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Enantioselective Synthesis of 2-Substituted 2-Phenylethylamines by Lithiation−Substitution Sequences: Synthetic Development and Mechanistic Pathway

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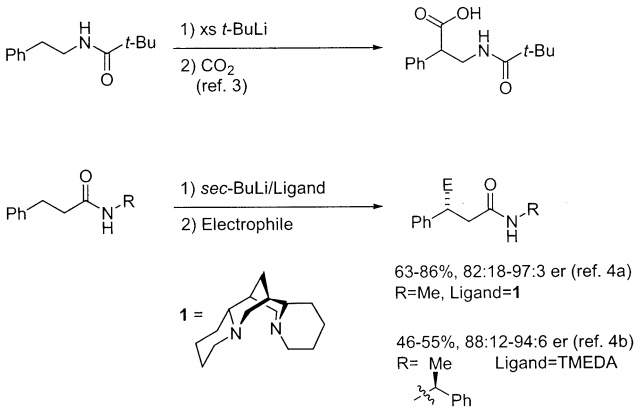
The lithiation and asymmetric substitution of *N*-(2-phenylethyl)isobutyramide (**2**) with selected electrophiles, under the influence of (−)-sparteine, provides benzylically substituted products in 58−90% yields with enantiomeric ratios (ers) from 72:28 to 91:9. Syntheses of enantioenriched dihydroisoquinolines (*S*)-**18** and (*S*)-**19** and a tetrahydroisoquinoline (*4S*)-**20** provide examples of synthetic applications. Mechanistic investigations suggest the enantiodetermining step at −78 °C is a dynamic thermodynamic resolution.

Introduction

The 2-phenylethylamine framework is a recurrent pharmacophore which is found in many acyclic and heterocyclic bioactive compounds. The development of methodology for the synthesis and modification of 2-phenylethylamines as well as for dihydro- and tetrahydroisoquinoline derivatives is of continuing interest.[1]

We have previously reported lithiation−substitution sequences in the presence of (−)-sparteine (**1**) for asymmetric replacement of prochiral hydrogens adjacent to nitrogen and/or in benzylic or allylic positions.[2] We now report application of this methodology to the synthesis of 2-substituted 2-phenylethylamines with good yields and enantiomeric ratios. We establish the enantiodetermining step to be a dynamic thermodynamic resolution in which the less stable diastereoisomeric complex is the more reactive species.

Benzylic lithiations β to amide activating groups have been previously reported. In 1991 Simig and Schlosser reported that reaction of *N*-pivaloyl-2-phenylethylamine with excess *tert*-butyllithium (*t*-BuLi) followed by reaction with carbon dioxide provided 2-phenyl-3-(*N*-pivaloylamino)propionic acid.[3] The Swiss workers also found lithiation to occur at the benzylic position with a methoxy group on the aromatic ring using *t*-BuLi. However, if *n*-butyllithium (*n*-BuLi) or a mixture of *n*-BuLi and potassium *tert*-butoxide was used as the base, lithiation was directed adjacent to the methoxy group of the aromatic ring regioselectively but at different sites with each base. In 1993, we reported asymmetric lithiation substitutions of *N*-methyl-3-phenylpropionamide with *sec*-butyllithium/(−)-sparteine ((*sec*-BuLi)/**1**) and subsequently of (*S*)-*N*-(1-phenylethyl)-3-phenylpropionamide with *sec*-BuLi to provide enantiomerically and diastereomerically enriched products.[4] The β-lithiations in these reactions may be viewed as a manifestation of the complex induced proximity effect.[2,5]



Results and Discussion

Asymmetric lithiation−substitution sequences of *N*-(2-phenylethyl)isobutyramide (**2**) have been investigated as prototypical for the 2-phenylethylamine framework. The amide **2** was selected because of structural analogy to earlier cases for directed asymmetric β-lithiations and for its amenability for further transformations.

(1) Urban, J. J.; Cronin, C. W.; Roberts, R. R.; Famini, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 12292 and references therein. Shamma, M. *The Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic Press: New York, 1972.

(2) Weisenberger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522. Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(3) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1991**, *32*, 1963. Schlosser, M.; Simig, G. *Tetrahedron Lett.* **1991**, *32*, 1965.

(4) (a) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542. (b) Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2.

(5) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

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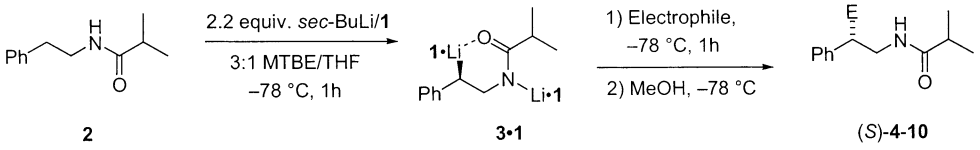
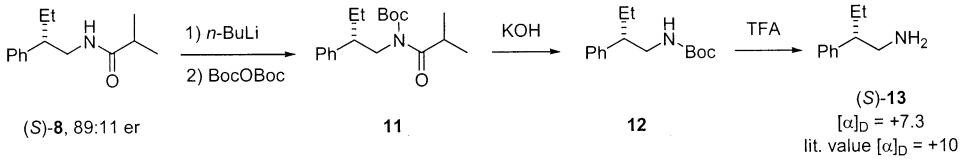
TABLE 1. Yields and Enantiomeric Ratios of Products 4−10



Entry	Electrophile	E	Product	Yield (%)	er[a]
1	Me_3SiCl	Me_3Si	(*S*)-**4**	90	91:9
2	Bu_3SnCl	Bu_3Sn	(*S*)-**5**	86	88:12
3	$PhCH_2Br$	$PhCH_2$	(*S*)-**6**	82	83:17
4	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	(*S*)-**7**	68	91:9
5	CH_3CH_2I	CH_3CH_2	(*S*)-**8**	73	88:12
6	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	(*S*)-**9**	58	72:28
7	PhCHO	PhCH(OH)	(*S*)-**10**	70	78:22[b]

[a]enantiomeric ratios were determined using chiral stationary phase HPLC (CSP-HPLC) by comparison with racemic compounds
[b]diastereomeric ratio of 79:21 was determined by ^{1}H NMR (er is for the major isomer)

SCHEME 1



Lithiation−Substitution. Treatment of *N*-(2-phenylethyl)isobutyramide (**2**) in 3:1 MTBE/THF with 2.2 equiv of *sec*-BuLi/**1** at −78 °C for 1 h forms the dilithiated species **3·1**.[6] Reaction of this complex with selected electrophiles followed by quenching with methanol at −78 °C yields the substituted products in moderate to good yields with enantiomeric ratios (ers) of 72:28−91:9, as shown in Table 1.

Reactions of chlorotrimethylsilane and chlorotributylstannane with **3·1** provide the benzylic substituted products (*S*)-**4** and (*S*)-**5** in 90% and 86% yields with ers of 91:9 and 88:12, respectively. Reactions of benzyl bromide, allyl bromide and iodoethane afford products (*S*)-**6**, (*S*)-**7**, and (*S*)-**8** in slightly lower yields of 68−82% and with similar enantiomeric ratios of 83:17 to 91:9. Reaction of the ketone electrophile cyclohexanone with **3·1** affords alcohol (*S*)-**9** in 58% yield with an er of 72:28. With benzaldehyde as the electrophile, the alcohol (2*S*)-**10** is obtained in 70% yield with a 79:21 dr and a 78:22 er for the major diastereomer.

The absolute configuration of (*S*)-**8** was determined by hydrolysis to the primary amine and comparison of the optical rotation to (*S*)-**13** with a value of $[\alpha]_D = +7.3$, to a literature value of $[\alpha]_D = +10$ as shown in Scheme 1.[7] Formation of the *N*-Boc amide **11**, followed by hydrolysis of the substituted amide affords **12**. Deprotection of the Boc group with trifluoroacetic acid (TFA) provides the primary amine (*S*)-**13**. The absolute configurations for (*S*)-**4**, (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** in Table 1 are assigned to be the same by analogy.

The absolute configuration of (2*S*)-**10** and the relationship of the stereochemical course of reaction of **3·1** with alkyl halides and with carbonyl electrophiles were addressed by the conversion of **10** to **6** (Scheme 2). Comparison of the CSP−HPLC trace of **6** obtained from reaction of **3·1** with benzyl bromide and reaction of **3·1** with benzaldehyde followed by deoxygenation shows identity.

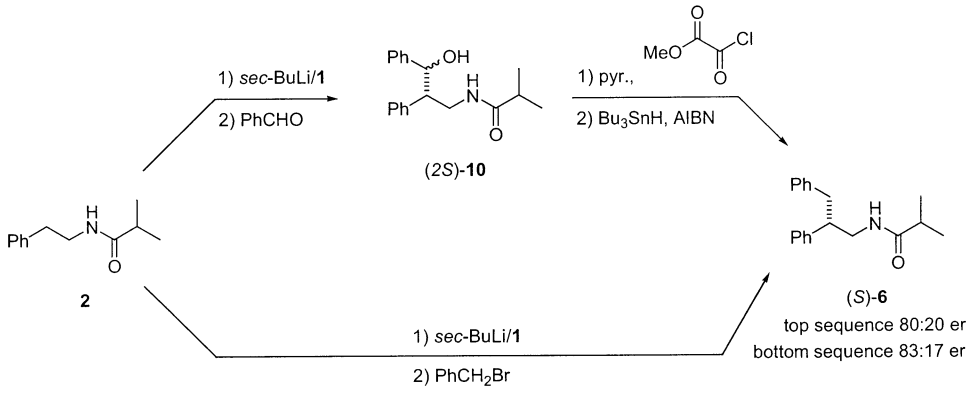
The assignment of absolute configuration to (2*S*)-**10** demonstrates that C−C bond formation affords products with the same sense of configuration at the newly formed stereogenic center for both alkyl halides and carbonyl compounds. The assignment of the absolute configuration to (*S*)-**9** is provisional and made by analogy to the reaction with benzaldehyde. Our working hypothesis is that fast reacting electrophiles or electrophiles which do not have the ability to coordinate to the lithiated species react with inversion of configuration, and that slow reacting electrophiles which can coordinate to the lithiated species react with retention of configuration. The present results can be rationalized if benzaldehyde is considered to react with **3·1** rapidly with inversion of configuration at the anionic center. However, the lower enantioselectivity for the carbonyl electrophiles may be attributed to a competitive pathway involving coordination of the carbonyl oxygen to the lithiated species and reaction with retention of configuration.

2-Phenylethylamine Derivatives. The asymmetric lithiation−substitution of *N*-(2-(3-methoxyphenyl)ethyl)-isobutyramide (**14**) illustrates the versatility of this methodology for ring substituted 2-phenylethylamine derivatives.

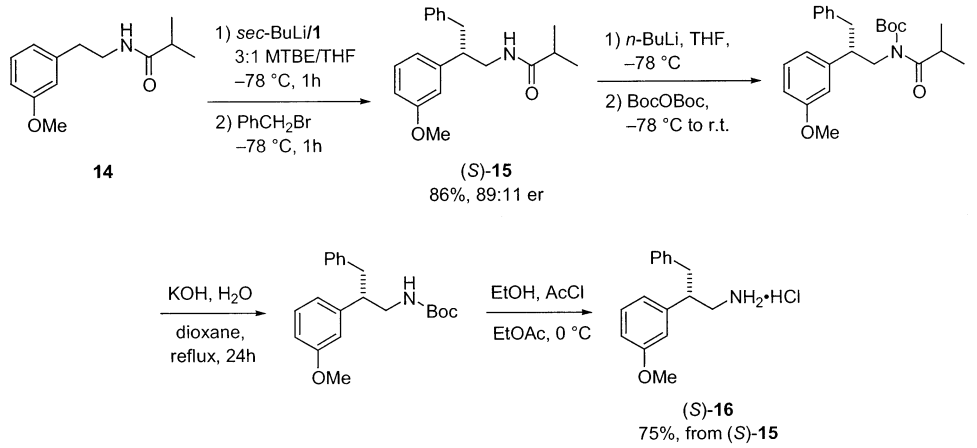
Treatment of **14** with 2.2 equiv of *sec*-BuLi/**1** in a 3:1 MTBE/THF solvent mixture at −78 °C for 1 h followed

(6) The absolute configuration of **3·1** is provisional and based on the assumption of reaction with electrophiles with inversion of configuration as is observed with related systems.[2]
(7) Pettersson, K. *Ark. Kemi* **1957**, *10*, 297.

SCHEME 2



SCHEME 3



by reaction with benzyl bromide at −78 °C for 1 h provides the benzylated product (*S*)-**15** in 86% yield with an er of 89:11. The absolute configuration of (*S*)-**15** is assigned by analogy to (*S*)-**6**.

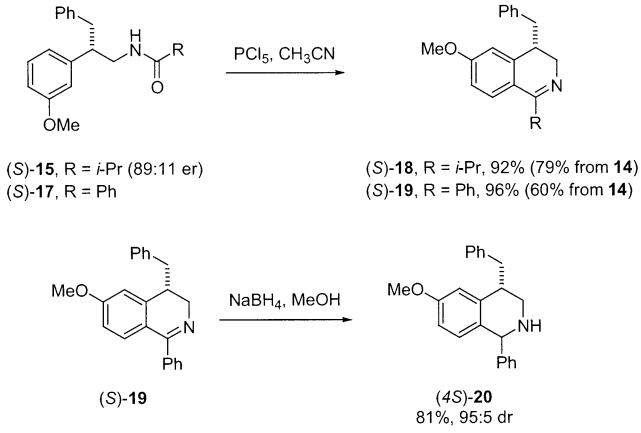
A variation of the hydrolysis procedure used in the synthesis of (*S*)-**13** is illustrated by the synthesis of the easily isolable hydrochloride salt (*S*)-**16** from (*S*)-**15** (Scheme 3). Activation of the amide with BocOBoc, basic hydrolysis, and removal of the Boc group is carried out with an aqueous workup after each step. The overall yield from (*S*)-**15** to (*S*)-**16** is 75%.

The amide (*S*)-**15** and the benzamide (*S*)-**17**, which can be obtained in 97% yield from reaction of (*S*)-**16** with benzoyl chloride, have been used to prepare isoquinoline derivatives. Cyclization of (*S*)-**15** with phosphorus pentachloride affords (4*S*)-4-benzyl-6-methoxy-1-isopropyl-3,4-dihydroisoquinoline ((*S*)-**18**) in 92% yield (Scheme 4). Cyclization of the corresponding benzamide (*S*)-**17** is achieved using phosphorus pentachloride, providing (4*S*)-4-benzyl-6-methoxy-1-phenyl-3,4-dihydroisoquinoline ((*S*)-**19**) in 96% yield.

The dihydroisoquinoline (*S*)-**19** has been reduced with sodium borohydride to give (4*S*)-4-benzyl-6-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((4*S*)-**20**) in 81% yield with a 95:5 dr, as shown in Scheme 4. However, the absolute configuration at C-1 remains unassigned.[8]

(8) The absolute configuration of **20** could not be assigned by analogy to a similar compound reported by Jullian, V.; Quirion, J.-C.; Husson, H.-P. *Eur. J. Org. Chem.* **2000**, 1319, nor did NOE NMR experiments provide elucidation of the absolute configuration.

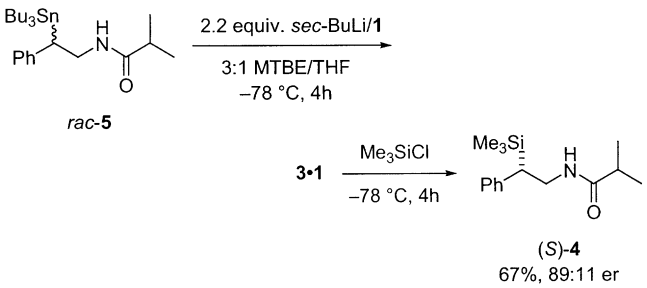
SCHEME 4



Reaction Pathway. The two limiting pathways for asymmetric replacement of a prochiral hydrogen in a lithiation−substitution sequence are: asymmetric deprotonation in which one of the prochiral hydrogens is selectively removed to give a configurationally stable organolithium anion which reacts stereoselectively with electrophiles, or asymmetric substitution in which the enantiomeric ratio is established in a step after the initial deprotonation.[2]

To differentiate between these two pathways for the present case, the racemic lithiated intermediate was generated through tin−lithium exchange of *rac*-**5** and allowed to react with an electrophile in the presence of

SCHEME 5



(−)-sparteine to determine if the product is enantiomerically enriched. Racemic *N*-(2-tributylstannyl-2-phenylethyl)isobutyramide (**5**) was synthesized in 76% yield using chlorotributylstannane as the electrophile after lithiation of **2** with *sec*-BuLi/TMEDA. Transmetalation of *rac*-**5** using 2.2 equiv of *sec*-BuLi/**1** followed by reaction with chlorotrimethylsilane affords (*S*)-**4** with an er of 89:11. Unreacted **5** was isolated, analyzed by CSP−HPLC, and determined to be racemic, ruling out a kinetic resolution in the initial tin−lithium exchange. The fact that asymmetric induction arises from a racemic starting material in the presence of the chiral ligand shows that the enantiodetermining step is an asymmetric substitution (Scheme 5).

For reaction pathways of asymmetric substitution, there are two limiting modes of stereoinduction: a dynamic thermodynamic resolution in which the diastereomeric lithiated complexes may equilibrate on the time scale of metalation, but not on the time scale of reaction with the electrophile, or a dynamic kinetic resolution in which the diastereomeric lithiated complexes equilibrate rapidly relative to the rate of reaction with electrophile.[2] The "poor man's Hoffmann test" using different amounts of the electrophile may be used to differentiate between a dynamic thermodynamic resolution and a dynamic kinetic resolution.[2] In the present case reaction of **3·1** with 1.1 equiv of chlorotrimethylsilane and 0.1 equiv of chlorotrimethylsilane afforded (*S*)-**4** with the ers shown in Table 2.

In the case of a dynamic kinetic resolution, the enantiomeric ratio depends solely on $\Delta\Delta G^{\ddagger}$ and would be independent of the amount of electrophile. However, for a dynamic thermodynamic resolution if the two diastereomeric lithiated complexes have different energy barriers for reaction with an electrophile, the amount of the electrophile can affect the degree of enantioenrichment in the product. Entries 1 and 2 in Table 2 show (*S*)-**4** is obtained with different enantiomeric ratios with different amounts of chlorotrimethylsilane, suggesting the mode of enantioinduction for the present reaction is a dynamic thermodynamic resolution.[9] However, the difference is close to our conservative experimental error for er determinations of ±3%. Entries 3 and 4 provide further data in support of this reaction pathway, albeit for reactions at −100 °C. The decrease in enantiomeric ratio of (*S*)-**4** with the limited amount of the electrophile shows that the more stable diastereomeric complex has a higher energy barrier to reaction with chlorotrimethylsilane.

Benzyl bromide has also been tested as an electrophile in the "poor man's Hoffmann test" with **3·1**. The results shown in Table 3 for entries 1 through 4 show there is no difference in the products' enantiomeric ratios with excess and limited amounts of the electrophile. This is consistent with a dynamic thermodynamic resolution in which the energies of activation for the reactions of each diastereomer are indistinguishable.

However, another possibility is that there are higher barriers for reaction of the diastereomeric intermediates with benzyl bromide than with chlorotrimethylsilane. In effect this would allow a change in the reaction pathway from a dynamic thermodynamic resolution with chlorotrimethylsilane to a dynamic kinetic resolution with benzyl bromide.[2] To evaluate this issue, a competitive reaction was carried out in which **3·1** was cooled to −100 °C and allowed to react with a mixture of 2 equiv of benzyl bromide and 2 equiv of chlorotrimethylsilane. The products were (*S*)-**6** in 50% yield with a 96:4 er and (*S*)-**4** in 13% yield with an 88:13 er.[10] This product ratio establishes that the activation barrier for the reaction with benzyl bromide is lower than for the reaction with chlorotrimethylsilane. The reaction pathway with benzyl bromide therefore is assigned as a dynamic thermodynamic resolution with indistinguishable barriers for reaction of each diastereomeric complex.

Lithiation−substitution reactions of **2** also have been carried out at −100 °C. Two separate sets of experiments were performed, one using chlorotrimethylsilane as the electrophile and the second using benzyl bromide as the electrophile. After lithiation in the presence of **1**, the lithiated intermediates were then allowed to react with either 1.1 or 0.1 equiv of electrophile.

The results with benzyl bromide are consistent with the above analysis. However, the results with chlorotrimethylsilane as the electrophile shown in Table 2 as entry 6 suggested a more complex situation.

The ers of (*S*)-**4** from lithiation at −78 °C with reaction at −78 °C and at −100 °C are comparable (entries 1−4, Table 2). Both of these sets of sequences are consistent with a dynamic thermodynamic resolution with the less populated diastereomeric intermediate having a lower barrier to reaction with chlorotrimethylsilane. When the entire sequence is carried out at −100 °C using an excess amount of chlorotrimethylsilane (entry 5), the product is obtained with an er of 52:48. This result could be taken to suggest that the initial deprotonation is unselective and that the diastereomeric lithiated intermediates do not equilibrate at −100 °C. If the diastereomeric intermediates formed by lithiation at −78 °C are the same as those obtained on lithiation at −100 °C, addition of a deficient amount of chlorotrimethylsilane to the −100 °C lithiation should provide more (*R*)-**4** than is observed in entry 6.

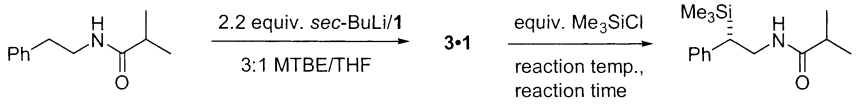
This result is not consistent with a straightforward dynamic thermodynamic resolution in which the same complexes are formed by cooling from −78 °C to −100 °C, and by carrying out the whole sequence at −100 °C.[11] The results in entry 5 suggest that unequilibrated

(9) To determine whether a halide effect could influence the er of the product, the reaction was run with 0.1 equiv of chlorotrimethylsilane and 1.0 equiv of LiCl. The results were unchanged.

(10) The increased er of (*S*)-**6** is noted and of interest.

(11) For an investigation which shows more than one initial prelithiation complex can be present in a lithiation, see: Pippel, D. J.; Weisenburger, G. A.; Fabish, N. A.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919.

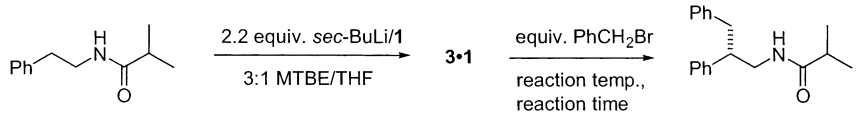
TABLE 2. Effect of Lithiation and Reaction Temperatures on the Enantioselectivity of Lithiation−Substitution of 2 Using Chlorotrimethylsilane as the Electrophile



2 (*S*)-**4**

Entry	Lithiation Temp.	equiv. Me_3SiCl	Reaction Temp.	Reaction Time	er
1	–78 °C	1.1	–78 °C	1h	91:9
2	–78 °C	0.1	–78 °C	1h	85:15
3	–78 °C	1.1	–100 °C	1h	94:6
4	–78 °C	0.1	–100 °C	10 min	86:14
5	–100 °C	1.1	–100 °C	1h	52:48
6	–100 °C	0.1	–100 °C	10 min	52:48

TABLE 3. Effect of Lithiation and Reaction Temperature on the Enantioselectivity of Lithiation−Substitution of 2 Using Benzyl Bromide as the Electrophile



2 (*S*)-**6**

Entry	Lithiation Temp.	equiv. $PhCH_2Br$	Reaction Temp.	Reaction Time	er
1	–78 °C	1.1	–78 °C	1h	83:17
2	–78 °C	0.1	–78 °C	1h	82:18
3	–78 °C	1.1	–100 °C	1h	85:15
4	–78 °C	0.1	–100 °C	10 min	85:15
5	–100 °C	1.1	–100 °C	1h	55:45
6	–100 °C	0.1	–100 °C	10 min	56:44

diastereomeric complexes are present and provide, on reaction with the electrophile, essentially racemic products. If these complexes were the same species that are present for entries 3 and 4, reaction with 0.1 equiv of the chlorotrimethylsilane should provide products enriched in the *R* isomer rather than the almost racemic products observed.

In an effort to clarify the source of this discrepancy, we have carried out an evaluation of the configurational stability of the epimeric center by generation of complexes with known configurations by tin−lithium exchanges. Tin−lithium exchange of (*S*)-**5** which has an er of 88:12 by *sec*-BuLi/**1** was carried out at −78 °C and −100 °C in 3:1 MTBE/THF prior to cooling to −100 °C. After lithiation at −78 °C and cooling to −100 °C, reaction with chlorotrimethylsilane at −100 °C provided (*S*)-**4** with a reduced er of 77:23. When the entire sequence was carried out at −100 °C, (*S*)-**4** was obtained with an even more reduced er of 63:37. In the later case recovered (*S*)-**5** had an er of 88:12. These results show that in the tin−lithium exchange epimerization does occur, and there is more epimerization at the carbanionic center at lower temperature. The pathway for the formation of the organolithium from Sn−Li/**1** exchange must be subtly different from the deprotonative pathway of **2** to form **3•1**. A rational possibility is that the initially formed organolithium from the tin−lithium exchange is relatively free of the ligand, and there is insufficient thermal energy to fully form the same complexes as from the deprotonative pathway. This indication of differences rationalizes the inconsistency of the "poor man's Hoffmann test" of entry 6 of Table 2. Whether this is an isolated case or a general phenomenon will require an investigation of the structures of these complexes and the relative rates of lithiation, epimerization, and complexation.[2,4,11]

In summary, asymmetric lithiation−substitution sequences of *N*-(2-phenylethyl)isobutyramide can be achieved at the benzylic position in the presence of (−)-sparteine to provide 2-substituted 2-phenylethylamines with good enantioenrichments in good yields. The reaction profile is consistent with a dynamic thermodynamic resolution, albeit with the formation of different species under different lithiation conditions.

Experimental Section

All lithiation−substitution reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen with freshly distilled solvents. Tetrahydrofuran (THF) and methyl *tert*-butyl ether (MTBE) were distilled from sodium and benzophenone. Dichloromethane was distilled from CaH_2. (−)-Sparteine (1) was obtained from a commercial source and distilled under reduced pressure over CaH_2 and stored under nitrogen. Commercial *sec*-BuLi (solution in cyclohexane) and *n*-BuLi (solution in hexane) were titrated prior to use against *N*-pivaloyl-*o*-toluidine according to literature procedure.[12] All other commercial reagents were used without further purification unless otherwise indicated.

(12) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

The purity of compounds reported herein is either established by CHN combustion analysis or high-resolution mass spectrometry (HRMS) supported by a ^{13}C NMR spectrum. In cases where microanalytical data was not available, the purity of compounds is estimated to be >95% based on ^{1}H and ^{13}C NMR spectroscopic data.

Product enantiomeric purity was determined by comparison of chiral stationary phase (CSP) HPLC traces of both racemic and enantioenriched compounds. Analytical CSP−HPLC was carried out using a Rainin HPLX pump system on either Whelk-O (Regis Chemical Co., 25 cm × 4.6 mm i.d.) or Chiralpak-AD (Chiral Technologies Inc. 25 cm × 4.6 mm i.d.) chiral columns. The obtained ers are given a degree of uncertainty of ±1%. Mixtures of 2-propanol and hexane were used as the mobile phase.

Optical rotations were obtained on a JASCO Model DIP-370 Digital Polarimeter (JASCO Inc., Easton, MD, 21601) in a cylindrical glass cell (3.5 mm i.d. × 50 mm) with quartz windows.

General Lithiation−Substitution Procedure for 2. To a flame-dried flask, purged with N_2 and charged with **2** (0.095 g, 0.50 mmol), were added MTBE (4.5 mL or 6 mL) and THF (1.5 mL or 2 mL), maintaining the concentration of **2** between 0.06 and 0.08 M, followed by (−)-sparteine (1) (0.25 mL, 1.09 mmol). The solution was cooled to −78 °C in a dry ice−acetone bath, and *sec*-BuLi (0.80 mL, 1.36 M in cyclohexane, 1.09 mmol) was added dropwise. The dark yellow reaction mixture was stirred at −78 °C for 1 h before the electrophile (1.1−1.2 equiv) was added. The reaction was quenched with 2 mL of CH_3OH after stirring at −78 °C for an additional 1 h. Stirring was continued as the solution was allowed to warm to room temperature. The solution was poured into 5% H_3PO_4 (10 mL), and 10 mL of ether was added. The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined ether layers were dried over $MgSO_4$, and the solvent was removed in vacuo to afford the crude product. Racemic compounds were prepared using a similar procedure with TMEDA as the ligand.

(*S*)-*N*-(2-Trimethylsilyl-2-phenylethyl)isobutyramide (4). The general lithiation procedure was followed using 1.1 equiv of chlorotrimethylsilane (70.0 μL, 0.55 mmol) as the electrophile to provide crude (*S*)-**4**. The crude product was purified using flash chromatography (40% EtOAc/hexane) to give (*S*)-**4** (131 mg, 90%) as a white solid, mp 72−73 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ -0.02 (s, 9H, $Si(CH_3)_3$), 0.97 (d, J = 7.8 Hz, 3H, $CHCH_3$), 0.99 (d, J = 7.0 Hz, 3H, $CHCH_3$), 2.13 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 2.34 (dd, J = 12.6, 4.2 Hz, 1H, $PhCHCH_2N$), 3.57 (td, J = 13.4, 4.0 Hz, 1H, PhCHCHHN), 3.85 (ddd, J = 14.0, 6.3, 4.3 Hz, 1H, PhCHCHHN), 5.25 (bs, 1H, NH), 7.02−7.29 (m, 5H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.09 (CH_3), 19.28 (CH_3), 19.36 (CH_3), 35.34 (CH), 37.34 (CH), 39.15 (CH_2), 125.04 (Ar−H), 127.56 (Ar−H), 128.33 (Ar−H), 140.49 (Ar), 176.85 (C=O). Anal. Calcd %C: 68.39, %H: 9.56, %N: 5.32. Found %C: 68.35, %H: 9.38, %N: 5.52. The enantiomeric ratio of (*S*)-**4** was determined to be 91:9 by CSP−HPLC on a Whelk-O column with 5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 14.1 and 16.2 min, respectively.

(*S*)-*N*-(2-Tributylstannyl-2-phenylethyl)isobutyramide (5). The general lithiation procedure was followed using Bu_3SnCl as the electrophile to provide crude (*S*)-**5**. The crude product was purified using flash chromatography (25% EtOAc/hexane) to give (*S*)-**5** (200 mg, 86%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.80 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.84 (t, J = 7.2 Hz, 9H, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.99 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.01 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.23 (sext, J = 7.3 Hz, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.37 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$), 2.16 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 2.77 (dd, J = 12.6, 5.0 Hz, 1H, $PhCHCH_2N$), 3.75−3.90 (m, 2H, $PhCHCH_2N$), 5.35 (bs, 1H, NH), 7.01−7.24 (m, 5H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.92 (CH_2), 13.56 (CH), 19.46 (CH_3), 19.50 (CH_3), 27.32 (CH_2), 28.88 (CH_2) 33.64 (CH_3), 35.50 (CH), 40.80 (CH_2), 124.10 (Ar−H), 126.28 (Ar−H), 128.56 (Ar−H), 143.33 (Ar), 176.79 (C=O). Anal. Calcd %C: 60.01, %H: 9.02, %N: 2.92. Found %C: 60.08, %H: 9.37, %N: 3.09. The enantiomeric ratio of (*S*)-**5** was determined to be 88:12 by CSP−HPLC on a Whelk-O column with 1.5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 21.9 and 24.1 min, respectively.

(*S*)-*N*-(2,3-Diphenylpropyl)isobutyramide (6). The general lithiation procedure was followed using benzyl bromide as the electrophile to provide crude (*S*)-**6**. The crude product was flushed through a plug of silica with EtOAc and purified using HPLC (50% EtOAc/hexane) to give (*S*)-**6** (115 mg, 82%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.00 (d, J = 6.8 Hz, 3H, $CHCH_3$), 2.14 (sept, J = 7.0 Hz, 1H, $CH(CH_3)_2$), 2.93 (m, 1H, $PhCH_2$), 3.12 (m, 1H, $PhCHCH_2N$), 3.33 (ddd, J = 13.4, 9.2, 5.1 Hz, 1H, PhCHCHHN), 3.71 (ddd, J = 13.2, 6.5, 5.7 Hz, 1H, PhCHCHHN), 5.26 (bs, 1H, NH), 7.05−7.31 (m, 10H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.28 (CH_3), 19.40 (CH_3), 35.37 (CH), 40.65 (CH_2), 43.99 (CH_2), 47.29 (CH), 125.95 (Ar−H), 126.70 (Ar−H), 127.72 (Ar−H), 128.11 (Ar−H), 128.46 (Ar−H), 128.87 (Ar−H), 139.39 (Ar), 141.97 (Ar), 176.71 (C=O). Anal. Calcd %C: 81.10, %H: 8.24, %N: 4.98. Found %C: 80.99, %H: 8.18, %N: 5.08. The enantiomeric ratio of (*S*)-**6** was determined to be 83:17 by CSP−HPLC on a Whelk-O column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 16.3 and 18.7 min, respectively.

(*S*)-*N*-(2-Phenyl-4-pentenyl)isobutyramide (7). The general lithiation procedure was followed using allyl bromide as the electrophile to provide crude (*S*)-**7**. The crude product was purified using flash chromatography (50% EtOAc/hexane) to give (*S*)-**7** (78 mg, 68%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.04 (d, J = 6.8 Hz, 3H, $CHCH_3$), 2.19 (sept, J = 6.8 Hz, 1H, $CH(CH_3)_2$), 2.40 (m, 2H, $CH_2CH{=}CH_2$), 2.88 (quint, J = 7.4 Hz, 1H, $PhCHCH_2N$), 3.20 (ddd, J = 13.4, 9.0, 4.6 Hz, 1H, PhCHCHHN), 3.74 (ddd, J = 13.6, 7.1, 5.9 Hz, 1H, PhCHCHHN), 4.97 (m, 2H, $CH_2CH{=}CH_2$), 5.32 (bs, 1H, NH), 5.68 (m, 1H, $CH_2CH{=}CH_2$), 7.16−7.34 (m, 5H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.42 (CH_3), 19.56 (CH_3), 35.54 (CH), 38.24 (CH_2), 44.15 (CH_2), 45.37 (CH), 116.58 (CH_2), 126.78 (Ar−H), 127.75 (Ar−H), 128.61 (Ar−H), 135.83 (CH), 142.16 (Ar), 176.75 (C=O). HRMS (EI) $C_{15}H_{21}NO$: Calcd 231.1623 Found 231.1623 The enantiomeric ratio of (*S*)-**7** was determined to be 91:9 by CSP−HPLC on a Chiralpak-AD column with 5% IPA/hexane mobile phase; retention times for the major and minor enantiomers were 11.3 and 18.3 min, respectively.

(*S*)-*N*-(2-Phenylbutyl)isobutyramide (8). The general lithiation procedure was followed using ethyl iodide as the electrophile to provide crude (*S*)-**8**. The crude product was purified using prep-HPLC (45% EtOAc/hexane) to give (*S*)-**8** (61 mg, 73%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.80 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.00 (d, J = 7.3 Hz, 3H, $CHCH_3$), 1.02 (d, J = 7.1 Hz, 3H, $CHCH_3$), 1.58 (m, 1H, $CHHCH_3$), 1.70 (m, 1H, $CHHCH_3$), 2.18 (sept, J = 6.8 Hz, 1H, $CH(CH_3)_2$), 2.67 (tt, J = 9.4, 5.0 Hz, 1H, $PhCHCH_2N$), 3.16 (ddd, J = 13.3, 9.4, 4.6 Hz, 1H, PhCHCHHN), 3.71 (ddd, J = 13.4, 7.1, 5.9 Hz, 1H, PhCHCHHN), 5.32 (bs, 1H, NH), 7.13−7.32 (m, 5H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.80 (CH_3), 19.39 (CH_3), 19.54 (CH_3), 26.62 (CH_2), 35.49 (CH), 44.44 (CH_2), 47.50 (CH), 126.60 (Ar−H), 127.78 (Ar−H), 128.53 (Ar−H), 142.57 (Ar), 176.71 (C=O). HRMS (EI) $C_{14}H_{21}NO$: Calcd 219.1623 Found 219.1623 The enantiomeric ratio of (*S*)-**8** was determined to be 88:12 by CSP−HPLC on a Whelk-O column with 2.5% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 40.8 and 43.5 min, respectively.

(*S*)-*N*-(2-(1′-Cyclohexanol)-2-phenylethyl)-isobutyramide (9). The general lithiation procedure was followed using cyclohexanone as the electrophile to provide crude (*S*)-**9**. The crude product was purified using flash chromatography (3%

MeOH/ CH_2Cl_2) to give (*S*)-**9** (84 mg, 58%) as a white solid, mp 143−145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (d, J = 6.8 Hz, 3H, $CHCH_3$), 0.98 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.64 (bs, 1H, OH), 1.10−1.80 (m, 10H, $(CH_2)_5$), 2.14 (sept, J = 6.8 Hz, 1H, $CH(CH_3)_2$), 2.87 (dd, J = 10.0, 5.1 Hz, 1H, $PhCHCH_2N$), 3.48 (ddd, J = 14.2, 9.8, 4.4 Hz, 1H, PhCHCHHN), 4.00 (ddd, J = 13.1, 6.5, 5.3 Hz, 1H, PhCHCHHN), 5.42 (bs, 1H, NH), 7.25−7.33 (m, 5H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.28 (CH_3), 19.54 (CH_3), 21.71 (CH_2), 21.87 (CH_2), 25.52 (CH_2), 35.52 (CH), 36.00 (CH_2), 36.04 (CH_2), 37.34 (CH), 39.13 (CH_2), 72.89 (CH), 127.01 (Ar−H), 128.37 (Ar−H), 129.67 (Ar−H), 139.48 (Ar). Anal. Calcd %C: 74.70, %H: 9.26, %N: 4.84. Found %C: 74.58, %H: 9.51, %N: 4.99. The enantiomeric ratio of (*S*)-**9** was determined to be 72:28 by CSP−HPLC on a Chiralpak-AD column with 10% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 11.1 and 12.8 min, respectively.

(2*S*)-*N*-(3-Hydroxy-2,3-diphenylethyl)isobutyramide (10). The general lithiation procedure was followed using benzaldehyde as the electrophile to provide crude (2*S*)-**10**. The crude product was purified using prep-HPLC (70% EtOAc/hexane) to give two diastereomers of (2*S*)-**10** in a dr of 79:21 (82 mg, 70%) as viscous oils. ^{1}H NMR major diastereomer ($CDCl_3$, 400 MHz): δ 1.06 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.08 (d, J = 6.9 Hz, 3H, $CHCH_3$), 2.28 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.10 (dt, J = 8.6, 5.6 Hz, 1H, $PhCHCH_2N$), 3.51 (dt, J = 13.9, 5.2 Hz, 1H, PhCHCHHN), 3.72 (bs, 1H, OH), 3.92 (dt, J = 14.1, 6.5 Hz, 1H, PhCHCHHN), 4.81 (d, J = 8.6 Hz, 1H, PhCHOH), 6.01 (bs, 1H, NH), 7.02−7.20 (m, 10H, Ar−H). ^{13}C NMR major diastereomer ($CDCl_3$, 100 MHz): δ 19.34 (CH_3), 19.53 (CH_3), 35.47 (CH), 41.62 (CH_2), 53.29 (CH), 75.96 (CH), 126.53 (Ar−H), 126.76 (Ar−H), 127.21 (Ar−H), 127.94 (Ar−H), 128.35 (Ar−H), 128.44 (Ar−H), 140.09 (Ar), 142.46 (Ar), 177.94 (C═O). Anal. Calcd %C: 76.74, %H: 7.80, %N: 4.71. Found major diastereomer %C: 76.55, %H: 7.58, %N: 4.66. The enantiomeric ratio of the major diastereomer of (2*S*)-**10** was determined to be 78:22 by CSP−HPLC on a Whelk-O column with 15% IPA/hexane mobile phase; retention times for the major and minor enantiomers were 10.6 and 13.5 min, respectively.

^{1}H NMR minor diastereomer ($CDCl_3$, 400 MHz): δ 1.04 (d, J = 7.1 Hz, 3H, $CHCH_3$), 1.05 (d, J = 7.1 Hz, 3H, $CHCH_3$), 2.32 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.07 (td, J = 7.8, 5.9 Hz, 1H, $PhCHCH_2N$), 3.33 (ddd, J = 13.8, 7.4, 5.6 Hz, 1H, PhCHCHHN), 3.76 (ddd, J = 13.9, 8.2, 6.8 Hz, 1H, PhCHCHHN), 4.89 (d, J = 5.7 Hz, 1H, PhCHOH), 5.72 (bs, 1H, NH), 7.13−7.32 (m, 10H, Ar−H).

***N*-(2-(*m*-Methoxyphenylethyl)isobutyramide (14).** To a solution of CH_2Cl_2 (400 mL) and triethylamine (50 mL) was added *m*-methoxyphenethylamine (25 g, 165 mmol) followed by dropwise addition of isobutyryl chloride (18.5 mL, 177 mmol) in CH_2Cl_2 (170 mL). The reaction mixture was allowed to stir at room temperature for 24 h. The solution was poured into 2 M HCl (∼500 mL), the layers were separated, and the CH_2Cl_2 layer was washed with 5% $NaHCO_3$ (∼200 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to provide an off-white solid. The crude product was recrystallized from hexane/ethyl acetate to provide pure **14** (31.3 g, 86%), mp 57−58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 2.28 (sept, J = 6.8 Hz, 1H, $CH(CH_3)_2$), 2.76 (t, J = 7.1 Hz, 2H, $PhCH_2CH_2N$), 3.45 (q, J = 6.5 Hz, 2H, $PhCH_2CH_2N$), 3.74 (s, 3H, OCH_3), 5.93 (bs, 1H, NH), 6.70−6.75 (m, 3H, Ar−H), 7.18 (t, J = 7.8 Hz, 1H, Ar−H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.43 (CH_3), 35.32 (CH), 35.57 (CH_2), 40.25 (CH_2), 54.92 (CH_3), 111.62 (Ar−H), 114.24 (Ar−H), 120.91 (Ar−H), 129.36 (Ar−H), 140.46 (Ar), 159.59 (Ar), 176.91 (C═O). Anal. Calcd %C: 70.56, %H: 8.65, %N: 6.33. Found %C: 70.61, %H: 8.67, %N: 6.47.

(*S*)-*N*-(2-*m*-Methoxyphenyl-3-phenylpropyl)isobutyramide (15). The general lithiation procedure of **2** was utilized for the lithiation-substitution of **14** using benzyl bromide as the electrophile to provide crude (*S*)-**15**. The crude product was purified using flash chromatography (40% EtOAc/hexane) to give (*S*)-**15** (134 mg, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.04 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.06 (d, J = 6.6 Hz, 3H, $CHCH_3$), 2.19 (sept, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 2.95 (m, 2H, $PhCH_2$), 3.13 (m, 1H, $ArCHCH_2N$), 3.35 (ddd, J = 13.4, 9.3, 4.9 Hz, 1H, ArCHCHHN), 3.75 (ddd, J = 13.4, 6.7, 5.7 Hz, 1H, ArCHCHHN), 3.80 (s, 3H, OCH_3), 5.33 (bs, 1H, NH), 6.71−6.82 (m, 3H, Ar−H), 7.10−7.30 (m, 6H, Ar−H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.66 (CH_3), 19.81 (CH_3), 35.79 (CH), 40.97 (CH_2), 44.23 (CH_2), 47.66 (CH), 55.39 (CH_3), 112.31 (Ar−H), 113.91 (Ar−H), 120.40 (Ar−H), 126.39 (Ar−H), 128.54 (Ar−H), 129.28 (Ar−H), 129.87 (Ar−H), 139.75 (Ar), 144.09 (Ar), 160.03 (Ar), 177.04 (C═O). HRMS (EI) $C_{20}H_{25}NO_2$: Calcd 311.1885 Found 311.1878 The enantiomeric ratio of (*S*)-**15** was determined to be 89:11 by CSP−HPLC on a Whelk-O column with 8% IPA/hexane mobile phase; retention times for the minor and major enantiomers were 31.6 and 35.3 min, respectively.

(*S*)-*N*-(2-(*m*-Methoxyphenyl)-3-phenylpropylamine Hydrochloride Salt (16). To a flask containing (*S*)-**15** (6.10 g, 19.59 mmol) dissolved in THF (150 mL) at −78 °C was added *n*-BuLi (1.5 M, 15.0 mL, 22.50 mmol). After the solution was allowed to stir for 2 h, Boc anhydride (5.0 mL, 21.74 mmol) was added. The solution was allowed to slowly warm to room temperature, and stirring was continued for 12 h. The solution was poured into water (150 mL), the layers were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The ethereal layers were combined, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to provide crude the crude Boc-amide. The crude Boc-amide was dissolved in dioxane (150 mL). To the solution was added aqueous KOH (16.48 g, 294 mmol in 100 mL of H_2O). The reaction mixture was stirred at reflux for 18 h. The solution was poured into H_2O (200 mL) and then extracted with ether (3 × 100 mL). The ethereal layers were combined, dried ($MgSO_4$), and filtered. The solvent was removed in vacuo to provide the crude Boc-amine. To the crude Boc-amine dissolved in EtOAc (200 mL) was added EtOH (11.0 mL, 190 mmol). The solution was cooled to 0 °C, and acetyl chloride (13.5 mL, 190 mmol) was added dropwise. The solution was allowed to slowly warm to room temperature, and stirring was continued for 19 h. The solution was concentrated in vacuo to approximately one-half the original volume. EtOAc (50 mL) was added to the heterogeneous mixture followed by cooling to −25 °C. The mixture was stirred at −25 °C for 10 min, and the solid was isolated by filtration (washing with cold EtOAc) to provide pure (*S*)-**16** (5.085 g, 77%), mp 141−143 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.82 (dd, J = 13.7, 9.0, Hz, 1H, ArCHCHHN), 3.01 (d, J = 7.3 Hz, 2H, $PhCH_2$), 3.12 (dd, J = 13.7, 6.3 Hz, 1H, ArCHCHHN), 3.27 (quint, J = 7.0 Hz, 1H, $ArCHCH_2N$), 3.70 (s, 3H, OCH_3), 6.75−6.82 (m, 3H, Ar−H), 7.07−7.21 (m, 6H, Ar−H), 8.19 (bs, 3H, NH_3^+). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.59 (CH_2), 43.93 (CH_2), 45.68 (CH), 55.63 (CH_3), 113.06 (Ar−H), 114.42 (Ar−H), 120.95 (Ar−H), 126.69 (Ar−H), 128.80 (Ar−H), 129.63 (Ar−H), 130.20 (Ar−H), 139.93 (Ar), 142.79 (Ar), 159.97 (Ar), 172.73 (C═O). Anal. Calcd %C: 69.18, %H: 7.26, %N: 5.04. Found %C: 69.25, %H: 7.28, %N: 5.17.

(*S*)-*N*-(2-(*m*-Methoxyphenyl)-3-phenylpropyl)benzamide (17). To a solution of CH_2Cl_2 (40 mL) and triethylamine (3.0 mL) was added (*S*)-**16** (1.211 g, 4.36 mmol). The solution was cooled to 0 °C followed by dropwise addition of benzoyl chloride (0.60 mL, 5.17 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was allowed to stir at room temperature for 24 h. The solution was poured into 2 M HCl (∼50 mL), the layers were separated, and the CH_2Cl_2 layer was washed with 5% $NaHCO_3$ (∼20 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to provide crude (*S*)-**17**. The crude product was purified using flash chromatography (30% EtOAc/hexane) to give (*S*)-**17** (1.469 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.01 (m, 2H, $PhCH_2$), 3.24 (m, 1H, $ArCHCH_2N$), 3.55 (ddd, J = 13.5, 8.9, 4.9 Hz, 1H, ArCHCHHN), 3.77 (s, 3H, OCH_3), 3.93 (dt, J = 13.5, 6.3 Hz, 1H, ArCHCHHN), 6.07 (bs,

1H, NH), 6.75−6.83 (m, 3H, Ar−H), 7.12−7.57 (m, 11H, Ar−H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 40.65 (CH_2), 44.65 (CH_2), 47.32 (CH), 55.06 (CH_3), 112.15 (Ar−H), 113.51 (Ar−H), 120.02 (Ar−H), 126.11 (Ar−H), 128.28 (Ar−H), 128.37 (Ar−H), 128.96 (Ar−H), 129.67 (Ar−H), 131.24 (Ar−H), 134.48 (Ar), 139.41 (Ar), 143.71 (Ar), 159.77 (Ar), 167.28 (C═O). HRMS (EI) $C_{23}H_{23}NO_2$: Calcd 345.1729 Found 345.1721.

(*S*)-4-Benzyl-6-methoxy-1-isopropyl-3,4-dihydroisoquinoline (18). In a round-bottom flask was dissolved (*S*)-**15** (134 mg, 0.43 mmol) in CH_3CN (8 mL). The solution was cooled to 0 °C, and phosphorus pentachloride (716 mg, 3.44 mmol) was added in three portions, allowing the solution to warm to room temperature between each addition. After the reaction mixture was stirred at room temperature for 14 h and cooled to 0 °C, NaOH was added (10 mL, 6 M). The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined CH_2Cl_2 layers were dried over Na_2SO_4, and the solvent removed in vacuo to afford crude (*S*)-**18**. The crude product was purified using flash chromatography (60:35:5 hexane/EtOAc/Et_3N) to give (*S*)-**18** (116 mg, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (d, J = 6.8 Hz, 3H, $CHCH_3$), 1.28 (d, J = 6.6 Hz, 3H, $CHCH_3$), 2.65−2.82 (m, 3H, ArCH, $PhCH_2$), 3.29 (sept, J = 6.7 Hz, 1H, $CH(CH_3)_2$), 3.42 (ddd, J = 15.5, 5.2, 1.4 Hz, 1H, ArCHCHHN), 3.71 (s, 3H, OCH_3), 3.89 (dd, J = 15.6, 3.2 Hz, 1H, PhCHCHHN), 6.41 (d, J = 2.7 Hz, 1H, Ar−H), 6.80 (dd, J = 8.5, 2.7 Hz, 1H, Ar−H), 7.07 (m, 2H, Ar−H), 7.17−7.28 (m, 3H, Ar−H), 7.50 (d, J = 8.5 Hz, 1H, Ar−H). ^{13}C NMR: δ 20.17 (CH_3), 21.43 (CH_3), 31.51 (CH), 38.73 (CH_2), 38.78 (CH), 50.08 (CH_2), 55.11 (CH_3), 112.28 (Ar−H), 112.54 (Ar−H), 121.34 (Ar), 126.01 (Ar−H), 126.52 (Ar−H), 128.17 (Ar−H), 128.93 (Ar−H), 129.23 (Ar−H), 139.69 (Ar), 143.54 (Ar), 160.49 (Ar), 170.80 (C═N). HRMS (EI) $C_{20}H_{23}NO$: Calcd 293.1780 Found 293.1780.

(*S*)-4-Benzyl-6-methoxy-1-phenyl-3,4-dihydroisoquinoline (19). In a round-bottom flask was dissolved (*S*)-**17** (1.423 g, 4.12 mmol) in CH_3CN (70 mL). The solution was cooled to 0 °C, and phosphorus pentachloride (6.835 g, 32.8 mmol) was added in three portions, allowing the solution to warm to room temperature between each addition. After the reaction mixture was stirred at room temperature for 14 h and cooled to 0 °C, NaOH was added (70 mL, 6 M). The reaction mixture was stirred at 0 °C for 1 h followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude (*S*)-**19**. The crude product was purified using flash chromatography (solvent gradient, 10% EtOAc/hexane increased to 35% EtOAc/hexane) to give (*S*)-**19** (1.291 g, 96%) as a yellow oil. ^{1}H NMR (acetone-d_6, 500 MHz): δ 2.74 (dd, J = 13.3, 9.0 Hz, 1H, PhCHH), 2.89 (dd, J = 13.2, 6.8 Hz, 1H, PhCHH), 2.98 (m, 1H, $PhCH_2CH$), 3.46 (dd, J = 15.7, 5.4 Hz, 1H, CHCHHN), 3.75 (s, 3H, OCH_3), 3.95 (dd, J = 15.7, 3.4 Hz, 1H, CHCHHN), 6.73 (d, J = 2.8 Hz, 1H, Ar−H), 6.81 (dd, J = 8.6, 2.6 Hz, 1H, Ar−H), 7.16−7.29 (m, 6H, Ar−H), 7.43−7.46 (m, 3H, Ar−H), 7.60−7.62 (m, 2H, Ar−H). ^{13}C NMR (acetone-d_6, 125 MHz): δ 39.59 (CH_2), 39.59 (CH), 51.87 (CH_2), 55.94 (CH_3), 112.95 (Ar−H), 113.87 (Ar−H), 122.45 (Ar), 127.21 (Ar−H), 129.09 (Ar−H), 129.36 (Ar−H), 129.41 (Ar−H), 129.94 (Ar−H), 130.12 (Ar−H), 130.43 (Ar−H), 130.54 (Ar−H), 140.79 (Ar), 141.13 (Ar), 145.61 (Ar), 162.38 (Ar), 162.38 (Ar), 166.88 (C═N). HRMS (EI) $C_{23}H_{21}NO$ (M-1 scanned): Calcd 326.1545 Found 326.1537.

(4*S*)-4-Benzyl-6-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (20). In a round-bottom flask was dissolved (*S*)-**19** (0.1251 g, 0.38 mmol) in MeOH (2.0 mL). The solution was cooled to 0 °C, and $NaBH_4$ (41.6 m g, 1.10 mmol) was added. The reaction mixture was stirred at 0 °C for 18 h. The reaction mixture was concentrated in vacuo followed by addition of H_2O (∼10 mL). The aqueous solution was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ layers were dried over Na_2SO_4, and the solvent was removed in vacuo to afford crude (4*S*)-**20**. The crude product was purified using prep-HPLC (50% EtOAc/hexane) to give a diastereomixture of (4*S*)-**20** (101.9 mg, 81%, 95:5 dr by ^{1}H NMR) as a yellow oil. ^{1}H NMR major diastereomer ($CDCl_3$, 400 MHz): δ 1.84 (bs, 1H, NH), 3.03 (m, 1H, $PhCH_2CH$), 3.13 (d, J = 2.9 Hz, 2H, $PhCH_2$), 3.17 (dd, J = 13.4, 5.4 Hz, 1H, CHCHHN), 3.30 (dd, J = 13.4, 9.8 Hz, 1H, CHCHHN), 3.76 (s, 3H, OCH_3), 5.06 (s, 1H, PhCHN), 6.69 (m, 3H, Ar−H), 7.28−7.40 (m, 11H, Ar−H). ^{13}C NMR major diastereomer ($CDCl_3$, 100 MHz): δ 40.75 (CH), 42.66 (CH_2), 45.90 (CH_2), 55.05 (CH_3), 62.46 (CH), 112.40 (Ar−H), 113.42 (Ar−H), 125.99 (Ar−H), 127.35 (Ar−H), 128.30 (Ar−H), 128.36 (Ar−H), 128.90 (Ar−H), 128.95 (Ar−H), 129.46 (Ar−H), 130.88 (Ar), 140.30 (Ar), 140.69 (Ar), 145.17 (Ar), 157.54 (Ar). HRMS (EI) $C_{23}H_{23}NO$ (M-1 scanned): Calcd 328.1701 Found 328.1698.

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Supporting Information Available: Experimental procedures for the synthesis of starting materials, absolute configuration determination, and mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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