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Effect of Ligand Structure on the Asymmetric Cyclization of Achiral Olefinic Organolithiums

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The ability of a large and chemically diverse set of 30 chiral ligands to effect asymmetric cyclization of 2-(*N*,*N*-diallylamino)phenyllithium (**1**), derived from *N*,*N*-diallyl-2-bromoaniline (**2**) by low-temperature lithium−bromine exchange, has been investigated in an attempt to elucidate the structural motifs required to provide high enantiofacial selectivity in the ring closure. Although none of the ligands examined in this study afforded 1-allyl-3-methylindoline in significantly higher ee than previously observed for the cyclization of **1** in the presence of the benchmark ligand (−)-sparteine, several ligands, structurally unrelated to sparteine and available in either enantiomeric form, were found to match the utility of (−)-sparteine in this chemistry.

The conversion of achiral materials into chiral, nonracemic compounds is one of the most intensely studied areas of modern organic chemistry. Although a substantial portion of such study has focused on transition-metal-mediated methods,[1] significant progress has been made in the exploitation of main group metals for this purpose. Thus, for example, the chiral organolithium complexes generated by the enantioselective deprotonation of *Boc*-protected amines or carbamoyl-protected alcohols with *s*-BuLi/(−)-sparteine provide a powerful method for the installation of a stereogenic center adjacent to a nitrogen[2] or oxygen[3] atom in both cyclic and alicyclic systems. The asymmetric intermolecular carbometalation of olefins with either organolithium[4] or other organometallic[4a,5] reagents has also been a productive area of research. Recently, the *intra*molecular carbolithiation of an olefinic organolithium has been found to proceed in a highly enantioselective fashion in the presence of (−)-sparteine,[6] and the two techniques of enantioselective deprotonation and anionic cyclization have been combined[7] to provide highly functionalized systems with good enantioselectivity.

A vexing problem with all sparteine-mediated chemistry arises from the fact that only the (−)-enantiomer of the compound is commercially available. The (+)-enantiomer has been prepared by resolution of the racemate, obtained from *rac*-lupanine,[8] and recently by asymmetric total synthesis;[9] however, at this time neither approach is a particularly attractive solution to the "missing enantiomer" quandary. A clever technique, involving invertive metal−metal exchange,[2a] was introduced by Beak to circumvent this problem in the asymmetric deprotonation chemistry; unfortunately, no such technique is available for the anionic cyclization methodology, as the stereogenic center is introduced in an irreversible carbon−carbon bond-forming step.[10] For this reason, we have explored the ability of a variety of chemically diverse chiral ligands, available in most cases in either enantiomeric form from the chiral pool, to act as surrogates for sparteine in effecting the asymmetric cyclization of an achiral olefinic organolithium. Where possible, we have attempted to draw conclusions about the effect of the ligand structure on the enantioselectivity of the cyclization.

The well-studied 5-*exo* cyclization of 2-(*N*,*N*-diallylamino)phenyllithium (**1**) to (1-allyl-3-indolinyl)methyllithium (**4**), which proceeds in an enantioselective fashion when

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TABLE 1. Yields and Product Distribution from Ligand Screening Studies

		products, yield[a] (% d_1)[b]		
entry	ligand/solvent[c]	**6**	**5**	% ee[d]
1	**3**/A	11(L)	89(L)	80
2	**7**/A	39(M)	61(M)	−16
3	**8**/B	*e*	16(L)	0
4	**9**/B	77(L)	23(L)	60
5	**10**/A	21(L)	79(H)	62
6	**11**/A	27(L)	73(L)	−44
7	**12**/A	100(L)	0	
8	**13**/A	41(M)	59(H)	−78
9[f]	**14**/A	55	45	−52
10	**15**/A	100(H)	0	
11	**16**/A	95(H)	5(L)[e]	27
12	**17**[g]/B	78(H)	22(H)	−12
13	**18**/A	83(M)	17(M)	−18
14	**19**/B	14(L)	86(H)	30
15	**20**/B	100(L)	0	
16	**21**/A	22(L)	78(H)	80
17	**22**/A	37(L)	63(H)	78
18	**23**/A	46(L)	54(H)	76
19	**24**/A	25(L)	75(H)	68
20	**25**/A	41(L)	59(L)	68
21	**26**/B	53(H)	47(H)	76
22[f]	**27**/B	45	55	−52
23	**28**/B	71	29(M)	−32
24	**29**/A	76(M)	24(H)	6
25	**30**/A	85(H)	15(H)	0
26	**31**/A	73(H)	27(H)	2
27	**32**/B	90(H)	10(H)	12
28	**33**/B	91(H)	9(H)	10
29	**34**/B	92(H)	8(H)	2
30	**35**[h]/B	100(H)	0	

[a] Yields determined by GC analysis of reaction mixtures assuming identical detector response for the isomeric products. [b] Due to the large $M^+ - 1$ fragment, % d_1 is listed as a range: L = 0−29%; M = 30−59%; H = 60−100%. [c] Solvent system A: *n*-C_5H_{12}−Et_2O (9:1 v/v); solvent system B: Et_2O. [d] A positive ee indicates the major enantiomer posesses the (*R*)-configuration, a negative ee indicates that the major enantiomer has the (*S*)-configuration. [e] The product coelutes with the ligand. [f] The reaction was quenched with MeOH. [g] The ligand is only partially soluble in pure diethyl ether. [h] The ligand was added as a suspension in pentane.

conducted in the presence of (−)-sparteine (**3**),[6] was selected as the model system for our investigation. As noted previously, the rate of cyclization of an olefinic organolithium is strongly temperature-dependent;[11] however, the addition of a lithiophilic ligand, such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), accelerates the cyclization reaction.[12,13] Thus, in the presence of (−)-sparteine, the rearrangement of **1** to **4** occurs at −40 °C in 1.5 h to furnish, after quench with CH_3OD, (*R*)-1-allyl-3-deuteriomethylindoline [(*R*)-**5**] in ca. 80% yield with 86% ee.[6a] It should be noted that in the absence of a ligand the cyclization is very slow at −40 °C and only trace amounts of 1-allyl-3-methylindoline (**5**) are produced after a reaction time of 1.5 h. It is also important to note that the exploratory reactions described below were conducted under identical conditions to assess the enantioselectivity imparted by each ligand; consequently, with one exception (vide infra), no attempt was made to optimize product yield for reaction involving a particular ligand.

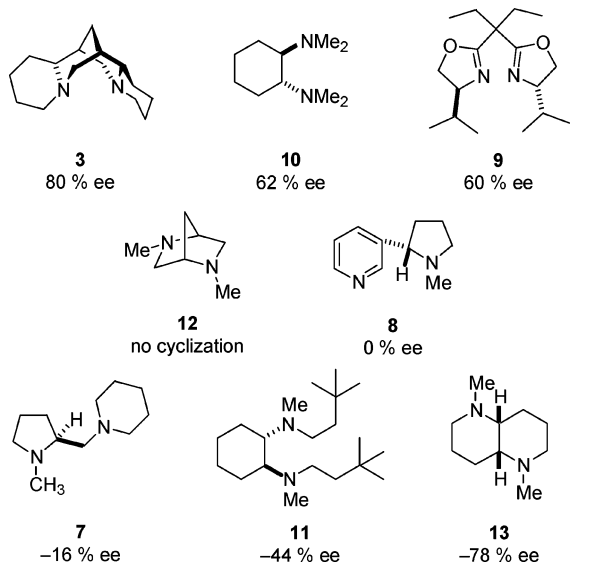

FIGURE 1. Enantioselectivity in the cyclization of **1** imparted by diamine ligands.

Results and Discussion

Following a convenient convention introduced by Beak in another context,[2b] the effectiveness of a ligand in promoting enantiofacially selective cyclization is expressed as positive when it leads to preferential formation of (*R*)-**5**, the predominant enantiomer obtained using (−)-sparteine; a negative ee indicates preferential formation of (*S*)-**5**. Using this convention, the results from experiments involving a diverse set of ligands are summarized, from highest (*R*)-selectivity to highest (*S*)-selectivity, in Figures 1−4. Chemical yield, product distribution, and enantioselectivities for all experiments are reported in Table 1.

Chiral Diamine Ligands. Cursory inspection of the data displayed in Figure 1 reveals that none of the diamine ligands studied surpasses the enantioselectivity imparted by (−)-sparteine (**3**). However, several of the diamines are reasonably effective ligands. The pyrrolidine ligands, such as **7** and (*S*)-(−)-nicotine (**8**), are poorly suited to this process. Indeed, in the presence of nicotine, the conversion to **5** was quite poor (Table 1, entry 3), and numerous byproducts were formed, most likely as a result of well-known reactions of an organolithium with the pyridine ring.[14] The reaction mediated by the amino acid derived *i*-Pr-Box ligand (**9**) proceeded with reasonable enantioselectivity; however, the unnatural amino acid would be required to complement the (−)-sparteine-mediated chemistry. The *trans*-diaminocyclohexane ligands (**10** and **11**) lead to moderate enantioselectivity, but the more sterically demanding ligand **11** appears to be less effective than **10**. The rigid, bicyclic diamine **12** led to no cyclization, presumably because of competitive consumption of the organolithium species via a metalation−elimination sequence. The *cis*-1,5-diazadecalin ligand (**13**), which has been used by Kozlowski's group as an adjuvant in asymmetric lithiation-substitution chemistry,[15] is nearly as effective as is (−)-sparteine in the

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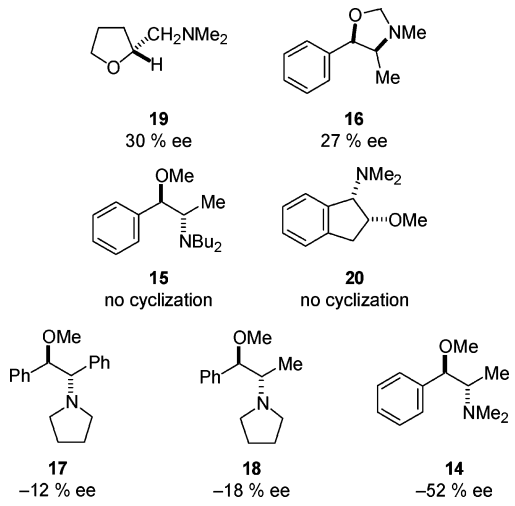
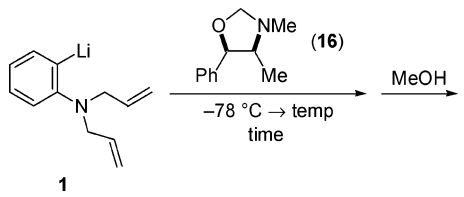


FIGURE 2. Enantioselectivity in the cyclization of **1** imparted by aminoether ligands.

TABLE 2. Effect of Temperature and Ligand Stoichiometry on the Cyclization of 1 in the Presence of Oxazolidine 16



			products, relative yield		
entry	cond[a]	ligand, equiv	**6**[b]	(*R*)-**5**	% ee
1	A	2.5	42	58	12
2	A	4.5	59	41	20
3	B	2.0	~95	~5	27
4	B	4.7	93	7	

[a] Reaction conditions: A = +22 °C, 1.0 h; B = −40 °C, 1.5 h. [b] X = H.[6a]

asymmetric cyclization of **1** (Table 1, entry 8). Unfortunately, **13** is not commercially available, and its synthesis requires a resolution.[15]

Aminoether Ligands. The results of a screening of a series of aminoethers, derived primarily from commercially available (1*R*,2*S*)-(−)-norephedrine, are summarized in Figure 2. It might be noted that the enantiomer, (1*S*,2*R*)-(+)-norephedrine, is also commercially available. Evidently, the cyclization of **1** is sensitive to even slight changes in the norephedrine structure. Cyclization of **1** in the presence of ligand **14** is modestly enantioselective; however, in the presence of **15**, which differs only in chain length of the alkyl group on nitrogen, cyclization was completely suppressed (Table 1, entry 10). Somewhat unexpectedly, connecting the nitrogen and oxygen atoms of the (1*R*,2*S*)-ephedrine skeleton by a methylene tether to give **16** led to a reversal of the enantioselectivity of the cyclization. It is possible that oxazolidine **16** binds to the lithium of **1** in an η_1 fashion; the cyclization of **1** in the presence of **16** is sluggish at −40 °C, and as illustrated in Table 2 (entries 3 and 4), less than 10% of cyclized product is formed. The cyclization is more rapid at room temperature, but it appears that the presence of >4 equiv of ligand decreases the rate of the cyclization (Table 2, cf. entries 1 and 2).

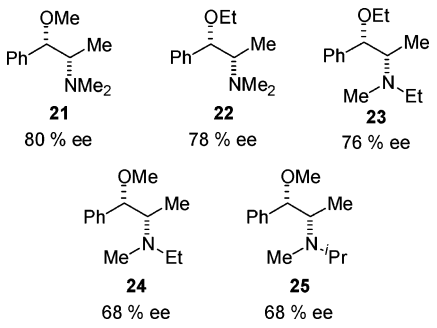


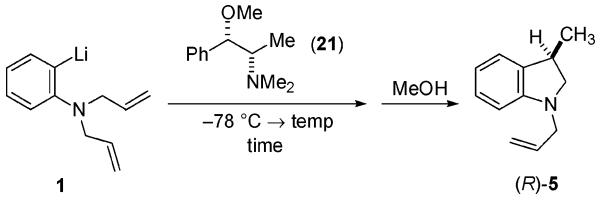
FIGURE 3. Systematic structural variation of the (1*S*,2*S*)-(+)-pseudoephedrine substitution pattern.

The aminoethers that incorporate a pyrrolidine unit (**17** and **18**) are poor ligands for use in this chemistry (Table 1, entries 12 and 13). Not only is the cyclization of **1** slow in the presence of **17** or **18**, but the enantioselectivity is low as well (Figure 2). The tetrahydrofurfuralamine ligand **19** also gives product in low ee, while the use of aminoindanol-derived ligand **20** results in quench of organolithium **1** (Table 1, entry 15).

A more successful result with ligands derived from (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine led us to conduct a systematic investigation into the influence of nitrogen and oxygen substituents on that core structure. The results of these experiments are summarized in Figure 3; the ligands are arranged in the order of decreasing enantioselectivity. Remarkably, the most effective ligand, **21**, matches the enantioselectivity observed in the presence of (−)-sparteine and is the simplest in relation to the substitution pattern. Increasing the size of the oxygen substituent appears to have little influence on the enantioselectivity, as evidenced by the result observed in the presence of ligands **22** and **23**. In general, it appears that substitution on nitrogen is better tolerated if the alkyl chain on oxygen is also lengthened (cf. ligand **23** and ligands **24** and **25**). Be that as it may, none of the "functionalized" pseudoephedrine derivatives participated more effectively in the asymmetric cyclization of **1** than the simple permethylated ligand, **21**.

Given the reasonably high enantioselectivity observed for the cyclization of a *n*-pentane-diethyl ether solution of **1** at −40 °C in the presence of (1*S*,2*S*)-*N*,*O*-dimethylpseudoephedrine (**21**), the effect of several experimental variables on the yield and selectivity of this ring closure was explored. The results are summarized in Table 3. Not surprisingly, the yield of cyclized product may be increased by simply allowing the reaction mixture to stand for a longer time at −40 °C (Table 3, cf. entries 4 and 5); after standing for 3 h at this temperature a yield of 86% is obtained. At temperatures lower than ca. −40 °C, the cyclization is rather slow but the enantioselectivity is somewhat increased (Table 3, entries 9 and 10). At temperatures higher than −40 °C, a more rapid cyclization is purchased at the expense of enantioselectivity (Table 3, entries 1−3). Nonetheless, even at room temperature, cyclization of **1** in the presence of **21** is fairly selective. Significantly, as was the case for cyclization of **1** conducted in the presence of (−)-sparteine,[6a] solvent has a profound effect on the enantioselectivity of the

TABLE 3. Effect of Temperature and Solvent on the Enantioselective Cyclization of 1 in the Presence of Ligand 21



entry	temp, °C	time, h	solvent[a]	yield, % (*R*)-**5**	% ee
1	+25	1.0	*n*-C_5H_{12}−Et_2O	89	64
2	0	1.0	*n*-C_5H_{12}−Et_2O	87	68
3	−20	2.0	*n*-C_5H_{12}−Et_2O	89	74
4	−40	1.5	*n*-C_5H_{12}−Et_2O	78	80
5	−40	3.0	*n*-C_5H_{12}−Et_2O	86	78
6	−40	3.0	Et_2O	87	80
7	−40	3.0	*n*-C_5H_{12}	61	72
8	−40	3.0	THF	48	8
9	−60	6.0	*n*-C_5H_{12}−Et_2O	52	82
10	−78	8.0	*n*-C_5H_{12}−Et_2O	10	86

[a] The relative proportion of *n*-C_5H_{12}−Et_2O mixtures was 9:1 by vol.

process: pentane-diethyl ether mixtures (Table 3, entries 4 and 5), diethyl ether (Table 3, entry 6), and to a lesser extent, pure pentane (Table 3, entry 7) are effective media for the reaction, but THF should be avoided because it leads to essentially racemic product (Table 3, entry 8).

Ether Ligands. The results of a more extensive survey of chiral ethers as ligands are summarized in Figure 4. The C_2-symmetric dimethyl ether of hydrobenzoin (**26**) is nearly as effective as is (−)-sparteine in promoting the asymmetric cyclization of **1**. Several carbohydrate derivatives were explored as potential ligands because they were either commercially available or could be readily prepared.

The carbohydrate-derived ligands (**27**, **28**, **32**−**34**) were insoluble in pentane−diethyl ether (9:1 v/v) solvent at low temperature. For this reason, these ligands were used in pure diethyl ether solvent (Table 1, entries 22, 23, 27−29). Commercially available isosorbide dimethyl ether (**27**) afforded product in reasonable ee and is as effective as is aminoether **14**; however, isomannide dimethyl ether (**28**), the diastereomer of **27** having a *cis*-orientation of the ether moieties, is considerably less effective as a ligand for the cyclization of **1**. Other carbohydrate-derived ethers, such as **32**−**34**, are essentially ineffective in promoting the asymmetric cyclization of **1**. Moreover, ligands **29**−**31**, which are subunits of **32**−**34**, do not impart enantiofacial selectivity in the cyclization of **1**. The chiral BINOL derivative **35** also proved ineffective at facilitating the cyclization, most likely as a result of the poor solubility of the ligand-substrate complex.

Complications: Ligand−Substrate Interactions. We have noted elsewhere that the ability of a chiral ligand to facilitate the cyclization of an achiral, unsaturated organolithium is not sufficient to render the cyclization enantioselective.[6a] More recently it has become apparent that complexation of a ligand with the lithium atom of a substrate may, in fact, hinder the cyclization. A particularly striking example of this phenomenon is

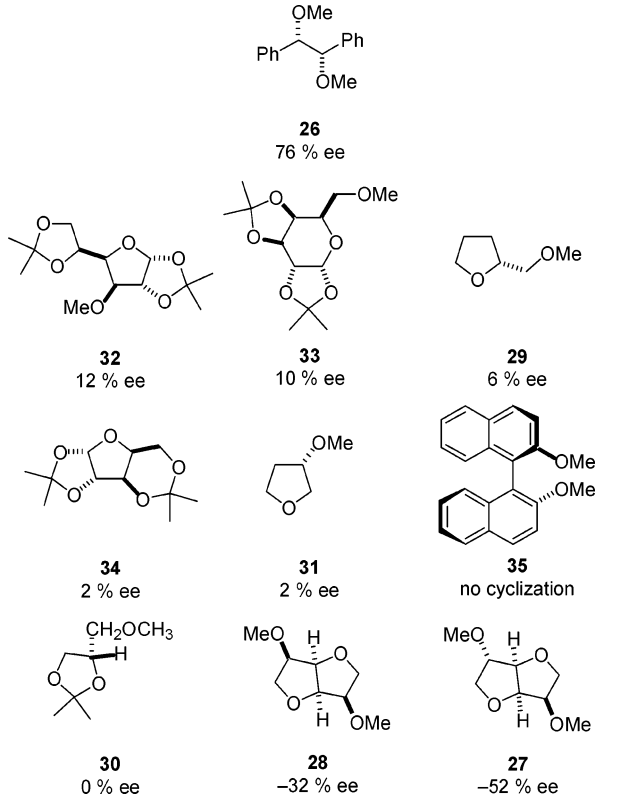
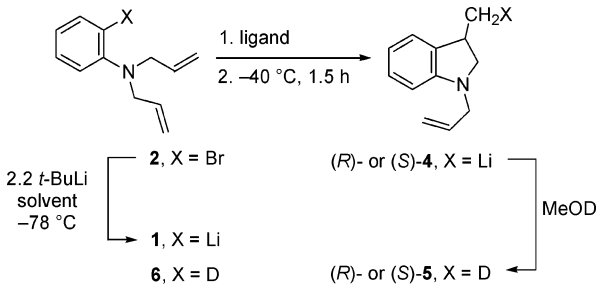


FIGURE 4. Enantioselectivity in the cyclization of **1** imparted by ether ligands.

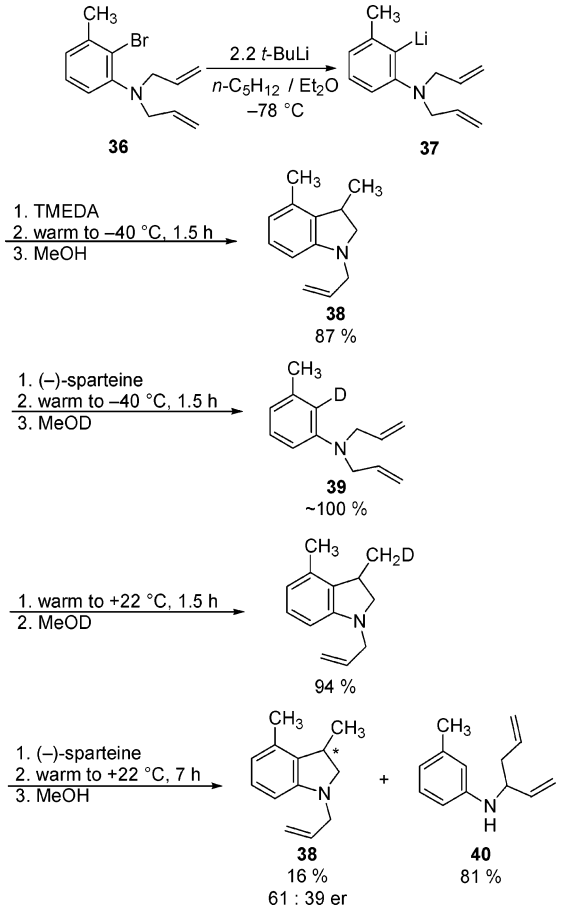
SCHEME 1



provided by the behavior of the organolithium derived from *N*,*N*-diallyl-2-bromo-3-methylaniline (**36**).

An approximately 0.1 M solution of [2-(*N*,*N*-diallylamino)-6-methyl]phenyllithium (**37**) in *n*-pentane−diethyl ether (9:1 v/v) was prepared, as illustrated in Scheme 2, by treatment of **36** with 2.2 molar equiv of *t*-BuLi at −78 °C. When 2.2 molar equiv of TMEDA was added and the resulting mixture was then allowed to stand at −40 °C for 1.5 h, 1-allyl-3,4-dimethylindoline (**38**) was isolated in 87% yield following quench of the reaction mixture with MeOH. In striking contrast to this result, an analogous experiment conducted in the presence of 2.2 molar equiv of (−)-sparteine and quenched with MeOD led exclusively to the formation of *N*,*N*-diallyl-2-deuterio-3-methylaniline (**39**). Given the rapid cyclization of **37** in the presence of TMEDA, the failure to observe any cyclic product when the reaction is conducted in the presence of (−)-sparteine was a surprise. One possibility, of course, is that sparteine does not form a complex with **37**. This does not appear to be the case.

SCHEME 2



As illustrated in Scheme 2, [2-(*N*,*N*-diallylamino)-6-methyl]phenyllithium (**37**) readily cyclizes in the absence of diamine ligand upon standing at room temperature for 1.5 h to give, after quench with MeOH, a 94% yield of 1-allyl-3,4-dimethylindoline (**38**). However, when 2 molar equiv of (−)-sparteine was added to **37** and the mixture was allowed to stand for an extended period (7 h) at room temperature, only 16% of the indoline was obtained; the major product (81%) was secondary amine **40**. The formation of **40** is likely the result of a [2,3]-sigmatropic rearrangement of the allylic anion initiated by removal of an allylic proton when the reaction mixture is warmed for an extended period.[16]

The cyclization of **37** does proceed in reasonable yield and with modest enantioselectivity when conducted in the presence of (1*R*,2*R*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (**10**). As illustrated in Scheme 3, (−)-1-allyl-3,4-dimethylindoline (**38**) is the major product of the reaction when **37** is allowed to stand for 1.5 h at −40 °C in the presence of 2 molar equiv of **10**. Moreover, the enantioselectivity of the cyclization (er = 85:15) is comparable to that observed for the cyclization of [2-(*N*,*N*-diallylamino)phenyl]lithium (**1**) in the presence of this ligand (Figure 1).

An unexpected feature of the cyclization of **37** is the fact that, whereas ring closure in the presence of (−)-sparteine produces (+)-**38**, the cyclization mediated by **10** affords the (−)-enantiomer. As noted above, cyclization

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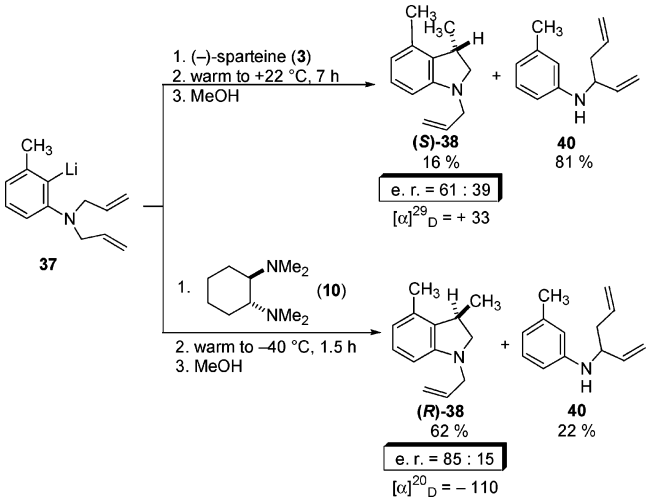
SCHEME 3



of the parent [2-(*N*,*N*-diallylamino)phenyl]lithium (**1**) in the presence of either (−)-sparteine or (1*R*,2*R*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (**10**) afforded the same product, viz., (*R*)-(−)-1-allyl-3-methylindoline (Figure 1 and Table 1, entries 1 and 5). On the assumption that cyclization of **37** in the presence of the cyclohexanediamine ligand (**10**) proceeds with the same facial selectivity as does the cyclization of **1** in the presence of this ligand, the absolute configurations of (+)- and (−)-1-allyl-3,4-dimethylindoline (**38**) are tenatively assigned as shown in Scheme 3.

Conclusions

The ability of a diverse set of chiral ligands to effect enantiofacially selective cyclization of 2-(*N*,*N*-diallylamino)phenyllithium (**1**) has been investigated. Although (−)-sparteine remains the best ligand for enantioselective cyclization of **1**, three structurally unrelated ligands, *cis*-1,5-diazadecalin (**13**), (1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane (**26**), and (1*S*,2*S*)-*N*,*O*-dimethylpseudoephedrine (**21**), which are available in either enantiomeric form, approach the efficiency of sparteine in this reaction. The *N*,*O*-dimethylpseudoephedrine ligand (**21**) is a particularly effective surrogate for sparteine, affording 1-allyl-3-methylindoline in good yield and high ee. The fact that seemingly minor variation in substrate structure (viz., **1** and **37**) may have a pronounced effect on the ability of a given ligand to facilitate the cyclization suggests that caution should be exercised in generalizing the results of this study to other substrates.

Experimental Section

Procedure for Ligand Screening in the Asymmetric Cyclization of [2-(*N*,*N*-Diallylamino)phenyl]lithium (1). A one-necked round-bottomed flask, fitted with a rubber septum and a magnetic spinbar was flame-dried under a stream of argon. The cooled, dry flask was charged with *N*,*N*-diallyl-2-bromoaniline (**2**) (typically 1.7−3.0 mmol) and sufficient solvent (Table 1) to give a 0.1 M solution of the aniline. The resulting solution was cooled to −78 °C in a dry ice−acetone bath, 2.2 molar equiv of *t*-BuLi in heptane was added dropwise over 5 min, and the solution was allowed to stir for approximately 10 min during which time a white precipitate was observed to form. The ligand (2.1−2.5 molar equiv) was

then added dropwise, and the cloudy, white-to-yellow mixture was stirred for an additional 7 min. The reaction vessel was then transferred to a constant-temperature bath maintained at −40 °C and stirred for 90 min prior to quench with 1.0 mL of dry, deoxygenated MeOD. The reaction mixture was poured onto 25 mL of water, residual material was transferred with 25 mL of diethyl ether, and the layers were separated. The aqueous layer was discarded, and the organic phase was washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Relative yields and the extent of deuterium incorporation, summarized in Table 1, were determined by GC and GC−MS analysis of an aliquot that was concentrated under a stream of nitrogen. Concentration of the remaining solution by rotary evaporation and medium-pressure chromatography of the residue on silica gel (9:1 hexanes−dichloromethane, $R_f = 0.21$) gave 1-allyl-3-methylindoline (**5**)[6a] as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.09−7.04 (m, 2H), 6.71−6.66 (m, 1H), 6.51 (d, J = 7.64 Hz, 1H), 5.98−5.84 (m, 1H), 5.32−5.16 (m, 2H), 3.82−3.52 (m, 3H), 3.30−3.27 (m, 1H), 2.84 (apparent t, J = 8.54 Hz, 1H), 1.28 (app d, J = 7.73 Hz, 2H). The enantiomeric excess was determined by CSP-GC as described in Supporting Information: the (*S*)-enantiomer eluted after 27.1 min, followed by the (*R*)-enantiomer at 28.2 min.

Procedure A: Eschweiler−Clarke Methylation of Amines. Tertiary amines were prepared following the procedure of Clarke[17] and worked up by the method of Cope.[18] Thus, 5.0 molar equiv of 96% aqueous formic acid was cooled to ∼0 °C in an ice−water bath, and 1.0 equiv of the amine was added slowly. A 37% aqueous formaldehyde solution (2.2 molar equiv) was then added in one portion, and the solution was heated until carbon dioxide evolution began at which time heating was discontinued. Once the formation of gas was no longer apparent, heating was resumed for 14−22 h. The cooled reaction mixture was then poured onto 1.1 molar equiv of ice-cold 10% aqueous hydrochloric acid and washed with four portions of diethyl ether. The pH of the aqueous phase was adjusted to 10 by the addition of solid NaOH pellets, and the solution was extracted with two portions of diethyl ether. The combined organic portions were dried over a potassium hydroxide−sodium sulfate mixture and concentrated by rotary evaporation. Rigorous drying of the product by heating with sodium metal and subsequent Kugelrohr distillation from fresh sodium provided the tertiary amines.

Procedure B: *O*-Methylation of *N,N*-Dialkylnorephedrines. A mixture of *N,N*-dialkylnorephedrine (1.0 equiv) and potassium *tert*-butoxide (1.2 equiv) was diluted at room temperature with enough THF to give a 0.1−0.5 M solution. After 15 min, iodomethane (1.3 equiv) was added dropwise and a white precipitate was observed to form after a few seconds. On a scale greater than 10 mmol, iodomethane should be added at 0 °C as precipitate formation is accompanied by a mild exotherm. The mixture was stirred for 1 h at room temperature and then concentrated by rotary evaporation. The residue was partitioned between water and ether, the phases were separated, and the organic portion was washed with brine, dried over sodium sulfate, and concentrated by rotary evaporation. In some cases the residue was purified by Kugelrohr distillation from sodium metal; however, in several instances, decomposition was evident upon addition of sodium.

(1*S*,2*S*)-(+)-*N,N*′-Bis(3,3-dimethylbutyl)-*N,N*′-dimethyl-1,2-diaminocyclohexane (11). Following Procedure A, 0.99 g (3.5 mmol) of (1*S*,2*S*)-(+)-*N,N*′-bis(3,3-dimethylbutyl)-1,2-cyclohexanediamine[19] gave 0.75 g (68%) of the title compound as a clear, colorless oil: bp 140−145 °C (5 mm); ^{13}C NMR ($CDCl_3$) δ 62.7, 50.1, 42.2, 37.0, 29.8, 29.6, 25.9, 25.2; $[\alpha]^{28}_D$ = +23.1 (*c* 1.71, CH_2Cl_2). Anal. Calcd for $C_{20}H_{42}N_2$: C, 77.35; H, 13.63; N, 9.02. Found: C, 77.07; H, 13.28; N, 9.09.

(1*S*,4*S*)-(+)-2,5-Dimethyl-2,5-diazabicyclo[2.2.1]-heptane (12). A solution of 10.8 g (39.3 mmol) of (1*S*,4*S*)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide[19] in 5.0 mL of water was cooled to 0 °C and the pH was adjusted to ∼8 by addition of 6 M aqueous sodium hydroxide. To this solution was slowly added 16.9 mL (393 mmol) of 96% aqueous formic acid, followed by 6.44 mL (86.5 mmol) of 37% aqueous formaldehyde solution, and the solution was heated until carbon dioxide evolution began at which time heating was discontinued. Once the formation of gas was no longer apparent, heating was resumed for 12 h, and the cooled reaction mixture was poured onto 30.0 mL (87.0 mmol) of ice-cold 10% aqueous hydrochloric acid and washed with four 30-mL portions of diethyl ether. The pH of the aqueous phase was adjusted to 10 by the addition of solid NaOH pellets, and this solution was continuously extracted with diethyl ether for 18 h. The organic portion was dried over a potassium hydroxide−sodium sulfate mixture and concentrated by rotary evaporation. Rigorous drying of the product by heating with sodium metal and subsequent Kugelrohr distillation from fresh sodium gave 2.24 g (45%) of a clear, colorless oil: bp 55−60 °C (13 mm); ^{1}H NMR ($CDCl_3$) δ 3.18 (m, 2H), 2.78−2.76 (m, 2H), 2.64−2.61 (m, 2H), 2.37 (s, 6H), 1.71 (app s, 2H); ^{13}C NMR ($CDCl_3$) δ 63.8, 57.0, 40.9, 33.2; $[\alpha]^{28}_D$ = +65.8 (*c* 2.97, CH_2Cl_2); HRMS calcd for $C_7H_{14}N_2$ 126.1157, found 126.1170.

(1*R*,2*S*)-(−)-*N,N*-Dibutyl-*O*-methylnorephedrine (15). Following General Procedure B, 4.74 g (20.1 mmol) of (1*R*,2*S*)-(+)-*N,N*-dibutylnorephedrine[19] afforded 4.01 g (72%) of the title compound as a yellow oil that was used without further purification. An analytical sample was prepared by preparative GC (10 ft, 10% SE-30, 190 °C): ^{1}H NMR ($CDCl_3$) δ 7.33−7.29 (m, 2H), 7.26−7.21 (m, 3H), 4.12 (d, J = 5.60 Hz, 1H), 3.20 (s, 3H), 2.85 (5-line pattern, J = 6.54 Hz, 1H), 2.41−2.37 (m, 4H), 1.28−1.12 (m, 8H), 1.03 (d, J = 6.71 Hz, 3H), 0.83 (t, J = 7.15 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 142.0, 127.8, 127.2, 126.9, 86.3, 60.7, 56.8, 50.4, 30.2, 20.5, 14.2, 9.3; $[\alpha]^{23}_D$ = −12.7 (*c* 1.61, CH_2Cl_2). Anal. Calcd for $C_{18}H_{31}NO$: C, 77.92; H, 11.26; N, 5.05. Found: C, 78.01; H, 11.03; N, 5.20.

(1*R*,2*S*)-(−)-1-Methoxy-1-phenyl-2-pyrrolidinylpropane (18). Following General Procedure B, 5.10 g (24.8 mmol) of (1*R*,2*S*)-(+)-1-phenyl-2-pyrrolidinyl-1-propanol[20] gave 4.30 g (79%) of the title compound as a clear, slightly yellow oil contaminated with ca. 5% of the starting alcohol (δ 0.79 (d, J = 6.64 Hz, 3H)). An analytically pure sample was prepared by preparative GC on a 10 ft, 10% SE-30 on Anakrom A (40 mesh) column: ^{1}H NMR ($CDCl_3$) δ 7.36−7.23 (m, 5H), 4.52 (d, J = 2.60 Hz, 1H), 3.32 (s, 3H), 2.71−2.65 (m, 4H), 2.42−2.40 (m, 1H), 1.86−1.78 (m, 4H), 0.97 (d, J = 6.68 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.5, 128.0, 126.9, 126.8, 84.4, 65.1, 57.2, 51.6, 23.4, 11.0; $[\alpha]^{22}_D$ = −59.6 (*c* 2.22, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.32; H, 9.47; N, 6.42.

(*R*)-(+)-*N,N*-Dimethyltetrahydrofurfurylamine (19). Following General Procedure A, 2.01 g (19.9 mmol) of (*R*)-(−)-tetrahydrofurfurylamine[19] afforded 1.85 g (72%) of the title compound as a clear, colorless oil: bp 60−65 °C (18 mm) [lit.[21] (racemate) bp 50 °C (13 mm)]; ^{1}H NMR ($CDCl_3$) δ 4.01−3.95 (m, 1H), 3.90−3.84 (m, 1H), 3.77−3.71 (m, 1H), 2.45−2.40 (m, 1H), [overlapping patterns, 2.32−2.27 (m, 1H), 2.28 (s, 6H)], 2.03−1.95 (m, 1H), 1.91−1.84 (m, 2H), 1.54−1.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 76.9, 67.8, 64.2, 46.0, 30.1, 25.4; $[\alpha]^{24}_D$ = +4.21 (*c* 1.76, CH_2Cl_2).

(1*S*,2*R*)-(−)-1-Dimethylamino-2-methoxyindan (20). The amino-ether was prepared according to General Procedure B. Thus, 2.84 g (16.0 mmol) of (1*S*,2*R*)-(+)-1-(dimethylamino)-2-indanol[22] and 2.20 g (19.6 mmol) of potassium *tert*-butoxide

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were combined under an atmosphere of argon and diluted with 32 mL of THF. After 15 min of stirring, the reaction vessel was cooled to 0 °C, and 1.30 mL (20.8 mmol) of iodomethane was added via syringe. The cooling bath was then removed, and stirring was continued for 1 h. After concentration and standard workup, 3.09 g (>100%) of 93% pure material was obtained (remainder starting alcohol). Preparative GC (10 ft, 10% SE-30, 200 °C) afforded an analytically pure sample of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.32−7.31 (m, 1H), 7.26−7.21 (m, 3H), 4.24−4.16 (m, 2H), 3.47 (s, 3H), 3.09−2.96 (m, 2H), 2.39 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.5, 139.5, 127.9, 126.3, 126.2, 125.0, 82.9, 69.1, 57.6, 42.2, 37.0; $[\alpha]^{23}_D = -96.7$ (*c* 1.47, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.04; H, 8.83; N, 7.39.

(1*S*,2*S*)-(+)-*N*-Methyl-*O*-ethylpseudoephedrine (22). Following a modification of General Procedure B, a solution of 3.34 g (18.6 mmol) of (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine[19] in 37 mL of THF was treated with 5.22 g (46.6 mmol) of potassium *tert*-butoxide for 15 min at 0 °C. A 3.48 mL (46.6 mmol) portion of ethyl bromide was added dropwise via syringe, and the reaction mixture was allowed to stir at room temperature for 1 h. After concentration and workup in the usual way, 3.22 g (83%) of a clear, pale yellow oil was obtained: bp 150 °C (6 mm); ^{1}H NMR ($CDCl_3$) δ 7.34−7.24 (m, 5H), 4.16 (d, J = 8.60 Hz, 1H), 3.35−3.23 (m, 2H), 2.94−2.87 (m, 1H), 2.39 (s, 6H), 1.14 (t, J = 7.01 Hz, 3H), 0.66 (d, J = 6.79 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.6, 128.1, 127.8, 127.5, 84.1, 63.7, 63.5, 41.0, 15.3, 11.2; $[\alpha]^{27}_D = +82.7$ (*c* 7.35, CH_2Cl_2); HRMS−FAB $[M + 1]^+$ calcd for $C_{13}H_{22}NO$ 208.1701, found 208.1707.

(1*S*,2*S*)-(+)-*N*-Ethyl-*O*-ethylpseudoephedrine (23). The amino ether was prepared by modification of General Procedure B. Thus, a solution of 5.96 g (30.8 mmol) of (1*S*,2*S*)-(+)-*N*-ethylpseudoephedrine[23] in 123 mL of THF was treated with 8.63 g (77.0 mmol) of potassium *tert*-butoxide for 15 min at 0 °C. A 5.75 mL (77.0 mmol) portion of ethyl bromide was added dropwise via syringe, and the reaction mixture was allowed to warm to room temperature and stir for 1 h. After standard workup and concentration, the crude product was found to be a ~7:3 mixture of product and starting material, as determined by GC−MS analysis. This material was resubjected to the conditions described above and purified in the usual way to afford 4.64 g (68%) of a clear, pale yellow oil: bp 155 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 7.37−7.22 (m, 5H), 4.18 (d, J = 8.43 Hz, 1H), 3.34−3.21 (m, 2H), 3.03−2.96 (m, 1H), 2.72−2.53 (m, 2H), 2.37 (s, 3H), 1.13 (t, J = 7.01 Hz, 3H), 1.08 (t, J = 7.14 Hz, 3H), 0.70 (d, J = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.0, 128.3, 128.0, 127.6, 84.7, 64.0, 62.7, 48.0, 37.7, 15.6, 14.1, 12.7; $[\alpha]^{23}_D = +92.4$ (*c* 3.95, CH_2Cl_2). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.71; H, 10.65; N, 6.51.

(1*S*,2*S*)-(+)-*N*-Ethyl-*O*-methylpseudoephedrine (24). Following General Procedure B, 4.82 g (24.9 mmol) of (1*S*,2*S*)-(+)-*N*-ethylpseudoephedrine[23] afforded 3.95 g (77%) of the title compound as a clear, pale yellow oil: bp 150 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 7.37−7.24 (m, 5H), 4.03 (d, J = 8.83 Hz, 1H), 3.14 (s, 3H), 3.05−2.98 (m, 1H), 2.70−2.61 (m, 1H), 2.54−2.46 (m, 1H), 2.33 (s, 3H), 1.10 (t, J = 7.15 Hz, 3H), 0.64 (d, J = 6.80 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.2, 128.3, 127.9, 127.7, 86.4, 62.2, 56.5, 47.6, 37.3, 13.9, 10.7; $[\alpha]^{22}_D = +103$ (*c* 4.50, CH_2Cl_2); HRMS−FAB $[M + 1]^+$ calcd for $C_{13}H_{22}NO$ 208.1701, found 208.1711.

(1*S*,2*S*)-(+)-*N*-Isopropyl-*O*-methylpseudoephedrine (25). Following General Procedure B, 4.11 g (19.8 mmol) of (1*S*,2*S*)-(+)-*N*-isopropylpseudoephedrine[23] afforded 2.16 g (49%) of the title compound as a clear, pale yellow oil: bp 150 °C (2 mm); ^{1}H NMR ($CDCl_3$) δ 7.37−7.24 (m, 5H), 4.02 (d, J = 7.60 Hz, 1H), 3.16 (s, 3H), 3.14−3.06 (m, 1H), 2.97 (app sep, J = 6.47 Hz, 1H), 2.24 (s, 3H), 1.07 (d, J = 6.47 Hz, 3H), 1.02 (d, J = 6.47 Hz, 3H), 0.75 (d, J = 6.87 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 141.6, 128.2, 128.1, 127.6, 87.2, 59.4, 56.9, 52.4, 32.6, 21.0, 20.0, 13.5; $[\alpha]^{27}_D = +90.6$ (*c* 4.40, CH_2Cl_2). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.59; H, 10.10; N, 6.31.

***N*,*N*-Diallyl-2-bromo-3-methylaniline (36).** Following the general procedure of Tidwell and Buchwald,[24] 1.79 g (9.63 mmol) of 2-bromo-3-methylaniline,[25] 4.08 g (38.5 mmol) of sodium carbonate, and 3.33 mL (38.5 mmol) of allyl bromide were added to 40 mL of dry DMF, and the resulting mixture was heated at reflux under an atmosphere of argon for 8 h. Upon cooling, the salts were removed by filtration, and the mother liquor was partitioned between diethyl ether and water. The layers were separated, and the aqueous phase was extracted twice with diethyl ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated. The crude yellow oil was purified by Kugelrohr distillation to give 2.29 g (89%) of the clear, slightly yellow oil: bp 82−86 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 7.09 (apparent t, J = 7.76 Hz, 1H), 6.94−6.86 (m, 2H), 5.89−5.76 (m, 2H), 5.21−5.07 (m, 4H), 3.66−3.64 (m, 4H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.3, 139.6, 135.0, 126.5, 125.7, 124.4, 121.6, 117.4, 55.6, 24.2. Anal. Calcd for $C_{13}H_{16}NBr$: C, 58.66; H, 6.06; N, 5.26. Found: C, 58.50; H, 6.08; N, 5.36.

(±)-1-Allyl-3,4-dimethylindoline (38). A solution of 323 mg (1.21 mmol) of *N*,*N*-diallyl-2-bromo-3-methylaniline (**36**) in 10.9 mL of *n*-pentane and 1.2 mL of diethyl ether was cooled to −78 °C under an atmosphere of argon, and 1.34 mL of a 1.99 M solution of *t*-BuLi in heptane (2.67 mmol) was added dropwise over a 5 min period. The resulting mixture was stirred at −78 °C for 10 min before addition of 0.40 mL (2.67 mmol) of TMEDA. After 10 min at −78 °C, the mixture was transferred to a thermostated bath at −40 °C and stirred for 1.5 h before addition of 1.2 mL of dry, deoxygenated MeOH. The reaction mixture was partitioned between 15 mL of water and 15 mL of diethyl ether, and the organic portion was washed with water, saturated aqueous ammonium chloride, and brine. After drying over magnesium sulfate, concentration by rotary evaporation gave 0.201 g (89%) of 85% pure indoline. Preparative GC (10 ft, 10% FFAP, 200 °C) afforded analytically pure clear and colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.98 (apparent t, J = 7.70 Hz, 1H), 6.48 (d, J = 7.56 Hz, 1H), 6.35 (d, J = 7.80 Hz, 1H), 5.94−5.84 (m, 1H), 5.29−5.23 (m, 1H), 5.18−5.15 (m, 1H), 3.79 (m, 1H), 3.58 (m, 1H), 3.35 (apparent t, J = 8.49 Hz, 1H), 3.31−3.23 (m, 1H), 3.09 (dd, J = 8.49, 2.61 Hz, 1H), 2.25 (s, 3H), 1.23 (d, J = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.2, 134.3, 133.6, 133.4, 127.5, 119.5, 117.0, 105.0, 60.8, 51.8, 34.2, 19.0, 18.1. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.13; H, 9.51; N, 7.39.

Preparation of (*S*)-(+)-1-Allyl-3,4-dimethylindoline [(*S*)-38]: An Unexpected [2,3]-Sigmatropic Rearrangement in the Presence of (−)-Sparteine. A solution of 385 mg (1.45 mmol) of *N*,*N*-diallyl-2-bromo-3-methylaniline (**36**) in 13.1 mL of *n*-pentane and 1.4 mL of diethyl ether was cooled to −78 °C under an atmosphere of argon, and 1.60 mL of a 1.99 M solution of *t*-BuLi in heptane (3.18 mmol) was added dropwise over a 5 min period. A white precipitate formed, and after 10 min at −78 °C 0.800 g (3.41 mmol) of (−)-sparteine was added dropwise (the solution was noted to turn a cloudy yellow color). The mixture was stirred for an additional 10 min at −78 °C, the cooling bath was removed, and the solution was allowed to stir for 7 h at room temperature before quench with 1.4 mL of dry, deoxygenated MeOH. The mixture was partitioned between water and pentane, and the organic portion was washed with saturated aqueous ammonium chloride, and brine

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and dried over magnesium sulfate. Concentration afforded 0.180 g (66%) of an oil consisting of three isomeric compounds: *N*,*N*-diallyl-3-methylaniline (3%), (+)-1-allyl-3,4-dimethylindoline (16%), and *N*-(1-vinylbut-3-enyl)-3-methylaniline (81%). The minor products proved to be spectroscopically identical to independently prepared samples of *N*,*N*-diallyl-3-methylaniline (**39**)[26] and (±)-1-allyl-3,4-dimethylindoline (**38**). Isolation of the indoline by preparative GC (10 ft, 15% FFAP, 200 °C) and subsequent analysis by CSP-GC (30 m, G-TA, 110 °C) indicated an enantiomeric excess of 29.6%. A 22% ee sample of the indoline prepared under conditions differing from those described above had the following specific rotation: $[\alpha]^{29}_{D} = +33$ (*c* 0.33, CH_2Cl_2). The major product was identified as *N*-(1-vinylbut-3-enyl)-3-methylaniline (**40**) based upon the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ 7.04 (dd, *J* = 7.64, 7.64 Hz, 1H), 6.52−6.50 (m, 1H), 6.43 (m, 2H), 5.82−5.78 (m, 2H), 5.26−5.12 (m, 4H), 3.91−3.89 (m, 1H), 2.41−2.35 (m, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.5, 139.6, 138.9, 134.5, 129.0, 118.4, 118.0, 115.1, 114.3, 110.6, 54.9, 40.1, 21.6; HRMS calcd for $C_{13}H_{17}N$ 187.1361, found 187.1379.

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Supporting Information Available: General experimental methods and copies of the ^{1}H and ^{13}C NMR spectra of compounds **11**, **12**, **15**, **18**−**20**, **22**−**25**, **36**, **38**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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