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Synthesis of chiral C/N-functionalized morpholine alcohols: study of their catalytic ability as ligand in asymmetric diethylzinc addition to aldehyde

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Abstract—A broad variety of chiral C/N-functionalized morpholine alcohols sharing a common structural motif in the 3-(hydroxymethyl)morpholine **6** were prepared from enantiomerically pure serine for the purpose of studying their catalytic ligand properties. The asymmetric addition of diethylzinc to benzaldehyde in the presence of 10 mol % of chiral C/N-functionalized morpholine alcohols gave 1-phenyl-1-propanol in 59–81% yield with 10–30% ee. The addition of 10 mol % of *n*-butyl lithium to the reaction mixture resulted in a significant enhancement of the stereoselectivity in the case of ligands bearing the two geminal phenyl substituents on the backbone. In the presence of *n*-butyl lithium and using (*S*)-3-(hydroxydiphenylmethyl)morpholine (*S*)-**19** as the chiral promoter, (*S*)-1-phenyl-1-propanol was obtained in 81% yield with 76% ee. The geminal diphenyl-class of morpholine ligands was examined for the diethylzinc addition to four different aldehydes in the presence of *n*-butyl lithium. (*S*)-*N*-Benzyl-3-(hydroxydiphenylmethyl)morpholine (*S*)-**27** was found to be most enantioselective in the case of 4-methoxybenzaldehyde to give (*R*)-alcohol in 87% yield with 80% ee. Catalysts (*S*)-**19** and its *N*-methyl derivative (*S*)-**26** gave alcohols with an (*S*)-absolute configuration while the N-benzylated derivative (*S*)-**27** gave the opposite enantiomeric products. The tentative transition state models to account for the observed product stereoselectivity with morpholine ligands holding the geminal diphenyl group on the β-amino alcohol segment are proposed.

1. Introduction

Even until today, the asymmetric addition[1] of diethylzinc to aldehydes is considered as a classical test for the design of new ligands, particularly chiral amino alcohols for catalytic enantioselective syntheses. The reaction allows access to chiral alcohols that are ubiquitous in the structures of natural products and drug compounds. Generally, it is assumed that six-membered azacycloalkanes are less efficient chiral catalysts in comparison with the corresponding smaller ring compounds, due to the ring flexibility. However, if the six-membered ring contains a heteroatom, such as an oxygen atom in morpholine, then the presence of an extra coordination site in the catalyst may influence its ligand catalytic properties. Recently, Seto et al.[2] and Nugent[3] have reported morpholine based β-diamines, and β-amino alcohols, respectively, as efficient chiral promoters for the enantioselective addition of organozinc reagents to aldehydes. A common feature of these catalysts is the presence of an achiral morpholine ring moiety with the stereodirecting stereogenic center on the appended segment of the amine. To the best of our knowledge, there has not been a report on the synthesis of morpholine-based β-amino alcohols with chirality on the heterocyclic ring.[4] It is thus of interest to synthesize and study the stereoinducing ability of the morpholine-based β-amino alcohol ligands with the stereocontrolling stereogenic center on the heterocyclic ring. Previously, we have reported[5] the enantioselective synthesis of O-protected *trans*-3,5-bis(hydroxymethyl)morpholines with the objective of understanding the influence of the oxygen atom of the morpholine ring on the ligand catalytic properties.

Herein, we report the synthesis of a variety of chiral C/N-functionalized morpholine alcohols bearing a common 3-(hydroxymethyl)morpholine structural motif from the commercially available optically active serine (Fig. 1). The catalytic ability of these chiral morpholine ligands was studied in the asymmetric addition of diethylzinc addition to benzaldehyde. The addition reaction was also studied in the presence of an *n*-butyl lithium additive.

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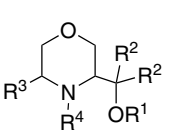


	R^1	R^2	R^3	R^4
5	H	H	H	H
10	H	H	CH_2OBn	H
11	H	H	$CH_2OTBDPS$	H
14	H	H	CH_2OBn	allyl

	R^1	R^2	R^3	R^4
15	H	H	CH_2OBn	COC_2H_5
18	Bn	H	CH_2OBn	$CH_2C(Ph)_2OH$
21	H	Ph	H	H
28	H	Ph	H	CH_3
29	H	Ph	H	Bn

Figure 1. Design of chiral ligands with 3-(hydroxymethyl)morpholine as a common structural unit.

These investigations would be informative for the future design of the morpholine-based ligand catalyst.

2. Results and discussion

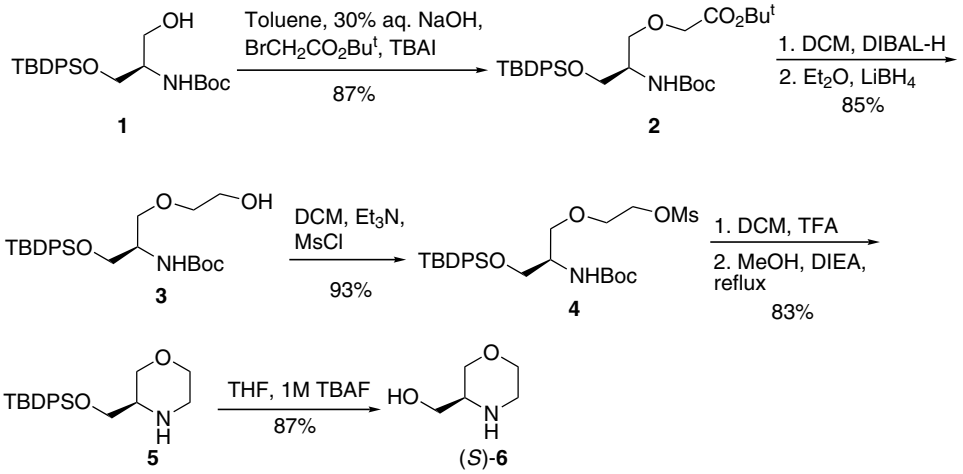
2.1. Synthesis of C/N-functionalized morpholine-based β-amino alcohols

The synthesis of (*S*)-3-(hydroxymethyl)morpholine,[6] (*S*)-**6** was envisaged from L-serine by involving coupling of a serinol derivative with *tert*-butyl bromoacetate as a key step.[7] One of the coupling components, (2*R*)-2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)-propan-1-ol **1**, was obtained[5] from L-*N*-Boc-serine methyl ester in 87% yield over two steps. Compound **1** was coupled with *tert*-butyl bromoacetate in a mixture of toluene and 30% aq NaOH containing catalytic TBAI to give ester **2** in 87% yield. $LiAlH_4$ reduction of **2** furnished alcohol **3** in only 45% yield, in an irreproducible manner in a large scale.

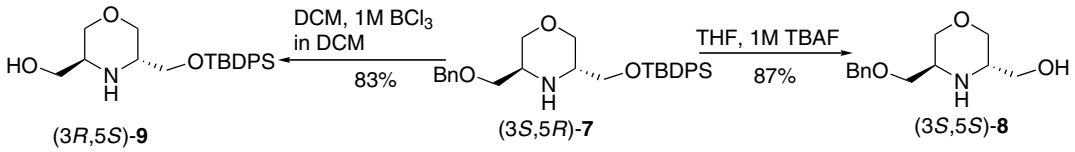
This problem was circumvented when a two-pot reduction procedure was employed to convert **2** to alcohol **3** in 85% yield. **2** was first reduced with DIBAL-H in DCM and the resulting crude aldehyde was further reduced to **3** with $LiBH_4$ in ether. **3** was converted to morpholine derivative **5** by the three-step sequence of O-mesylation, removal of the Boc-group from mesylate derivative **4**, and finally base-mediated cyclization at reflux in methanol (Scheme 1). Removal of silyl group from **5** with TBAF in THF gave (*S*)-**6** in 87% yield. The overall yield of (*S*)-**6** starting from **1** was 50%.

We felt that if (*S*)-**6** can share the benzyl/*tert*-butyldiphenylsilyloxymethyl structural motif at the C-5 position in a *trans* stereo-fashion then the resulting ligand may give valuable information on the influence of such substituents on the catalyst's chirality inducing properties in the asymmetric reactions. Thus, (3*S*,5*S*)-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-**8** and (3*R*,5*S*)-3-(*tert*-butyldiphenylsilyloxymethyl)-5-(hydroxymethyl)morpholine (3*R*,5*S*)-**9** were prepared from (3*S*,5*R*)-3-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)morpholine[5] (3*S*,5*R*)-**7** by selective cleavage of the *O*-*tert*-butyldiphenylsilyl, and *O*-benzyl group, respectively. (3*S*,5*R*)-**7** on treatment with 1 M TBAF in THF gave (3*S*,5*S*)-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-**8** in 87% yield. Initially, debenzylation of (3*S*,5*R*)-**7** by the palladium catalyzed hydrogenation failed to give the desired (3*R*,5*S*)-3-(*tert*-butyldiphenylsilyloxymethyl)-5-(hydroxymethyl)-morpholine (3*R*,5*S*)-**9**. Later, cleavage of *O*-benzyl group was achieved[8] in dichloromethane with 1 M solution of boron trichloride in dichloromethane to afford (3*R*,5*S*)-**9** in 83% yield (Scheme 2).

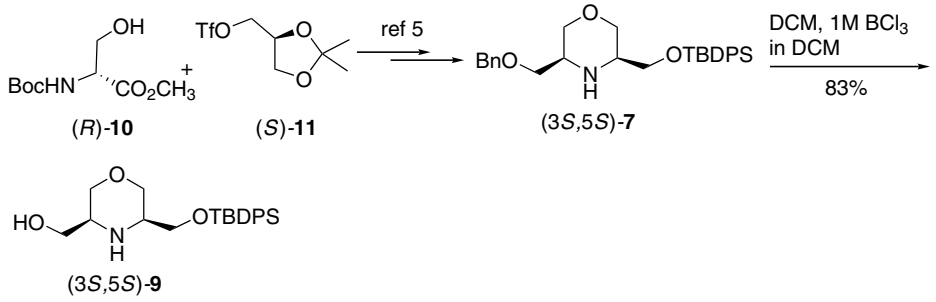
To understand the significance of the *trans*-stereochemistry of the substituents in (3*R*,5*S*)-**9** in an asymmetric reaction, we synthesized the *cis*-isomer of **9** from (3*S*,5*S*)-3-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)morpholine (3*S*,5*S*)-**7** by debenzylation with boron trichloride in 83% yield. Compound (3*S*,5*S*)-**7** was prepared from D-*N*-Boc-serine methyl ester (*R*)-**10** and (*S*)-2,3-*O*-isopropylideneglycerol triflate (*S*)-**11** in 42% overall yield following our standard[5] protocol (Scheme 3).



Scheme 1. Revised synthesis of (*S*)-**6**.



Scheme 2. Synthesis of (3*S*,5*S*)-**8** and (3*R*,5*S*)-**9**.

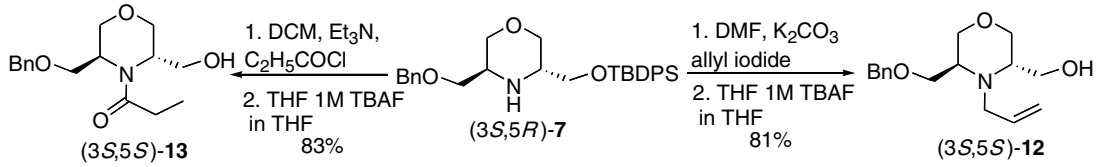


Scheme 3. Synthesis of (3*S*,5*S*)-**9**.

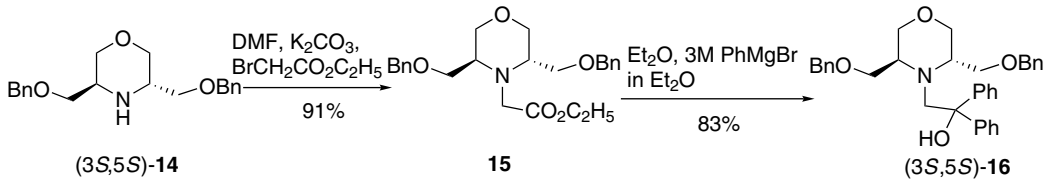
N-Derivatized morpholine ligands are useful for evaluating the steric role of the tertiary *N*-substituent on the transition state models in asymmetric reactions. Attempts to alkylating the morpholine nitrogen of (3*S*,5*R*)-**7** with methyl iodide and benzyl bromide/iodide in the presence of a base such as NaH, K_2CO_3, *n*-butyl lithium, etc. failed to give any *N*-alkylated product due to steric reasons. However, the use of allyl iodide in the presence of K_2CO_3 in DMF gave *N*-allylated derivative of (3*S*,5*R*)-**7** in 93% yield. Subsequent cleavage of the silyl protecting group with TBAF afforded (3*S*,5*S*)-*N*-allyl-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-**12** in 87% yield (81% yield over two steps). It was observed that the *N*-acylation of (3*S*,5*R*)-**7** in the presence of base was facile. Using propionyl chloride in the presence of triethylamine, *N*-propionylation of (3*S*,5*R*)-**7** and the subsequent removal of silyl protecting group from the resulting *N*-propionyl derivative with TBAF, furnished (3*S*,5*S*)-*N*-propionyl-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-**13** in 83% yield over two steps (Scheme 4).

The C_2-symmetric ligands obtained from the chiral scaffold of cyclic amines (azetidine and pyrrolidine) are known[9] to be excellent candidates for the enantioselective diethylzinc addition to aldehydes. The C_2-symmetric (3*S*,5*S*)-*N*-(2,2-diphenyl-2-hydroxyethyl)-3,5-bis(benzyloxymethyl)morpholine (3*S*,5*S*)-**16** was prepared from the chiral scaffold, (3*S*,5*S*)-3,5-bis(benzyloxymethyl)-morpholine (3*S*,5*S*)-**14** in two steps. The coupling of (3*S*,5*S*)-**14** with ethyl bromoacetate in the presence of K_2CO_3 in DMF gave ester **15** in 91% yield. The addition of phenylmagnesium bromide to **15** in ether gave (3*S*,5*S*)-**16** in 83% yield (Scheme 5).

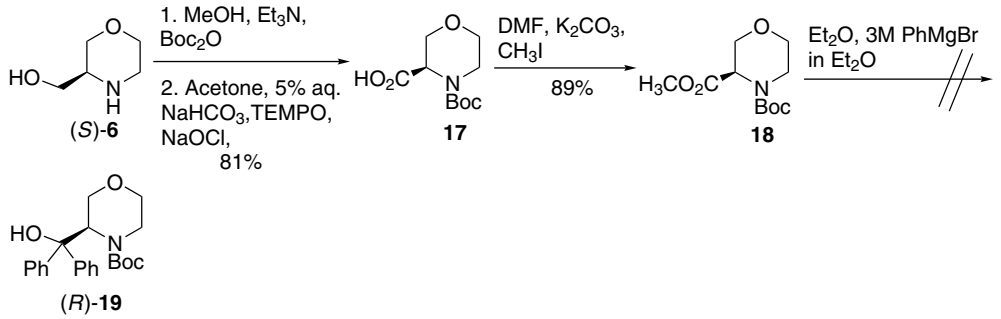
In the literature,[10] there are several examples of ligands, which share a flat/bulky phenyl structural motif, and promote asymmetric reactions. In this aspect, the synthesis of (*R*)-3-(hydroxydiphenylmethyl)morpholine[11] (*R*)-**19** was attempted by using the most obvious approach[12] from (*S*)-**6** (Scheme 6). The amino group of (*S*)-**6** was protected with Boc_2O, and the resulting *N*-Boc derivative of (*S*)-**6** was subjected to TEMPO-



Scheme 4. Synthesis of (3*S*,5*S*)-**12** and (3*S*,5*S*)-**13**.



Scheme 5. Synthesis of (3*S*,5*S*)-**16**.



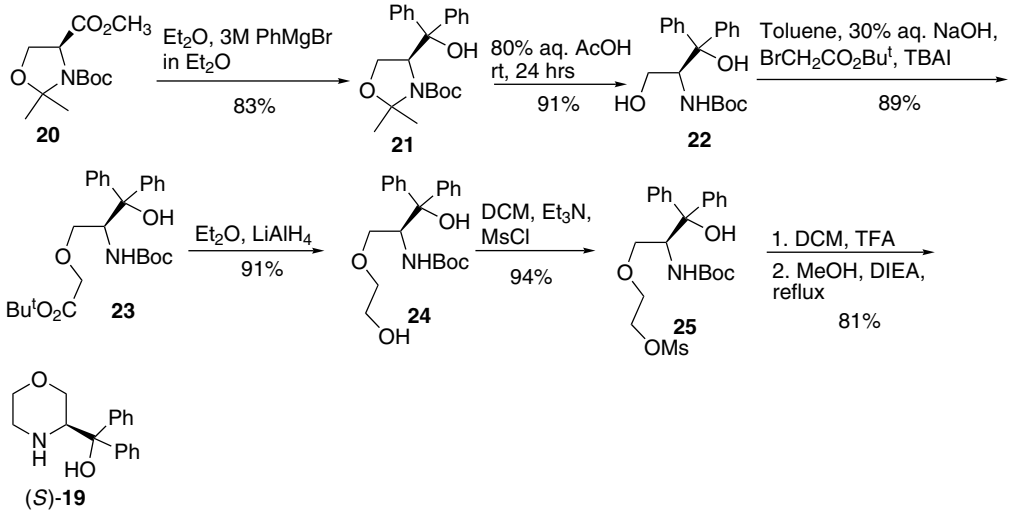
Scheme 6. Attempted synthesis of (*R*)-**19** from (*S*)-**6**.

mediated oxidation to afford acid **17** in 81% yield over two steps.

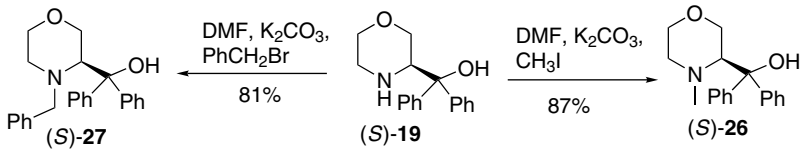
Esterification of **17** with methyl iodide in DMF in the presence of K_2CO_3 gave ester **18** in 89% yield. Unfortunately, the addition of phenylmagnesium bromide to ester **18** failed to give the desired (*R*)-**19** under various reaction conditions.

Failure of the above approach to access (*R*)-**19** prompted us to utilize a known addition reaction[13] of phenylmagnesium bromide to (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylate **20** to obtain (*S*)-**19**. Addition of phenylmagnesium bromide to **20** in ether gave *N*-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-(hydroxydiphenylmethyl)oxazolidine **21** in 83% yield. Cleavage of the oxazolidine moiety with 80% aq acetic acid and coupling of the resulting alcohol **22** with *tert*-butyl bromoacetate in a mixture of toluene and 30% aq NaOH solution gave ester **23**. $LiAlH_4$ reduction of **23** in THF gave alcohol **24** in 91% yield. The standard three step protocol of mesylation, deprotection of the amino group, and base-mediated cyclization gave (*S*)-**19** in 76% yield over three steps (Scheme 7).

To examine the role of the tertiary amine component of these ligands in the asymmetric reactions, *N*-substituted derivatives of (*S*)-**19** were prepared. Unlike 3,5-disubstituted morpholine, (*S*)-**19** underwent *N*-methylation with methyl iodide in the presence of potassium carbonate smoothly to give (*S*)-**26** in 87% yield. Similarly, when using benzyl bromide as an alkylating agent, (*S*)-**19** was converted to (*S*)-*N*-benzyl-3-(hydroxydiphenylmethyl)morpholine[14] (*S*)-**27** in 81% yield (Scheme 8).



Scheme 7. Synthesis of (*S*)-**19**.



Scheme 8. Synthesis of (*S*)-**26** and (*S*)-**27**.

2.2. Enantioselective diethylzinc addition

2.2.1. Enantioselective diethylzinc addition to benzaldehyde catalyzed by chiral morpholine-based β-amino alcohols. To begin with, ligands (*S*)-**6**, (3*S*,5*S*)-**8**, (3*R*,5*S*)-**9**, (3*S*,5*S*)-**9**, (3*S*,5*S*)-**12**, (3*S*,5*S*)-**13**, (3*S*,5*S*)-**16**, (*S*)-**19**, (*S*)-**26**, and (*S*)-**27** were tested for the asymmetric diethylzinc reaction with benzaldehyde as the reference substrate (Fig. 2). The results from these experiments are shown in Table 1.

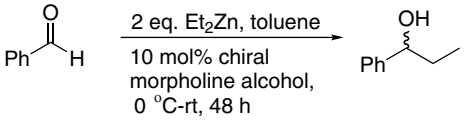


Figure 2. Diethylzinc addition to benzaldehyde catalyzed by β-amino alcohols bearing a morpholine moiety.

Table 1. Diethylzinc addition to benzaldehyde catalyzed by β-amino alcohol bearing chiral morpholine

Entry	Catalyst	Yield (%)[a]	Enantioselective ratio (*R*:*S*)	ee (%)[b]	Config. of alcohol[c]
1	(*S*)-**6**	80	40:60	20	*S*
2	(3*R*,5*S*)-**8**	71	43:57	14	*S*
3	(3*R*,5*S*)-**9**	75	36:64	28	*S*
4	(3*S*,5*S*)-**9**	74	37:63	26	*S*
5	(3*S*,5*S*)-**12**	61	55:45	10	*R*
6	(3*S*,5*S*)-**13**	59	56:44	12	*R*
7	(3*S*,5*S*)-**16**	81	58:42	16	*R*
8	(*S*)-**19**	79	43:57	14	*S*
9	(*S*)-**26**	77	42:58	16	*S*
10	(*S*)-**27**	78	65:35	30	*R*

[a] Isolated yield.
[b] HPLC analyses chiralcel OD column (10 μm, 4.6 × 250 mm), hexane/2-propanol 97.5/2.5, 1 ml/min, $t_R = 11.9$ (*R*) and 13.7 (*S*) min.
[c] Assigned from the sign of the specific rotation and from the elution order in HPLC analysis.

When benzaldehyde (1 mmol) was reacted with diethylzinc (2 mmol) in the presence of (*S*)-**6** (10 mol %) in toluene at room temperature for 48 h, (*S*)-1-phenylpropan-1-ol was obtained in 80% yield with 20% ee (entry 1).

The enantiomeric excess (ee) of the products was determined by chiral HPLC analysis and the absolute configuration of the major enantiomer assigned based on the sign of optical rotations and from the elution order in HPLC analysis. Compounds (3*R*,5*S*)-**8** and (3*R*,5*S*)-**9**, bearing benzyloxymethyl and *tert*-butyldiphenylsilyloxymethyl group, respectively, in a stereo-defined *trans* fashion when used as ligand, gave an alcohol with an (*S*)-configuration. Compound (3*R*,5*S*)-**9** with bulky TBDPS group yielded product with higher ee in comparison to (3*R*,5*S*)-**8** with a benzyl group (compare entries 2 and 3). Further, reversing the configuration of the stereogenic center bearing a *tert*-butyldiphenylsilyloxymethyl group (cis-form) did not show any significant change on the catalytic properties (entry 4). The tertiary amino alcohols, (3*S*,5*S*)-**12** and (3*S*,5*S*)-**13**, were relatively less efficient promoters in terms of both chemical yield as well as enantioselectivity (entries 5 and 6). Likewise, with C_2-symmetric morpholine-based amino alcohol, (3*S*,5*S*)-**16**, although it yielded the product in 81% yield, the ee was only 16% (entry 8). All the tertiary amine morpholine ligands, (3*S*,5*S*)-**12**, (3*S*,5*S*)-**13**, and (3*S*,5*S*)-**16** led to crossover in the product configuration. The promising ligand candidate (*S*)-**19**, with flat/bulky geminal phenyl substituents on the backbone, gave alcohol in 79% yield with just 14% ee (entry 8). Even, the *N*-methylated derivative, (*S*)-**26**, was equally less efficient (entry 9) in this catalytic reaction. Both (*S*)-**19** and (*S*)-**26** gave alcohol with (*S*) absolute configuration.

Interestingly, the *N*-benzylated ligand, (*S*)-**27**, was the best amongst the current series of morpholine ligands tested for the reaction. It led to a crossover in product configuration with 30% ee and 78% yield (entry 10). It is noteworthy that the sense of stereo-induction observed[15] for the product with (*S*)-**19** was reversed in comparison with that observed for (*S*)-**6**. This implies that the reaction involving the geminal diphenyl-class of morpholine ligand and (*S*)-**6** proceeds through different transition states.

The widely accepted mechanism[16] for this addition reaction involves the reaction of a β-amino alcohol with a molecule of diethylzinc to form ethylzinc-alkoxide chelate **A**, which subsequently coordinates with both the aldehyde and a second molecule of diethylzinc, allowing the addition of the ethyl group to the aldehyde carbonyl in a stereoselective manner. Monomeric zinc-alkoxide chelate **A** is the actual catalyst, which bears a Lewis acid site (Zn atom) to activate the aldehyde and a Lewis base site (O atom) to activate the zinc reagent (Fig. 3). Thus, the catalyst positions the two partners in close proximity and with the correct relative geometry, facilitating the reaction in a synergistic manner similar to catalysis by enzymes.

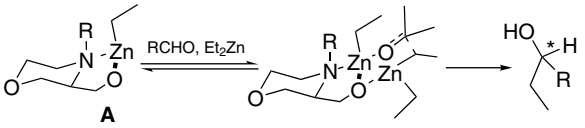


Figure 3. Mechanism for the addition of diethylzinc to aldehyde catalyzed by β-amino alcohol.

Similar bifunctional catalysts, such as lithium-alkoxide chelate,[16a,17] prepared from the reaction of a β-amino alcohol with *n*-butyl lithium are also known to catalyze the nucleophilic addition of organozinc reagent to aldehydes. Motivated by this precedence, the catalytic diethylzinc addition to benzaldehyde was reinvestigated in the presence of *n*-butyl lithium additive.

2.2.2. Enantioselective diethylzinc addition to benzaldehyde catalyzed by chiral morpholine-based β-amino alcohols in the presence of *n*-butyl lithium. Enantioselective diethylzinc addition to benzaldehyde catalyzed by chiral morpholine-based β-amino alcohols was studied in the presence of *n*-butyl lithium. First, to a toluene solution of (*S*)-**6** (1 mmol), *n*-butyl lithium (10 mol %), and diethylzinc (2 mmol) were sequentially added at −30 °C. The

mixture was warmed to 0 °C and after stirring for 30 min, benzaldehyde (1 mmol) was added. After 48 h of stirring at room temperature, (*S*)-1-phenylpropan-1-ol was isolated in 77% yield with 32% ee (Table 2, entry 1). With the monolithiated (*S*)-**6**, the sense of stereoinduction for product was same and there was no significant change in the chemical yield. Interestingly, the degree of stereoselectivity had enhanced by almost 50%. Following the same procedure, ligands (3*S*,5*S*)-**8**, (3*R*,5*S*)-**9**, (3*S*,5*S*)-**9**, (3*S*,5*S*)-**12**, (3*S*,5*S*)-**13**, (3*S*,5*S*)-**16**, (*S*)-**19**, (*S*)-**26**, and (*S*)-**27** were tested for asymmetric diethylzinc addition to the benzaldehyde in the presence of *n*-butyl lithium. The results from these experiments are summarized in Table 2.

Table 2. Diethylzinc addition to benzaldehyde catalyzed by β-amino alcohol bearing morpholine moiety in the presence of 10 mol % *n*-butyl lithium

Entry	Catalyst	Yield (%)[a]	Enantioselective ratio (*R*:*S*)	ee (%)[b]	Config. of alcohol[c]
1	(*S*)-**6**	77	34:66	32	*S*
2	(3*S*,5*S*)-**8**	55	47:53	6	*S*
3	(3*R*,5*S*)-**9**	71	38:62	24	*S*
4	(3*S*,5*S*)-**9**	67	39:61	22	*S*
5	(3*S*,5*S*)-**12**	35	44:56	12	*S*
6	(3*S*,5*S*)-**13**	69	43:57	14	*S*
7	(3*S*,5*S*)-**16**	74	61:39	22	*R*
8	(*S*)-**19**	81	12:88	76	*S*
9	(*S*)-**26**	73	27:73	46	*S*
10	(*S*)-**27**	79	84:16	68	*R*

[a] Isolated yield.
[b] HPLC analyses chiralcel OD column (10 μm, 4.6 × 250 mm), hexane/2-propanol 97.5/2.5, 1 ml/min, $t_R = 11.9$ (*R*) and 13.7 (*S*) min.
[c] Assigned from the sign of the specific rotation and from the elution order in HPLC analysis.

Compound (3*S*,5*S*)-**8** was an inefficient catalyst as it gave the product in 55% yield but with only 6% ee (entry 2). The presence of *n*-butyl lithium did not have any significant influence on the ligand catalytic properties of (3*R*,5*S*)-**9** and (3*S*,5*S*)-**9**, as product ee values and chemical yields were nearly the same as in the absence of the additive (compare entries 3 and 4 in Tables 1 and 2). *N*-Derivatized ligands, (3*S*,5*S*)-**12** and (3*S*,5*S*)-**13** were also poor promoters for the diethylzinc addition to benzaldehyde in the presence of *n*-butyl lithium (entries 5 and 6).

However, the interesting observation was that the configuration of the resulting alcohol was reversed. The C_2-symmetric morpholine-based amino alcohol, (3*S*,5*S*)-**16** was a better catalyst in its monolithiated form. The product was obtained in 74% yield with 22% ee (entry 7). Notably, ligands bearing a geminal diphenyl group on the backbone showed a dramatic enhancement in the ee of the product in the presence of *n*-butyl lithium. Compound (*S*)-**19** in the monolithiated form was the best amongst the series of morpholine ligands evaluated for the asymmetric diethylzinc addition to benzaldehyde and (*S*)-**19** gave the alcohol in 81% yield with 76% ee (entry 8). *N*-Methylated derivative, (*S*)-**26**, was relatively less efficient and afforded product in 73% yield with 46% ee (entry 9). As before, the use of *N*-benzylated derivative, (*S*)-**27**, as the ligand led to the reversal in the sense of stereoinduction, yielding 79% of product in 68% ee with *R* absolute configuration (entry 10). It is noteworthy that the sense of stereoinduction for the product with the morpholine ligands [except for (3*S*,5*S*)-**12** and (3*S*,5*S*)-**13**] was the same as with the case in the absence of *n*-butyl lithium additive.

2.2.3. Diethylzinc addition to aldehydes catalyzed by morpholine-based diphenyl-class of ligands, (*S*)-19, (*S*)-26, and (*S*)-27, in the presence of 10 mol % *n*-butyl lithium. Observing the significant enhancement in the ee of the product in the presence of *n*-butyl lithium additive, the use of diphenyl-class of ligands, (*S*)-**19**, (*S*)-**26**, and (*S*)-**27** was extended to the asymmetric ethylation of other aromatic, aliphatic, and α,β-unsaturated aldehydes (Table 3). The yields and enantioselectivites were 71–88% and 43–80%, respectively. Ligand (*S*)-**19**, which was the most enantioselective amongst the ligands tested for the benzaldehyde, was less efficient with other aldehydes except α,β-unsaturated aldehydes. It gave the best results for 3-phenylpropionaldehyde and *trans*-cinnamaldehyde, yielding the products with 68% ee (Table 3,

Table 3. Diethylzinc addition to aldehydes catalyzed by morpholine-based diphenyl-class of ligands, (*S*)-**19**, (*S*)-**26**, and (*S*)-**27**, in the presence of 10 mol % *n*-butyl lithium

Entry	Aldehyde	Catalyst	Yield (%)[a]	Enantioselective ratio *R*:*S*	ee (%)[b]	Config. of alcohol[c]
1	4-Methoxybenzaldehyde	(*S*)-**19**	79	18:82	64	S
2	4-Methoxybenzaldehyde	(*S*)-**26**	83	20:80	60	*S*
3	4-Methoxybenzaldehyde	(*S*)-**27**	87	90:10	80	*R*
4	2-Naphthaldehyde	(*S*)-**19**	78	18:82	64	*S*
5	2-Naphthaldehyde	(*S*)-**26**	84	24:76	52	*S*
6	2-Naphthaldehyde	(*S*)-**27**	88	87:13	74	*R*
7	3-Phenylpropionaldehyde	(*S*)-**19**	71	16:84	68	*S*
8	3-Phenylpropionaldehyde	(*S*)-**26**	73	21:79	58	*S*
9	3-Phenylpropionaldehyde	(*S*)-**27**	79	87:13	74	*R*
10	*trans*-Cinnamaldehyde	(*S*)-**19**	80	16:84	68	*S*
11	*trans*-Cinnamaldehyde	(*S*)-**26**	74	21:79	58	*S*
12	*trans*-Cinnamaldehyde	(*S*)-**27**	76	82:18	64	*R*

[a] Isolated yield.
[b] HPLC analyses chiralcel OD column.
[c] Assigned from the sign of the specific rotation and from the elution order in HPLC analysis.

entries 7 and 10). It also catalyzed the ethylation of cinnamaldehyde better than the other ligands tested (Table 3, compare entries 10–12). *N*-Methylated ligand, (*S*)-**26**, was a poor promoter in the ethylation reaction of the aldehydes. With 4-methoxybenzaldehyde, it gave the product with 60% ee in 83% yield (Table 3, entry 2). For 2-naphthaldehyde, 3-phenylpropionaldehyde, and *trans*-cinnamaldehyde, the ees were 52%, 58% and 58%, respectively (Table 3, entries 5, 8, and 11). The N-benzylated ligand, (*S*)-**26**, was the most enantioselective among the geminal diphenyl-class of catalyst for all the aldehydes, except *trans*-cinnamaldehyde. It catalyzed the diethylzinc addition to 4-methoxybenzaldehyde to furnish the (*R*)-configured alcohol in 87% yield with 80% ee (Table 3, entry 3). However, for 2-naphthaldehyde and 3-phenylpropionaldehyde, the enantioselection was lower, that is 74% for both (Table 3, entries 6 and 9). Cinnamaldehyde was a poor substrate for the (*S*)-**26** catalyzed ethylation reaction, giving the product with 64% ee (Table 3, entry 12).

The asymmetric addition of the organozinc reagent to the aldehyde in the presence of the β-amino alcohol is a well-documented reaction and several models explaining the sense of stereoinduction have been proposed.[18] The tentative transition state models for the reaction catalyzed by morpholine ligands bearing the geminal diphenyl group on the backbone was defined to explain the observed product configuration. The two chair-like transition states **A** and **B**, which account for the interaction of the *N*-substituent (X) with the morpholine ring segment, by reinforcement of the α-substituents (geminal phenyl groups), seem to be operational in the reaction (Fig. 4). This interaction dictates the approach and coordination of the aldehyde to the metal atom. In reactions with (*S*)-**19**, model **A** is operative. In this ligand, the geminal phenyl groups create a more crowded bottom face of the metallocycle. This allows for the coordination of the aldehyde from the top face and a *re* face ethyl addition to give the alcohol with an (*S*)-configuration. Model **B** becomes operative in the case of tertiary amine ligand (*S*)-**27** to neutralize the steric interaction of the *N*-substituent (benzyl) with the approaching aldehyde. In this complex, coordination of the aldehyde to the Lewis acid (metal atom) occurs on the less hindered bottom face while *si* face ethyl addition accounts for the observed (*R*)-configuration of the product. However, with *N*-methylated tertiary amine ligand (*S*)-**26**, the smaller methyl group is less effective in generating the steric interaction and thus the sense of stereoinduction is determined by model **A**.

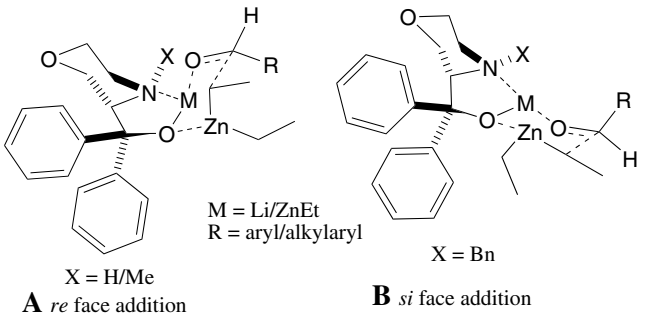


Figure 4. Transition state models for the diethylzinc reaction with benzaldehyde catalyzed by geminal diphenyl-class of morpholine ligands.

The higher enantioselectivity with the lithiated morpholine ligand, may be attributed to the stronger hard acid character of lithium compared to zinc.[19] Thus, the lithium can more easily coordinate with the oxygen atom (hard base) of the approaching aldehyde than zinc.[17b] Such a coordination of the lithium cation may control the steric course of the reaction to afford higher enantioselectivity.

3. Conclusion

In conclusion, a broad variety of chiral C/N functionalized morpholine catalysts sharing a common structural motif with 3-(hydroxymethyl)morpholine **6** were prepared from optically active serine in an efficient manner. The key step in the building of the chiral morpholine unit was the base-mediated coupling of the serinol derivative with *tert*-butyl bromoacetate or chiral 2,3-*O*-isopropylideneglycerol triflate. These morpholine-based β-amino alcohols in 10 mol % concentration catalyze the diethylzinc addition to benzaldehyde to afford 1-phenyl-1-propanol in 59–81% yield with 10–30% ee. Interestingly, the addition of 10 mol % of *n*-butyl lithium to the reaction mixture dramatically enhanced the ee of the product in the case of ligands bearing geminal diphenyl group on the backbone. In the presence of *n*-butyl lithium, the use of (*R*)-3-(hydroxydiphenylmethyl)morpholine (*S*)-**19** as a catalyst gave (*S*)-1-phenyl-1-propanol in 81% yield with 75% ee for the benzaldehyde. The ee amplification of the product with the 10 mol % of *n*-butyl lithium additive in the case of geminal diphenyl-class of ligands was 220–580% for benzaldehyde. Principally, such a dramatic improvement in the product enantioselectivity could not be explained by only considering the strong hard acid character of lithium atom of the lithiated morpholine ligand. It seems that there may be some sort of coordination of the oxygen atom of the morpholine ring with the lithium atom, thereby imparting rigidity to the catalyst system. To gain a precise understanding, parallel studies with the corresponding piperidine class of ligands need to be conducted. *N*-Benzylated morpholine ligand, (*S*)-**27** was found to be the most efficient catalyst among the diphenyl-class of ligands tested against other aldehydes except cinnamaldehyde. With 4-methoxybenzaldehyde, it gave an (*R*)-configured alcohol in 87% yield with 80% ee. Interestingly, catalyst (*S*)-**19** and its *N*-methyl derivative (*S*)-**26** gave alcohols with an (*S*)-configuration while the N-benzylated derivative (*S*)-**27** gave the opposite enantiomeric products for all the aldehydes. The transition state models proposed could explain this crossover in the product configuration. Experiments are currently underway to refine our proposed model, and to probe the role of the α-substituents on the hydroxymethylene group of the morpholine unit. For this purpose, the synthesis of (1*S*,3*R*)-3-(1-hydroxyethyl)morpholine from L-threonine is under progress.

Such a ligand having an extra chirality on the methylene carbon holding the hydroxyl group could provide more information on the design of new catalysts. We also plan to screen the morpholine ligands presented in this article against a variety of other aliphatic and aromatic aldehydes as substrates using various zinc reagents.

4. Experimental

4.1. General considerations

Tetrahydrofuran was distilled from sodium benzophenone ketyl and methylene chloride from P_2O_5 immediately prior to use. All reagents obtained from commercial sources were used without purification, unless otherwise mentioned. Diethylzinc (1 M in hexanes) and *n*-butyl lithium (1.6 M in hexanes) were supplied by Aldrich. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, E. Merck) and a stepwise solvent polarity gradient elution method was employed. Optical rotations and Infrared (IR) spectra were recorded on a JASCO P-1010 polarimeter and Perkin Elmer Spectrum BX spectrometer, respectively. High resolution mass spectra (HRMS) were run on Waters Micromass LCT with an electrospray source (ZQ) in positive mode ionization (ESI). Proton nuclear magnetic resonance (δ_H) spectra and carbon nuclear magnetic resonance spectra were recorded on Brucker AM-300. HPLC analyses were carried out on an Alliance (Waters 2695) using PDA detector (2996). Melting points were determined on a Buchi melting point apparatus and are uncorrected.

4.1.1. (*R*)-*tert*-Butyl 2-(2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propoxy)acetate 2. To a stirred solution of **1** (4.08 g, 9.5 mmol) in toluene (50 ml), 30% aq NaOH solution (50 ml), *tert*-butyl bromoacetate (2.8 ml, 19 mmol), and TBAI (1.736 g, 4.7 mmol) were sequentially added at 0–5 °C. After stirring for 3 h, the toluene layer was separated and the aq layer diluted with water (100 ml) before extracting with toluene (3×25 ml). The combined toluene layer was washed with 1 M HCl (25 ml), and brine (20 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a residue, which on silica gel flash column chromatographic purification (15% EtOAc in heptanes) afforded **2** (4.49 g, 87%) as a colorless oil: $[\alpha]_D^{23} = +4.7$ (*c* 1.1, $CHCl_3$); IR (neat) 3444, 3071, 2976, 2930, 2856, 1747, 1714, 1588, 1499, 1473, 1427, 1391, 1366, 1308, 1228, 1167, 1133, 1112, 1059, 1029, 997, 939, 885, 846, 824, 780, 740, 702, 691, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s, $SiC(CH_3)_3$), 1.42 (9H, s, $NCO_2C(CH_3)_3$), 1.47 (9H, s, $CO_2C(CH_3)_3$), 3.61 (H_a, dd, $J = 9.3$, 5.4 Hz, $COCH_aH_b$), 3.72 ($2H_b$, m, $COCH_aH_b$, $SiOCH_aH_b$), 3.79 (H_a, dd, $J = 10$, 4.3 Hz, $SiOCH_aH_b$), 3.88 (1H, m, NCH), 3.92 (2H, s, OCH_2-CO_2), 5.03 (1H, d, $J = 7.6$ Hz, NH), 7.37 (6H, m, PhH), 7.65 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.9, 28.1, 28.4, 51.4, 62.5, 68.9, 70, 79.2, 81.8, 127.7, 129.7, 133.3, 135.6, 155.5, 169.5; MS (ESI) *m*/*z* 566 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: *m*/*z* calcd for $C_{30}H_{45}NNaO_6Si$ 566.2908, found 566.2916.

4.1.2. (*R*)-2-(2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propoxy)ethanol 3. A solution of DIBAL-H (1.5 M) in toluene (21 ml) was added dropwise to a stirred solution of **2** (8.745 g, 15.6 mmol) in DCM (25 ml) at −78 °C and left to stir for 1 h. The solution was warmed to 0 °C and stirred for 2 h. Then, the mixture was again cooled to −78 °C and diluted with cold MeOH (3 ml) and cold 1 M HCl (30 ml). The DCM layer was separated and the aq layer extracted with DCM (2×25 ml). Combined DCM extract was washed with 5% aq $NaHCO_3$ (25 ml), brine (25 ml) and dried over Na_2SO_4. Evaporation of the solvent under vacuum gave the yellow residue (7.4 g), which was subjected to further reduction with $LiBH_4$ in ether without purification.

To a stirred solution of the above yellow residue in anhydrous ether (50 ml), $LiBH_4$ (0.34 g, 15.6 mmol) was added at 0–5 °C under argon. The cooling-bath was removed and stirring continued at room temperature for 12 h. The mixture was again cooled to 0–5 °C and quenched with water (40 ml) containing 6 M HCl (5 ml). The ether layer was separated and the aqueous layer was extracted with ether (2×25 ml). The combined ether layer was dried over Na_2SO_4 and evaporated to give a yellow residue, which on silica gel flash column chromatographic (40% EtOAc in heptanes) purification afforded **3** (6.275 g, 85%) as a colorless oil: $[\alpha]_D^{23} = +1.9$ (*c* 1.9, $CHCl_3$); IR (neat) 3445, 3070, 3048, 2930, 2857, 1710, 1695, 1589, 1499, 1472, 1427, 1390, 1364, 1313, 1246, 1170, 1111, 1058, 1029, 1007, 997, 969, 936, 884, 852, 823, 739, 700, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s, $SiC(CH_3)_3$), 1.44 (9H, s, $NCO_2C(CH_3)_3$), 2.18 (1H, br s, OH), 3.54 ($2H+H_a$, m, $H_2COCH_aH_b$), 3.68 ($4H+H_b$, m, $COCH_aH_b$, $SiOCH_2$, CH_2-hydroxyl), 3.88 (1H, m, NCH), 5.03 (1H, d, $J = 7.7$ Hz, NH), 7.41 (6H, m, PhH), 7.66 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.9, 28.4, 51.2, 61.8, 62.7, 69.9, 72.4, 79.5, 127.8, 129.8, 133.2, 135.6, 155.6; MS (ESI) *m*/*z* 496 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: *m*/*z* calcd for $C_{26}H_{39}NNaO_5Si$ 496.2490, found 496.2477.

4.1.3. (*R*)-(2-*tert*-Butoxycarbonylamino-3-(*tert*-butyldiphenylsilyloxy)propoxy)-2-(methanesulfonyloxy)ethane 4. To a stirred mixture of **3** (1.514 g, 3.2 mmol) and triethylamine (1.3 ml, 9.6 mmol) in DCM (25 ml), methanesulfonyl chloride (0.4 ml, 4.8 mmol) was added at −30 °C under argon. After addition, the cooling-bath was removed and the mixture stirred at room temperature for 2 h. The mixture was diluted with DCM (20 ml) and washed successively with water (10 ml), 1 M HCl (10 ml), satd aq $NaHCO_3$ solution (10 ml), and brine (10 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a yellow residue, which on silica gel flash column chromatographic (5% EtOAc in DCM) purification afforded **4** (1.64 g, 93%) as a colorless oil: $[\alpha]_D^{27} = +2.2$ (*c* 1.5, $CHCl_3$); IR (neat) 3390, 3070, 2957, 2930, 2856, 1711, 1588, 1503, 1471, 1454, 1427, 1390, 1353, 1311, 1246, 1173, 1111, 1059, 1021, 997, 970, 921, 852, 823, 803, 741, 702, 690, 620, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s, $SiC(CH_3)_3$), 1.44 (9H, s, $NCO_2C(CH_3)_3$), 2.95 (3H, s, SCH_3), 3.55

(H_a, dd, $J = 9.3$, 6.1 Hz, $COCH_aH_b$), 3.67 (2H+$2H_b$, m, $COCH_aH_b$, $SiOCH_aH_b$, $COCH_2$), 3.76 (H_a, dd, $J = 10$, 4 Hz, $SiOCH_aH_b$), 3.87 (1H, m, NCH), 4.29 (2H, dd, $J = 4.6$, 4.5 Hz, CH_2OMs), 4.85 (1H, d, $J = 7.7$ Hz, NH), 7.41 (6H, m, PhH), 7.65 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.9, 28.4, 37.6, 51.1, 62.6, 68.8, 69.9, 79.5, 127.8, 129.8, 133.1, 135.5, 155.4; MS (ESI) m/z 574 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{27}H_{41}NNaO_7SSi$ 574.2265, found 574.2250.

4.1.4. (*R*)-3-(*tert*-Butyldiphenylsilyloxymethyl)morpholine 5. To a stirred ice-cold solution of **4** (1.322 g, 2.4 mmol) in anhydrous DCM (20 ml), trifluoroacetic acid (5 ml) was added under argon. The cooling-bath was removed and the mixture stirred at room temperature for 1 h, after which TLC revealed the completion of the reaction. The mixture was concentrated under vacuum and the resulting residue was treated with satd aq $NaHCO_3$ solution (25 ml). The mixture was extracted with DCM (3×10 ml) and the combined DCM layer was dried (Na_2SO_4) and evaporated to give a yellow residue.

The residue was dissolved in MeOH (15 ml) and triethylamine (1 ml, 7.2 mmol) and *N*,*N*-diisopropylethylamine (1.3 ml, 7.2 mmol) added at room temperature. The mixture was refluxed at 80 °C under stirring for 4 h. The mixture was cooled, concentrated under vacuum, and treated with water (30 ml). The mixture was extracted with EtOAc (3×10 ml) and the combined EtOAc layer washed with brine (10 ml), dried over Na_2SO_4, and evaporated to give a yellow residue. Silica gel flash column chromatographic (EtOAc) purification of the residue afforded **5** (0.707 g, 83%) as a colorless oil: $[\alpha]_D^{25} = -0.3$ (*c* 1.2, $CHCl_3$); IR (neat) 3069, 3048, 2954, 2930, 2891, 2854, 1588, 1486, 1461, 1471, 1427, 1389, 1360, 1348, 1329, 1310, 1263, 1188, 1155, 1104, 1030, 1007, 997, 971, 956, 935, 883, 839, 823, 797, 740, 701, 690, 622, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s, $SiC(CH_3)_3$), 2.01 (1H, br s, NH), 2.96 (3H, m, NCH_2, NCH), 3.26 (H_a, dd, $J = 11.1$, 9.6 Hz, $COCH_aH_b$), 3.53 (2H+H_b, m, $SiOCH_2$, $COCH_aH_b$), 3.77 (H_c, t, $J = 3.2$ Hz, $COCH_cH_d$), 3.81 (H_d, t, $J = 3.4$ Hz, $COCH_cH_d$), 7.41 (6H, m, PhH), 7.65 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.9, 45.6, 56.2, 64.7, 67.8, 69.6, 127.8, 129.8, 133.3, 135.5; MS (ESI) m/z 378 $[M+Na]^+$, 356 $[M+H]^+$, 278, 200; HRMS (ESI) $(M+H)^+$: m/z calcd for $C_{21}H_{30}NO_2Si$ 356.2040, found 356.2037.

4.1.5. (*S*)-3-(Hydroxymethyl)morpholine (*S*)-6. Compound **5** was desilylated with TBAF using the previously described procedure to afford (*S*)-**6** as a colorless solid in 87% yield: mp 112 °C; $[\alpha]_D^{27} = -17.2$ (*c* 1.4, 1 M HCl); IR (neat) 3347, 2945, 2496, 1613, 1449, 1307, 1202, 1101, 1046, 988, 944, 863, 669, 648, 613 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 3.25 (2H, m, NCH_2), 3.38 (1H, m, NCH), 3.62 (H_a, dd, $J = 8.1$, 2.2 Hz, H_aH_b-$COCH_cH_d$), 3.66 (H_a, dd, $J = 8$, 2 Hz, CH_aH_b-hydroxyl), 3.74 (H_b+H_c, m, CH_aH_b-hydroxyl, $H_aH_bCOCH_cH_d$), 3.94 (H_d, t, $J = 3.4$ Hz, $H_aH_bCOCH_cH_d$), 3.98 (H_b, t, $J = 3.3$ Hz, $H_aH_bCOCH_cH_d$); ^{13}C NMR (75.5 MHz, MeOD) δ 44.2, 57.3, 59.2, 64.7, 66.8; MS (ESI) m/z 118 $[M+H]^+$; HRMS (ESI) $(M+H)^+$ HRMS (ESI) $(M+H)^+$: m/z calcd for $C_5H_{12}NO_2$ 118.0863, found 118.0865.

4.1.6. (3*S*,5*S*)-3-(Benzyloxymethyl)-5-(hydroxymethyl)-morpholine (3*S*,5*S*)-8. (3*S*,5*R*)-**7** was desilylated with TBAF using the previously described procedure to furnish (3*S*,5*S*)-**8** as a colorless oil in 87% yield: $[\alpha]_D^{26} = +3.7$ (*c* 1.0, MeOH); IR (neat) 3304, 2856, 1495, 1453, 1365, 1335, 1206, 1097, 1047, 925, 853, 796, 736, 696, 609 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 2.97 (1H, m, NCH), 3.17 (1H, m, NCH), 3.51 (2H+H_a, m, $COCH_2$, CH_aH_bOBn), 3.58 (2H+H_b, m, $COCH_2$, CH_aH_bOBn), 3.74 (2H, d, $J = 11.6$ Hz, CH_2-hydroxyl), 4.54 (H_a, d, $J = 12.2$ Hz, $PhCH_aH_b$), 4.57 (H_b, d, $J = 12.2$ Hz, $PhCH_aH_b$), 7.31 (1H, m, PhH), 7.36 (4H, m, PhH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 49.3, 51.4, 60.9, 68.1, 68.2, 69.6, 72.2, 127.3, 127.4, 128.2, 138.4; MS (ESI) m/z 260 $[M+Na]^+$, 238 $[M+H]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{13}H_{19}NNaO_3$ 260.1257, found 260.1255.

4.1.7. (3*R*,5*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-5-(hydroxymethyl)morpholine (3*R*,5*S*)-9. To a stirred solution of (3*S*,5*R*)-**7** (1.283 g, 2.7 mmol) in DCM (6 ml), 1 M solution of boron trichloride in DCM (5.4 ml, 5.4 mmol) was added at 0–5 °C under argon over a period of 10 min. The cooling-bath was removed and the mixture stirred at room temperature for 30 min. The mixture was quenched with MeOH (2 ml) and concentrated under vacuum. The resulting residue was diluted with DCM (25 ml, cooled to 0 °C and basified with triethylamine (1.9 ml). The mixture was concentrated under vacuum and the resulting brown residue was purified by silica gel flash column chromatography (EtOAc) to afford (3*R*,5*S*)-**9** (0.863 g, 83%) as a colorless oil: $[\alpha]_D^{24} = +11.5$ (*c* 1.1, MeOH); IR (neat) 3315, 3070, 2929, 2856, 2358, 2337, 1589, 1470, 1427, 1390, 1360, 1336, 1110, 998, 969, 932, 823, 740, 700, 614 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1 (9H, s, $SiC(CH_3)_3$), 2.77 (1H, m, NCH), 2.96 (1H, m, NCH), 3.29 (2H+H_a, m, $H_aH_bCOCH_cH_d$), CH_2-hydroxyl), 3.42 (H_c, dd, $J = 10.9$, 5.1 Hz, $H_aH_bCOCH_cH_d$), 3.59 (2H+H_b+H_d, m, $SiOCH_2$, $H_aH_bCOCH_cH_d$), 4.56 (1H, br s, NH), 7.46 (6H, m, PhH), 7.63 (4H, m, PhH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.8, 26.7, 51.3, 61.1, 63.3, 67.7, 68.4, 127.9, 129.8, 133, 135; MS (ESI) m/z 408 $[M+Na]^+$, 386 $[M+H]^+$, 308, 230; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{22}H_{31}NNaO_3Si$ 408.1965, found 468.1964.

4.1.8. (3*S*,5*S*)-3-(Benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)morpholine (3*S*,5*S*)-7. (3*S*,5*S*)-**7** was prepared from D-*N*-Boc-serine methyl ester (*R*)-**10** and (*S*)-2,3-*O*-isopropylideneglycerol triflate (*S*)-**11** employing our standard protocol:[5] $[\alpha]_D^{24} = +2.2$ (*c* 1.0, $CHCl_3$); IR (neat) 3069, 2929, 2854, 1588, 1471, 1453, 1427, 1389, 1361, 1336, 1308, 1240, 1209, 1101, 1028, 998, 968, 940, 822, 787, 737, 698, 641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s, $SiC(CH_3)_3$), 3.14 (4H, m, NCH, NCH, $COCH_2$), 3.32 (H_a, m, $BnOCH_aH_b$), 3.52 (H_b+2H, m, $BnOCH_aH_b$, $SiOCH_2$), 3.81 (2H, m,

$COCH_2$), 4.49 (H_a, d, $J = 11.9$ Hz, $PhCH_aH_b$), 4.53 (H_b, d, $J = 11.9$ Hz, $PhCH_aH_b$), 7.35 (11H, m, PhH), 7.64 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3, 26.8, 54.4, 56, 64.9, 69.4, 69.7, 71.1, 73.5, 127.8, 128.4, 129.8, 133.3, 135.6, 138; MS (ESI) m/z 476 $[M+H]^+$; HRMS (ESI) $(M+H)^+$: m/z calcd for $C_{29}H_{38}NO_3Si$ 476.2615, found 476.2610.

4.1.9. (3*S*,5*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-9. (3*S*,5*S*)-**7** was debenzylated with 1 M boron trichloride solution in DCM using the previously described procedure to give (3*S*,5*S*)-**9** as a colorless oil in 83% yield: $[\alpha]_D^{26} = -0.6$ (*c* 1.4, MeOH); IR (neat) 3304, 3069, 2929, 2854, 1588, 1470, 1461, 1426, 1389, 1360, 1335, 1240, 1209, 1103, 1006, 997, 937, 821, 788, 738, 699, 689, 621 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1 (9H, s, $SiC(CH_3)_3$), 2.76 (1H, m, NCH), 2.92 (3H, m, NCH, $COCH_2$), 3.22 (2H, m, CH_2-hydroxyl), 3.48 (2H, m, $SiOCH_2$), 3.72 (H_a, dd, $J = 10.5$, 2.9 Hz, $COCH_aH_b$), 3.79 (H_b, d, $J = 7.4$ Hz, $COCH_aH_b$), 4.58 (1H, br s, NH), 7.45 (6H, m, PhH), 7.61 (4H, m, PhH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.8, 26.6, 55.7, 56.1, 62.1, 64.9, 69.3, 69.4, 127.9, 129.9, 132.8, 132.9, 135; MS (ESI) m/z 408 $[M+Na]^+$, 386 $[M+H]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{22}H_{31}NNaO_3Si$ 408.1965, found 468.1964.

4.1.10. (3*S*,5*S*)-*N*-Allyl-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-12. To a solution of (3*S*,5*R*)-**7** (1.662 g, 3.5 mmol) in DMF (10 ml), K_2CO_3 (0.967 g, 7 mmol), and allyl iodide (0.5 ml, 5.3 mmol) were added at room temperature under argon. After stirring for 3 h, the mixture was diluted with EtOAc (100 ml), filtered, and the filtrate washed sequentially with water (15 ml), 1 M HCl (15 ml), satd $NaHCO_3$ (15 ml), and brine (15 ml). Drying over Na_2SO_4 and evaporation of solvent gave a residue, which on silica gel flash column chromatographic purification (DCM) afforded *N*-allyl derivative of (3*S*,5*R*)-**7** (1.677 g, 93%) as a colorless oil: $[\alpha]_D^{28} = +49.8$ (*c* 2.0, $CHCl_3$); IR (neat) 3069, 2928, 2854, 1588, 1471, 1453, 1427, 1360, 1111, 997, 919, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (9H, s, $SiC(CH_3)_3$), 2.88 (2H, m, $2 \times NCH$), 2.99 (H_a, dd, $J = 14.3$, 7.5 Hz, NCH_aH_b), 3.35 (H_b, ddt, $J = 14.3$, 5.1, 1.7 Hz, NCH_aH_b), 3.48 (2H, d, $J = 5.8$ Hz, $BnOCH_2$), 3.72 (6H, m, $SiOCH_2$, H_2COCH_2), 4.43 (H_a, d, $J = 11.9$ Hz, $PhCH_aH_b$), 4.49 (H_b, d, $J = 12.1$ Hz, $PhCH_aH_b$), 5.02 (2H, m, C=CH_2), 5.74 (1H, m, HCC=C), 7.33 (11H, m, PhH), 7.65 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 26.8, 53.5, 55.2, 57, 60, 67, 68.6, 69.1, 73.4, 116.8, 127.7, 128.4, 129.7, 133.5, 135.6, 136.2, 138.1; MS (ESI) m/z 538 $[M+Na]^+$, 516 $[M+H]^+$; HRMS (ESI) $(M+H)^+$: m/z calcd for $C_{32}H_{42}NO_3Si$ 516.2928, found 516.2916.

The *N*-allyl derivative of (3*S*,5*R*)-**7** was desilylated with TBAF using previously described procedure to afford (3*S*,5*S*)-1**2** as a colorless oil in 87% yield: $[\alpha]_D^{26} = +47$ (*c* 1.3, $CHCl_3$); IR (neat) 3418, 2856, 1641, 1495, 1454, 1418, 1306, 1129, 1094, 1075, 1047, 921, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.32 (1H, br s, OH), 2.81 (1H, m, BnOCCHN), 3.09 (1H, m, SiOCCHN), 3.19 (H_a, ddt, $J = 14.1$, 7.2, 1.1 Hz, NCH_aH_b), 3.46 (H_b, ddt, $J = 14.2$, 5.6, 1.5 Hz, NCH_aH_b), 3.53 (H_a, dd, $J = 11.3$, 3.8 Hz, CH_aH_b-hydroxyl), 3.64 (4H, m, $SiOCCH_2$, $COCH_2$), 3.76 (2H+H_b, m, $COCH_2$, CH_aH_b-hydroxyl), 4.47 (H_a, d, $J = 12.1$ Hz, $PhCH_aH_b$), 4.53 (H_b, d, $J = 12.1$ Hz, $PhCH_aH_b$), 5.13 (H_a, ddd, $J = 10.2$, 3.8, 1.5 Hz, C=CH_aH_b), 5.21 (H_b, ddd, $J = 17.2$, 3, 1.7 Hz, C=CH_aH_b), 5.84 (1H, m, CCH=C), 7.31 (5H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 52.4, 54.6, 55.8, 58.8, 66.1, 67.7, 68.2, 73.4, 117.5, 127.7, 128.4, 135.8, 138.1; MS (ESI) m/z 300 $[M+Na]^+$, 278 $[M+H]^+$; HRMS (ESI) $(M+H)^+$: m/z calcd for $C_{16}H_{24}NO_3$ 278.1751, found 278.1721.

4.1.11. (3*S*,5*S*)-*N*-Propionyl-3-(benzyloxymethyl)-5-(hydroxymethyl)morpholine (3*S*,5*S*)-13. To a stirred ice-cold solution of (3*S*,5*R*)-**7** (2.134 g, 4.5 mmol) in anhydrous DCM (45 ml), triethylamine (1.3 ml, 9 mmol), and propionyl chloride (0.6 ml, 6.7 mmol) were sequentially added under argon. After addition, the cooling-bath was removed and stirring continued at room temperature for 30 min. The mixture was diluted with DCM (50 ml) and washed subsequently with satd aq $NaHCO_3$ solution (20 ml) and brine (20 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a yellow residue, which on silica gel flash column chromatographic purification (10% EtOAc in heptanes) afforded the *N*-propionyl derivative of (3*S*,5*R*)-**7** (2.2 g, 92%) as a colorless oil: $[\alpha]_D^{29} = +40.8$ (*c* 1.0, $CHCl_3$); IR (neat) 2930, 2856, 1650, 1471, 1426, 1407, 1272, 1152, 1111, 1028, 997, 824, 739, 701, 614 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.86 (3H, t, $J = 7.3$ Hz, CH_3), 0.99 (9H, s, $SiC(CH_3)_3$), 2.24 (2H, br hump, $COCH_2Me$), 3.79 (10H, m, $4 \times COCH_2$, $2 \times NCH$), 4.51 (2H, s, $PhCH_2$), 7.32 (5H, m, PhH), 7.46 (6H, m, PhH), 7.62 (4H, m, PhH); ^{13}C NMR (75.5 MHz, MeOD) δ 10.1, 20.1, 27.3, 27.6, 52.7, 54.4, 55.9, 64.4, 65.1, 70.3, 71.8, 74.2, 128.8, 129.1, 129.5, 131.2, 134.3, 136.7, 136.8, 139.6, 176.9; MS (ESI) m/z 554 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{32}H_{41}NNaO_4Si$ 554.2697, found 554.2692.

The *N*-propionyl derivative of (3*S*,5*R*)-**7** was desilylated with TBAF using previously described procedure to afford (3*S*,5*S*)-**13** as a colorless oil in 90% yield (two rotamers): $[\alpha]_D^{24} = +22.2$ (*c* 1.6, $CHCl_3$); IR (neat) 3407, 3030, 2936, 2874, 1636, 1495, 1454, 1419, 1283, 1147, 1098, 1076, 1053, 947, 908, 843, 817, 740, 698, 634, 602 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 1.09 (3H, t, $J = 7.2$ Hz, CH_3), 2.47 (2H, q, $J = 7.5$ Hz, $COCH_2Me$), 3.89 (10H, m, $4 \times COCH_2$, $2 \times NCH$), 4.57 (2H, s, $PhCH_2$), 7.34 (5H, m, PhH); ^{13}C NMR (75.5 MHz, MeOD) δ 9.5, 10, 27.2, 27.6, 52.9, 54.8, 56, 62.4, 65.6, 70.3, 70.7, 74.2, 128.6, 128.8, 129.2, 129.3, 129.5, 130.5, 136, 139.6, 177.6; MS (ESI) m/z 316 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{16}H_{23}NNaO_4$ 316.1519, found 316.1484.

4.1.12. (3*S*,5*S*)-*N*-Ethoxycarbonylmethyl-3,5-bis(benzyloxymethyl)morpholine 15. To a solution of (3*S*,5*S*)-**14** (1.9 g, 5.8 mmol) in DMF (20 ml), K_2CO_3 (1.204 g, 8.71 mmol), and ethyl bromoacetate (0.8 ml, 7.0 mmol) were added at room temperature under argon. After

stirring for 12 h, the mixture was diluted with EtOAc (200 ml), filtered, and the filtrate washed sequentially with water (25 ml), 1 M HCl (25 ml), satd $NaHCO_3$ (25 ml), and brine (25 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a residue, which on silica gel flash column chromatographic purification (25% EtOAc in heptanes) afforded **15** (2.183 g, 91%) as a colorless oil: $[\alpha]_D^{23} = +26.9$ (*c* 1.2, $CHCl_3$); IR (neat) 2856, 1745, 1495, 1453, 1366, 1177, 1134, 1091, 1057, 933, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, t, $J = 7.2$ Hz, CH_3) 3.17 (2H, m, $2 \times NCH$), 3.62 (10H, m, NCH_2, $2 \times BnOCH_2$, $2 \times COCH_2$), 3.99 (2H, m, CO_2CH_2), 4.45 (4H, s, $2 \times PhCH_2$), 7.31 (10H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 54.2, 56.3, 60.4, 68.1, 69.1, 73.3, 127.6, 128.4, 137.6, 172.2; MS (ESI) *m*/*z* 382 $[M+Na]^+$, 360 $[M+H]^+$, 342, 167; HRMS (ESI) $(M+Na)^+$: *m*/*z* calcd for $C_{24}H_{31}NNaO_5$ 436.2094, found 436.2086.

4.1.13. (3*S*,5*S*)-*N*-(2,2-Diphenyl-2-hydroxyethyl)-3,5-bis(benzyloxymethyl)morpholine (3*S*,5*S*)-16. To a solution of **15** (1.2 g, 2.9 mmol) in THF (25 ml), 1 M solution of PhMgBr in THF (11.6 ml, 11.6 mmol) was added at −20 °C under argon over a period of 10 min. The mixture was warmed to room temperature and stirred for 3 h. Reaction was quenched with aq satd NH_4Cl solution (50 ml) and then extracted with ether (3×20 ml). Ether layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a yellow oil, which on silica gel flash column chromatographic purification (20% EtOAc in heptanes) afforded (3*S*,5*S*)-**16** (1.259 g, 83%) as a colorless oil: $[\alpha]_D^{23} = +35.2$ (*c* 1.0, $CHCl_3$); IR (neat) 3416, 3058, 3027, 2856, 1596, 1493, 1447, 1364, 1311, 1204, 1088, 1074, 1027, 1012, 953, 909, 778, 734, 694, 646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (1H, br s, OH), 2.71 (2H, m, $2 \times NCH$), 3.54 (H_a+ 8H, m, $2 \times BnOCH_2$, $2 \times COCH_2$, NCH_aH_b), 3.82 (H_b, d, $J = 14$ Hz, NCH_aH_b), 4.36 ($2H_a$, d, $J = 11.6$ Hz, $2 \times PhCH_aH_b$), 4.44 ($2H_b$, d, $J = 12.2$ Hz, $2 \times PhCH_aH_b$), 5.25 (1H, br s, NH), 7.27 (16H, m, PhH), 7.48 (2H, d, $J = 7.3$ Hz, PhH), 7.53 (2H, d, $J = 7.3$ Hz, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 56, 58.6, 67.8, 68.1, 73.2, 74.7, 125.9, 126.1, 126.6, 126.7, 127.7, 128, 128.1, 128.4, 137.9, 147, 147.2; MS (ESI) *m*/*z* 546 $[M+Na]^+$, 524 $[M+H]^+$, 506; HRMS (ESI) $(M+H)^+$: *m*/*z* calcd for $C_{34}H_{38}NO_4$ 524.2795, found 524.2798.

4.1.14. (*R*)-*N*-*tert*-Butoxycarbonyl morpholine-3-carboxylic acid 17. To a stirred ice-cold solution of (*S*)-**6** (3.7 g, 31.6 mmol) in methanol (35 ml), triethylamine (5.3 ml, 37.9 mmol), and di-*tert*-butyl dicarbonate (9.644 g, 44.2 mmol) were added under argon. The cooling-bath was removed and the mixture stirred at room temperature for 1 h. The mixture was concentrated under vacuum and the resulting residue was quenched with water (50 ml). The mixture was extracted with EtOAc (3×25 ml) and the combined EtOAc extract was washed with 1 M $KHSO_4$ (15 ml) and brine (15 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a residue, which on silica gel flash column chromatographic purification (30% EtOAc in heptanes) afforded the *N*-Boc derivative of (*S*)-**6** (6.654 g, 97%) as a colorless solid: mp 80 °C; $[\alpha]_D^{26} = +60.4$ (*c* 1.1, $CHCl_3$); IR (neat) 3448, 2974, 2862, 1692, 1454, 1411, 1365, 1297, 1277, 1236, 1169, 1122, 1054, 968, 912, 862, 710, 620, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s, $OC(CH_3)_3$), 2.22 (1H, br s, OH), 3.17 (H_a, td, $J = 12.7$, 3.2 Hz, NCH_aH_b), 3.46 (H_a, td, $J = 11.8$, 3 Hz, $COCH_aH_b$), 3.57 (H_b, dd, $J = 11.9$, 3.6 Hz, $COCH_aH_b$), 3.87 (5H+H_b, m, $COCH_2$, NCH, CH_2-hydroxyl, NCH_aH_b); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.4, 40.1, 52.2, 60.5, 66.4, 66.7, 80.5, 155.7; MS (ESI) *m*/*z* 240 $[M+Na]^+$, 184; HRMS (ESI) $(M+Na)^+$: *m*/*z* calcd for $C_{10}H_{19}NNaO_4$ 240.1206, found 240.1210.

To a solution of the *N*-Boc derivative of (*S*)-**6** (4 g, 18.4 mmol) in acetone (20 ml), an aq 5% solution of $NaHCO_3$ (62 ml) was added at room temperature. The heterogeneous mixture was cooled to 0 °C and treated sequentially with KBr (219 mg, 1.8 mmol) and TEMPO (3.163 g, 20.2 mmol). An aq 5% solution of sodium hypochlorite (27.4 ml, 18.4 mmol) was then added dropwise while the mixture was vigorously stirred and maintained at 0 °C. After 1 h, additional 5% aq NaOCl solution (27.4 ml, 18.4 mmol) was added and stirring was continued at 0 °C for another 1 h followed by addition of 5% aq $NaHCO_3$ solution. Acetone was removed under vacuum and the aq layer washed with ether (2×25 ml), acidified to pH 6 with 1 M $KHSO_4$ solution and extracted with EtOAc (3×50 ml). Drying over Na_2SO_4 and evaporation of EtOAc extract gave a pale yellow solid, which on silica gel flash column chromatographic purification (50% EtOAc in heptanes) afforded **17** (3.536 g, 83%, two rotamers) as a colorless solid: mp 181 °C; $[\alpha]_D^{24} = +73$ (*c* 1.1, MeOH); IR (neat) 3458, 3400–2700, 1730, 1745, 1694, 1680, 1650, 1476, 1454, 1392, 1367, 1324, 1300, 1267, 1255, 1226, 1164, 1113, 1066, 1022, 981, 950, 871, 834, 775, 754, 629 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.37, 1.47 (9H, two s, $OC(CH_3)_3$), 2.99 (H_a, td, $J = 12.7$, 3.7 Hz, NCH_aH_b), 3.17 ($0.5H_a$, td, $J = 12.4$, 3.3 Hz, NCH_aH_b), 3.37 (H_a, m, $COCH_aH_b$), 3.55 ($2H_b$, m, $COCH_aH_b$, NCH_aH_b), 3.78 (H_c, td, $J = 14.7$, 3.3 Hz, $COCH_cH_d$), 4.15 (H_d, t, $J = 11.6$ Hz, $COCH_cH_d$), 4.31 (1H, dd, $J = 15.2$, 2.7 Hz, NCH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.8, 27.9, 38.7, 40.3, 53.4, 54.8, 65.5, 65.8, 66.8, 67.3, 79.3, 79.5, 154.8, 171.4, 171.6; MS (ESI) *m*/*z* 254 $[M+Na]^+$, 198, 154; HRMS (ESI) $(M+Na)^+$: *m*/*z* calcd for $C_{10}H_{17}NNaO_5$ 254.0999, found 254.1033.

4.1.15. (*R*)-Methyl *N*-*tert*-butoxycarbonyl morpholine-3-carboxylate 18. To a solution of **17** (4 g, 17.3 mmol) in DMF (20 ml), K_2CO_3 (3.589 g, 26 mmol), and methyl iodide (1.6 ml, 26 mmol) were added at room temperature under argon. After stirring for 12 h, the mixture was diluted with EtOAc (100 ml), filtered, and the filtrate washed sequentially with water (15 ml), 1 M HCl (15 ml), satd $NaHCO_3$ (15 ml), and brine (15 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a residue, which on silica gel flash column chromatographic purification (15% EtOAc in heptanes) afforded **18** (3.774 g, 89%, two rotamers) as a pale yellow oil: $[\alpha]_D^{24} = +78.9$ (*c* 1.2, $CHCl_3$); IR (neat) 2975, 1747, 1699, 1454, 1395, 1365, 1328, 1299, 1267, 1220, 1198, 1166, 1109, 1067, 1027, 982, 872, 776 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 1.44, 1.48 (9H, two s, $OC(CH_3)_3$), 3.19 (0.5H_a, td, $J = 12.8$, 3 Hz, NCH_aH_b), 3.32 (0.5H_a, td, $J = 12.6$, 3 Hz, NCH_aH_b), 3.48 (H_a, t, $J = 11.9$ Hz, $COCH_aH_b$), 3.73 (2H_b+H_c, m, $H_cH_dCOCH_aH_b$, NCH_aH_b), 3.78 (3H, s, OCH_3), 4.36 (0.5H+H_d, m, NCH, $COCH_cH_d$), 4.59 (0.5H, m, NCH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3, 40.7, 41.9, 52.4, 54, 55.4, 66.4, 66.8, 67.3, 67.8, 80.7, 155.6, 155.8, 170.4, 170.7; MS (ESI) m/z 268 $[M+Na]^+$, 212, 168; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{11}H_{19}NNaO_5$ 268.1155, found 268.1136.

4.1.16. (*S*)-*N*-*tert*-Butoxycarbonyl-4-(hydroxydiphenylmethyl)-2,2-dimethyloxazolidine 21. Compound **21** was obtained as a colorless solid in 83% yield from **20** using the previously described procedure, except that 3 M PhMgBr solution in ether was used instead of 1 M solution in THF: mp 127 °C; $[\alpha]_D^{25} = -8.5$ (c 1.1, $CHCl_3$); IR (neat) 3290, 2976, 1696, 1656, 1478, 1446, 1395, 1364, 1249, 1205, 1168, 1113, 1069, 1046, 850, 813, 756, 699, 632, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, s, $OCCH_3$), 1.35 (9H, s, $NCO_2C(CH_3)_3$), 1.43 (3H, s, $OCCH_3$), 4.02 (H_a, dd, $J = 9.9$, 1.8 Hz, OCH_aH_b), 4.11 (H_b, dd, $J = 9.9$, 7.1 Hz, OCH_aH_b), 4.96 (H, dd, $J = 7$, 1.7 Hz, NCH), 6.26 (1H, br s, OH), 7.31 (8H, m, PhH), 7.49 (2H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8, 25.6, 28.1, 65.5, 66.2, 81.2, 81.3, 95.4, 127.1, 127.5, 127.9, 128, 143.6, 145.3, 154.8; MS (ESI) m/z 406 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{23}H_{29}NNaO_4$ 406.1989, found 406.1994.

4.1.17. (*S*)-2-*tert*-Butoxycarbonylamino-1,1-diphenylpropane-1,3-diol 22. A suspension of **21** (1.456 g, 3.8 mmol) in 80% aq acetic acid (20 ml) was stirred at room temperature for 24 h. The mixture was concentrated under vacuum below 50 °C and the resulting residue was purified by silica gel flash column chromatography (50% EtOAc in heptanes) to afford **22** (1.186 g, 91%) as a colorless oil: mp 123 °C; $[\alpha]_D^{28} = -63.9$ (c 1.4, $CHCl_3$); IR (neat) 3399, 2977, 1681, 1503, 1449, 1392, 1366, 1247, 1166, 1061, 965, 887, 853, 749, 701, 663, 640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (9H, s, $OC(CH_3)_3$), 2.24 (1H, br s, OH), 3.71 (H_a, ddd, $J = 11.3$, 5.2, 2.5 Hz, CH_aH_b), 3.83 (H_b, dt, $J = 10.7$, 3 Hz, CH_aH_b), 4.61 (1H, s, OH), 4.67 (1H, d, $J = 7.3$ Hz, NCH), 5.43 (1H, d, $J = 8.3$ Hz, NH), 7.25 (6H, m, PhH), 7.49 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3, 55.5, 63.9, 79.8, 81.7, 125.1, 125.4, 126.9, 127, 128.2, 128.5, 144.6, 145.4, 156; MS (ESI) m/z 366 $[M+Na]^+$; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{20}H_{25}NNaO_4$ 366.1676, found 366.1652.

4.1.18. (*S*)-*tert*-Butyl 2-(2-(*tert*-butoxycarbonylamino)-3-hydroxy-3,3-diphenylpropoxy)acetate 23. Compound **22** was coupled with *tert*-butyl bromoacetate using previously described procedure to furnish **23** as a colorless solid in 89% yield: mp 148 °C; $[\alpha]_D^{25} = -23.3$ (c 1.5, $CHCl_3$); IR (neat) 3439, 2976, 1705, 1492, 1391, 1366, 1246, 1163, 1126, 1054, 846, 749, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (9H, s, $NCO_2C(CH_3)_3$), 1.47 (9H, s, $CO_2C(CH_3)_3$), 3.47 (H_a, dd, $J = 9.5$, 2 Hz, $COCH_aH_b$), 3.59 (H_a, d, $J = 15.6$ Hz, $CH_aH_bCO_2$), 3.81 (H_b, dd, $J = 9.6$, 2.5 Hz, $COCH_aH_b$), 3.86 (H_b, d, $J = 15.8$ Hz, $CH_aH_bCO_2$), 4.78 (1H, d, $J = 8.9$ Hz, NCH), 5.2 (1H, s, OH), 5.58 (1H, d, $J = 8.7$ Hz, NH), 7.24 (6H, m, PhH), 7.53 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.1, 28.3, 54.5, 69.4, 72.9, 79.5, 81.1, 82.4, 125.2, 125.6, 126.7, 126.8, 128.1, 128.4, 144.6, 145.8, 155.8, 168.8; MS (ESI) m/z 480 $[M+Na]^+$, 424, 368; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{26}H_{35}NNaO_6$ 480.2357, found 480.2350.

4.1.19. (*S*)-2-(2-(*tert*-Butoxycarbonylamino)-3-hydroxy-3,3-diphenylpropoxy)ethanol 24. To an ice-cold stirred solution of **23** (2.67 g, 7.5 mmol) in ether (50 ml), $LiAlH_4$ (0.425 g, 11.2 mmol) was added under argon over a period of 30 min. After addition, the cooling-bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was again cooled to 0 °C and water (0.44 ml), 15% aq NaOH solution (0.44 ml) and again water (1.32 ml) were added sequentially. The mixture was stirred for 10 min and filtered through Celite. The filtrate was evaporated under vacuum and the resulting residue was subjected to silica gel flash column chromatographic purification (30% EtOAc in heptanes) to give **24** (2.642 g, 91%) as a colorless solid: mp 141 °C; $[\alpha]_D^{25} = -55.7$ (c 1.2, $CHCl_3$); IR (neat) 3425, 2976, 1681, 1494, 1448, 1391, 1366, 1249, 1167, 1120, 1063, 889, 858, 750, 702, 664, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (9H, s, $NCO_2C(CH_3)_3$), 2.42 (1H, br s, OH), 3.26 (H_a, m, $COCH_aH_b$), 3.41 (H_b, dt, $J = 10.6$, 4.2 Hz, $COCH_aH_b$), 3.81 (2H+H_a, m, $NCCH_aH_b$, CH_2-hydroxyl), 3.73 (H_b, dd, $J = 9.9$, 2.4 Hz, $NCCH_aH_b$), 4.79 (1H, d, $J = 9$ Hz, NCH), 4.91 (1H, br s, OH), 5.69 (1H, d, $J = 9.2$ Hz, NH), 7.26 (6H, m, PhH), 7.51 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3, 54.6, 61, 72.5, 72.9, 79.6, 81.3, 125, 125.5, 126.9, 127, 128.2, 128.5, 144.4, 145.6, 155.9; MS (ESI) m/z 410 $[M+Na]^+$, 354; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{22}H_{29}NNaO_5$ 410.1938, found 410.1932.

4.1.20. (*S*)-(2-*tert*-Butoxycarbonylamino-3-hydroxy-3,3-diphenylpropoxy)-2-(methanesulfonyloxy)ethane 25. Compound **24** was mesylated with methanesulfonyl chloride following the previously described procedure to afford **25** as a colorless solid in 94% yield: mp 161 °C; $[\alpha]_D^{27} = -43.3$ (c 1.2, $CHCl_3$); IR (neat) 3443, 2976, 1704, 1494, 1449, 1352, 1250, 1172, 1127, 1063, 1021, 970, 923, 858, 807, 751, 704, 662, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (9H, s, $NCO_2C(CH_3)_3$), 3.05 (3H, s, CH_3), 3.44 (H_a, m, $COCH_aH_b$), 3.57 (2H_b, m, $COCH_aH_b$, $NCCH_aH_b$), 3.73 (H_a, dd, $J = 9.7$, 2.4 Hz, $NCCH_aH_b$), 4.29 (2H, dd, $J = 5.1$, 3.8 Hz, CH_2OMs), 4.44 (1H, s, OH), 4.77 (1H, d, $J = 8.9$ Hz, NCH), 5.48 (1H, d, $J = 9$ Hz, NH), 7.25 (6H, m, PhH), 7.49 (4H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3, 37.7, 54.6, 67.8, 69.4, 72.9, 79.7, 81.1, 124.9, 125.5, 126.9, 127, 128.2, 128.5, 144.2, 145.4, 155.8; MS (ESI) m/z 488 $[M+Na]^+$, 432; HRMS (ESI) $(M+Na)^+$: m/z calcd for $C_{23}H_{31}NNaO_7S$ 488.1713, found 488.1718.

4.1.21. (*S*)-3-(Hydroxydiphenylmethyl)morpholine (*S*)-19. Compound (*S*)-**19** was obtained from **25** as a colorless solid in 81% yield following the previously

described procedure: mp 140 °C; $[\alpha]_D^{25} = -105.5$ (*c* 1.7, $CHCl_3$); IR (neat) 3434, 2852, 1596, 1492, 1449, 1350, 1316, 1172, 1143, 1106, 1058, 1032, 993, 963, 938, 893, 848, 813, 747, 703, 665, 635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (1H, br s, OH), 2.81 (H_a, ddd, $J = 11.4$, 2.4, 1.1 Hz, NCH_aH_b), 3.05 (H_b, td, $J = 11.3$, 3.4 Hz, NCH_aH_b), 3.46 ($2H_a+H_b$, m, H_bH_a-$COCH_aH_b$), 3.75 (H_b, ddd, $J = 11.3$, 3.3, 1.1 Hz, $COCH_aH_b$), 3.85 (H, dd, $J = 8.5$, 4.9 Hz, NCH), 4.25 (1H, s, NH), 7.26 (6H, m, PhH), 7.48 (2H, m, PhH), 7.59 (2H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 45.6, 59.3, 66.9, 68, 77.1, 125.2, 125.7, 126.8, 127.2, 128.2, 128.7, 142.8, 145.6; MS (ESI) *m*/*z* 270 $[M+H]^+$, 252; HRMS (ESI) $(M+H)^+$: *m*/*z* calcd for $C_{17}H_{20}NO_2$ 270.1489, found 270.1483.

4.1.22. (*S*)-*N*-Methyl-3-(hydroxydiphenylmethyl)morpholine (*S*)-26. Compound (*S*)-**26** was obtained from (*S*)-**19** in 87% yield as a colorless solid using the previously described procedure: mp 213 °C (decomp.); $[\alpha]_D^{29} = -157.2$ (*c* 0.9, $CHCl_3$); IR (neat) 3382, 2854, 2804, 1593, 1487, 1444, 1340, 1294, 1167, 1154, 1125, 1059, 1042, 1030, 988, 959, 899, 870, 789, 758, 748, 713, 696, 662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (3H, s, NCH_3), 2.63 (H_a, td, $J = 11.6$, 3.6 Hz, NCH_aH_b), 2.73 (H_b, ddd, $J = 12$, 2.5, 1.9 Hz, NCH_aH_b), 3.12 (H_a, dd, $J = 12.2$, 10.5 Hz, H_dH_cCO-CH_aH_b), 3.31 (H_b, ddd, $J = 12.1$, 4, 1.1 Hz, H_dH_cCO-CH_aH_b), 3.48 (H_c+1H, m, $H_dH_cCOCH_aH_b$, NCH), 3.76 (H_d, m, $H_dH_cCOCH_aH_b$), 7.22 (6H, m, PhH), 7.5 (2H, m, PhH), 7.7 (2H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 46.5, 55.3, 65.1, 66.5, 68.5, 75.5, 124.7, 125.4, 126.4, 128.1, 128.2, 144.6, 149.4; MS (ESI) *m*/*z* 266 $[(M-H_2O)+H]^+$, 167; HRMS (ESI) $[(M-H_2O)+H]^+$: *m*/*z* calcd for $C_{18}H_{20}NO$ 266.1539, found 266.1525.

4.1.23. (*S*)-*N*-Benzyl-3-(hydroxydiphenylmethyl)morpholine (*S*)-27. To a solution of (*S*)-**19** (1.076 g, 4 mmol) in DMF (15 ml), K_2CO_3 (1.106 g, 8 mmol) and benzyl bromide (0.7 ml, 6.0 mmol) were added at room temperature under argon. After stirring for 18 h, the mixture was diluted with EtOAc (100 ml), filtered, and the filtrate washed sequentially with water (20 ml), 1 M HCl (20 ml), satd $NaHCO_3$ (20 ml), and brine (20 ml). Drying over Na_2SO_4 and evaporation of the solvent gave a residue, which on silica gel flash column chromatographic purification (20% EtOAc in heptanes) afforded (*S*)-**27** (1.164 g, 81%) as a colorless solid: mp 102 °C; $[\alpha]_D^{28} = -81.4$ (*c* 1.0, $CHCl_3$); IR (neat) 3304, 3027, 2855, 1595, 1493, 1448, 1376, 1298, 1171, 1130, 1114, 1058, 1026, 1009, 956, 906, 875 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (H_a, ddd, $J = 12.9$, 9.4, 3.5 Hz, NCH_aH_b), 2.87 (H_a, d, $J = 13.2$ Hz, NCH_aH_bPh), 2.88 (H_b, m, NCH_aH_bC), 3.31 (H_a, dd, $J = 12.2$, 9.1 Hz, $H_dH_cCOCH_aH_b$), 3.45 (H_b+H_c, m, $H_dH_cCOCH_aH_b$), 3.71 (H_d, dt, $J = 11.4$, 3.6 Hz, $H_dH_cCOCH_aH_b$), 3.76 (1H, dd, $J = 9.1$, 4.4 Hz, NCH), 3.88 (H_b, d, $J = 13$ Hz, NCH_aH_bPh), 5.38 (1H, br s, OH), 7.11 (4H, m, PhH), 7.26 (7H, m, PhH), 7.55 (2H, m, PhH), 7.72 (2H, m, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 49.9, 60.5, 63.7, 66, 68, 77.2, 124.9, 125.6, 126.5, 126.6, 127.2, 128.2, 128.4, 128.8, 131.7, 138.3, 148.8; MS (ESI) *m*/*z* 382 $[M+Na]^+$, 360 $[M+H]^+$, 342, 167; HRMS (ESI) $(M+H)^+$: *m*/*z* calcd for $C_{24}H_{26}NO_2$ 360.1964, found 360.1956.

4.2. Typical reaction procedure for Et_2Zn addition to benzaldehyde in the presence of catalytic morpholine-based β-amino alcohol

To a solution/suspension of β-amino alcohol (0.38 mmol) in toluene (4 ml), diethylzinc (7.6 mm, 7.6 ml of 1 M hexane solution) was added at 0 °C under argon. After stirring for 30 min, benzaldehyde (403 mg, 3.8 mmol) was added and the reaction mixture stirred for 3 h at 0 °C. The cooling-bath was removed and the mixture stirred at room temperature for another 45 h. The reaction was quenched with 3% aq HCl solution (15 ml) and the organic product was extracted with EtOAc (3×25 ml). Combined EtOAc layer was dried (Na_2SO_4) and evaporated under vacuum. The resulting residue was purified by silica gel flash column chromatography (8% EtOAc in heptanes) to afford 1-phenyl-1-propanol as a colorless oil. The product was characterized by ^1H NMR and the enantiomeric excess was determined by HPLC. The absolute configuration of the major enantiomer was assigned based on the sign of optical rotations and from the elution order in HPLC analysis.

4.3. Typical reaction procedure for Et_2Zn addition to aldehydes in the presence of lithiated ligand

To a stirred solution of β-amino alcohol (0.38 mmol) in toluene (4 ml), *n*-butyl lithium (0.38 mm, 0.2 ml of 1.6 M hexane solution) was added under argon at −30 °C. The mixture was warmed to 0 °C and stirred for 10 min. The mixture was again cooled to −30 °C and diethylzinc (7.6 mm, 7.6 ml of 1 M hexane solution) was added over a period of 5 min. The mixture was warmed to 0 °C, stirred for 30 min and the aldehyde (3.8 mmol) was added. The reaction mixture was then stirred at room temperature for 48 h. The reaction mixture was quenched with 1 M aq HCl solution (15 ml) and the organic product extracted with EtOAc (3×25 ml). The combined EtOAc layer was dried over Na_2SO_4 and evaporated under vacuum. The resulting residue was purified by silica gel flash column chromatography (8% EtOAc in heptanes) to afford alcohol as a colorless oil. The product was characterized by ^1H NMR and the ee was determined by HPLC. The absolute configuration of the major enantiomer was assigned based on the sign of optical rotations and from the elution order in HPLC analysis.

4.4. Determination of alcohol enantiomeric excesses

Unless otherwise mentioned, ee values of ethylation products were determined by HPLC analysis using Chiralcel OD column (10 μm, 4.6×250 mm) as the chiral stationary phase. For 1-phenyl-1-propanol $t_R = 11.9$ and $t_S = 13.7$ min, flow 1.0 ml/min, hexane/2-propanol 97.5/2.5; 1-(4-methoxyphenyl)-1-propanol $t_R = 11.8$ and $t_S = 13.3$ min, flow 1.0 ml/min, hexane/2-propanol 96/4; 1-(2-naphthyl)-1-propanol $t_R = 10.4$ and $t_S = 9.2$ min, flow 1.0 ml/min, hexane/2-propanol 90/10;

1-phenyl-3-pentanol $t_R = 13.0$ and $t_S = 20.6$ min, flow 1.0 ml/min, hexane/2-propanol 97/3; 1-phenyl-1-penten-3-ol $t_R = 11.7$ and $t_S = 19.6$ min, flow 1.0 ml/min, hexane/2-propanol 95/5.

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