Asymmetric Synthesis of 4-Hydroxy-3-phenyltetrahydroisoquinoline Derivatives Using Enantiopure Sulfinimines (*N*-Sulfinyl Imines)

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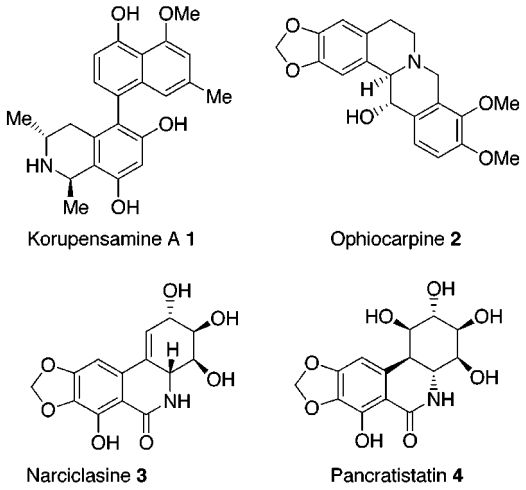
Addition of lateral lithiated amides and phthalide anions to enantiopure sulfinimines (*N*-sulfinyl imines) represents a new approach for the asymmetric synthesis of 3-substituted isoquinolones and 3-substituted 4-hydroxy isoquinolones, respectively, important chiral building blocks for isoquinoline alkaloid synthesis. In one example 3-phenylisoquinolone (−)-**15b** was prepared in >95% ee by treatment of amide ion **10b** with sulfinimine (*S*)-(+)-**11** and subsequent deprotection of the *N*-sulfinyl auxiliary and cyclization. Oxaziridine-mediated hydroxylation of the anion of **16** afforded 4-hydroxy isoquinolone **19**, which was transformed into 4-hydroxy-3-phenyltetrahydroisoquinoline (−)-**22**. In another approach **22** was prepared more directly by addition of phthalide ion **26** to (*S*)-(+)-**11**, creating the two stereogenic centers simultaneously. The selectivity proved to be highly counterion dependent.

Interest in 3-substituted 1,2,3,4-tetrahydroisoquinolines stems from their unique structure and diverse biological properties. Relevant examples include korupensamine A (**1**), ophiocarpine (**2**), and narciclasine (**3**), members of the naphthylisoquinoline,[1] protoberberine,[2] and amaryllidaceae[3] families, respectively (Scheme 1). Korupensamine A (**1**) is a subunit of the michellamines, which protect against HIV by inhibiting viral reverse transcriptase and cellular fusion.[1,4] Other naphthylisoquinolines show antimalarial, antifeedant, fungicidal, molluscicidal, and larvicidal properties.[1] The protoberberine alkaloids such as ophiocarpine (**2**) are widely distributed in nature and exhibit diverse biological activities.[2] Importantly, they also serve as the biosynthetic and synthetic precursors of related structures, including protopine, phthalidesioquinolines, and spirobenzylisoquinoline.[2a] The amaryllidaceae alkaloids narciclasine (**3**) and pancratistatin (**4**) are powerful antitumor agents that inhibit eukaryotic protein synthesis at the ribosomal level.[3]

Scheme 1



The cyclization of *β*-arylethylamino derivatives using the Bishler−Napieralski (B−N) and Pictet−Spengler (P−S) protocols has been the most widely employed route to isoquinolines.[1,5] Because nitrilium ion intermediates are involved, side reactions occur, and there are difficulties in controlling the regio- and stereoselective formation of the isoquinoline ring.[6,7] In the asymmetric synthesis of isoquinolines, the enantioselective synthesis of the *β*-arylethylamino precursors, as well as the compatibility of functionalized derivatives with the harsh B−N and P−S conditions,[5] can be a problem.

3-Substituted 1(2*H*)-isoquinolones **6** are potentially important chiral building blocks for the asymmetric construction of isoquinolines because they can be reductively transformed into a variety of substituted 1,2,3,4-tetrahydroisoquinolines **5** (Scheme 2). Clark and Jahangir described the synthesis of **6** by condensation of lateral lithiated amides **8**[8] with racemic imines.[9,10] This proce-

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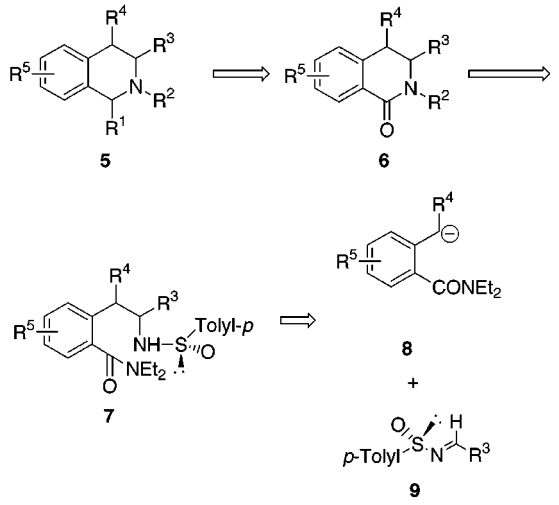
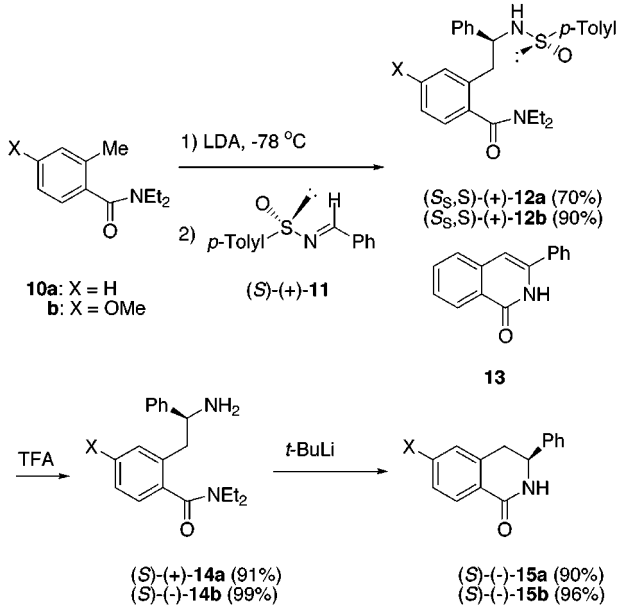
Scheme 2



Scheme 3



dure avoids many of the limitations of the B−N and P−S protocols and should provide isoquinolines with substitution patterns not readily accessible by other means. What has undoubtedly prevented the general application of this methodology to the asymmetric synthesis of **6** is the unreactivity of imines, the propensity of aliphatic examples to undergo α-deprotonation rather than addition, and the lack of suitable chiral examples.

Recent studies in our laboratory and elsewhere have demonstrated that the *N*-sulfinyl group in sulfinimines (*N*-sulfinyl imines) **9** is superior to other imine auxiliaries because it activates the C=N bond for addition to such an extent that α-deprotonation is not an important issue.[11−19] It is highly stereodirecting and easily removed under mild acidic conditions. We describe here the utility of sulfinimines for the asymmetric synthesis of new 1(2*H*)-isoquinolone **6** building blocks and their elaboration into 4-hydroxy-3-phenyltetrahydroisoquinoline derivatives, which are potential precursors of the 13-hydroxyprotoberberine alkaloids.[20]

Results and Discussion

From Lateral Lithiated Amides. Initially the addition of the lateral lithiated amide generated from *N*,*N*-diethyl-*o*-toluamide (**10a**) to (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**11**) was explored.[21] Thus, treatment of **10a** with 2 equiv of LDA at −78 °C gave an intensely colored burgundy solution of the lateral lithiated amide to which was added 1 equiv of (+)-**11** (Scheme 3). The desired sulfinamide (+)-**12a** was obtained in only 24% yield, and 3-phenyl-1(2*H*)-isoquinolone (**13**) was also isolated in 26% yield. Sulfinamide **12a** cannot be the source **13** because reaction with base, under the reaction conditions, produced none of the isoquinolone. However, Poindexter reported that **13** is formed by reaction of the amide ion of **10a** with benzonitrile.[22] Indeed, treatment of sulfinimine **11** with 2.0 equiv of LDA at −78 °C resulted in 1,2-elimination of *p*-toluenesulfenic acid anion (*p*-tolylSO$^-$) with formation of benzonitrile in 27% and 36% yield (HPLC) after 20 and 50 min, respectively.

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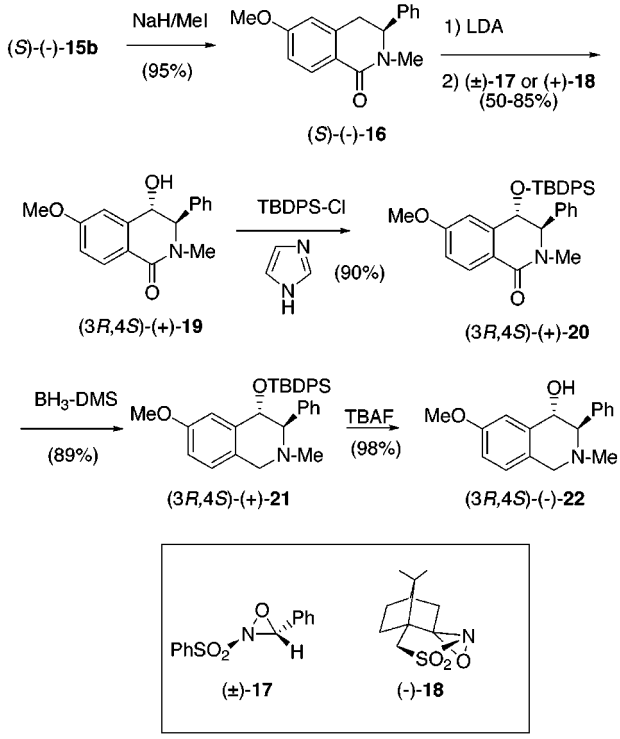
When 1.2 equiv of LDA was used to generate the anion of **10a**, the yield of (+)-**12a** increased to 70%. It proved difficult to determine the diastereomeric purity of sulfinamide (+)-**12a** by NMR. However, amine **14a** was obtained in >95% yield by treatment of **12a** with TFA/MeOH, and preparation of the Mosher amide from **14a** indicated that sulfinamide **12a** was formed as a single diastereoisomer (i.e., >95% de). Cyclization of **14a** to the isoquinolone (−)-**15a** was accomplished by treatment with 3 equiv of *tert*-butyllithium. Attempts to directly convert **12** to **15** under these conditions was unsuccessful, most likely as a result of the stability of the *N*-sulfinylamine anion.

Because suitable crystals for X-ray analysis of **12a** could not be obtained, it was necessary to determine the absolute configuration of the new stereogenic center by chemical means. In this context the enantioselective synthesis of 4-hydroxy-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**21**) was undertaken. Dominguez and co-workers reported the asymmetric synthesis of (3*S*,4*R*)-(+)-**22** in a series of steps from an enzyme-resolved cyanohydrin.[23] Hydroxy isoquinolines are potential precursors of the 13-hydroxyprotoberberines such as ophiocarpine (**2**) and exhibit diverse biological activities.[24−26]

Synthesis of the 6-methoxy analogue **15b** was accomplished in 86% yield for the three steps as outlined in Scheme 3. Interestingly, it was found that when about 50% of sulfinimine (+)-**11** was added to the lateral lithiated amide of **10b**, the color of the anion discharged.[27] If an additional equivalent of LDA was added, followed by the rest of (+)-**11**, the yield of sulfinamide (+)-**12b** was 85−90%, obtained as a single isomer.[27] Removal of the auxiliary and cyclization gave **15b** in 86% overall yield, which was *N*-methylated with NaH/MeI (Scheme 4). To introduce the C-4 hydroxy group into (−)-**16** we planned to carry out an oxaziridine-mediated hydroxylation of the corresponding C-4 anion, which was generated with 3 equiv of LDA.[28] Treatment with (±)-2-(phenylsulfonyl)-3-phenyloxaziridine **17**[20] or (camphorylsulfonyl)oxaziridine (−)-**18** afforded (+)-**19** as a single hydroxy diastereoisomer in 85% yield. The trans selectivity is consistent with our earlier findings that the hydroxylation stereochemistry is controlled by nonbonded steric interactions in the transition state such that the oxygen of the oxaziridine is delivered from the sterically least hindered direction[28a] and also is in agreement with the small 3,4-coupling constant of 2.1 Hz in (+)-**19**.[29] The synthesis of

Scheme 4



22 was completed by silylation with TBDPSCl/imidazole, reduction with BH_3·DMS, and desilylation with tetrabutylammonium fluoride (TBAF) to give (3*R*,4*S*)-(−)-**22** in 78% yield for the three steps. The enantiomeric purity of **22** was >95% ee as determined by a chiral shift ^{1}H NMR (500 MHz) experiment using Eu(hfc)$_3$. The spectral properties of this compound were identical in all respects with those reported previously, except that it had the opposite but equal sign of rotation. Therefore, the configuration of the initially formed stereocenter in sulfinamide (+)-**12b** and by analogy to (+)-**12a** is *S*.

Mechanistic details of heteroatom-facilitated lateral lithiation reactions are unknown.[8] However, studies by Beak et al.[30] and others[8] suggest that these species can be represented as *o*-quinodimethane resonance structures, e.g., **23** (Scheme 5). This is based on the intense colors of these anions, consistent with electronic delocalization, and the fact that *N*-ethyl-2-isopropylbenzamide does not form a tertiary benzylic species. In the latter example steric hindrance may inhibit formation of the planar anion. Steric and chelation control arguments have been used to rationalize the asymmetric induction for addition of organometallic reagents to sulfinimines with regard to the participation of the chiral sulfinyl group. Enolates,[14,17] allyl[14h] and alkyl[13d] Grignard reagents, DIBAL-H,[12c,14h] and Et_2AlCN[13b,c] are suggested to react with sulfinimines via six-membered chairlike transition states in which the metal ion is chelated to the sulfinyl oxygen. However, steric arguments have been evoked to explain the stereochemistry for additions of benzyl Grignard,[13a,c] metal phosphites,[15] α-metallo phosphonates,[16] chloromethyl phosphonate anions,[19] and 1,3-dipoles[18d] to sulfinimines. On the basis of these considerations and the assumption that the sulfinimine has the *E* geometry,[15a,21] a plausible rationalization for the pref-

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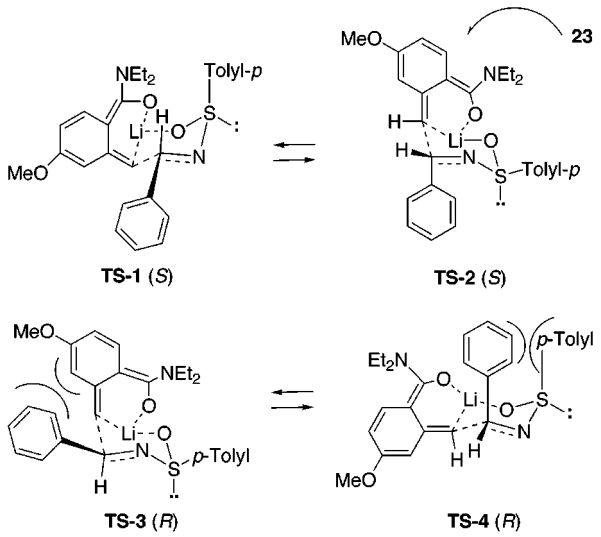
Scheme 5



erential formation of (*S*)-**14** in the addition of amide anion species **23** to (+)-**11** is depicted in Scheme 5. In this representation the lithium cation is chelated to the sulfinyl oxygen and the *o*-quinodimethane **23** in a six-member chairlike transition state **TS-1**−**TS-4** (Scheme 5). Transition states **TS-1** and **TS-2** are expected to be lower in energy than **TS-3** and **TS-4**, in which the interactions between the bulky amide anion and the phenyl group and/or the phenyl and the *p*-tolyl groups are unfavorable.

From Phthalide Anions. Dodsworth et al. reported that phthalide anions add to imines to give mixtures of *cis*- and *trans*-4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolines.[31] In a related study Marsden and MacLean described the synthesis of 13-hydroxytetrahydroprotoberberines via the addition of phthalide anions to 1,4-dihydroisoquinolines.[32] Addition of phthalide anions to enantiopure sulfinimines could therefore provide direct access to enantiomerically enriched 4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolones such as **19** because the two chiral centers are formed in a single operation. However, in principle four stereoisomeric products could result.

Passing gaseous CH_2O through a solution of the *o*-lithiobenzamide of **24**, prepared by treatment of the amide with *s*-BuLi/TMEDA, afforded **25** in 72% yield (Scheme 6). The alcohol was converted in 74% yield to 6-methoxyphthalide (**26**) by refluxing in toluene for 9 h with *p*-toluenesulfonic acid. The phthalide anion of **26** was generated at −78 °C, and a solution of (*S*)-(+)-**11** at −78 °C was added via cannula (sequential addition). Alternatively, the base was added to equivalent amounts of **26** and (*S*)-**11** at −78 °C (one portion). Flash chromatography produced two diastereomeric products **27** as indicated by the presence of two methoxy absorptions at δ 3.79 and 3.84 ppm, respectively, in the ^{1}H NMR spectrum. Significantly, the product selectivity proved to be counterion dependent, with lithium reagents (LDA, LiHMDS) affording (S_S,*S*,*R*)-**27a** (Table 1, entries 1−6) and sodium and potassium reagents (NaHMDS, KHMDS) giving (S_S,*R*,*S*)-**27b** (Table 1, entries 7−13). The one-portion method gave better ratios and cleaner products than the sequential method (Table 1, compare entries 1 and 2, 7 and 8). Furthermore, the potassium enolate gave a reaction mixture having fewer side products. Solvent also played a role, with THF/Et_2O (1:1) giving better selectivity (Table 1, entries 2 and 3, 8 and 9). However, in pure ether the reaction mixture was complex, consisting of multiple products, **27** and **28**, that were impossible to separate.

That the two diastereoisomers produced in the reaction of (+)-**11** with the anion of **26** are epimeric at the carbon centers was determined by cyclizing the mixture with NaH to give a single hydroxy isoquinolone **28**. Furthermore, the pure diastereoisomers (S_S,*S*,*R*)-(−)-**27a** and (S_S,*R*,*S*)-(−)-**27b**, isolated by flash chromatography, were individually cyclized with 2.5 equiv of NaH to give the same 3,4-*trans*-hydroxyisoquinolines (3*S*,4*R*)-(−)-**28** and (3*R*,4*S*)-(+)-**28**, respectively, with identical spectral properties but opposite optical rotations. The absolute configuration of (3*R*,4*S*)-(+)-**28** was established by silylation with TBDPSCl and *N*-methylation to give (3*R*,4*S*)-(+)-*N*-methyl-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (**20**), whose stereochemistry was determined in the preceding section (vide supra).

An explanation for the observed stereochemistry is given in Scheme 7. The preference for the (S_S,*S*,*R*)-(−)-**27a** is consistent with chelation control in which the lithium ion is associated with the sulfinyl oxygen as in **TS-5** and the phthalide ion approaches the *si* face of **11**. Conversely, formation of (S_S,*R*,*S*)-(−)-**27b** would involve attack of phthalide anion at the less sterically hindered *re* face of **11** as in **TS-6**. Thus chelation control by the Li ion vs steric control with the poorer chelating Na and K ions appears to be responsible for the reversibility of the stereochemistry. Consistent with this hypothesis is the observation that addition of *N*,*N*′-dimethylpropyleneurea (DMPU), known to disrupt metal ion chelation, has no effect on the stereoselectivity with NaHMDS, whereas the selectivity was reversed with LiHMDS (Table 1, compare entries 4 and 10).

In summary, the addition of lateral lithiated amides and phthalide anions to enantiopure sulfinimines represents a new methodology for asymmetric synthesis of isoquinolones and hydroxy isoquinolones, important building blocks for isoquinoline alkaloid synthesis.

Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 microns) purchased from Analtech Inc. TLC plates were visualized with UV, in an iodine chamber or with phosphomolybdic acid unless noted otherwise. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. *N*,*N*-Diethyl-*o*-toluamide (**10a**) and 4-methoxy-*N*,*N*-diethyl-*o*-toluamide (**10b**) were prepared as previously described.[33]

General Procedure for the Addition of Lithium *o*-Toluamide Anions to Sulfinimines. (S_S,*S*)-(+)-*N*-[1-Phenyl-2-(2-*N*,*N*-diethylbenzamido)ethyl]-*p*-toluenesulfinamide (12a). To a stirring solution of 1.14 g (6 mmol) of *N*,*N*-diethyl-*o*-toluamide in THF (12 mL), in a 50 mL two neck

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Scheme 6

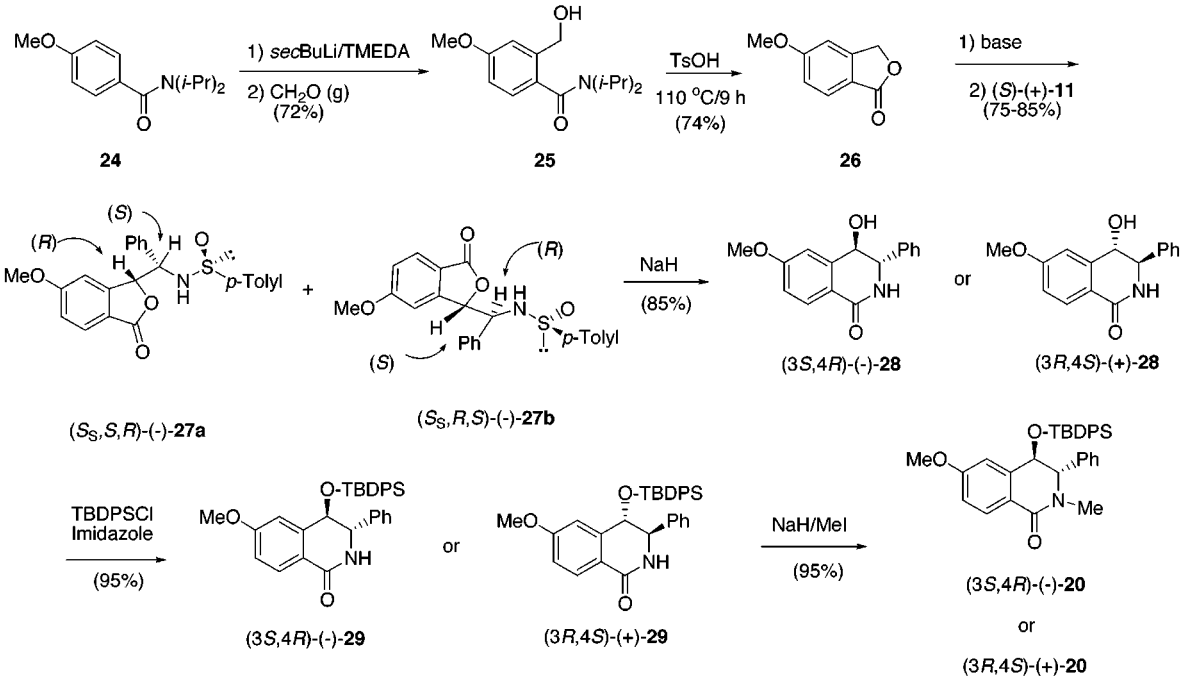
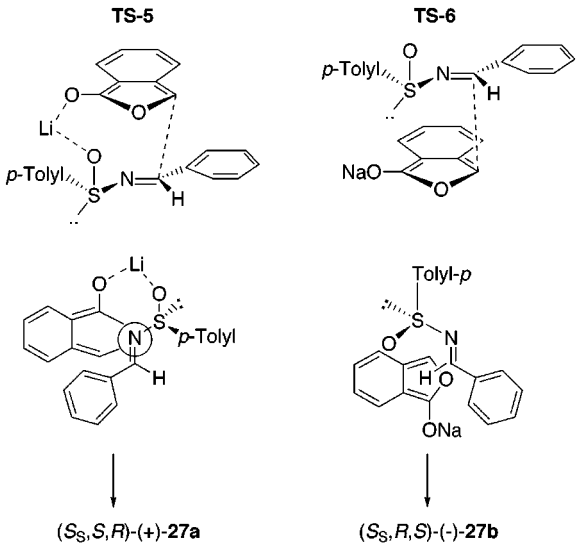


Table 1. Addition of Phthalide 26 to Sulfinimine (*S*)-(+)-11 at −78 °C

entry	base	solvent	conditions	(S_S,*S*,*R*)-**27a**/(S_S,*R*,*S*)-**27**[a]	% yield[b]
1	LiHMDS	THF	sequential[a]	7:1	76
2	LiHMDS	THF	one portion[b]	10:1	80
3	LiHMDS	THF/Et_2O (1:1)	one portion	8:1	85
4	LiHMDS/DMPU[e]	THF	one portion	1:2	40
5	LDA	THF	sequential	4:1	75
6	LDA	THF	one portion	complex mixture	
7	NaHMDS	THF	sequential	complex mixture[f]	
8	NaHMDS	THF	one portion	1:10	80
9	NaHMDS	THF/Et_2O (1:1)	one portion	1:15	80
10	NaHMDS/DMPU[e]	THF/Et_2O (1:1)	one portion	1:14	75
11	NaHMDS	Et_2O	one portion	1:15	ca. 30[f]
12	KHMDS	THF/Et_2O (1:1)	one portion	1:14	70
13	KHMDS	THF/Et_2O (2:1)	one portion	1:18	85

[a] Determined by NMR integration of the OMe groups in **27**. [b] Isolated yields. [c] Sulfinimine **11** added to the anion of **26**. [d] Base added to **11** and **26**. [e] Two equivalents added. [f] Complex reaction mixture; **28** also detected.

Scheme 7



round-bottomed flask equipped with a stirring bar and rubber septum under argon at −78 °C, was added 3.9 mL (1.5 M in cyclohexane, 6.0 mmol, 1 equiv) of lithium diisopropylamide (LDA). After 10 min a −78 °C solution of (*S*)-(+)-**11**[21] (0.73 g, 3 mmol) in THF (2 mL) was added via cannula. The reaction mixture was quenched after 15 min by addition of saturated NH_4Cl (5 mL) at −78 °C, and the solution was extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel flash chromatography (4:6 EtOAc/hexane) to give 1.0 g (77%) of **12a**: >98% de; mp 100−101 °C; $[\alpha]^{20}_D$ 13.75 (c 1.6, MeOH); IR (KBr) 3151, 1610, 1438, 1093, 1067 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55−6.8 (m, 13H Ar), 4.6 (m, 1H), 3.7−3.4 (m, 2H), 3.4−3.0 (m, 2H), 2.9−2.7 (m, 2H), 2.2 (s, 3H), 1.3 (t, 3H, J = 7 Hz), 1.0 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.0, 21.0, 39.4, 41.8, 43.2, 54.8, 125.3, 125.9, 126.3, 126.4, 126.5, 127.8, 128.4, 129.4, 130.4, 134.9, 136.3, 139.8, 141.0, 144.5, 171.4. Anal. Calcd for $C_{26}H_{29}NO_2S$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.45; H, 6.98; N, 6.42.

Treatment of *N*-(Benzylidene)-*p*-toluenesulfinamide (11) with LDA. In a 25 mL two-neck round-bottomed flask equipped with stirring bar and rubber septa under argon was placed 0.072 g (0.296 mmol) of **11** in 3 mL of THF. To the reaction mixture at −78 °C was added dropwise 0.40 mL (1.5 M, 2 equiv) of LDA. After 20 min an aliquot was withdrawn and quenched with saturated NH_4Cl (1 mL). The rest of the reaction mixture was stirred for a total of 50 min and then quenched with NH_4Cl (1 mL). HPLC (benzophenone standard) of the reaction mixture for the molar ratio of benzonitrile and

unreacted **11** indicated a ratio of 27:73 for the 20 min reaction and 36:64 for the 50 min reaction. The crude material was purified by preparative TLC to provide 0.027 g (38%) of **11**, 0.008 g (19%) of *p*-tolyl *p*-toluenethiosulfonate, and 0.015 g (41%) of *p*-toluenedisulfide, the sulfenic acid decomposition products.[34]

(S_S,*S*)-(+)-*N*-[1-Phenyl-2-(5-methoxy-2-*N*,*N*-diethylbenzamido)-ethyl]-*p*-toluenesulfinamide (12b). To a solution of 0.426 (1.92 mmol) of **10b** in THF (8 mL) at −78 °C was added 1.3 mL (1.5 M in cyclohexane, 1 equiv) of LDA. After 15 min a −78 °C solution of 0.467 g (1.92 mmol) of (*S*)-(+)-**11** in THF (2 mL) was added dropwise via cannula until the color of the anion was discharged. An additional amount of LDA (0.5 mL, 0.4 equiv) was added, and to the resulting burgundy colored solution was cannulated the solution of (+)-**11**. The reaction mixture was quenched at −78 °C after 15 min with saturated NH_4Cl (10 mL), and the solution was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), concentrated, and purified by silica gel column flash chromatography (4:6 EtOAc/hexane) to give 0.801 g (90%) of **12b**: >98% de; mp 143−144 °C; $[\alpha]^{20}_D$ 10.58 (*c* 1.2, $CHCl_3$); IR (KBr) 1617, 1424, 1286, 1092, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−6.80 (12H), 4.7 (br, 1H) 4.80−3.40 (bm, 5H) 3.20−2.80 (bm, 4H), 2.23 (s, 3H) 1.62 (s, 1H) 1.29 (t, J = 6.9 Hz, 3H) 1.02 (t, J = 7 Hz, 3H); ^{13}C NMR δ 171.5, 141.3, 140.0, 128.7, 127.8, 127.0, 126.8, 126.7, 126.5, 125.9, 115.8, 112.45, 112.38, 112.32, 112.29, 112.24, 55.0, 43.3, 42.0, 39.5, 21.1, 14.1, 12.9. Anal. Calcd for $C_{27}H_{32}N_2O_3S$: C, 69.80; H, 6.94; N, 6.03. Found: C, 69.62; H, 6.98; N, 5.83.

General Procedure for the Hydrolysis of *p*-Toluenesulfinamides to the Amine. (*S*)-(+)-*N*,*N*-Diethyl-2-(2-amino-2-phenylethyl)benzamide (14a). To a solution of 0.077 g (0.177 mmol) of **12a** in dry MeOH (1.5 mL) at 0 °C was added dropwise 0.9 mL (0.89 mmol, 5 equiv) of trifluoroacetic acid (TFA) in MeOH (0.2 mL). After 2 h, the solvent was evaporated, and the residue was dissolved in EtOAc (20 mL), washed with 5% aqueous NaOH (10 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (1:4:0.1 MeOH/EtOAc/TEA) afforded 0.047 g (91%) of the amine as a thick oil: $[\alpha]^{20}_D$ 10.65 (*c* 3.1, $CHCl_3$); IR (neat) 3294, 3367, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5−6.2 (m, 9H), 4.4−4.2 (m, 2H), 3.9−3.6 (m, 1H), 3.45−3.20 (m, 1H), 3.2−2.8 (m, 3H), 2.7 (dd, 1H, J = 9 Hz), 1.83 (s, 2H, NH, 1.27 (t, 3H, J = 7 Hz), 1.0 (t, 3H, J = 7 Hz). Spectral properties were identical with literature values.[9a]

(*S*)-(−)-*N*,*N*-Diethyl-4-methoxy-2-(2-amino-2-phenylethyl)benzamide (14b). Purification by silica gel column chromatography (1:4:0.1 MeOH/EtOAc/Et_3N) afforded 0.473 g (99%) of the amine as a thick oil: $[\alpha]^{20}_D$ −4.10 (*c* 1.10, $CHCl_3$); IR (neat) 3372, 3304, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3−7.1 (m, 6H), 7.04 (d, J = 8.5, 1H), 6.68 (d, J = 8.5 Hz, 1H), 6.62 (bs, 1H), 4.16 (br, 1H), 3.64 9 (s, 3H), 3.5−2.76 (brm, 3H), 2.64 (dd, J = 6.75, 4.75 Hz, 1H), 1.52 (br, 2H), 1.17 (t, J = 7 Hz), 0.92 (t, J = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.3, 145.8, 137.3, 129.7, 128.2, 127.0, 126.8, 126.2, 115.5, 111.8, 55.0, 44.0, 42.7, 38.7, 13.8, 12.7; HRMS calcd for $C_{20}H_{26}N_2O_2$ (M + H) 327.1994, found 327.207.

Preparation of the Mosher Amides. The Mosher acid chloride (1.2 equiv) was added to the crude amine in CH_2Cl_2 (5 mL) and 20% aqueous NaOH (2 mL). After 20 min of stirring the organic phase was dried ($MgSO_4$) and concentrated, and the ^{19}F NMR was determined and compared with racemic material.

General Procedure for the Base-Induced Cyclizations. (3*S*)-(−)-3-Phenyl-3,4-dihydro-1(2*H*)-isoquinolone (15a). To a solution of 0.020 g, (0.067 mmol) of (+)-**14a** dissolved in of THF (1 mL) at −78 °C was added dropwise *tert*-butyllithium (1.7 M in pentane, 0.12 mL, 0.20 mmol, 3 equiv). After 30 min of stirring, the dark-brown mixture was quenched with a saturated solution of NH_4Cl (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic portions were washed with saturated NH_4Cl (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (3:7 EtOAc/hexane) to give 0.014 g (90%) of **15a**: mp 130−131 °C [lit.[9a] mp 130−131 °C]; $[\alpha]^{20}_D$ −203.4 (*c* 1.03 $CHCl_3$); IR (KBr), 3402, 1664, 909, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12, (d, J = 7.5 Hz, 1H), 7.5−7.2 (m, 8H), 6.0 (bs, 1H), 4.86 (dd, J = 11.5, 4.5 Hz, 1H, NH) 3.20 (dd, J = 16, 11.5 Hz, 1H), 3.25 (dd, J = 16, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.2, 140.9, 137.5, 132.4, 128.9, 128.3, 128.0, 127.3, 127.2, 126.4, 56.1, 50.7, 37.4.

(3*S*)-(−)-6-Methoxy-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (15b). Purification by flash chromatography (3:7 EtOAc/hexane) gave 0.350 g (96%) of a solid: mp 127−128 °C; $[\alpha]^{20}_D$ −131.6 (*c* 1.36, $CHCl_3$); IR (KBr) 3466, 1669 cm^{-1}; NMR ($CDCl_3$) δ 8.08 (d, 1H, J = 8.5 Hz), 7.41−7 (m, 5H), 6.89 (dd, J = 6.5, 2 Hz 1H), 6.67 (d, J = 2.5 Hz, 1H), 5.79 (bs, 1H), 4.84 (dd, J = 15.5, 4.5 Hz, 1H), 3.85 (s, 3H, OMe), 3.18 (dd, J = 15.5, 11.5 Hz, 1H), 3.10 (dd, J = 15.5, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.2, 162.6, 141.0, 139.5, 129.9, 128.7, 128.0, 126.2, 121.1, 112.4, 112.2, 55.7, 55.2, 37.4. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.85; H, 6.00; N, 5.48.

(3*S*)-(−)-6-Methoxy-*N*-methyl-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (16). To a stirring suspension of 0.416 g of NaH (60% w/w in mineral oil, 10.4 mmol, 10 equiv) and 0.264 g (1.04 mmol) of (−)-**15b** in THF (5 mL) at room temperature was added 0.32 mL (5.12 mmol, 5 equiv) of iodomethane. After 1 h the reaction mixture was filtered through Celite, and the filtrate was washed with cold saturated NH_4Cl (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica gel, hexane followed by 1:1 EtOAc/hexane) to give 0.262 g (94%) of **16**: mp 124−125 °C; $[\alpha]^{20}_D$ −136.5 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 9 Hz, 1H), 7.26−7.20 (m, 3H), 7.10−7.08 (d, J = 8 Hz, 2H), 6.82 (dd, J = 8.5, 2.5 Hz, 1H), 6.5 (s, 1H), 4.74 (dd, J = 6.5, 2.5 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, J = 16, 6.5 Hz, 1H), 3.08 (s, 3H), 2.97 (dd, J = 16, 2.5 Hz, 1H); ^{13}C NMR δ.164.8, 162.3, 140.0, 137.1, 129.8, 128.6, 127.5, 126.2, 122.1, 112.4, 112.3, 61.8, 55.1, 35.9, 34.1. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.49; H, 6.61; N, 5.03.

(3*R*,4*S*)-(+)-4-Hydroxy-6-methoxy-*N*-methyl-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (19). To a stirring solution of 0.04 g (0.158 mmol) of (−)-**16** in THF (3 mL) at −78 °C was added dropwise 0.21 mL (1.5 M, 3 equiv) of LDA. After 20 min 0.054 g (0.237 mmol, 1.5 equiv) of (camphorylsulfonyl)oxaziridine[35] (−)-**18** in THF (1 mL), cooled to −78 °C, was cannulated until the deep purple color was discharged. After 20 min saturated NH_4Cl (5 mL) was added, and the reaction mixture was extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (silica gel, 1:1 EtOAc/hexane) provided 0.032 g (85%) of a gum: $[\alpha]^{20}_D$ 91.93 (*c* 0.86, $CHCl_3$); IR (neat) 3315, 1635, 1475, 1281, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (d, J = 8.66 Hz, 1H), 7.28−7.20 (m, 3H), 7.08−7.05 (m, 2H), 6.82 (dd, J = 8.71, 2.51 Hz, 1H), 6.70 (d, J = 2.45 Hz, 1H), 4.89 (d, J = 2.1 Hz, 1H), 4.67 (d, J = 2.1 Hz, 1H), 3.81 (s, 3H, OMe), 3.12 (s, 3H, NMe); ^{13}C NMR ($CDCl_3$), δ 164.1, 162.4, 138.4, 136.8, 129.4, 128.7, 127.7, 126.4, 120.5, 114.5, 112.9, 72.0, 70.3, 55.2, 34.6; HRMS calcd for $C_{17}H_{17}NO_3$ (M + H) 284.1208, found 284.1215

(3*R*,4*S*)-(+)-4-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-*N*-methyl-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (20). To a stirring solution of 0.025 g (0.088 mmol) of (+)-**19** and 0.018 g (0.28 mmol, 3 equiv) of imidazole in CH_2Cl_2 (1.5 mL) at room temperature was added 0.073 g (0.27 mmol, 3 equiv) of *tert*-butylchlorodiphenylsilane (TBDPSCl). After 3 h, CH_2Cl_2 (2 × 10 mL) was added, and the crude mixture was washed with saturated NH_4Cl (10 mL). The organic portion was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica gel, hexane and then 1:9 ethyl acetate/hexane) to give 0.043 g (95%): mp 187−188 °C; $[\alpha]^{20}_D$ 120.5 (*c* 0.6, $CHCl_3$); IR (KBr) 2960, 1646, 1254, 1047, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.60−7.36 (m,

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8H), 7.20−7.0 (m, 3H), 6.90 (dd, 8.5, 2.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.5 (d, J = 1.5 Hz, 1H), 4.58 (d, J = 2.5 Hz, 1H), 4.54 (d, J = 2 Hz, 1H), 3.62 (s, 3H), 3.1 (s, 3H), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 164.0, 161.9, 137.6, 136.4, 135.9, 133.5, 132.9, 130.2, 129.9, 128.5, 128.1, 127.7, 127.5, 126.3, 122.0, 114.7, 113.1, 72.9, 69.9, 55.1, 34.4, 26.7, 19.2. Anal. Calcd for $C_{33}H_{35}NO_3Si$: C, 75.97; H, 6.76; N, 2.68. Found: C, 75.91; H, 6.98; N, 2.63. HRMS calcd for $C_{33}H_{35}NO_3Si$ (M + H) 508.2593, found 508.2695.

(3*R*,4*S*)-(+)-4-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (21). To a stirring solution of 0.070 g (0.134 mmol) of (−)-**20** in THF (3 mL) at room temperature was added 0.67 mL (2 M, 10 equiv) of BH_3·DMS. After 5 h of heating at reflux, the solvent was evaporated, the residue was dissolved in diethyl ether (3 mL), and 0.035 g (0.574 mmol) of ethanolamine was added. After 12 h at room temperature the precipitated solid was filtered and washed with diethyl ether, and the combined organic phases were filtered through Celite and concentrated. Purification by flash chromatography (silica gel, 3:7 EtOAc/hexane) gave 0.067 g (98%) of an oil: $[\alpha]^{20}_D$ 33.53 (*c* 2.75, $CHCl_3$); IR (neat) 1615, 1506, 1266, 111, 1053, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.45−7.15 (m, 9H), 6.70−7.0 (m, 3H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 4.95 (d, J = 4.5 Hz, 1H), 3.74 (d, J = 14 Hz, 1H), 3.71 (d, J = 4.5 Hz, 1H), 3.60 (d, J = 14 Hz, 1H), 3.28 (s, 3H), 2.21 (s, 3H), 0.86 (s, 9H); ^{13}C NMR δ 157.7, 139.6, 136.9, 136.8, 133.8, 133.2, 129.7, 129.3, 128.9, 128.1, 127.6, 127.3, 127.2, 126.8, 114.8, 113.1, 74.8, 73.3, 55.4, 54.7, 43.6, 26.7, 19.5. Anal. Calcd for $C_{33}H_{37}NO_2Si$: C, 78.06; H, 7.34; N, 2.76. Found: C, 77.71; H, 7.33; N, 2.48.

(3*R*,4*S*)-(−)-4-Hydroxy-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (22). To a stirred solution of 0.060 g (0.118 mmol) of **21** in of THF (10 mL) at room temperature was added 1.0 mL (1 M, THF, 8.5 equiv) of TBAF. After 12 h, H_2O (10 mL) was added, and the crude mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated, and the residue was purified by silica gel flash chromatography (1:1 EtOAc/hexane) to provide 0.031 g (98%) of the product: mp 116−117 °C; $[\alpha]^{20}_D$ −59.75 (*c* 0.80 $CHCl_3$) [lit.[23] $[\alpha]^{20}_D$ 59 (*c* 1.0 $CHCl_3$) for the (3*S*,4*R*)-enantiomer]; [lit.[23] mp 87−88 °C]; ^{1}H NMR δ 7.40−7.22 (m, 5H), 7.05 (d, J = 2.6, 1H), 7.01 (d, J = 8.5, 1H), 6.83 (dd J = 8.5, 2.6, 1H), 4.79(d, J = 6.5, 1H), 3.84 (s, 3H), 3.74 (d, J = 15.2,1H), 3.55 (d, J = 15.2, 1H), 3.43 (d, J = 6.5, 1H), 2.21 (s, 3H); ^{13}C NMR δ 158.6, 137.8, 137.4, 129.0, 128.6, 128.0, 126.8, 126.4, 114.5, 111.6, 72.9, 72.5, 56.0, 55.3, 43.3.

2-Hydroxymethyl-4-methoxy-*N*,*N*-diisopropylbenzamide (25). To a stirred solution of 0.945 g (4.0 mmol) of 4-methoxy-*N*,*N*-diisopropylbenzamide (**24**)[33] and 1.2 mL (2 equiv) of TMEDA in THF (20 mL) in a 100 mL two-neck round-bottomed flask equipped with stirring bar and rubber septum cooled to −78° C was added dropwise 6.2 mL (1.3 M solution, 2 equiv) of *s*-BuLi. After 30 min a THF solution of formaldehyde at −40 °C was added dropwise via syringe. The formaldehyde solution was prepared by cracking 0.6 g (20 mmol, 5 equiv) of paraformaldehyde with a heat gun, which was bubbled into THF (15 mL) at −78 °C. After 2 h of stirring, the reaction temperature was raised to room temperature over 8 h, saturated aqueous NH_4Cl (15 mL) was added, and the solution was extracted with EtOAc (2 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated, and the crude material was purified by silica gel flash chromatography (7:3 hexane/EtOAc) to provide 0.77 g (72%) of the product as an oil: IR (KBr) 3286, 1613.4, 1453 cm^{-1}; ^{1}H NMR δ 7.10 (d, J = 8 Hz, 2H), 6.95 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 4.61 (br, 1H), 4.35 (br, 1H), 2.89 (br, 1H), 3.83 (s, 3H), 3.52 (br, 1H), 1.53 (br, 6H), 1.18 (br, 3H); ^{13}C NMR ($CDCl_3$) δ 171.29, 159.82, 140.29, 129.87, 125.05, 126.38, 114.54, 112.85, 63.80, 55.21, 51.20, 45.97, 20.92, 20.65, 20.49, 20.26. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.59; H, 8.85; N, 5.12.

6-Methoxyphthalide (26). A stirring solution of 0.594 g (2.2 mmol) of **25** and 0.10 g (0.58 mmol) of *p*-TsOH in toluene (10 mL) in a 25 mL round-bottomed flask was heated at reflux for 9 h. The solvent was removed, and the residue was diluted with CH_2Cl_2 (10 mL) and filtered through a short pad of silica gel to give 0.267 g (74%) of a solid: mp 110−111 °C; IR (KBr) 1759, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83, (d, J = 8.5 Hz, 1H), 7.05, (dd, J = 8 Hz, 2.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 5.26 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ, 170.80, 164.64, 149.32, 127.10, 116.46, 105.91, 69.05, 55.79. Anal. Calcd for $C_9H_8O_3$: C, 65.85; H 4.91; Found: C, 65.91; H, 4.97.

Addition of 6-Methoxyphthalide Anion to (*S*)-(+)-11 To Give 27 [Sequential Addition]. To a stirring solution of 0.108 g (0.66 mmol) of **26** in THF (3 mL) in a 25 mL two-neck round-bottomed flask under argon at −78 °C was added dropwise 1.32 mL (1.32 mmol of a 1 M solution) of LiHMDS. After 15 min 0.148 g (0.61 mmol) of (*S*)-**11** in THF (1.5 mL) at −78 °C was added to the orange solution via cannula. After 15 min, saturated NH_4Cl (10 mL) was added, and the reaction mixture was extracted with EtOAc (2 × 15 mL). The organic portion was dried ($MgSO_4$) and concentrated to give 0.250 g of an oil containing two diastereomers, (S_S,*S*,*R*)-**27a** and (S_S,*R*,*S*)-**27b**, in the ratio of 7:1 determined by integration of the MeO absorptions at δ 3.79 and 3.84 ppm, respectively. Silica gel flash chromatography (4:1 hexane/EtOAc) provided the major diastereoisomer as a white powder, which was further purified by dissolving in diethyl ether and trituration with hexane to provide 0.190 g (76%) of (S_S*S*,*R*)-(−)-**27a**; mp 143−145 °C; $[\alpha]^{20}_D$ −62.4 (*c* 1.20, $CHCl_3$); IR (neat) 3444, 1765, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.6 (d, J = 8 Hz, 2H), 7.52 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8 Hz), 7.18 (m, br, 5H), 6.86 (dd, J = 2, 8.5 Hz, 1H), 6.65 (d, J = 1.5 Hz), 5.58, (d, J = 3 Hz), 5.11 (d, J = 8 Hz), 5.03 (dd, J = 7.5, 3 Hz, 1H), 3.8 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.4, 164.2, 148.4, 141.7, 141.1, 135.2, 129.6, 128.2, 127.9, 127.0, 125.7, 118.7, 116.7, 106.6, 82.5, 59.5, 55.7, 21.3. Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.59; H, 5.36; N, 3.68.

General Procedure for the Addition of Base to Phthalide 26 and (*S*)-(+)-11 [One Portion] To Give 27b. To a stirring solution of 0.075 g (0.46 mmol) of **26** and 0.11 g (0.46 mmol) of (*S*)-(+)-**11** in 2:1 THF/Et_2O (10 mL) in a 100 mL two-neck round-bottomed flask cooled to −78 °C was added 1.8 mL (0.092 mmol) of KHMDS. After 20 min the reaction mixture was quenched by addition of saturated NH_4Cl (10 mL) followed by EtOAc (20 mL). The organic phase was dried ($MgSO_4$) and concentrated to give an oil containing (S_S,*S*,*R*)-**27a** and (S_S,*R*,*S*)-**27b** in the ratio of 1:18. The material was purified by silica gel column chromatography (3:7 EtOAc/CH_2Cl_2) to provide 0.16 g (86%) of (S_S*S*,*R*)-(−)-**27b**: mp 127−130; $[\alpha]^{20}_D$ −72.0 (*c* 0.58, $CHCl_3$); IR (KBr) 3444, 1764, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 7.12−7.10 (m, 3H), 6.97 (d, J = 1.5 Hz, 1H), 6.95 (d, J = 3 Hz, 1H), 6.86 (dd, J = 9 Hz, 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 5.00 (d, J = 8.5 Hz, 1H), 4.97 (dd, J = 8.5 Hz, 3 Hz, 1H), 3.79 (s, 3 H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.49, 164.19, 148.43, 141.32, 140.53, 135.29, 129.4, 127.78, 127.51, 126.90, 126.05, 118.80, 116.6, 106.59, 82.96, 58.66, 55.74. Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.80; H, 5.58; N, 3.09.

NaH-Induced Cyclization of 27 to (3*S*,4*R*)-(−)-4-Hydroxy-6-methoxy-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (28). To a stirring solution of 0.160 g (0.393 mmol) of (S_S,*S*,*R*)-(−)-**27** in THF (4 mL) in a 25 mL two-neck round-bottomed flask under argon at room temperature was added 0.023 g (0.983 mmol, 2.5 equiv) of NaH. After stirring for 3 h the crude mixture was filtered through Celite, and the filtrate was diluted with EtOAc (25 mL), washed with saturated NH4Cl (10 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography (1:1 EtOAc/hexane) gave 0.09 g (85%) of (3*S*,4*R*)-**28** as a gum: $[\alpha]^{20}_D$ −19.6 (*c* 1.12 $CHCl_3$); IR (KBr) 3264, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 1H), 7.31−7.27 (m, 5H), 6.92 (d, J = 2.5 Hz, 1H), 6.64 (dd, J = 9 Hz, 2.5 Hz, 1H), 4.96 (d, J = 5.5 Hz), 4.80 (d, J = 5.5 Hz), 3.83 (s, 3H). ^{13}C NMR δ 166.11, 162.20, 140.88, 138.40, 129.52, 128.92, 128.32, 127.07, 119.65, 114.28, 111.36, 71.94, 62.67, 55.42; HRMS calcd for $C_{16}H_{15}NO_3$ (M + H) 270.1126, found 270.1125. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.00; H, 5.55; N, 5.10.

(3*R*,4*S*)-(+)-4-Hydroxy-6-methoxy-3-phenyl-3,4-dihydro-1(2*H*)-isoquinolone (28): 76%, gum; $[\alpha]^{20}_D$ 24.25 (*c* 1.60 $CHCl_3$); IR (KBr) 3264, 1666 cm^{-1}; ^1H NMR (CD_3OD) δ 7.90 (d, J = 8.5 Hz, 1H), 7.31−7.27 (m, 5 H),7.02 (d, J = 2.5 Hz 1H), 6.91 (dd, J = 8.5 Hz, 2.5 Hz), 4.82 (d, J = 8 Hz), 4.64 (d, J = 8 Hz), 3.83 (s, 3H); ^{13}C NMR (CD_3OD) δ 167.67, 165.0, 143.52, 140.46, 130.69, 129.64, 129.05, 128.33, 121.29, 115.06, 112.78, 72.48, 63.51, 56.01.

(3*S*,4*R*)-(−)-4-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (29). To a stirring solution of 0.120 g (0.446 mmol) of (−)-**28** in CH_2Cl_2 (5.0 mL) in a 25 mL two-neck round-bottomed flask at room temperature was added 0.184 g (0.670 mmol, 1.5 equiv) of TBDPSCl followed by 0.091 g (2.01 mmol, 3 equiv) of imidazole. After stirring for 1.5 h the reaction mixture was filtered through a short column of silica gel (CH_2Cl_2 followed by 1:5 EtOAc/CH_2Cl_2) to provide 0.197 g (97%) of a solid: mp 221−222 °C; $[\alpha]^{20}_D$ −62.4 (*c* 1.20, $CHCl_3$); IR (KBr) 3380, 1667, 1608, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (d, J = 9 Hz, 1H), 7.81 (d J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.52−7.34 (m, 6H), 7.10−7.07 (m, 3H), 6.90 (dd, J = 10 Hz, 2.5 Hz, 1H), 6.65 (d, J = 9 Hz, 2H), 6.26 (d, J = 2.5 Hz, 1H), 6.08 (d, J = 4 Hz, 1H), 4.72 (dd, J = 4.5 Hz, 3 Hz), 4.70 (m, br, 1H), 3.59 (s, 3H), 1.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.21, 162.44, 138.76, 138.35, 135.92, 133.32, 133.00, 130.0, 129.84, 129.79, 128.35, 128.03, 127.62, 127.43, 126.28, 121.14, 114.84, 113.18, 73.09, 62.20, 55.10, 26.68, 11.24. Anal. Calcd for $C_{32}H_{33}NO_3Si$: C, 75.70; H, 6.55; N, 2.76. Found: C, 75.25; H, 6.60; N, 2.77.

(3*R*,4*S*)-(+)-4-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (29): 78% yield; mp 220−221 °C; $[\alpha]^{20}_D$ 67.7 (*c* 1.18, $CHCl_3$); IR (KBr) 3380, 1667, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 9 Hz, 1H), 7.83 (dd J = 8 Hz, 1.5 Hz, 1H), 7.53−7.35 (m, 6H), 7.10−7.07 (m, 3H), 6.90 (dd, J = 16 Hz, 7 Hz, 1H), 6.46 (dd, J = 8.5 Hz, 6.6.22 (d, J = 9 Hz, 2H), 6.26 (d, J = 2.5 Hz, 1H), 6.08 (d, J = 4 Hz, 1H), 4.72 (dd, J = 4.5 Hz, 3 Hz), 4.70 (m, br, 1H), 3.59 (s, 3H), 1.00 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.11, 162.54, 138.82, 138.37, 135.97, 133.40, 133.04, 130.16, 129.89, 129.79, 128.43, 128.06, 127.67, 127.54, 126.33, 121.15, 114.89, 113.26, 73.17, 62.21, 55.16, 26.73, 19.29.

(3*S*,4*R*)-(−)-4-(*tert*-Butyldiphenylsiloxy)-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (20). To a stirred solution of 0.078 g (0.153 mmol) of (−)-**29** in THF (3.0 mL) in a 25 mL two-neck round-bottomed flask under argon at room temperature was placed 0.031 g (0.765 mmol, 5 equiv) of *n*-hexane-washed NaH (60% in mineral oil). A 0.109 g (5 mmol) portion of MeI was added. After 0.5 h the crude mixture was filtered through Celite, and the solution was concentrated and dissolved in CH_2Cl_2 (5 mL). The solution was filtered through a short pad of silica gel and concentrated to give 0.078 g (97%) of a solid: mp 187−188 °C; $[\alpha]^{20}_D$ −125.0 (*c* 0.20, $CHCl_3$). This compound had spectral properties identical to those of the enantiomer (3*R*,4*S*)-(+)-**20** prepared above.

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Supporting Information Available: IR and ^1H and ^{13}C NMR spectra of (−)-**14b** and (+)-**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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