO_4$, the solvent was removed at reduced pressure to give crude methanesulfonate (*S*,*R*)-**12b** which was dissolved in methanol (20 mL) and treated with solid K_2CO_3 (2.76 g, 20 mmol). After heating at reflux for 5 h, and following the general procedure, morpholine (*S*,*S*)-**4b** was isolated by column chromatography.

(*S*,*S*)-**4b**: 1.64 g (85% yield), (AcOEt/PE, 1:3) $[\alpha]^{23}_D$ −23.3 (*c* 0.79, $CHCl_3$); HPLC (CHIRALPAK AD; hexane/*i*-PrOH 80:20; t_R (*meso*) = 14.0, t_R (*S*,*S*) = 16.1, t_R (*R*,*R*) = 23.2, ee 98%. ^{1}H NMR identical to that reported in ref 8 for (*R*,*R*)-**4b**.

2,6-Bis-(hexyl)-4-tosylmorpholine (4c). Et_3N (1.6 mL, 11.5 mmol) was added to a stirred solution of carbamate (*S*,*R*)-**9c** (3.69 g, 7 mmol) in CH_2Cl_2 (20 mL). Methanesulfonyl chloride (0.85 mL, 11 mmol) was added over 3 min at 0 °C, and the temperature was allowed to reach room temperature. After 24 h, water (5 mL) was added, and the separated organic phase was washed with 0.5 M HCl (5 mL) and brine (2 × 5 mL). After drying over $MgSO_4$, the solvent was removed at reduced pressure to give crude methanesulfonate **12c** which was dissolved in methanol (25 mL) and treated with solid K_2CO_3 (4.84 g, 35 mmol). After heating at reflux for 9 h, and following the general procedure, morpholine **4c** was isolated by column chromatography.

Two diastereoisomeric morpholines have been separated (AcOEt/PE, 1:19). 2.32 g (81% yield).

(*RR*+*SS*)-**4c**: 1.16 g, mp 39−40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2 H, J = 8.2), 7.35 (d, 2 H, J = 8.1), 3.80 (m, 2 H), 2.98 (dd, 2 H, J = 3.2 and 11.2), 2.71 (dd, 2 H, J = 5.8 and 11.2), 2.45 (s, 3 H), 1.26 (m, 20 H), 0.87 (m, 6 H).^{13}C NMR ($CDCl_3$) δ 143.6 (C), 132.6 (C), 129.6 (CH), 127.7(CH), 69.6 CH), 49.4 (CH_2), 31.7 (CH_2), 31.2 (CH_2), 29.1 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 14.0 (CH_3).

(*meso*)-**4c**: 1.15 g, mp 55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2 H, J = 8.2), 3.59−3.48 (m, 4 H), 2.46 (s, 3 H), 1.96 (dd, 2 H, J = 10.7 and 10.7), 1.41−1.28 (m, 20 H), 0.90

(m, 6 H). ^{13}C NMR ($CDCl_3$) δ 143.6 (C), 132.6 (C), 129.7 (CH), 127.8 (CH), 75.2 CH), 50.1 (CH_2), 33.2 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 14.0 (CH_3).

(*R*,*R*)-2,6-Bis-(allyloxymethyl)-4-tosylmorpholine (4d). Et_3N (0.80 mL, 5.76 mmol) was added to a stirred solution of carbamate (*R*,*S*)-**9d** (1.80 g, 3.6 mmol) in CH_2Cl_2 (20 mL). Methanesulfonyl chloride (0.42 mL, 5.4 mmol) was added over 3 min at 0 °C, and the temperature was allowed to reach room temperature. After 18 h, water (5 mL) was added, and the separated organic phase was washed with 0.5 M HCl (5 mL) and brine (2 × 5 mL). After drying over $MgSO_4$, the solvent was removed at reduced pressure to give crude methanesulfonate (*R*,*S*)-**12d** which was dissolved in methanol (20 mL) and treated with solid K_2CO_3 (2.49 g, 18 mmol). After heating at reflux for 4 h, and following the general procedure, morpholine (*R*,*R*)-**4d** was isolated by column chromatography.

(*R*,*R*)-**4d**: 0.93 g (80% yield), $[\alpha]^{23}_D$: +22.4 (*c* 0.97, $CHCl_3$); HPLC (CHIRALPAK AD; hexane/*i*-PrOH, 80:20); t_R (*R*,*R*) = 11.5, t_R (*S*,*S*) = 8.2, t_R (*meso*) = 7.6, ee 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 2 H, *J* = 8.1), 7,37 (d, 2 H, *J* = 8.1), 5.96−5.85 (m, 2 H), 5.32−5.20 (m, 4 H), 4.04−3.99 (m, 6 H), 3.66−3.56 (m, 4 H), 3.13−3.08 (dd, 2 H, *J* = 3.6 and 11.8), 2.98−2.92 (dd, 2 H, *J* = 5.9 and 11.5), 2.47 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 143.9 (C), 134.4 (CH), 132.3 (C), 129.7 (CH), 127.8 (CH), 117.4 (CH_2), 72.4 (CH_2), 69.7 (CH), 68.8 (CH_2), 46.7 (CH_2), 21.5 (CH_3). APCI-MS: *m*/*z* = 322 $[M + H]^+$.

Alternative Synthesis of *tert*-Butyl 1-(*N*-(2-Hydroxy-3-phenoxypropyl)-4-methylphenylsulfonamido)-3-phenoxypropan-2-yl Carbonate 9a. *Method A.* Epoxide **1a** (150 mg, 1 mmol) was added to a mixture of **8a** (421 mg, 1 mmol), K_2CO_3 (14 mg, 0.1 mmol) and TEBA (23 mg, 0.1 mmol). After heating at 90 °C for 2 h the reaction mixture was directly purified by column chromatography (AcOEt/PE, 1:4) to generate 434 mg of the title compound, 96% yield.

Method B. Epoxide **1a** (150 mg, 1 mmol) was added to a mixture of **10a** (420 mg, 1 mmol), K_2CO_3 (14 mg, 0.1 mmol) and TEBA (23 mg, 0.1 mmol). After heating at 90 °C for 2 h the reaction mixture was directly purified by column chromatography (AcOEt/PE, 1:4) to generate 457 mg of the title compound, 97% yield.

Alternative Synthesis of Carbonate (*S*,*R*)-9b. *Step 1.* (*S*)-Benzyl glycidol (164 mg, 1 mmol) was added to a mixture of TsNHBoc (326 mg, 1.2 mmol), K_2CO_3 (14 mg, 0.1 mmol) and TEBA (23 mg, 0.1 mmol). After heating at 90 °C for 2 h the reaction mixture was directly purified by column chromatography (AcOEt/PE, 1:4) to generate 318 mg of (*S*)-**10b**, 73% yield. $[\alpha]^{23}_D$ + 0.29 (*c* 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$) δ, 7.90−7.83 (m, 4 H), 7.36−7.25 (m, 5 H), 4.59 (s, 2 H), 4.18−4.03 (m, 3 H), 3.94 (dd, 1 H, *J* = 3.3 and 14.3), 3.61 (dd, 1 H, *J* = 4.0 and 9.9), 3.52 (dd, 1 H, *J* = 4.9 and 9.9), 2.44 (s, 3 H), 1.30 (s, 9 H).

Step 2. (*R*)-Benzyl glycidol (115 mg, 0.7 mmol) was added to a mixture of (*S*)-**10b** (305 mg, 0.7 mmol), K_2CO_3 (10 mg, 0.07 mmol) and TEBA (16 mg, 0.07 mmol). After heating at 90 °C for 2 h the reaction mixture was directly purified by column chromatography (AcOEt/PE, 1:4) to generate 399 mg of the title compound, 95% yield.

(*S*,*R*)-**9b**: $[\alpha]^{23}_D$: +11.0 (*c* 0.93, $CHCl_3$), HPLC (CHIRALCEL OD; hexane/*i*-PrOH, 80:20) t_R (*S*,*R*) = 25.0, ee 98%.

Acknowledgment

Financial support from MIUR (Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali) and CNR is gratefully acknowledged.

Received for review February 10, 2010.

OP1000435