Asymmetric Synthesis of Both Diastereomers of α,α′-disubstituted Iminodiacetic Acid Derivatives Using Stereoselective Nucleophilic Substitution of α-Bromo Esters

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Received January 24, 2018, Accepted March 9, 2018

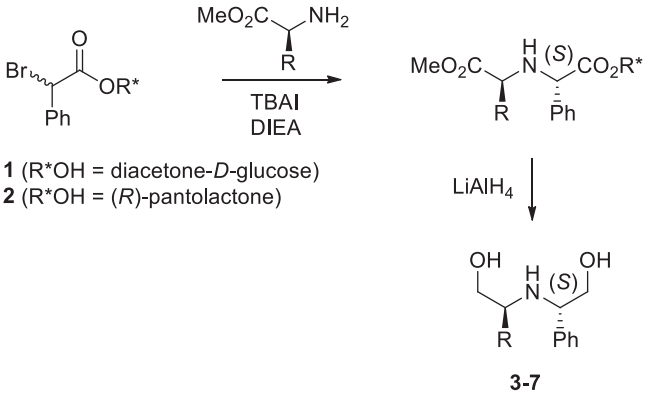
Keywords: Dynamic kinetic resolution, Nucleophilic substitution, Stereoselectivity, Chiral auxiliary, Morpholine

α,α′-Disubstituted iminodiacetic acids are structurally interesting and biologically relevant natural products.[1] Their scaffolds also constitute a part of important chiral drugs such as Enalapril, Enalkiren and Captopril. Furthermore, their derivatives such as α,α′-disubstituted iminodiethanols and morpholines have been widely utilized in organic synthesis for their sterically congested and highly functionalized scaffold.[2] However, asymmetric synthetic approaches toward these types of compounds in the conventional literature are usually limited in scope, as they afford symmetrically disubstituted products and can be used only for the generation of one diastereomer.[3] Herein, we report our efforts to synthesize both diastereomers of unsymmetrically disubstituted iminodiacetic acid derivatives by stereoselective nucleophilic substitution of chiral auxiliary-derived α-bromo phenylacetates.

Diacetone-*D*-glucose-mediated nucleophilic substitution of α-bromo arylacetates with amine nucleophiles has been developed in our laboratory for stereoselective preparation of α-amino acid derivatives.[4] The chiral information of *D*-glucose is transferred via dynamic kinetic resolution in the substitution at α-bromo carbon center with amine nucleophiles. The α-bromo stereogenic center of diacetone-*D*-glucose-derived α-bromoacetate (**1**) undergoes rapid epimerization in the presence of epimerization agents, and (α*R*)-**1** reacts with an amine nucleophile preferentially to afford (α*S*)-substitution product.

We first attempted to use this methodology with *L*-amino ester nucleophiles for asymmetric syntheses of α,α′-disubstituted iminodiacetic acid derivatives. As shown in Table 1, the treatment of two diastereomeric mixture (1:1) of α-bromo acetate **1** with *L*-phenylalanine methyl ester nucleophile (1.2 equiv) in the presence of tetrabutyl ammonium iodide (TBAI, 1.0 equiv) and diisopropyl ethylamine (DIEA, 1.2 equiv) for 20 h in CH_2Cl_2 provided the substitution product in 87% yield with 99:1 diastereomeric ratio (dr, α*S*:α*R*). The observed dr and yield of iminodiacetate suggest that the α-bromo stereogenic center is configurationally labile with respect to the rate of substitution and two diastereomers of **1** are dynamically resolved under the reaction conditions. Subsequent reductive removal of the chiral auxiliary with $LiAlH_4$ at room temperature gave highly diastereoenriched (*S,S*)-diol **3** in 58% overall yield (entry 1). The scope of the two-step (*S,S*)-diol formation was investigated using four different *L*-amino ester nucleophiles. The substitutions with *L*-alanine, *L*-leucine, *L*-valine, and *L*-phenylglycine methyl esters were examined as shown in entries 2–5. Treatment of **1** with *L*-alanine

Table 1. Chiral auxiliary-mediated nucleophilic substitution for the preparation of iminodiethanols.



1 (R*OH = diacetone-*D*-glucose)
2 (R*OH = (*R*)-pantolactone)

3-7

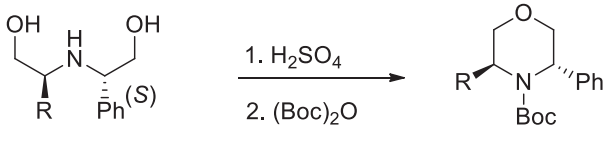
Entry[a]	Reactant	R	Overall yield (%)[b]	Dr (α*S*:α*R*)[c]
1	**1**	$PhCH_2$	58 (**3**)	99:1
2	**1**	Me	62 (**4**)	95:5
3	**1**	isoBu	40 (**5**)	95:5
4	**1**	isoPr	33 (**6**)	94:6
5	**1**	Ph	51 (**7**)	99:1
6	**2**	$PhCH_2$	62 (**3**)	99:1
7	**2**	Me	66 (**4**)	98:2
8	**2**	isoBu	70 (**5**)	97:3
9	**2**	isoPr	61 (**6**)	99:1

[a] All substitutions were carried out in CH_2Cl_2 at rt.
[b] Isolated yields.
[c] The drs were determined by 1H NMR of the reaction mixture.

methyl ester, TBAI, and DIEA and following reduction of the iminodicarboxylic ester with $LiAlH_4$ provided diol **4** in 62% overall yield with 95:5 dr (α*S*:α*R*). The same high selectivities ranging from 99:1 dr to 94:6 dr were observed with *L*-leucine, *L*-valine, and *L*-phenylglycine-derived methyl esters in 51–33% overall yields. To improve the overall yield and dr of diols, we next examined the stereocontrolling ability of (*R*)-pantolactone auxiliary under the same reaction conditions.[5] The reactions of (*R*)-pantolactone-derived α-bromo acetate **2** with *L*-amino ester nucleophiles took place with higher yields, affording diols **3–6** in 70–61% yields. We are pleased to observe higher stereoselectivities to produce **3–6** with drs ranging from 99:1 to 97:3 (entries 6–9). In addition, we attempted the reaction of α-bromo propionate with *L*-phenylalanine methyl ester under the same conditions and found that corresponding diol was afforded in 32% yield with 71:29 dr. The reactions of α-bromo acetate bearing other aliphatic R substituents showed much lower selectivities under identical reaction conditions.

The iminodiethanols **3–6** then be transformed to morpholines **8–11** through acid (H_2SO_4)-catalyzed ether formation as shown in Scheme 1. The cyclization occurred during heating to 140 °C of diol **3** with concentrated sulfuric acid. 3-Benzyl-5-phenylmorpholine was isolated and treated with di-*tert*-butyl dicarbonate to produce stable *N*-Boc derivative **8** in 27% overall yield. This strategy should provide access to a broad array of enantiopure *trans*-3,5-disubstituted morpholines that are difficult to generate using existing methods.[3d-f] The same acid-catalyzed cyclization and following *N*-Boc protection of diols **4–6** successfully provided highly diastereoenriched *trans*-3,5-disubstituted morpholines **9–11** in 31–23% overall yields.[6] Our further attempts to improve the overall yields using Mitsunobu cyclizations with PPh_3 and DEAD in THF failed to give a higher yield.

Having successfully developed an asymmetric synthetic method for the preparation of (*S,S*)-disubstituted imino diacetic acid derivatives, we next focused our attention on the preparation of (*S,R*)-α,α′-disubstituted iminodiacetic acid derivatives using *L*-amino ester nucleophiles. In the reaction with *L*-amino ester nucleophiles, the chiral information of not only a chiral auxiliary, but also the chiral nucleophile can be transferred to the new C—N bond formation. When the racemic α-bromo methyl ester **12** was treated with



3-6

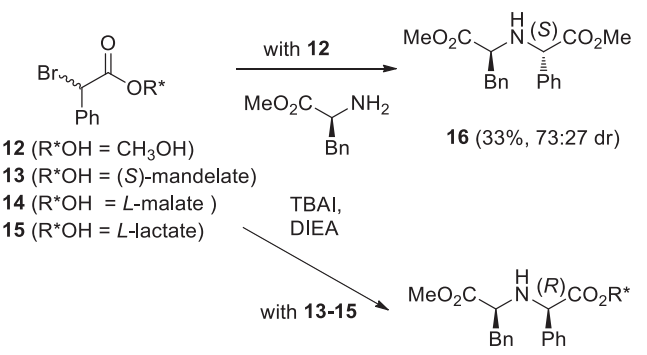
8 (R = Bn) 27%, 99:1 dr
9 (R = Me) 31%, 99:1 dr
10 (R = i-Bu) 25%, 99:1 dr
11 (R = i-Pr) 23%, 99:1 dr

Scheme 1. Synthesis of *N*-Boc-*trans*-morpholines **8–11**.

L-phenylalanine methyl ester, TBAI and DIEA at room temperature, iminodiacetate **16** was produced with a selectivity of 73:27 dr (α*S*:α*R*) as shown in Scheme 2. The result indicates that the *L*-amino ester nucleophile slightly prefers (α*S*)-product in the substitution with α-bromo phenylacetate and may experience mismatching in the substitution for the synthesis of (α*R*)-product.

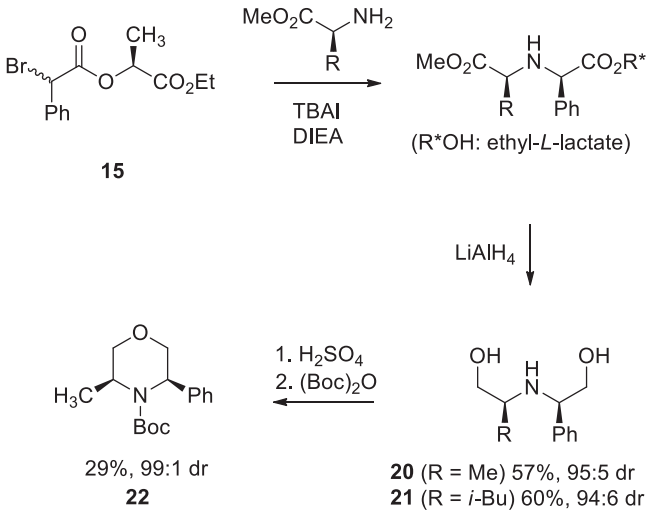
Three different chiral alcohols known to give (α*R*)-product, such as *L*-mandelate, *L*-malate and *L*-lactate have been tested for their stereocontrolling ability in dynamic kinetic resolution of α-bromo esters.[7,8] Initial studies were carried out with methyl *L*-mandelate. When the diastereomeric mixture (1:1) of α-bromo ester **13** was treated with TBAI (1.0 equiv), DIEA (1.2 equiv), and *L*-phenylalanine methyl ester (1.2 equiv) in CH_2Cl_2 at room temperature for 20 h, the substitution produced (α*R*)-**17** in 51% yield with 89:11 dr. In an effort to improve the stereoselectivity, we examined substitution reactions of α-bromo acetates **14** and **15** derived from *L*-malate and *L*-lactate, respectively. Nucleophilic substitutions of **14** and **15** were conducted under the same reaction conditions as that used for **13**. A lower stereoselectivity was observed in the reaction of **14** with *L*-phenylalanine methyl ester to produce **18** in a ratio of 81:19. The reaction of ethyl *L*-lactate-derived **15** took place with a higher stereoselectivity, affording **19** with a ratio of 91:9 and 72% yield. In the stereo mismatching reactions of **13–15** with *L*-amino ester, the stereochemistry of the major products was dominated by the chiral auxiliary and (α*R*)-**17–19** were produced with drs ranging from 91:9 to 81:19 as shown in Scheme 2.

With the identification of ethyl *L*-lactate as appropriate stereocontrolling auxiliary for dynamic kinetic resolution of α-bromo phenylacetate, we examined the scope of this methodology with two different *L*-amino ester nucleophiles as shown in Scheme 3. Treatment of **15** (50:50 dr) with alanine methyl ester (1.2 equiv), TBAI (1.0 equiv), and DIEA (1.2 equiv) and following reduction gave **20** in 57% overall yield with 95:5 dr. This methodology is also practical for



17 (51%, 89:11 dr, from **13**)
18 (25%, 81:19 dr, from **14**)
19 (72%, 91:9 dr, from **15**)

Scheme 2. Nucleophilic substitution of *L*-phenylalanine with α-bromo acetates.



Scheme 3. Synthesis of *N*-Boc-*cis*-morpholine.

the preparation of iminodiethanol **21** with 94:6 dr in 60% overall yield from *L*-leucine methyl ester nucleophile. Highly diastereoenriched **20** (95:5 dr) was used for the asymmetric synthesis of *cis*-3,5-disubstituted morpholine **22** as shown in Scheme 3. Acid-catalyzed dehydrative cyclization of the diol and *N*-protection with di-*tert*-butyl dicarbonate gave *cis*-3,5-disubstituted *N*-Boc morpholine **22** with 99:1 dr in 29% yield over the two steps.[6]

We have developed a convenient synthetic method for asymmetric syntheses of both diastereomers of unsymmetrically disubstituted iminodiethanols and morpholines through dynamic kinetic resolution of α-bromo arylacetates. The highly stereoselective substitutions of (*R*)-pantolactone-derived α-bromo esters provide iminodiesters with the "*S*" stereochemistry predominating at the newly formed asymmetric center. The "*R*" stereochemistry can be obtained utilizing *L*-ethyl lactate although stereoselectivities in the substitutions are lowered in comparison to (*R*)-pantolactone-mediated substitutions. This asymmetric synthetic approach using easily available chiral auxiliaries appears to offer a substantial advantage over previously reported methodologies for α,α′-disubstituted iminodiacetic acid derivatives.

Experimental

General Procedure for the Synthesis of Iminodiethanols 3–7 and 20–21. To a solution of diastereomeric mixture (1:1) of α-bromo-α-arylacetate (**1**, **2**, **13**, **14**, and **15**) in CH_2Cl_2 (0.1 M) at room temperature was added *L*-amino ester (1.2 equiv), TBAI (1.0 equiv) and DIEA (3.0 equiv). The resulting reaction mixture was stirred at room temperature for 20 h. The solvent in mixture was evaporated and the crude product was purified by short column chromatography on silica gel to give iminodiesters. To a solution of iminodiester in THF (0.5 M) was added $LiAlH_4$ (1.0 M in THF, 3 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Chromatographic separation on silica gel afforded highly diastereoenriched diols.

(2*S*)-2-[(2-Hydroxy-(1*S*)-1-Phenylethyl)Amino]-3-Phenyl Propanol (3). A pale yellow oil was obtained in 62% overall yield from **2**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36–7.10 (m, 10H), 3.90 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.65 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.52 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.41 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.26 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.89–2.79 (m, 2H), 2.66–2.62 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.34 (br, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.6, 138.6, 129.3, 128.8, 128.5, 127.8, 127.5, 126.4, 67.2, 64.2, 62.1, 57.8, 37.8; HRMS: calcd. For $C_{17}H_{22}NO_2$ [M^+ + 1] 272.1651; found 272.1650.

(2*S*)-2-[(2-Hydroxy-(1*S*)-1-Phenylethyl)Amino]Propanol (4). A pale yellow oil was obtained in 66% overall yield from **2**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32–7.25 (m, 5H), 3.95 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.72 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.55 (dd, *J* = 10.8, 9.2 Hz, 1H), 3.50 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.28 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.73–2.68 (m, 1H), 2.04 (br, 3H), 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.9, 128.7, 127.7, 127.5, 66.9, 66.6, 61.2, 51.0, 15.9.

(2*S*)-2-[(2-Hydroxy-(1*S*)-1-Phenylethyl)Amino]-4-MethylPentanol (5). A yellow oil was obtained in 70% overall yield from **2**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36–7.27 (m, 5H), 3.91 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.67 (m, 1H), 3.55 (dd, *J* = 10.8, 9.2 Hz, 1H), 3.48 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.22 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.84 (br, 3H), 2.61–2.55 (m, 1H), 1.54 (m, 1H), 1.40 (m, 1H), 1.22–1.16 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.9, 128.7, 127.8, 127.4, 67.2, 64.8, 61.9, 54.5, 41.1, 25.1, 23.5, 22.4.

(2*S*)-2-[(2-Hydroxy-(1*S*)-1-Phenylethyl)Amino]-3-MethylButanol (6). A yellow oil was obtained in 61% overall yield from **2**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36–7.26 (m, 5H), 3.92 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.54 (dd, *J* = 10.4, 9.2 Hz, 1H), 3.44 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.30 (dd, *J* = 10.4, 8.4 Hz, 1H), 2.54 (br, 3H), 2.44–2.40 (m, 1H), 1.95–1.90 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.8, 128.7, 127.8, 127.4, 67.4, 62.3, 61.4, 61.1, 28.3, 19.4, 17.5.

(2*S*)-2-[(2-Hydroxy-(1*S*)-1-Phenylethyl)Amino]-2-Phenyl Ethanol (7). A yellow oil was obtained in 51% overall yield from **1**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.34–7.20 (m, 10H), 3.64–3.51 (m, 6H), 2.84 (br, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.1, 128.7, 128.6, 127.5, 127.3, 66.0, 62.0.

(2*S*)-2-[(2-Hydroxy-(1*R*)-1-Phenylethyl)Amino]Propanol (20). A colorless oil was obtained in 57% overall yield from **15**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.25 (m, 5H), 3.89 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.72–3.56 (m, 6H), 3.32 (dd, *J* = 11.2, 5.2 Hz, 1H), 2.76 (br, 1H), 0.97 (d,

J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.0, 128.7, 127.7, 127.3, 66.8, 64.7, 62.7, 52.5, 18.5; HRMS: calcd. For $C_{11}H_{18}NO_2$ [M^+ + 1] 196.1338; found 196.1338.

(2*S*)-2-[(2-Hydroxy-(1*R*)-1-Phenylethyl)Amino]-4-MethylPentanol (21). A yellow oil was obtained in 60% overall yield from **15**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.26 (m, 5H), 3.90 (dd, J = 8.0, 3.6 Hz, 1H), 3.76–3.57 (m, 3H), 3.31 (dd, J = 11.2, 4.0 Hz, 1H), 3.3 (br, 3H), 2.60 (m, 1H), 1.60–1.57 (m, 1H), 1.28–1.22 (m, 2H), 0.80 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), 141.2, 128.6, 127.6, 127.3, 67.1, 63.0, 62.1, 53.9, 42.1, 24.6, 23.0, 22.4.

General Procedure for the Synthesis of *N*-Boc Morpholines 8, 9, 10, 11 and 22. Diol was stirred in a thick-walled sealable tube as 1.0 mL of conc. H_2SO_4 was added slowly. The tube was sealed and heated at 140 °C. After 7 h, the dark brown mixture was cooled to room temperature and then poured portion-wise into an ice-cold solution of KOH. To the solution was added di-*tert*-butyl dicarbonate (3.0 equiv) and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with diethyl ether and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic separation on silica gel afforded highly diastereoenriched morpholines.

(3*S*,5*S*)-*N*-Boc-*trans*-3-Benzyl-5-Phenylmorpholine (8). A yellow oil was obtained in 27% overall yield from **3**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33–7.22 (m, 10H), 4.57 (dd, J = 10.0, 4.4 Hz, 1H), 4.15 (d, J = 11.6 Hz, 1H), 3.92 (dd, J = 12.0, 4.4 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.57 (d, J = 11.6 Hz, 1H), 3.39 (m, 1H), 3.17 (m, 1H), 2.88 (dd, J = 12.8, 2.8 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.3, 141.9, 138.6, 129.7, 128.6, 128.3, 126.9, 126.5, 126.1, 80.4, 73.1, 66.6, 56.1, 55.0, 35.9, 27.4; HRMS: calcd. For $C_{22}H_{28}NO_3$ [M^+ + 1] 354.2069; found 354.2067.

(3*S*,5*S*)-*N*-Boc-*trans*-3-Methyl-5-Phenylmorpholine (9). A yellow oil was obtained in 31% overall yield from **4**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32–7.21 (m, 5H), 4.51 (dd, J = 9.6, 4.8 Hz, 1H), 4.17 (m, 1H), 3.87–3.74 (m, 3H), 3.37 (dd, J = 12.0, 10.0 Hz, 1H), 1.33 (d, J = 6.4 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.4, 142.0, 128.3, 126.8, 126.2, 80.1, 72.8, 71.3, 55.6, 48.6, 27.9, 16.2.

(3*S*,5*S*)-*N*-Boc-*trans*-3-Isobutyl-5-Phenylmorpholine (10). A yellow oil was obtained in 25% overall yield from **5**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32–7.20 (m, 5H), 4.49 (dd, J = 10.0, 4.4 Hz, 1H), 4.04 (d, J = 10.4 Hz, 1H), 3.93 (d, J = 11.6 Hz, 1H), 3.85 (dd, J = 12.0, 4.4 Hz, 1H), 3.74 (m, 1H), 3.38 (m, 1H), 2.00 (m, 1H), 1.64–1.61 (m, 2H), 1.16 (s, 9H), 0.97 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.1, 141.9, 128.3, 126.8, 126.1, 80.0, 72.8, 67.8, 55.9, 51.3, 38.6, 27.9, 25.1, 23.9, 21.5.

(3*S*,5*S*)-*N*-Boc-*trans*-3-Isopropyl-5-Phenylmorpholine (11). A yellow oil was obtained in 23% overall yield from **6**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31–7.21 (m, 5H), 4.50 (d, J = 4.4 Hz, 1H), 4.06 (m, 1H), 3.86–3.75 (m, 3H), 3.44 (m, 1H), 2.42 (m, 1H), 1.07 (s, 9H), 1.04 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.0, 142.0, 128.2, 126.8, 126.4, 79.8, 72.5, 67.5, 57.8, 56.9, 29.0, 27.7, 20.5, 19.0.

(3*S*,5*R*)-*N*-Boc-*cis*-3-Methyl-5-Phenylmorpholine (22). A yellow oil was obtained in 29% overall yield from **20**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.59–7.21 (m, 5H), 5.14 (d, J = 3.6 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 4.14 (m, 1H), 3.77 (dd, J = 12.1, 3.4 Hz, 1H), 3.71 (m, 2H), 1.51 (s, 9H) (br, 4H), 0.91 (d, J = 7.2 Hz, 3H). The spectral data of **22** were identical to those of the authentic material reported previously.[6]

Acknowledgments. This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A1B03035502)

Supporting Information. Additional supporting information is available in the online version of this article.

References

1. (a) H. A. Bates, A. Kaushal, P.-N. Deng, D. Sciaky, *Biochemistry* **1984**, *23*, 3287. (b) R. Nakashima, N. Hayashi, T. Mizutani, N. Ueda, J. Yamamoto, Y. Kimura, *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1514.
2. (a) R. Dave, N. A. Sasaki, *Tetrahedron Asymmetry* **2006**, *17*, 388. (b) H. Li, R. Xu, D. Cole, J. W. Clader, W. J. Greenlee, A. A. Nomeir, L. Song, L. Zhang, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6606.
3. (a) M. A. Sclaldone, A. I. Myers, *Tetrahedron Lett.* **1994**, *35*, 7533. (b) F. Berre'e, A. Debache, Y. Marsac, B. Collet, P. G. Bleiz, B. Carboni, *Tetrahedron* **2006**, *62*, 4027. (c) C. M. Shafer, T. F. Molinski, *J. Org. Chem.* **1996**, *61*, 2044. (d) R. Dave, N. A. Sasaki, *Org. Lett.* **2004**, *6*, 15. (e) M. D'hoogh, T. Vanlangendonck, K. W. To¨rnroos, N. De Kimpe, *J. Org. Chem.* **2006**, *71*, 4678. (f) M. L. Leathen, B. R. Rosen, J. P. Wolfe, *J. Org. Chem.* **2009**, *74*, 5107.
4. H. J. Kim, Y. Kim, E. T. Choi, M. H. Lee, E. S. No, Y. S. Park, *Tetrahedron* **2006**, *62*, 6303.
5. R. N. Ben, T. Durst, *J. Org. Chem.* **1999**, *64*, 7700.
6. In references 4 and 5, it was established that (αS)-products were provided in the substitution of both **1** and **2** with various amine nucleophiles. We confirmed the relative configuration of morpholine **22** by comparing the NMR spectra with those of previously reported F. Segat-Dioury, O. Lingibe, B. Graffe, M.-C. Sacquet, G. Lhommet, *Tetrahedron* **2000**, *56*, 233.
7. (a) J. Baek, J. I. Jang, Y. S. Park, *Bull. Korean Chem. Soc.* **2011**, *32*, 4067. (b) Y. Kim, K. J. Park, Y. S. Choi, M. Lee, Y. S. Park, *Bull. Korean Chem. Soc.* **2013**, *34*, 2531.
8. Y. M. Lee, K. H. Kang, H.-M. Min, H. J. Lim, E.-H. Park, Y. S. Park, *Arkivoc* **2010**, *ii*, 1.

