Asymmetric Lithiation-Substitutions of *N*-Boc Benzylamines Using RLi/Chiral Ligand Complex

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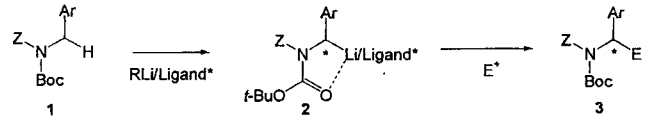
Introduction

The elaboration of benzylamines *via* dipole-stabilized carbanions has become a useful synthetic method. Recent studies, which have established that reactions of organolithium species complexed to optically pure ligands can lead to highly enantioenriched products, provide a basis for new approaches to asymmetric syntheses of α-substituted benzylamines.[2] Recently, we reported that *N*-Boc-*N*-(*p*-methoxyphenyl) benzylamines **1** can be lithiated enantioselectively with *n*-BuLi/(-)-sparteine as a chiral base and that the generated configurationally stable intermediate **2** reacts with electrophiles quite stereospecifically with inversion or retention to provide highly enantioenriched α-substituted benzylamines **3**.[3] In the present work we report the effects of solvents, *N*-alkyl groups, phenyl ring substituents and chiral ligands on regioselectivity and enantioselectivity of lithiation-alkylations of *N*-Boc-*N*-alkyl or *N*-aryl benzylamines **1**.



Results and Discussion

The sequence with *N*-Boc-*N*-methyl benzylamine **4** was carried out by treating **4** with 1.2 equiv of *s*-BuLi/(-)-sparteine at -78 °C for 4 h, followed by addition of methyl iodide. The solvent effects on regioselectivity and enantioselectivity of the reaction are shown in Table 1. The highest enantiomeric ratio (er) and regioselectivity are observed in toluene. The product was obtained with 95 : 5 er in toluene, 83 : 17 er in cumene, 79 : 21 er in pentane, 75 : 25 er in *t*-BuOMe and 72 : 28 er in ether. In THF, **5** was obtained with an er of 32 : 68 with a configuration which is opposite to that obtained in the reaction in toluene (entry 6).[4] In all solvents, except toluene, the reaction was not regioselective. The products **6** and **7** which result from lithiation-substitution at the *N*-methyl group were obtained as minor products in the ratios shown in Tabele 1.[5] Primary α-deprotonation over secondary α-deprotonation in an unsymmetrical acylic *N*-Boc amines has been reported.[6] When TMEDA was used in toluene, regioselectivity in toluene was also poor (entry 7). However, when (-)-sparteine was used in toluene, only the benzylic substituted product **5** was obtained and **6** and **7** were not observed (entry 1).

The low conversion for the reaction with 1.2 equiv of *s*-BuLi/(-)-sparteine in toluene was improved by using an excess (1.5-2.0 equiv) of *s*-BuLi/(-)-sparteine and longer lithiation time (8 h) as shown in Table 2 (entry 1).

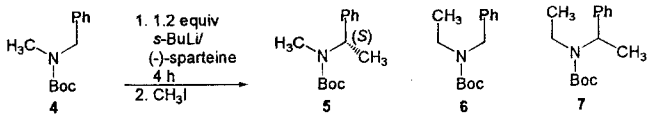


Table 1. Solvent effects on regioselectivity and enantioselectivity

Entry	Solvent	Ligand	**5 : 6 : 7**[a]	Yield (%)[a]	er(*S* : *R*)[b]
1	toluene	(-)-sparteine	100:0:0	20	95:5
2	cumene	(-)-sparteine	53:35:12	94	83:17
3	pentane	(-)-sparteine	57:24:19	95	79:21
4	*t*-BuOMe	(-)-sparteine	55:26:19	94	75:25
5	ether	(-)-sparteine	59:32:9	95	72:28
6	THF	(-)-sparteine	57:43:0	99	32:68
7	toluene	TMEDA	56:41:3	95	-

[a] The ratios and yields shown are based on GC. [b] The ers were determined by CSP-HPLC and absolute configuration was determined by comparison of the CSP-HPLC retention time with that of authentic (*S*)-enantiomer. The errors in er are judged to be ± 2 unless otherwise noted.

Significantly lower enantioselectivity was observed with $(CH_3O)_2SO_2$ as the electrophile (73 : 27 er) as compared to methyl iodide (96 : 4 er). A *p*-Cl substituent on phenyl ring gave lower enantioselectivity (90 : 10 er) while OMe gave high enantioselectivity (98 : 2 er) as compared to the reaction of **4**. When the *N*-alkyl group was ethyl, allyl, or benzyl and the electrophile was MeI, the products **7, 16**, and **17** were obtained with 95 : 5 er, 78 : 22 er, and 94 : 6 er respectively (entry 5-7). With an *N*-cyclopropyl and ethyl iodide as the electrophile **18** was obtained with 78 : 22 er. The reactions of **6, 11** and **12** were carried out in several different solvents under the same reaction conditions. When **6** was treated with *s*-BuLi/(-)-sparteine in THF, **7** was obtained in 93% yield with 42 : 58 er and a configuration which is opposite to that obtained in the reaction in toluene. From the reaction of Boc-*N*,*N*-dibenzylamine **11**, *N*-Boc-*N*-(α-phenylethyl) benzylamine **17** with a 75 : 25 er was obtained in ether. The enantiomeric purity of **18** was 87 : 13 er in pentane (13% yield), 72 : 28 er in ether (21% yield), and 54 : 46 er in THF (80% yield). The reaction of **12** in THF did not show the solvent controlled reversal of enantioselectivity recently reported by Schlosser for reactions of lithiated *N*-Boc-*N*-methyl benzylamine.[4]

These results which show that the lithiation-substitution in toluene gives higher enantioselectivity and regioselectivity than in other solvents led us to use toluene for asymmetric lithiation-substitution reactions of the *N*-Boc benzylamines, even though the reactions in toluene are slower and give lower conversion.

As we have reported previously, we extended our investigation to asymmetric syntheses of α-substituted primary

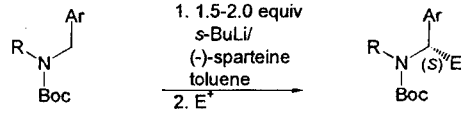


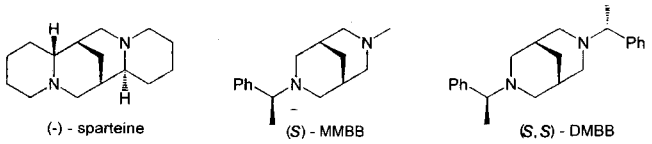
Table 2. Effects of *N*-Alkyl group and substituent on phenyl ring

Entry	S.M.	R	Ar	E^+	Product	Yield[a]	er[b] (*S*:*R*)
1	**4**	Methyl	Ph	CH_3I	**5**	79	96:4
2	**4**	Methyl	Ph	$(CH_3O)_2SO_2$	**5**	64	73:27
3	**8**	Methyl	*p*-ClPh	CH_3I	**14**	74	90:10
4	**9**	Methyl	*p*-MeOPh	CH_3I	**15**	58	98:2
5	**6**	Ethyl	Ph	CH_3I	**7**	25	95:5
6	**10**	Allyl	Ph	CH_3I	**16**	50	78:22
7	**11**	Benzyl	Ph	CH_3I	**17**	47	94:6
8	**12**	Cyclopropyl	Ph	CH_3CH_2I	**18**	27	78:22
9	**13**	H	Ph	CH_3I	**19**	32	63:37

[a] The yields are based on GC. [b] The ers were determined by CSP-HPLC and absolute configurations of **5, 7, 16, 17** and **19** were determined by comparison of the CSP-HPLC retention time with that of authentic (*S*)-enantiomer. The absolute configurations of **14, 15** and **18** were assigned by analogy.

benzylamines by asymmetric alkylation of an activated and protected secondary benzylamine with the removable amine substituent, *p*-methoxyphenyl group.[3] We reported that **19** was produced with 97:3 er in 81% yield using *n*-BuLi/(-)-sparteine and MeOTf and after removing *p*-methoxyphenyl group with ceric ammonium nitrate (Table 3, entry 3).[3d] We investigated a more direct route with *N*-Boc-*N*-benzylamine **13**. However, reaction of **13** with 2.2 equiv of *s*-BuLi/(-)-sparteine and methyl iodide gave **19** with only 63:37 er in toluene and 56:44 er in ether (Table 2, entry 9).

In search for new synthetically useful chiral ligands which would be readily available in both enantiomeric forms, two different bispidine ligands which contain the core diaza[3.3.1] ring system of sparteine were investigated.[7] The [3.3.1] ring system incorporated into a chiral complex mimics the core structure of (-)-sparteine and should provide rigidity which reduces conformational possibilities in the enantiodetermining transition state. Use of (*S*)-MMBB ((*S*)-3-methyl-7-(1'-phenylethyl)-3,7-diazabicyclic[3.3.1]-nonane) as a ligand for the reaction of **20** in toluene provided (*R*)-**19** with 19:81 er and 30:70 er with *s*-BuLi or *n*-BuLi, and methyl iodide respectively with a configuration which is opposite to that obtained with (-)-sparteine (entry 4, 5). (*S,S*)-DMBB ((*S*)-3,7-di(1'-phenylethyl)-3,7-diazabicyclic[3.3.1]-nonane) provided (*R*)-**19** with 11:89 er in 88% yield, when treated with *n*-BuLi and MeOTf in toluene (entry 7). Neither ligand provided an enantioselectivity as high as (-)-sparteine although DMBB gave a promising result. The substituent on phenyl ring was found to affect the enantioselectivity of the reaction only slightly. Reaction of **21** with a *p*-F group showed slightly lower enantioselectivity and reaction of **22** with *m*-OMe electron-donating substituent group showed slightly higher enantioselectivity (entry 8, 10) compared to the reaction of **20** (entry 2). In toluene, the lithiation did not take place without the diamine ligand (entry 11).



Studies of asymmetric lithiation-substitution of *N*-Boc-*N*-alkyl or *N*-aryl benzylamines, showed toluene to be the best solvent and that *N*-subsituent affects the enantioselectivity of the reaction. When the *N*-substituent was allyl or cyclopropyl, lower enantioselectivity was observed (78:22 er) compared to the reaction with methyl, ethyl, benzyl and *p*-methoxyphenyl *N*-substituents. Without an *N*-substituent (R= H), lowest enantioselectivity (63:37 er) was observed. Substituents on the phenyl ring change the enantioselectivity only slightly. (*S*)-MMBB and (*S,S*)-DMBB provided lower enantioselectivity than (-)-sparteine. Based on our mechanistic studies of lithiation-substitution of *N*-Boc-*N*-(*p*-methoxyphenyl) benzylamine **20** and the fact that the *S*-enantiomer is major enantiomer in the reactions of all *N*-Boc *N*-alkyl or aryl benzylamines used in this work, we suggest the lithiated configurationally stable intermediate **2** has the (*R*) configuration and reacts with invertive substitution with CH_3I in toluene.[3a]

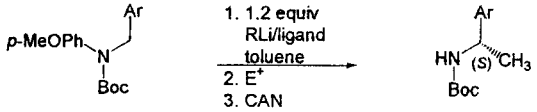


Table 3. Effects of chiral ligand and subtituent on phenyl ring

Entry	S.M.	Ar	RLi	Ligand	E^+	Product	Yield[a]	er[b] (*S*:*R*)
1	**20**	Ph	*s*-BuLi	sparteine	CH_3I	**19**	75	92:8
2	**20**	Ph	*n*-BuLi	sparteine	CH_3I	**19**	80	94:6
3	**20**	Ph	*n*-BuLi	sparteine	CH_3OTf	**19**	81	97:3
4	**20**	Ph	*s*-BuLi	MMBB	CH_3I	**19**	87	19:81
5	**20**	Ph	*n*-BuLi	MMBB	CH_3I	**19**	83	30:70
6	**20**	Ph	*s*-BuLi	DMBB	CH_3OTf	**19**	78	20:80
7	**20**	Ph	*n*-BuLi	DMBB	CH_3OTf	**10**	88	11:89
8	**21**	*p*-F-Ph	*n*-BuLi	sparteine	CH_3I	**23**	89	90:10
9	**22***m*-MeOPh		*n*-BuLi	sparteine	CH_3I	**24**	77	95:5
10	**22***m*-MeOPh		*s*-BuLi	sparteine	CH_3I	**24**	72	91:9
11	**20**	Ph	*n*-BuLi	none	CH_3I	**19**	N.R.	-

[a] Isolated yields. [b] The ers were determined by CSP-HPLC and absolute configuration of **19** was determined by comparison of the CSP-HPLC retention time with that of authentic (*S*)-enantiomer. The absolute configurations of **23** and **24** were assigned by analogy.

Experimental

General Procedure for the Asymmetric Syntheses of *N*-Boc-*N*-Alkyl or *N*-Aryl-α-Substituted Benzylamines. To a solution of (-)-sparteine (1.2 equiv) in toluene (*ca.* 0.1 M) at −78 °C was added *n*-BuLi (1.2 equiv). The reaction mixture was stirred for 15 min at −78 °C and then a solution of a starting material (1.0 equiv) in toluene (*ca.* 0.2 M) was transferred to the above solution at −78 °C. The resulting reaction mixture was stirred at −78 °C for 1-10 h, and then an electrophile (1.2 equiv) in toluene (*ca.* 0.2 M) was added after precooling. After stirring for 3 h at −78 °C, this mixture was allowed to slowly warm to room temperature. Workup consisted of addition of saturated

NH_4Cl solution, extraction with diethyl ether three times, drying over anhydrous $MgSO_4$, filteration and concentration *in vacuo*. The crude material was purified by chromatography to give the product.

Removal of the *p*-Methoxyphenyl Group by CAN. (for **19, 23** and **24**): The product was dissolved in CH_3CN-H_2O (4 : 1 *ca.* 0.05 M) and CAN (ceric ammonium nitrate, 2.2 equiv) was added at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was diluted with diethyl ether, poured into water and was extracted with diethyl ether. The extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was further purified by chromatography to give a pure product.

***N*-(*tert*-Butyloxycarbonyl)-*N*-methyl-α-phenethylamine (5).** From 110 mg of **4**, 40 mg (34% isolated yield) of **5** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.20 (m, 5H, *Ph*), 5.48 (br, 1H, N-C*H*-Ph), 2.57 (s, 3H, N-CH_3), 1.49 (s, 9H, C(CH_3)$_3$), 1.48 (d, *J*=6.4 Hz, 3H, CH-CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 141.3, 128.1, 126.8, 126.7, 79.2, 52.3, 28.3, 28.2, 16.2; Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H 8.99; N, 5.95. Found: C, 71.59; H, 9.12; N, 6.56. The enantiomeric ratio of **5** was determined to be 96 : 4 in favor of the *S* enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methylbenzylamine. (Whelk-0 column; 0.5% 2-propanol in hexane; 1.25 mL/min; The *S*-enantiomer (major) had a retention time of 10.1 min, and the *R*-enantiomer (minor) had a retention time of 9.1 min).

***N*-(tert-Butyloxycarbonyl)-*N*-ethyl-α-phenethylamine (7).** From 193 mg of **6**, 18 mg (9% isolated yield) of **7** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.16 (m, 5H, *Ph*), 5.42 (br, 1H, N-C*H*-Ph), 3.08 (br, 1H, N-CH_aH$_b$CH$_3$), 2.90 (br, 1H, N-CH$_a$H$_b$CH$_3$), 1.50 (d, *J*=7.1 Hz, 3H, CHCH_3), 1.45 (s, 9H, C(CH_3)$_3$), 0.95 (br, 3H, N-CH$_a$H$_b$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 141.9, 128.9, 128.0, 126.7, 79.1, 53.7, 37.9, 28.2, 17.3, 15.0; HRMS Calcd for $C_{15}H_{23}NO_2$: 249.1729 Found: 249.1730. The enantiomeric ratio of **7** was determined to be 95 : 5 in favor of the *S* enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methyl-benzylamine. (Whelk-0 column; 0.5% 2-propanol in hexane; 1.0 mL/min; The *S*-enantiomer (major) had a retention time of 12.1 min, and the *R*-enantiomer (minor) had a retention time of 9.8 min).

***N*-(*tert*-Butyloxycarbonyl)-*N*-methyl-α-*p*-chlorophenethylamine (14).** From 95 mg of **8**, 50 mg (50% isolated yield) of **14** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.12 (m, 4H, *Ph*), 4.38 (br, 1H, N-C*H*-Ph), 2.56 (s, 3H, N-CH_3), 1.48 (br, 12H, CH-CH_3+C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 139.8, 132.8, 128.3, 79.6, 51.6, 28.3, 28.2, 16.0; HRMS Calcd for $C_{14}H_{20}NO_2Cl$: 269.1183, Found: 269.1183. The enantiomeric ratio of **14** was determined to be 90 : 10 by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by analogy. (Whelk-0 column; 1.0% 2-propanol in hexane; 1.25 mL/min; The *S*-enantiomer (major) had a retention time of 7.9 min, and the *R*-enantiomer (minor) had a retention time of 6.8 min).

***N*-(*tert*-Butyloxycarbonyl)-*N*-methyl-α-*p*-methoxyphenethylamine (15).** From 84 mg of **9**, 17 mg (22% isolated yield) of **15** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20-6.83 (m, 4H, *Ph*), 4.35 (brs, 1H, N-C*H*-Ph), 3.78 (s, 3H, OCH_3), 2.54 (s, 3H, N-CH_3), 1.48 (s, 9H, C(CH_3)$_3$), 1.45 (d, *J*=7.3 Hz, 3H, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 155.8, 133.3, 128.0, 113.5, 79.3, 55.1, 51.6, 28.4, 28.3, 16.2; HRMS Calcd for $C_{15}H_{23}NO_3$: 265.1678, Found: 265.1675. The enantiomeric ratio of **15** was determined to be 98 : 2 by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by analogy. (Whelk-0 column; 1.5% 2-propanol in hexane; 1.25 mL/min; The *S*-enantiomer (major) had a retention time of 11.9 min, and the *R*-enantiomer (minor) had a retention time of 10.6 min).

***N*-(*tert*-Butyloxycarbonyl)-*N*-allyl-α-phenethylamine (16).** From 28 mg of **10**, 8 mg (28% isolated yield) of **16** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.19 (m, 5H, *Ph*), 5.72-5.65 (br, 1H, C*H*=CH$_2$), 5.38 (br, 1H, N-C*H*-Ph), 5.04-4.97 (m, 2H, CH=CH_2), 3.73 (br, 1H, N-CH_aH$_b$), 3.46 (br, 1H, N-CH$_a$H$_b$), 1.52 (d, *J*=7.4 Hz, 3H, CHCH_3), 1.45 (s, 9H, C(CH_3)$_3$). The spectral data of **16** were identical to those of authentic material reported previously. The enantiomeric ratio of **16** was determined to be 78 : 22 in favor of the *S* enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methylbenzylamine. (Whelk-0 column; 0.5% 2-propanol in hexane; 1.25 mL/min; The *S*-enantiomer (major) had a retention time of 9.2 min, and the *R*-enantiomer (minor) had a retention time of 6.7 min).

***N*-(*tert*-Butyloxycarbonyl)-*N*-benzyl-α-phenethylamine (17).** From 323 mg of **11**, 71 mg (21% isolated yield) of **17** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.03 (m, 10H, *Ph*), 5.58 (br, 1H, N-CH_aH$_b$-Ph), 4.43 (br, 1H, N-CH$_a$H$_b$-Ph), 4.03 (br, 1H, C*H*Ph), 1.44 (d, *J*=7.2 Hz, 3H, CHCH_3), 1.38 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 141.7, 139.9, 128.2, 128.0, 127.0, 126.8, 126.7, 126.4, 79.8, 53.6, 47.2, 28.3, 17.8; Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H 8.10; N, 4.50. Found: C, 77.08; H, 8.14; N, 4.47. The enantiomeric ratio of **17** was determined to be 94 : 6 in favor of the *S*-enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methylbenzylamine. (Whelk-0 column; 0.5% 2-propanol in hexane; 0.75 mL/min; The *S*-enantiomer (major) had a retention time of 23.8 min, and the *R*-enantiomer (minor) had a retention time of 15.1 min).

***N*-(*tert*-Butyloxycarbonyl)-*N*-(1-phenpropyl)-α-cyclopropylamine (18).** From 111 mg of **12**, 14 mg (11% isolated yield) of **18** was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.21 (m, 5H, *Ph*), 4.92 (t, *J*=7.8 Hz, 1H, C*H*Ph), 2.31 (m, 1H, N-C*H*(CH$_2$)$_2$), 2.13 (m, 2H, PhCHCH_2), 1.44 (s, 9H, C(CH_3)$_3$), 1.00 (t, *J*=7.3 Hz, 3H, CH$_2$CH_3), 0.56 (m, 4H, CH(CH_2)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 142.2, 127.9, 127.1, 126.6, 79.4, 62.1, 28.3, 27.8, 24.1, 11.4, 7.9, 7.1; Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H 9.15; N, 5.09. Found: C, 73.82; H, 9.40; N, 5.48.

The enantiomeric ratio of **18** was determined to be 78 : 22 in favor of the *S*-enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by analogy. (Whelk-0 column; 0.05% 2-propanol in hexane; 1.25 mL/min; The *S*-enantiomer (major) had a retention time of 18.4 min, and the *R*-enantiomer (minor) had a retention time of 24.6 min).

***N*-(*tert*-Butyloxycarbonyl)-α-methylbenzylamine (19).** From 619 mg of **20**, 354 mg (81%) of **19** was obtained as a white solid (Table 3, Entry 3). mp 68.5-70.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.21 (m, 5H, *Ph*), 4.90-4.77 (br, 2H, N*H*+N-C*H*-Ph), 1.44-1.42 (s and d, 12H, CHCH_3+C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 144. 0, 128.4, 127.0, 125.8, 79.2, 50.1, 28.3, 22.6; Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H 8.65; N, 6.33. Found: C, 70.47; H, 8.60; N, 6.40. The enantiomeric ratio of **19** was determined to be 97 : 3 in favor of the *S*-enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-α-methylbenzylamine. (Whelk-0 column; 20% 2-propanol in hexane; 2.0 mL/min; The *S*-enantiomer (major) had a retention time of 8.0 min, and the *R*-enantiomer (minor) had a retention time of 5.7 min).

***N*-(*tert*-Butyloxycarbonyl)-α-methyl-*p*-fluorobenzylamine (23).** From 150 mg of **21**, 96 mg (89%) of **23** was obtained as a white solid. mp 99-100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-6.95 (m, 4H, *Ph*), 4.87 (br, 1H), 4.75 (br, 1H), 1.40 (br, 12H, CHCH_3+C(CH_3)$_3$); ^{13}C NMR (two rotomers $CDCl_3$, 100 MHz) δ (162.9, 160.4), 154.9, 139.7, (127.3, 127.2), (115.2, 115.0), 79.3, 49.4, 28.2, 22.6; HRMS Calcd for $C_{13}H_{18}FNO_2$: 239.1322 Found: 239.1323. The enantiomeric ratio of **23** was determined to be 90 : 10 by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative on a Pirkle column packed with (*S*)-*N*-naphthylleucine using racemic material as a standard and the absolute configuration was assigned by analogy. (30% 2-propanol in hexane; 2.0 mL/min; The *S*-enantiomer (major) had a retention time of 4.6 min, and the *R*-enantiomer (minor) had a retention time of 3.9 min).

***N*-(*tert*-Butyloxycarbonyl)-α-methyl-*m*-methoxybenzylamine (24).** From 211 mg of **22**, 119 mg (77%) of **24** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-6.77 (m, 4H, *Ph*), 4.78 (brs, 2H), 3.80 (s, 3H, OCH_3), 1.45 (d, *J*=5.3 Hz, 3H, CHCH_3) 1.42 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 155.1, 129.57, 129.56, 118.1, 112.3, 111.7, 79.4, 55.2, 45.5, 28.4, 22.7; HRMS Calcd for $C_{14}H_{21}NO_3$: 251.1521 Found: 251.1524. The enantiomeric ratio of **24** was determined to be 95 : 5 by chiral HPLC analysis of the corresponding 3,5-dinitrobenzoyl derivative on a Pirkle column packed with (*S*)-*N*-naphthylleucine using racemic material as a standard and the absolute configuration was assigned by analogy. (20% 2-propanol in hexane; 2.0 mL/min; The *S*-enantiomer (major) had a retention time of 12.3 min, and the *R*-enantiomer (minor) had a retention time of 7.6 min).

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4. This result is similar to the result reported by Schlosser group.[2c] They reported that deprotonation of **4** with *s*-BuLi/(-)-sparteine is highly asymmetric but racemization is rapid and that the configuration of the subsequent asymmetric substitution is highly solvent dependent. They reported 10 : 90 er in THF with methyl iodide and we observed 32 : 68 er.
5. Voyer and Roby reported that when **4** was treated with *s*-BuLi/(-)-sparteine and CO_2 in ether, *N*-methyl substituted product was obtained in 5% yield along with the benzyl substituted product in 52% yield with 80 : 20 er.[2d]
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