Stereo- and Regioselective Synthesis of Chiral Diamines and Triamines from Pseudoephedrine and Ephedrine

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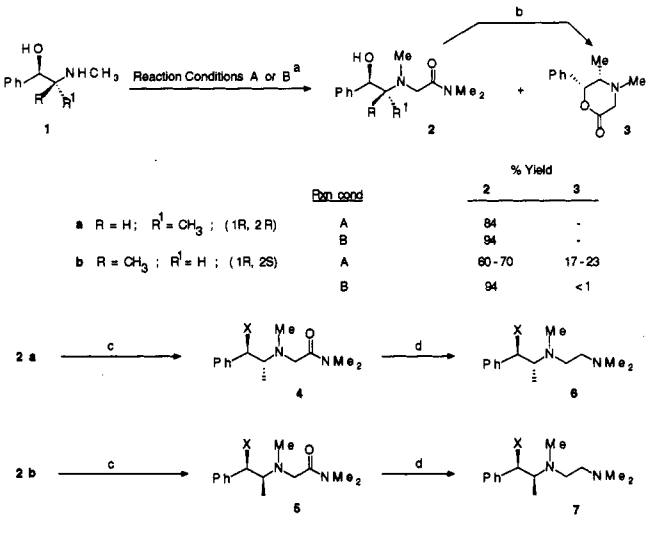
N-Alkylated derivatives of (1*R*,2*R*)-(−)-pseudoephedrine and (1*R*,2*S*)-(−)-ephedrine afford, upon reaction with methanesulfonyl chloride, mixtures of 1-chloro- and 2-chloroamines which undergo stereospecific and regiospecific substitution reactions with sodium azide, amines, imides, thiols, thiolacetic acid, *N*-hydroxyphthalimide, and diphenylphosphine to give, in each case, a single isomeric product. These substitution reactions proceed with net retention of configuration. The procedure is not readily extended to nonbenzylic systems which give widely varying yields and regioisomeric ratios. The methodology provides for a facile synthesis of chiral diamines, triamines, aminohydroxylamines, aminothiols, aminosulfides, and aminophosphines from chiral 1,2-amino alcohols wherein either the amine or alcohol functionality is benzylic.

Introduction and Background

Vicinal diamines are an important class of compounds useful as chelating agents in radiopharmaceuticals,[1] precursors in the synthesis of azamacrocycles[2] and heterocyclic compounds,[3] and in medicinal chemistry.[4] Chiral vicinal diamines and their derivatives have been used as chiral auxiliaries in a variety of asymmetric transformations involving chiral phosphonamides,[5] Lewis acids[6a] or electrophiles,[6b-3] metal enolates,[7] dienophiles,[8] and transition-metal reagents.[9] Synthetic routes to these compounds are often limited in scope, and few procedures provide for regio- and stereoselective control during synthesis. Chiral vicinal diamines and bis-vicinal triamines have also proven to be useful ligands in asymmetric organocopper conjugate addition reactions.[10]

Vicinal diamines can be prepared by reduction of α-aminoamides[1b,11] or nitriles,[12] bisamides of oxalic acid,[13] diimines[14] and bisoximes[15] derived from 1,2-diketones, and by reductive amination of α-amino ketones.[16] α-Amino amides are readily available from α-amino acids and provide a convenient route to chiral vicinal diamines which can also be prepared via intermediate α-amino aldehydes.[17] Symmetrical vicinal diamines can be constructed very rapidly by metal (Ti,[18] Nb,[19] alkali metals,[20a,b] and alkali earth metals[20c]) catalyzed coupling reactions of imines to afford *dl* and meso mixtures of diastereomers. Separation of diastereomers and resolution of the *dl*-diastereomer affords the chiral diamines. An alternative to transition-metal-mediated coupling is the addition of Grignard reagents to or reduction of mixed aminals derived from glyoxal, benzotriazole, and a primary or secondary amine.[21]

Scheme I[a]



[a] Key: (a) A = $ClCH_2CONMe_2$, Na_2CO_3 (1.5 equiv), NaI (1.5 equiv), PhH, reflux, 20 h; B = $ClCH_2CONMe_2$, PhH, Et_3N, reflux; (b) Na_2CO_3, xylene, reflux; (c) (i) Mesyl chloride; (ii) RNH_2 or NaN_3; (d) $LiAlH_4$.

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Since the synthetic routes involving carbon–carbon bond formation generate racemic material, asymmetric synthesis of chiral vicinal diamines is heavily dependent upon functional group substitution chemistry of chiral starting materials derived from the chiral pool or by asymmetric synthesis. Nucleophilic opening of aziridines has been utilized in a recent synthesis of 1,2-diaminopropanes from 1,3-diamino-2-propanol.[1a] Primary vicinal diamines have been prepared by reduction of diazides prepared from olefins,[22a] dihalides,[22b] or cyclic sulfates.[23] The latter procedure allows for the preparation of chiral diamines since the cyclic sulfates are derived from chiral diols available by asymmetric hydroxylation.[9d,e,24] The cyclic sulfates can also be converted to aziridines which can be opened by amines.[25] Chiral vicinal diamines have also been prepared by a multistep synthesis involving asymmetric iodoamination.[26]

During the course of our work on asymmetric induction in organocopper conjugate addition reactions we required a series of chiral di- and triamines for use as ligands.[10a] A highly stereo- and regioselective route to these compounds from ephedrine and pseudoephedrine was developed.[27] In this the full account of our work, we describe in detail the conversion of ephedrine and pseudoephedrine into a series of di- and triamines and the examination of this methodology in the utilization of vicinal amino alcohols derived from α-amino acids. The scope and generality of the method is also explored with a variety of nucleophiles.

Results

The β-hydroxy-*tert*-amines **2a,b** used in this study were readily obtained by alkylation of (1*R*,2*R*)-(−)-pseudoephedrine (**1a**) and (1*R*,2*S*)-(−)-ephedrine (**1b**), respectively, with α-chloro-*N*,*N*-dimethylacetamide[28] (Scheme I). Pseudoephedrine cleanly afforded amide **2a** with either Na_2CO_3 or Et_3N while ephedrine gave substantial amounts of **3** which could be completely avoided by use of Et_3N. Cyclization of **2b** to **3** could be effected with Na_2CO_3 in xylene heated to reflux, and **3** could also be prepared by treatment of the ethyl ester corresponding to **2b** with *p*-TsOH in hot benzene according to an established procedure.[29]

Initial attempts to mesylate (CH_3SO_2Cl, Et_3N, THF) **2b** gave only recovered starting alcohol upon aqueous workup while **2a** gave predominantly a single compound which neat or in solution slowly changed into a mixture of products that did not display ^1H NMR or IR absorptions for the methanesulfonyl group. Reaction of the single compound or of the mixture with aniline gave a single diamino amide **4b**. X-ray analysis[30] confirmed that the substitution reaction had proceeded regiospecifically and stereospecifically with retention of configuration. Similarly clean results were obtained with *n*-butylamine and cyclohexylamine to afford diamino amides **4c,d** (Table I). Treatment of **2a** with mesyl chloride followed by sodium azide afforded azide **4a** in lower but good yield. Compounds **4a–d** display in the ^1H NMR spectra vicinal coupling constants of 9.7–10.0 Hz for the benzylic proton which is characteristic of the pseudoephedrine relative stereochemistry in this series.

Table I. Synthesis of Chiral Triamines from Pseudoephedrine and Ephedrine

amino alcohol	procedure[a]	substitution product (% yield)[b]	triamine[c] (% yield)[d]
2a	A	**4a** (70)	**6a** (60)
	B	**b** (90)	**b** (70)
	B	**c** (92)	**c** (83)
	B	**d** (90)	**d** (82)
2b	A	**5a** (66)	**7a** (60)
	B	**b** (89)	**b** (70)
	B	**c** (94)	**c** (82)
	B	**d** (90)	**d** (82)

[a] A = i. Et_3N, CH_3SO_2Cl, THF. ii. NaN_3, HMPA, 80 °C, 12 h. B = i. Et_3N, CH_3SO_2Cl, THF. ii. RNH_2, PhH, Et_3N, reflux, 12 h. [b] Yields are based upon crude products >95% pure by ^1H NMR. [c] The triamines are prepared by $LiAlH_4$ redn. of the amides. [d] Overall yields from **2a** or **2b** are based upon isolated purified products.

Similarly, sequential treatment of **2b** with mesyl chloride and sodium azide or an amine gave amides **5a–d** in good to excellent yields (Table I). That the substitution had proceeded with retention of configuration was confirmed by single-crystal X-ray analysis[30] of amide **5b**. Compounds **5a–d** display in the ^1H NMR spectra vicinal coupling constants of 4.1–8.1 Hz for the benzylic proton and these smaller values, in contrast to the larger values observed in the pseudoephedrine derivatives, are characteristic of the ephedrine relative stereochemistry in this series. Reduction of azides **4a** and **5a** and amides **4b–d** and **5b–d** with lithium aluminum hydride proceeded uneventfully to afford triamines **6a–d** and **7a–d**, respectively, in good yields (60–83%).

These procedures were also readily extended to (1*R*,2*S*)-*N*-ethylephedrine (**8**), (1*R*,2*S*)-*N*-methylephedrine (**9**), (1*R*,2*R*)-*N*-ethylpseudoephedrine (**10**), and the N,N-bis-protected (2*R*)-phenylglycinol **11** (Table II). The *N*-ethyl derivatives were readily prepared by N-acylation followed by lithium aluminum hydride reduction while **11** was prepared by $LiAlH_4$ reduction of the phthalimide of (*R*)-(−)-2-phenylglycine. The yields in this series proved to be significantly lower (20%) with the amine nucleophiles. Phthalimide was examined as an alternative source of a masked "NH_2" unit and gave an excellent yield of the substitution product **15b**. Amino alcohol **11**, in contrast to amino alcohol **9**, gave a good yield of the substitution product **17** with *n*-$BuNH_2$. The NMR spectra of compounds **14a,b**, **15a**, and **16** display characteristically smaller coupling constants for the benzylic proton in the ephedrine series (**14a,b**, **15a**: J = 4.2–5.2 Hz) than in the pseudoephedrine series (**16**: J = 9.9 Hz). The phthalimide derivatives of **14a** and **16** display vicinal coupling constants for the benzylic proton comparable to that of **15b** (J = 10.5–11.7 Hz) so that relative stereochemistry cannot be assigned on the basis of coupling constants in this series.

Amino alcohol **12** was prepared by bis-methylation[31] of 2-amino-2-methylpropanol, and **13** was prepared by $LiAlH_4$

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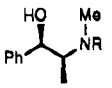
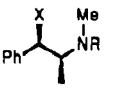
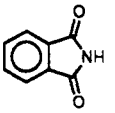
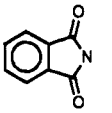
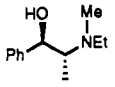
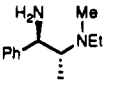
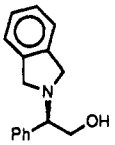
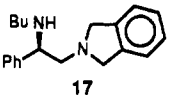
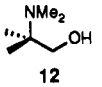
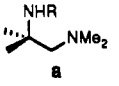
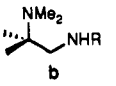
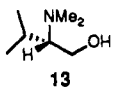
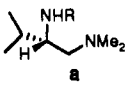
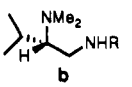
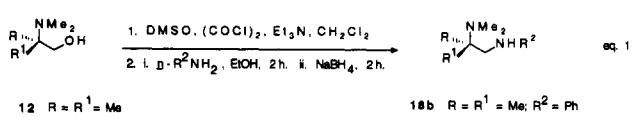
Table II. Reaction of Amino Alcohols with Mesyl Chloride and Various Nucleophiles

amino alcohol	nucl	proc[a]	product	% yield[b] (ratio a:b)
				
8, R = Et	NaN_3	A	**14a**, X = NH_2	72
	c-$C_6H_{11}NH_2$	B	**b**, X = c-C_6H_{11}NH	70
9, R = Me	*n*-$BuNH_2$	B	**15a**, X = *n*-BuNH	50
		B	**b**, X = 	96
	NaN_3	A		70
10			**16**	
	*n*-$BuNH_2$	B		85
11			**17**	
				
12			**a**	**b**
	$PhNH_2$	A	**18**, R = Ph	63 (100:0)
	n-$BuNH_2$	C	**19**, R = *n*-Bu	45 (50:50)
				
13			**a**	**b**
	$PhNH_2$	C	**20**, R = Ph	55 (mixture)[c]
	n-$BuNH_2$	C	**21**, R = *n*-Bu	45 (22:78)

[a] A = i. MsCl, Et_3N, THF. ii. NaN_3, HMPA, 80 °C, 12–16 h. iii. $LiAlH_4$, THF. B = i. MsCl, Et_3N, THF. ii. PhH, Et_3N, nucleophile, reflux. C = i. *n*-BuLi, PhH. ii. MsCl. iii. RNH_2, Et_3N, 25 °C. [b] Yields are based upon isolated purified products. [c] This reaction gave varied results for several experiments.

reduction of (*S*)-(+)-valine followed by bis-methylation. Sequential treatment of **12** with mesyl chloride and aniline afforded a single isomer in good yield that was initially assumed to be the rearranged regioisomer. Utilization of an aliphatic amine, however, gave two regioisomers **19a** and **19b** as a 1:1 mixture. Less basic nitrogen nucleophiles such as phthalimide afforded no substitution product in marked contrast to the excellent yield of **15b** obtained from **9**.

Treatment of (*S*)-*N*,*N*-dimethylvalinol (**13**) under the standard conditions did not afford a substitution product with aniline and gave a complex mixture of products with butylamine. The reactions could be achieved by carrying the reaction sequence out at room temperature to afford a 50:50 mixture of regioisomers **20a** and **20b** with aniline and a 22:78 mixture of regioisomers with *n*-butylamine. The reaction of aniline with **13** was problematic and sometimes yielded predominantly a product that appeared to be the rearranged amino alcohol. The formation of a single product from reaction of **12** with aniline and two isomers from reaction with *n*-butylamine required a procedure to distinguish between the two possible regioisomers. That rearrangement had indeed occurred was confirmed by synthesis of the unrearranged regioisomers **18b**, and **21b** (eq 1). This was achieved by oxidation[32] of amino



eq 1

12 R = R^1 = Me
13 R = ^{i}Pr; R^1 = H
18b R = R^1 = Me; R^2 = Ph
21b R = ^{i}Pr; R^1 = H; R^2 = *n*-Bu

Table III. Reaction of Amino Alcohols with Mesyl Chloride and Various Nucleophiles

amino alcohol	nucleophile	procedure[a]	product[b]	% yield
9	*N*-hydroxyphthalimide	A	**22**	98
	CH_3COSH	A	**23**	73
	n-PrSH	A	**24**	96
	Ph_2PH	A	**25**[c]	49
13	*n*-PrSH	A or B	**26**	70–80

[a] A = i. MsCl, Et_3N, THF. ii. PhH, Et_3N, nucleophile, reflux. B = i. *n*-BuLi, PhH. ii. MsCl. iii. nucleophile, Et_3N, 24 h. [b] Overall yields from **9** or **13** are based upon isolated products. [c] Isolated as the phosphine oxide.

alcohols **12** and **13** to the amino aldehydes followed by reductive amination[33] to afford regiospecifically the diamines **18b** and **21b**, respectively. The spectroscopic data for **18b** were inconsistent with diamine **18a** obtained from **12** confirming that rearrangement had occurred, while **21b** was identical with the major isomer obtained from **13**.

The reaction of (1*R*,2*S*)-(−)-*N*-methylephedrine (**9**) and (2*S*)-(+)-*N*,*N*-dimethylvalinol (**13**) with mesyl chloride followed by a variety of non-nitrogen nucleophiles was briefly examined (Table III). N-hydroxyphthalimide,

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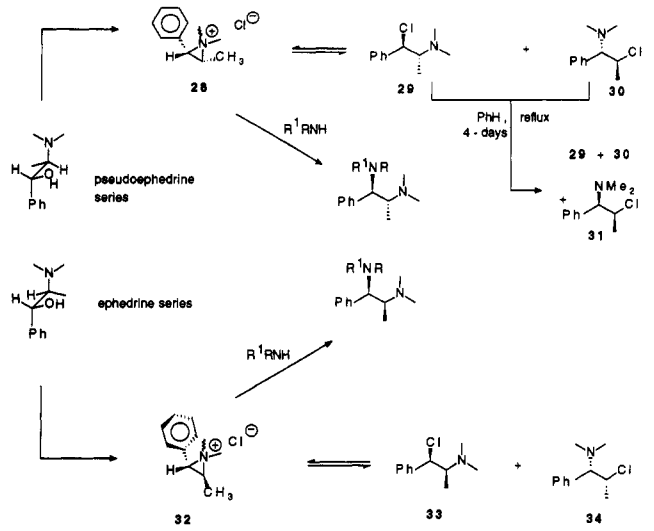
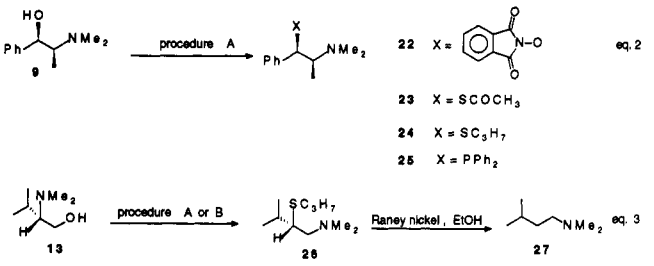
(33) Saavedra, J. *J. Org. Chem.* **1985**, *50*, 2271.

Scheme II



thiolacetic acid, and propanethiol all gave good yields of the corresponding substitution products from **9** (eq 2).



The small vicinal coupling constant (J = 6.4 Hz) for the benzylic proton in alkoxyamine **22** is consistent with the ephedrine relative stereochemistry indicating that the substitution proceeded with retention of configuration as previously observed with amine nucleophiles. Modest yields were obtained with diphenylphosphine as the nucleophile. Sequential treatment of **13** with mesyl chloride and propanethiol afforded predominantly one regioisomer tentatively assigned as the rearranged isomer **26**. This was confirmed by Raney nickel desulfurization to afford **27** (eq 3).

Discussion

The net retention of configuration observed in these substitution reactions suggests neighboring-group participation by either the tertiary amine or amide functionality in **2a,b** while only the tertiary amine functionality is available for participation in amino alcohols **8–13**. The cis cyclization product **3** derived from ephedrine is inconsistent with formation by intramolecular participation of the amide carbonyl. The cis substitution parttern in **3** was established from ^{1}H NMR coupling constants ($J_{ax,eq}$ = 3.5 Hz for the benzylic proton) and by alternative modes of preparation requiring nucleophilic acyl substitution of the amide functionality by the benzylic hydroxyl group.

Neighboring-group participation of the tertiary amine functionality in amino alcohols **2** and **8–13** provides the most plausible explanation for the observed stereo- and regioselectivities in these substitution reactions. Treatment of the amino alcohols with mesyl chloride affords an unstable mesylate that undergoes reaction with the neighboring tertiary amine to afford an aziridinium ion (e.g., **28** or **32**, Scheme II). Aziridinium ions have been postulated in substitution reactions of amino tosylates[34a] and in the Mitsunobu reaction[34b] of amino alcohols. Although an aziridinium salt is postulated as the intermediate undergoing reaction with the amine nucleophiles, the experimental evidence suggests a more complicated sequence.

Although a crude mixture of two principal intermediates can be obtained from either the ephedrine or pseudoephedrine derivatives upon attempted mesylation under nonaqueous workup conditions, aqueous workup affords only starting alcohol in the ephedrine series and a varying proportion of the two intermediates in the pseudoephedrine series. Treatment of the pseudoephedrine-derived amide **2a** with mesyl chloride and Et_3N affords predominantly a single product showing characteristic benzylic (δ 4.77, J = 9.0 Hz, 1 H) and methyl (δ 0.80, d, J = 7.2 Hz) absorptions in the ^{1}H NMR spectrum with a trace of a minor component showing significantly different absorptions for the benzylic (δ 3.63, d, J = 9.9 Hz) and methyl (δ 1.29, d, J = 6.3 Hz) absorptions. The methyl absorption at δ 1.29 in the minor component is characteristic of a methyl group on a carbon bearing a chlorine atom[35a] (δ 1.33 for CH_3 in CH_3CH_2Cl). The increase in the minor component over time and the complementary downfield shift of the methyl group and upfield shift of the benzylic proton are suggestive of a rearrangement from chloroamine **29** to chloroamine **30** (Scheme II). In fact, rather similar reaction conditions have been employed in the preparation of alkyl chlorides from alcohols.[36] The occurrence of these rearranged products in both series was confirmed by treating **9** and the N-methyl analogue of **10** with $MsCl/Et_3N/PhH$ in an NMR tube and monitoring the mixtures over time. Both samples displayed methyl and benzylic absorptions consistent with unrearranged (from **9**, Me: δ 1.10, d, J = 6.4 Hz. PhCH: δ 4.60, d, J = 8.1 Hz. From the N-methyl analogue of **10**, Me: δ 0.53, d, J = 6.7 Hz. PhCH: δ 4.63, d, J = 8.8 Hz) and rearranged (from **9**, Me: δ 1.35, d, J = 6.6 Hz. PhCH: δ 3.00, d, J = 7.3 Hz. From the N-methyl analogue of **10**; Me: δ 1.20, d, J = 6.6 Hz. PhCH: δ 3.26, d, J = 8.0 Hz) chloroamines. Although, in general, the ephedrine series displays a smaller vicinal coupling constant for the benzylic proton than that observed in the pseudoephedrine derivatives, the magnitude of this difference varies widely depending upon the electronegativity[35b] and orientation of the substituent and on the carbon-substituent bond length. The ephedrine and pseudoephedrine derivatives containing the phthalimide substituent or substituents with third row atoms (e.g., Cl and S) display vicinal coupling constants of comparable magnitude for the benzylic proton. These considerations demand caution in using coupling constants to assign relative stereochemistry in these series of compounds.

Since both **29** and **30** react with amines to give the same product, the absolute configurations of the stereogenic centers in the rearranged chloroamine **30** can be assigned as 1*S*,2*S* requiring inversion at both centers consistent with anchimeric assistance. Chloroamines **29** and **30** can only give the same substitution product if **30** is converted into **29** prior to reaction with nucleophiles or if **29** and **30** undergo reaction with nucleophiles via the common aziridi-

(34) (a) Rosen, T.; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis* **1988**, 40 and references cited therein. (b) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670.

(35) (a) Jackman, L. M.; Sternhell, S. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd ed.; Pergamon Press Ltd: London, 1969; Chapter 32, p 164; (b) *Ibid.* Chapter 4-2, p 283–284.

(36) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295.

nium ion **28** which seems far more likely. The instability to aqueous workup of the chloroamines derived from the ephedrine series and the initial absence of rearranged chloroamine **34** in the ephedrine series can be accounted for on the basis of aziridinium ion stability and hence reaction rates. These observations are consistent with the increased stability of **32** relative to **28** as a result of steric interactions and perhaps electronic effects involving resonance interaction with the phenyl ring in the trans-substituted aziridinium ion **32** generated from the ephedrine derivatives. Steric hindrance in the cis-substituted aziridinium ion **28** derived from the pseudoephedrine derivatives raises the energy barrier leading to its formation by simple steric effects and perhaps by an electronic effect arising from a diminished overlap of the aromatic π-system with the aziridinium-C–N bond. In either event, conformational steric effects or electronic effects will diminish the rate of nucleophilic attack on aziridinium ion **28** relative to **32** resulting in competitive attack at the nonbenzylic position of **28** leading to the rearranged product **30**. Formation of the thermodynamically or kinetically more stable nonbenzylic halide provides the driving force for the rearrangement in both series. Prolonged heating of **29** and **30** in benzene affords after 4 days a mixture of **29**, **30**, and **31**. The formation of **31** requires epimerization at one of the stereogenic centers in **29** or **30**, and **31** is assigned as the enantiomer of **34** assuming that epimerization occurs at the benzylic carbon.

This picture is also consistent with the results obtained in the aliphatic series involving amino alcohols **12–13**. With strong nucleophiles (e.g., *n*-$BuNH_2$) a mixture of regioisomers is obtained while weaker nucleophiles (e.g., $PhNH_2$) give either the rearranged product (with **12**) or a mixture of the two regioisomers (with **13**). Less basic nucleophiles such as propanethiol give predominantly the rearranged product with **13**. The products then are a result of a subtle balance between the effects of aziridinium ion stability, nucleophilicity of the nucleophile, and steric factors upon the relative reaction rates for the paths leading to the regioisomeric substitution products and/or side products.

Summary

Reaction of 1-phenyl or 2-phenyl-1,2-*N*,*N*-dialkylamino alcohols with methanesulfonyl chloride under a variety of conditions affords 1,2-chloroamines which undergo stereo- and regiospecific substitution reactions with nitrogen, sulfur, phosphorous, and oxygen nucleophiles with net retention of configuration. Although the benzyl alcohols lead to unstable benzyl chlorides which rearrange to afford a mixture of the benzyl and nonbenzylic chlorides, both the unrearranged and rearranged chloroamines react with nucleophiles via a common aziridinium ion intermediate to afford the same product. The method works well only for the benzylic derivatives since aliphatic amino alcohols give widely varying yields and regioselectivities. This method should be useful for the preparation of chiral bi- and tridentate ligands from the chiral pool using substrates that complement the amino acids.

Experimental Section

NMR spectra were recorded as $CDCl_3$ solutions and obtained on spectromers operating at 90 and 300 MHz for ^1H NMR and at 22.5 and 75.5 MHz for ^{13}C NMR and are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS). The carbon NMR chemical shifts are referenced with respect to internal $CDCl_3$ (δ 77.0 for center line). Melting points are uncorrected. Elemental analyses were determined by Atlanta Microlab Inc., Atlanta, GA. The optical rotations observed for compounds obtained by metal hydride reductions must be used with caution.[37] Tetrahydrofuran and diethyl ether were distilled from sodium–benzophenone ketyl at atmospheric pressure immediately prior to use. All the amines used were purified by fractional distillation. Methane sulfonyl chloride, hexamethylphosphoramide (HMPA), sodium azide, and triethylamine were purchased from Aldrich and used without further purification. Diamines and triamines could be purified by chromatography (silica gel, ethyl acetate/5% triethyl amine, v/v).

General Procedure A: Synthesis of Amido Alcohols 2a and 2b. α-Chloro-*N*,*N*-dimethylacetamide (0.05 mol, 6.08 g) and ephedrine (or pseudoephedrine) (0.05 mol, 8.25 g) were dissolved in 150 mL of benzene. Triethylamine (11–15 mL) was added in one portion at room temperature, and the resulting solution was heated at reflux under a nitrogen atmosphere for 6–8 h with vigorous stirring. The organic layer was washed with brine (50 mL) and dried over anhydrous K_2CO_3 and the solvent was removed in vacuo to give a colorless glassy liquid. Dry THF (50 mL) was added, and the resulting suspension was filtered. After removal of THF, a white crystalline solid was obtained which was used without purification.

General Procedure B: Synthesis of Chloroamines. To a solution of amino alcohols **2a** or **2b** (0.01 mol) in dry THF (40 mL) was added triethylamine (0.03 mol, 4.18 mL) at 0 °C. Methanesulfonyl chloride (0.02 mol, 1.57 mL) in THF (20 mL) was then added dropwise via a dropping funnel under a nitrogen atmosphere with vigorous stirring. A white or pale yellow precipitate resulted upon addition. The reaction mixture was stirred for 1 h, and the solvent was removed in vacuo. The residue was used in the next step immediately. This intermediate can be stored overnight in a refrigerator or under a nitrogen atmosphere without any decomposition.

General Procedure C: Synthesis and Reduction of Azido Amines 4a and 5a. To the chloroamine intermediate prepared from **2a** and **2b** by procedure B (assumed to be 0.01 mol) was added sodium azide (0.03 mol, 65 g) as a solid. HMPA (25 mL) was then added, and the resulting suspension was heated at 80 °C for 12 h. After the mixture was cooled, water (25 mL) was added to the suspension. The aqueous solution was then extracted with Et_2O (4 × 30 mL). The combined ether extracts were washed with water (3 × 20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo. The residue was used in the next step without further purification.

The solution of azide **4a** or **5a** in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (4.0 equiv) in THF. The resulting suspension was heated at reflux under a nitrogen atmosphere for 10 h. The reaction was quenched by the following sequence after cooling: First, "*n*" mL of H_2O was added slowly for *n* g of $LiAlH_4$ used, followed by *n* mL of 10% KOH and 3*n* mL of H_2O. The resulting thick paste was filtered. The filterate was dried over anhydrous K_2CO_3, and the solvent was removed in vacuo.

General Procedure D: Synthesis of Triamines. To the chloroamine intermediate prepared by procedure B (0.01 mol) in 50 mL of benzene was added Et_3N (0.02 mol, 2.02 g) in one portion. The required primary amine was then added, and the resulting suspension was heated at reflux under a nitrogen atmosphere for 12 h. Fifteen percent aq NaOH (10 mL) was added after the mixture was cooled. The organic layer was washed with brine (20 mL) and then dried over anhydrous K_2CO_3, and the solvent was removed in vacuo. The resulting amine can be purified by column chromatography on silica gel with 5% (v/v) Et_3N–EtOAc as eluent.

The product obtained from the above reaction was dissolved in THF (15 mL), and the resulting solution was added dropwise to a suspension of $LiAlH_4$ (3.0 equiv) in THF under a nitrogen atmosphere. After the addition was complete, the resulting suspension was heated at reflux for 10 h. On cooling, the reaction was quenched carefully by the following sequence: For *n* g of $LiAlH_4$ used, first *n* mL of H_2O was added followed by *n* mL of 10% KOH and 3*n* mL of water. The thick white precipitate was filtered and the filtrate dried over anhydrous K_2CO_3. The solvent

(37) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.

was removed in vacuo to yield the required amine.

(1*R*,2*R*)-2-[(β-Hydroxy-α-methylphenethyl)methylamino]-*N*,*N*-dimethylacetamide (2a). General procedure A was employed and (1*R*,2*R*)-pseudoephedrine was used as the starting material. Compound **2a** was obtained in 94% yield (≥95% pure by NMR): mp 75 °C; $[\alpha]^{25}_D$ −85.1 (*c* = 0.11, $CHCl_3$); IR (KBr) 3342 (s, br), 3063 (w), 3030 (w), 1636 (s) cm^{-1}; ^1H NMR (90 MHz) δ 0.75 (d, *J* = 6.6 Hz, 3 H), 2.38 (s, 3 H), 2.97 (s, 3 H), 3.02 (s, 3 H), 2.77–3.20 (m, 1 H), 3.34 (s, 2 H), 4.26 (d, *J* = 9.5 Hz, 1 H), 5.16 (br s, 1 H), 7.27–7.34 (m, 5 H); ^{13}C NMR δ 8.3, 35.7, 36.4, 36.6, 55.9, 65.2, 75.3, 127.3 (2C), 127.5, 128.1 (2C), 142.1, 170.2; mass spectrum (*m*/*z*) (intensity) CI 251.2 (66, $M^+ + 1$), 233.2 (44), 143.1 (100, −PhCHOH); EI 143.1 (100, −PhCHOH), 70.1 (65), 56.2 (10).

(1*R*,2*S*)-2-[(β-Hydroxy-α-methylphenethyl)methylamino]-*N*,*N*-dimethylacetamide (2b). General procedure A was employed with (−)-(1*R*,2*S*)-ephedrine as the starting material. Compound **2b** was obtained in 94% yield (≥95% pure by NMR): $[\alpha]^{25}_D$ −12.9 (*c* = 0.1, $CHCl_3$); mp 98 °C; IR (KBr) 3369 (s, br), 3063 (w), 3031 (w), 1629 (s) cm^{-1}; ^1H NMR (90 MHz) δ 0.94 (d, *J* = 7.01 Hz, 3 H), 2.38 (s, 3 H), 2.82 (s, 3 H), 2.91 (s, 3 H), 2.72–3.20 (m, 1 H), 3.42 (s, 2 H), 4.34 (br, 1 H), 4.81 (d, *J* = 4.4 Hz, 1 H), 7.27–7.34 (m, 5 H); ^{13}C NMR δ 9.8, 35.6, 36.4, 39.5, 56.3, 63.8, 73.7, 126.2 (2 C), 126.8, 127.9 (2 C), 142.6, 170.8; mass spectrum (*m*/*z*) CI 251.2 (100, $M^+ + 1$), 143.1 (84, −PhCHOH); EI 143.1 (100, −PhCHOH), 70.1 (50).

Lactone **3** was obtained as a byproduct in the reaction of (−)-ephedrine with α-chloro-*N*,*N*-dimethylacetamide in the presence of Na_2CO_3/NaI in benzene, and it was purified by column chromatography (R_f = 0.52, 50% ethyl acetate–petroleum ether (v/v)) (colorless liquid): $[\alpha]^{25}_D$ −3.0 (*c* = 0.02, $CHCl_3$); IR (neat) 3063 (w), 3030 (w), 1748 (s) cm^{-1}; ^1H NMR (300 MHz) δ 0.75 (d, *J* = 6.6 Hz, 3 H), 2.38 (s, 3 H), 2.9–3.15 (m, 1 H), 3.47 (AB quartet, δ_A = 3.53, δ_B = 3.39, J_{AB} = 18.0 Hz, 2 H), 5.63 (d, *J* = 3.5 Hz, 1 H), 7.25–7.46 (m, 5 H); ^{13}C NMR δ 5.68, 41.3, 52.6, 56.9, 83.9, 126.1 (2 C), 128.1, 128.3 (2 C), 136.5, 168.1. The structure was confirmed by two alternate syntheses of this compound as shown below.

(1) **2b** was heated to reflux in xylene with 2.0 equiv of anhydrous Na_2CO_3 for 24 h. The reaction mixture was filtered upon cooling, and the solvent was removed in vacuo. Column chromatography with 50% ethyl acetate–petroleum ether (R_f −0.52) on silica gel afforded a colorless liquid in 88% yield which showed identical ^1H and ^{13}C NMR spectra as **3**.

(2) William's procedure[29] was followed: To a solution of (1*R*,2*S*)-ephedrine (1.65 g, 10.0 mmol) in 25 mL of THF was added ethyl bromoacetate (1.11 mL, 10.0 mmol) followed by addition of triethylamine (4.2 mL, 30.0 mmol) at room temperature. After being stirred vigorously for 18 h, the mixture was filtered. The filtrate was evaporated under vacuum. To the colorless oil thus obtained were added *p*-toluenesulfonic acid (0.2 g, 1.0 mmol) and benzene (40 mL), and the reaction mixture was heated at reflux with a Dean-Stark trap for 24 h. After the mixture was cooled, 25 mL of water was added and the organic layer was washed with 25 mL of brine and dried over anhydrous K_2CO_3. The solvent was removed on a rotary evaporator to give a colorless liquid (1.0 g, 50%). The spectral data for this compound matched those of **3**.

(1*R*,2*R*)-2-[[β-(*N*-Phenylamino)-α-methylphenethyl]methylamino]-*N*,*N*-dimethylacetamide (4b). It was synthesized from **2a** by using general procedures B and D in 90% yield, and purification was done by recrystallization from methanol: $[\alpha]^{25}_D$ +10.5 (*c* = 0.11, $CHCl_3$); mp 94–95 °C; IR (KBr), 3250 (w) cm^{-1}; ^1H NMR (300 MHz) δ 0.82 (d, *J* = 3.6 Hz, 3 H), 2.29 (s, 3 H), 2.70–2.86 (m, 1 H), 2.97 (s, 3 H), 3.08 (s, 3 H), 3.28 (s, 2 H), 3.88 (d, *J* = 9.9 Hz, 1 H), 5.80 (br, s, 1 H), 6.40–7.49 (m, 10 H); ^{13}C NMR δ 8.4, 35.7, 36.4, 36.9, 55.9, 62.3, 63.5, 113.8, 116.9, 127.2, 127.8, 128.5, 128.8, 143.3, 148.6, 170.2.

(1*R*,2*S*)-2-[[β-(*N*-Phenylamino)-α-methylphenethyl]methylamino]-*N*,*N*-dimethylacetamide (5b). It was synthesized from **2b** by general procedures B and D in 89% yield. Further purification was carried out by recrystallization from methanol: $[\alpha]^{25}_D$ −17.5 (*c* = 0.10, $CHCl_3$); mp 113 °C; IR (KBr pellet) 3256 (m) cm^{-1}; ^1H NMR (90 MHz) δ 1.12 (d, *J* = 6.8 Hz, 3 H), 2.51 (s, 3 H), 2.76 (s, 3 H), 2.92 (s, 3 H), 2.50–2.90 (m, 1 H), 3.48 (s, 2 H), 4.42 (d, *J* = 4.4 Hz, 1 H), 5.70 (br s, 1 H), 6.42–7.36 (m, 10 H); ^{13}C NMR δ 6.3, 10.7, 35.5, 36.6, 39.4, 55.9, 59.6, 63.0, 113.6, 117.3, 127.3, 128.4, 129.0, 141.0, 147.4, 169.0.

Spectral Data for Azides 4a,5a and Amides 4c,d and 5c,d. These compounds were obtained crude in ≥95% purity (^1H NMR) and used without purification. Selected data are provided.

4a: IR (neat) 3065 (w), 3030 (w), 2101 (s), 1649 cm^{-1}; ^1H NMR (300 MHz) δ 0.76 (d, *J* = 6.7 Hz, 3 H), 2.34 (s, 3 H), 2.93 (s, 3 H), 3.11 (s, 3 H), 2.80–3.20 (m, 1 H), 3.34 (s, 2 H), 4.33 (d, *J* = 9.7 Hz, 1 H), 7.24–7.40 (m, 5 H). **4c:** IR (neat) 3302 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.63 (d, *J* = 7.9 Hz, 3 H), 0.9 (t, *J* = 9.7, 3 H), 1.18–1.40 (m, 4 H), 2.24 (s, 3 H), 2.18–2.30 (m, 2 H), 2.60–2.87 (m, 2 H), 2.97 (s, 3 H), 3.14 (s, 3 H), 3.30 (s, 2 H), 3.58 (d, *J* = 9.9 Hz, 1 H), 7.22–7.38 (m, 5 H); ^{13}C NMR δ 8.1, 13.8, 20.2, 32.1, 34.9, 35.3, 37.1, 47.2, 58.1, 63.4, 66.7, 126.9, 127.1 (2C), 127.9 (2C), 142.6, 170.2. **4d:** IR (neat) 3302 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.63 (d, *J* = 6.8 Hz, 3 H), 0.8–2.36 (m, 11 H), 2.22 (s, 3 H), 2.37–3.45 (m, 2 H), 2.95 (s, 3 H), 3.11 (s, 3 H), 3.25 (s, 2 H), 3.58 (d, *J* = 10.0 Hz, 1 H), 7.22–7.48 (m, 5 H); ^{13}C NMR δ 8.1, 24.8, 25.0, 25.9, 32.5, 34.3, 34.9, 35.3, 37.1, 53.3, 58.2, 63.2, 63.4, 126.7, 127.8 (2 C), 128.2 (2 C), 143.2, 170.1.

5a: ^1H NMR (90 MHz) δ 1.13 (d, *J* = 6.7 Hz, 3 H), 2.28 (s, 3 H), 2.47 (s, 3 H), 2.81 (s, 3 H), 2.78–2.94 (m, 1 H), 3.22 (s, 2 H), 4.53 (d, *J* = 8.1 Hz, 1 H), 7.20–7.42 (m, 5 H). **5c:** IR (neat) 3301 (w), 1650 (s) cm^{-1}; ^1H NMR (90 MHz) δ 0.85 (t, *J* = 9.0 Hz, 3 H), 1.04 (d, *J* = 9.1 Hz, 3 H), 1.25–1.40 (m, 5 H), 2.24 (s, 3 H), 2.32–2.47 (m, 3 H), 2.51 (s, 3 H), 2.80 (s, 3 H), 3.20 (s, 2 H), 3.63 (d, *J* = 6.7 Hz, 1 H), 7.19–7.36 (m, 5 H); ^{13}C NMR δ 9.98, 13.9, 20.4, 32.4, 35.3, 36.3, 37.1, 45.6, 58.7, 62.9, 65.7, 126.4, 127.6 (2C), 127.9 (2C), 143.6, 170.6. **5d:** IR (neat) 3284 (br), 1647 (s), cm^{-1}; ^1H NMR (300 MHz) δ 1.05 (d, *J* = 6.6 Hz, 3 H), 0.90–1.20 (m, 7 H), 1.38–1.62 (m, 4 H), 2.22 (s, 3 H), 2.47 (s, 3 H), 2.80 (s, 3 H), 2.68–2.82 (m, 2 H), 3.20 (s, 2 H), 3.78 (d, *J* = 5.9 Hz, 1 H), 7.18–7.31 (m, 5 H); ^{13}C NMR δ 9.8, 24.5, 24.9, 26.1, 32.6, 34.8, 35.2, 36.2, 36.7, 53.3, 58.7, 61.9, 62.9, 126.1, 127.4 (2 C), 127.7 (2 C), 144.3, 170.4.

(1*R*,2*R*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]ethyl]benzylamine (6a). Compound **6a** was synthesized from (1*R*,2*R*)-pseudoephedrine by using general procedures B and C and was purified by flash chromatography (R_f = 0.1, ethyl acetate/5% triethylamine (v/v)) in 60% yield: $[\alpha]^{25}_D$ −47.5 (*c* = 0.09, $CHCl_3$); IR (neat) 3375 (w), 3302 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.6 (d, *J* = 7.0 Hz, 3 H) 2.39 (s, 9 H), 2.27–2.70 (m, 7 H), 3.7 (d, *J* = 10.5 Hz, 1 H), 7.27–7.34 (m, 5 H); ^{13}C NMR δ 8.1, 36.6, 45.7 (2 C), 51.7, 58.4, 59.0, 64.9, 127.0, 127.6 (2 C), 128.1 (2 C), 143.9; mass spectrum (*m*/*e*) CI 236 (42, $M^+ + 1$), 129.2 (100, $-PhCHNH_2$); EI 129 (100, $-PhCHNH_2$), 72 (72).

The phthalimide derivative was prepared by treatment of **6a** with an equimolar amount of phthalic anhydride in toluene by heating for 12 h and removing H_2O with a Dean-Stark trap and was purified by flash chromotography (R_f = 0.5): $[\alpha]^{25}_D$ −0.86 (*c* = 0.1, $CHCl_3$); mp 91.4–92.2 °C; IR (neat) 1715 (s) cm^{-1}; ^1H NMR (300 MHz) δ 0.84 (d, *J* = 6 Hz, 3 H), 2.11 (s, 6 H), 2.20 (s, 3 H), 1.80–2.92 (m, 4 H), 3.90–4.45 (m, 1 H), 5.16 (d, *J* = 12 Hz, 1 H), 6.90–7.88 (m, 9 H); ^{13}C NMR δ 9.6, 36.7, 45.7 (2 C), 51.3, 57.1, 58.4, 58.7, 122.8, 127.9, 128.5 (2 C), 129.4 (2 C), 132.1, 133.5, 138.4, 166.5 (2 C); mass spectrum (*m*/*e*) EI 129.3 (60, −PhCHNPHth). Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.29; H, 7.45. Found: C, 72.17; H, 7.48.

(1*S*,2*S*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]ethyl]benzylamine. It was synthesized from (1*S*,2*S*)-pseudoephedrine by using procedures B and C and was purified by flash chromatography (R_f = 0.11, ethyl acetate/5% triethylamine (v/v)) in 62% yield: $[\alpha]^{25}_D$ +51.8 (*c* = 0.11, $CHCl_3$).

(1*R*,2*R*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]ethyl]-*N*-phenylbenzylamine (6b). Triamine **6b** was synthesized from (1*R*,2*R*)-pseudoephedrine and aniline by general procedures B and D and was purified by flash chromatography (R_f = 0.24, ethyl acetate, 5% triethylamine) in 70% yield: $[\alpha]^{25}_D$ −2.3 (*c* = 0.69, EtOH); IR (neat) 3256 (br s) cm^{-1}; ^1H NMR (90 MHz) δ 0.77 (d, *J* = 6.6 Hz, 3 H), 2.23 (s, 9 H), 1.96–2.94 (m, 5 H), 3.83 (d, *J* = 10.0 Hz, 1 H), 6.20–7.50 (m, 11 H); ^{13}C NMR δ 7.9, 36.5, 45.7 (2 C), 51.0, 58.0, 62.0, 63.4, 113.8, 116.8, 127.0, 127.7, 128.4, 128.7, 143.6, 148.8; mass spectrum (*m*/*e*) CI 312 (26, $M^+ + 1$), 129 (100, −PhCHNHPh).

(1*R*,2*R*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]ethyl]-*N*-butylbenzylamine (6c). Triamine **6c** was synthesized from (1*R*,2*R*)-pseudoephedrine and *n*-butylamine by general procedures B and D. The amine was purified by column chro-

matography (R_f = 0.22, ethyl acetate/5% triethyl amine (v/v)) and obtained in 83% yield: $[\alpha]^{25}_D$ −44.1 (c = 0.1, $CHCl_3$); IR (neat) 3303 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.59 (d, J = 6 Hz, 3 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.98–1.56 (m, 4 H), 2.26 (s, 9 H), 1.92–3.04 (m, 8 H), 3.32 (d, J = 10 Hz, 1 H), 6.92–7.29 (m, 5 H); ^{13}C NMR δ 8.2, 13.9, 20.4, 32.2, 36.2, 45.9 (2 C), 47.5, 51.2, 58.6, 64.0, 67.0, 126.9, 127.9, 128.3, 143.1; mass spectrum (m/z) CI 292 (55%, M^+ + 1), 129 (100, −PhCHNHBu); EI 129.3 (22, −PhCHNHBu), 72.2 (100, $-CH_2CH_2NMe_2$), 58.2 (55).

(1*R*,2*R*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]-ethyl]-*N*-cyclohexylbenzylamine (6d). Triamine **6d** was synthesized from (1*R*,2*S*)-pseudoephedrine and cyclohexylamine by procedures B and D and was purified by column chromatography (R_f = 0.23, ethyl acetate/5% triethyl amino (v/v)): $[\alpha]^{25}_D$ −96.4 (c = 0.12, $CHCl_3$); IR (neat) 3300 (m), 3030 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.58 (d, J = 6.5 Hz, 3 H), 0.91–1.30 (m, 6 H), 1.32–1.70 (m, 4 H), 2.24 (s, 3 H), 2.27 (s, 6 H), 1.71–2.90 (m, 7 H), 3.52 (d, J = 9.8 Hz, 1 H), 7.27–7.34 (m, 5 H); ^{13}C NMR 8.1, 25.0, 25.2, 26.1, 32.8, 35.1, 36.7, 45.9 (2C), 51.5, 53.8, 58.6, 63.6, 64.2, 126.7, 127.8 (2 C), 128.3, (2 C), 143.9; mass spectrum (m/e) CI 318 (19, M^+ + 1), 129.2 (100, −PhCHNH C_6H_{11}); EI 129.2 (100), 72.2 (49, $-CH_2CH_2NMe_2$). Anal. Calcd for $C_{20}H_{35}N_3$: C, 75.66; H, 11.11. Found: C, 74.86; H, 10.79.

(1*R*,2*S*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]-ethyl]benzylamine (7a). Triamine **7a** was synthesized from (1*R*,2*S*)-ephedrine by using general procedures B and C, and purification was done by column chromatography (R_f = 0.11, ethyl acetate 5% triethyl amino (v/v)) in 60% yield: $[\alpha]^{25}_D$ −0.83 (c = 0.11, $CHCl_3$); IR (neat) 3363 (w), 3309 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.98 (d, J = 6.8 Hz, 3 H), 2.20 (s, 9 H), 1.82–2.86 (m, 7 H), 4.02 (d, J = 5.6 Hz, 1 H), 7.27–7.34 (m, 5 H); ^{13}C NMR δ 10.1, 38.9, 45.7 (2 C), 52.7, 57.8, 60.0, 64.2, 126.4, 126.8 (2 C), 127.9 (2 C), 144.9; mass spectrum (m/z) CI 236 (42, M^+ + 1), 129.2 (53, $-PhCHNH_2$); EI 129.2 (82, $-PhCHNH_2$), 72.2 (100, $-CH_2CH_2NMe_2$), 58.1 (45).

The phthalimide derivative was prepared from **7a** by reaction with phthalic anhydride (equimolar amount) in toluene for 12 h by using a Dean-Stark trap. It was purifed by flash chromatography (R_f = 0.3 ethyl acetate/5% triethyl amine) followed by recrystallization from ether to yield colorless crystals (75% yield): $[\alpha]^{25}_D$ −4.6 (c = 0.11, $CHCl_3$); mp 141.5–142.9; IR (KBr) 1716 (s) cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (d, J = 3 Hz, 3 H), 2.21 (s, 6 H), 2.24 (s, 3 H), 2.08–2.30 (m, 2 H), 2.40–2.65 (m, 2 H), 4.20–4.40 (m, 1 H), 5.22 (d, J = 12 Hz, 1 H), 7.20–7.35 (m, 4 H), 7.50–7.80 (m, 5 H); ^{13}C NMR δ 10.0, 36.5, 45.8 (2 C), 52.1, 56.9, 58.0 (2 C), 123.2 (2 C), 127.6, 128.1 (2 C), 129.3 (2 C), 131.8, 133.9 (2 C), 139.2, 168.4 (2 C); mass spectrum (m/e) EI 129.3 (60.8, −PhCHNPhth), 58.1 (100). Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.29; H, 7.45. Found: C, 72.12; H, 7.44.

(1*R*,2*S*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]-ethyl]-*N*-phenylbenzylamine (7b). Triamine **7b** was synthesized by general procedures B and D using (1*R*,2*S*)-ephedrine and purified by flash chromatography (R_f = 0.21, ethyl acetate 5% triethylamine) in 70% yield: $[\alpha]^{25}_D$ +38.9 (c = 0.69, EtOH); IR (neat) 3355 (br, m) cm^{-1}; ^1H NMR (90 MHz) δ 0.98 (d, J = 6.6 Hz, 3 H), 2.09 (s, 3 H), 2.22 (s, 6 H), 1.87–2.72 (m, 5 H), 4.34 (d, J = 4.4 Hz, 1 H), 5.50 (br s, 1 H), 6.12–7.41 (m, 10 H); ^{13}C NMR (22.5 MHz) δ 11.4, 39.6, 45.6 (2 C), 53.0, 57.3, 60.1, 62.1, 113.4, 116.5, 126.7, 127.6, 128.0, 128.9, 141.4, 147.9; mass spectrum (m/e) CI 312 (8, M^+ + 1), 129 (100, −PhCHNHPh).

(1*R*,2*S*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]-ethyl]-*N*-butylbenzylamine (7c). General procedures B and D were employed, and purification of **7c** was achieved by column chromatography (R_f = 0.23, ethyl acetate/5% triethylamine (v/v)) in 82% yield: $[\alpha]^{25}_D$ = −31.2 (c = 0.12, $CHCl_3$); IR (neat) 3309 (w) cm^{-1}; ^1H NMR (90 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 0.96 (d, J = 5.7 Hz, 3 H), 1.10–1.57 (m, 4 H), 2.19 (s, 3 H), 2.22 (s, 6 H), 1.96–3.00 (m, 8 H), 3.77 (d, J = 4.7 Hz, 1 H), 6.90–7.34 (m, 5 H); ^{13}C NMR, 10.5, 13.6, 20.1, 32.1, 38.8, 45.4 (2 C), 47.3, 52.4, 57.2, 63.7, 64.7, 128.9, 127.3 (4 C), 142.6; mass spectrum (m/e) CI 129.2 (100, −PhCHNHBu); EI 129.3 (25), 72.2 (100, $CH_2CH_2NMe_2$).

(1*R*,2*S*)-α-[1-[[2-(Dimethylamino)ethyl]methylamino]-ethyl]-*N*-cyclohexylbenzylamine (7d). Triamine **7d** was synthesized from **5d** by the general procedures B and D in 82% yield and was further purified by column chromatography (R_f = 0.22): $[\alpha]^{25}_D$ −20.4 (c = 0.09, $CHCl_3$); IR (neat) 3329 (w) cm^{-1}; ^1H NMR (300 MHz) δ 0.95 (d, J = 6.9 Hz, 3 H), 1.01–1.21 (m, 5 H), 1.32–1.81 (m, 5 H), 2.18 (s, 6 H), 2.22 (s, 3 H), 1.90–2.79 (m, 7 H), 3.90 (d, J = 5.4 Hz, 1 H), 7.27–7.35 (m, 5 H); ^{13}C NMR δ 10.8, 24.7, 25.1, 26.2, 32.8, 34.9, 39.1, 45.8 (2 C), 52.6, 53.7, 57.5, 61.5, 64.1, 126.2, 127.7 (4 C), 129.6, 143.8; mass spectrum (m/e) CI 318.3 (81.4, M^+ + 1), 129.1 (100, $-PhCHNHC_6H_{11}$); EI 129.2 (100, $-PhCHNHC_6H_{11}$), 72.2 (95, $-CH_2CH_2NME_2$). Anal. Calcd for $C_{20}H_{35}N_3$: C, 75.66; H, 11.11. Found C, 74.71; H, 10.88.

(1*R*,2*S*)-α-[1-(Ethylmethylamino)ethyl]benzylamine (14a). It was synthesized from **8** by the general procedures B and C and was purified by flash chromatography (R_f = 0.41) in 72% overall yield: $[\alpha]^{25}_D$ −4.63 (c = 0.12, $CHCl_3$); IR (neat) 3369 (w), 3296 (w) cm^{-1}; ^1H NMR δ 0.92 (d, J = 5.6 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3 H), 1.75 (br s, 2 H), 2.20 (s, 3 H), 2.50 (q, J = 7.0 Hz, 2 H), 2.63–2.89 (m, 1 H), 4.06 (d, J = 5.2 Hz, 1 H), 7.10–7.38 (m, 5 H); ^{13}C NMR δ 9.8, 12.2, 38.0, 48.1, 57.3, 62.9, 126.3, 126.7 (2 C), 127.7 (2 C), 144.8; mass spectrum (m/e) CI 193.1 (100, M^+ + 1); EI 86.2 (100, $-PhCHNH_2$).

The phthalimide derivative was prepared from **14a** by refluxing an equimolar quantity of phthalic anhydride in toluene using a Dean-Stark trap and was purified by flash chromatography (R_f = 0.51) in 90% yield: $[\alpha]^{25}_D$ = −49.4 (c = 0.11, $CHCl_3$); mp = 141–143 °C; IR (KBr) 1707 (s) cm^{-1}; ^1H NMR (300 MHz) δ 0.92 (t, J = 6 Hz, 3 H), 0.96 (d, J = 8.4 Hz, 3 H), 2.18 (s, 3 H), 2.29–2.70 (m, 2 H), 3.90–4.52 (m, 1 H), 5.24 (d, J = 10.5 Hz, 1 H), 7.15–7.90 (m, 9 H); ^{13}C NMR δ 9.5, 13.6, 35.7, 47.6, 55.4, 57.9, 123.2 (2 C), 127.5, 128.1 (2 C), 129.2 (2 C), 131.8, 133.9 (2 C), 139.2, 166.4 (2 C); mass spectrum (m/e) CI 323.2 (100, M^+ + 1); EI 86.2 (100, −PhCHN Phth). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.9. Found: C, 74.44; H, 6.93.

(1*R*,2*S*)-α-[1-(Ethylmethylamino)ethyl]-*N*-cyclohexylbenzylamine (14b). It was synthesized from **8** in 70% yield, and further purification was carried out by column chromatography: $[\alpha]^{25}_D$ −16.6 (c = 0.06, $CHCl_3$); IR 3296 (w) cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (d, J = 6.6 Hz, 3 H), 0.94 (t, J = 6.9 Hz, 3 H), 0.92–1.21 (m, 6 H), 1.43–1.72 (m, 5 H), 1.86–2.00 (m, 1 H), 2.22 (s, 3 H), 2.38–2.68 (m, 3 H), 3.97 (d, J = 4.5 Hz, 1 H), 7.19–7.32 (m, 5 H); ^{13}C NMR δ 10.6, 11.8, 24.9, 25.3, 26.2, 32.9, 35.1, 38.3, 48.0, 53.8, 60.9, 62.9, 126.2, 127.7 (2 C), 127.8 (2 C), 143.9.

(1*R*,2*S*)-α-[1-(Dimethylamino)ethyl]-*N*-butylbenzylamine (15a). General procedures B and D were followed on 1 mmol of *N*-methylephedrine. The 1,2-diamine was obtained in 50% yield (≥95% by NMR). Further purification was achieved by column chromatography (R_f 0.41, EtOAc 4% Et_3N (v/v)) followed by bulb-to-bulb distillation: $[\alpha]^{25}_D$ −43.2 (c = 0.95, $CHCl_3$); IR (neat) 3309 (w) cm^{-1}; ^1H NMR δ 0.85–0.92 (m, 6 H), 1.28–1.36 (m, 2 H), 1.42–1.51 (m, 2 H), 1.80 (br, 1 H), 2.29 (s, 6 H), 2.31–2.51 (m, 3 H), 3.87 (d, J = 4.2 Hz, 1 H), 7.19–7.39 (m, 5 H); ^{13}C NMR δ 11.2, 14.1, 20.6, 32.5, 43.4 (2 C), 48.2, 64.1, 66.1, 126.4, 127.8 (2 C), 128.0 (2 C), 143.0. Anal. Calcd for $C_{15}H_{26}N_2$: C, 76.86; H, 11.12; N, 11.95. Found: C, 76.71; H, 11.11; N, 11.95.

(1*R*,2*S*)-α-[1-(Ethylmethylamino)ethyl]-*N*-phthalimidobenzylamine (15b). General procedures B and D were followed to obtain **15b** in 96% yield (≥95% by NMR). Recrystallization from diethyl ether afforded an analytically pure sample of **15b**: $[\alpha]^{25}_D$ −21.48 (c = 0.025, $CHCl_3$); mp 156–157 °C; IR ($CHCl_3$) 2952 (m), 1735 (s), 1714 (s) cm^{-1}; ^1H NMR δ 0.95 (d, J = 6.5 Hz, 3 H), 2.20 (s, 6 H), 4.21–4.31 (m, 1 H), 5.20 (d, J = 11.6 Hz, 1 H), 7.20–7.80 (m, 9 H); ^{13}C NMR δ 8.4, 39.8, 56.6, 57.5, 123.1, 127.6, 128.2, 128.9, 131.7, 133.8, 138.9, 168.2. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 73.99; H 6.54. Found C, 73.96; H, 6.52.

(1*R*,2*R*)-α-[1-(Ethylmethylamino)ethyl]benzylamine (16). It was synthesized from **10** by general procedures B and C and was purified by flash chromatography (R_f = 0.3) in 70% yield: $[\alpha]^{25}_D$ −68.6 (c = 0.08, $CHCl_3$); IR (neat) 3389 (w), 3302 (w), 3030 (m) cm^{-1}; ^1H NMR δ 0.58 (d, J = 6.6 Hz, 3 H), 1.12 (t, J = 6.7 Hz, 3 H), 2.23 (s, 3 H), 2.18–2.93 (m, 5 H), 3.70 (d, J = 9.9 Hz, 1 H), 7.01–7.56 (m, 5 H); ^{13}C NMR δ 7.9, 13.9, 35.6, 47.5, 58.9, 64.2, 127.0, 127.7 (2 C), 128.2 (2 C), 144.4, mass spectrum (m/e) CI 193.1 (100, M^+ + 1); EI 86.2 (100, $-PhCHNH_2$).

The phthalimide derivative was prepared from **16** by refluxing with an equimolar quantity of phthalic anhydride in toluene using a Dean-Stark trap and was purified by column chromatography (R_f = 0.55): $[\alpha]^{25}_D$ −25.8 (c = 0.02, $CHCl_3$); IR (KBr), 1707 (s) cm^{-1}; ^1H NMR (300 MHz) δ 0.81 (d, J = 6.3 Hz, 3 H), 0.85 (t, J = 6.9 Hz, 3 H), 2.15 (s, 3 H), 2.27–2.58 (m, 2 H), 3.82–4.26 (m,

1 H), 5.17 (d, J = 11.7 Hz, 1 H), 7.18–7.82 (m, 9 H); ^{13}C NMR δ 9.4, 13.8, 35.8, 47.1, 56.4, 58.8, 122.9 (2 C), 127.9, 128.6 (2 C), 129.4 (3 C), 133.5, 132.2, 138.5 (2 C), 168.6 (2 C); mass spectrum (m/e) CI 323.2 (100, M^+ + 1); EI 86.2 (100, –PhCHNPhth). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.9. Found: C, 74.42; H, 6.91.

***N*-[2-(*N*-Butylamino)-2-phenylethyl]-1,3-dihydroisoindole (17).** General procedures B and D were used to obtain **17** in 85% yield (≥95% by NMR). Further purification was achieved by column chromatography (R_f = 0.32, 90% EtOAc, 8% Et_3N, 2% MeOH (v/v)) followed by bulb-to-bulb distillation: $[\alpha]^{25}_D$ = +1.56 (c = 2.5, $CHCl_3$); IR (neat) 3310 (w) cm^{-1}; ^{1}H NMR δ 0.85 (t, 3 H, J = 7.3 Hz, 3 H), 1.25–1.50 (m, 4 H), 2.33 (br, 1 H), 2.46–2.72 (m, 4 H), 3.80 (d, d, J = 3 Hz, 1 Hz, 1 H), 3.99 (ABq, δ_A = 4.04, δ_B = 3.97, J_{AB} = 10.8 Hz, 4 H), 7.17–7.43 (m, 9 H); ^{13}C NMR δ 14.0, 20.6, 32.5, 47.7, 59.2 (2 C), 62.3, 63.8, 122.3 (2 C), 126.7 (2 C), 127.1 (2 C), 128.3 (2 C), 128.7 (2 C), 140.1, 143.1. Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.50. Found: C, 80.69; H, 8.53; N, 9.29.

2-Methyl-2-(*N*-phenylamino)-3-(*N*,*N*-dimethylamino)-propane (18a). **18a** was synthesized from **12** following general procedures B and D. Purification using column chromatography (100% EtOAc, followed by 90% EtOAc, 8% Et_3N, 2% MeOH) gave 63% yield of pure compound: IR (neat) 3303 (m) cm^{-1}; ^{1}H NMR δ 1.27 (s, 6 H), 2.34 (s, 6 H), 2.37 (s, 2 H), 6.74–7.16 (m, 5 H); ^{13}C NMR δ 26.7 (2 C), 48.4 (2 C), 54.7, 69.9, 117.9 (2 C), 116.3, 128.8 (2 C), 147.2.

2-Methyl-2-(*N*,*N*-dimethylamino)-1-(*N*-butylamino)-propane (18b). Compound **18b** was prepared by oxidation[32] of **12** to the aldehyde followed by reductive amination:[33] ^{1}H NMR δ 1.06 (s, 6 H), 2.17 (s, 6 H), 2.91 (d, J = 5.7 Hz, 2 H, s after shaking with D_2O), 4.50 (br, 1 H), 6.57–7.17 (m, 5 H); ^{13}C NMR δ 20.8 (2 C), 38.04 (2 C), 52.5, 55.6, 112.4 (2 C), 116.5, 129.1 (2 C), 148.8.

General Procedure E. To the solution of 1 mmol of amino alcohol in dry benzene (5 mL) was added 1 mmol of n-BuLi at 5 °C. After the solution was stirred for 15 min, 1 mmol of methane sulfonyl chloride was added dropwise with vigorous stirring. The resulting gel-like suspension was allowed to stir for another 30 min at room temperature. Triethylamine (1.5 mmol) and the appropriate nucleophile (1.2 mmol) were then added, and the reaction mixture was allowed to stir for another 24–48 h. After completion of the reaction, the mixture was taken in Et_2O and washed with saturated $NaHCO_3$ solution (10 mL) followed by brine (10 mL). The organic extracts were dried over anhydrous K_2CO_3, and the solvent was removed in vacuo.

2-Methyl-2-(*N*-butylamino)-1-(*N*,*N*-dimethylamino)-propane (19a) and 2-Methyl-2-(*N*,*N*-dimethylamino)-1-(*N*-butylamino)propane (19b). General procedure E was used which gave 45% yield of a 50:50 mixture of **19a** and **19b**. The two regioisomers were not separated: ^{1}H NMR δ 0.90 (t, J = 4.2 Hz, 6 H), 0.94–1.02 (m, 8 H), 2.19 (s, 6 H), 2.22 (s, 2 H), 2.31 (s, 6 H), 2.46 (s, 2 H), 2.49 (t, J = 9.0 Hz, 2 H), 2.58 (t, J = 9.1 Hz, 2 H); ^{13}H NMR δ 14.0 (2 C), 20.6, 20.7, 21.01 (2 C), 25.28 (2 C), 32.2, 32.3, 38.3 (2 C), 41.9, 48.7 (2 C), 50.6, 53.8, 56.0, 58.8, 68.8.

(2*S*)-3-Methyl-2-(*N*-butylamino)-1-(*N*,*N*-dimethylamino)butane (21a) and (2*S*)-3-Methyl-1-(*N*-butylamino)-2-(*N*,*N*-dimethylamino)butane (21b). General procedure E was followed on 1 mmol of **11**, which gave 45% yield of a mixture of **21a** and **21b**. No attempt was made to separate the two regioisomers. The optical purity was further confirmed by treating these two diamines with Johnson's reagent,[38] 2-chloro-1,3,2-oxazaphospholidine 2-sulfide derived from l-ephedrine. The resulting phosphoramides gave only one peak for each of these compounds in ^{31}P NMR suggesting that no racemization occurred in the formation of **21a** and **21b**: ^{1}H NMR δ 0.89–1.02 (m, 18 H), 1.34–1.54 (m, 8 H), 1.65–1.91 (m, 2 H), 2.22–2.34 (m, 2 H), 2.36 (s, 12 H), 2.37–2.66 (m, 8 H); ^{13} NMR δ 13.9, 19.8, 20.5, 22.3, 27.3, 29.5, 32.2, 41.2, 42.2, 47.8, 49.9, 53.2, 55.1, 66.3, 68.8.

(2*S*)-3-Methyl-1-(*N*-butylamino)-2-(*N*,*N*-dimethylamino)butane (21b). Compound **21b** was synthesized by converting amino alcohol **13** into the corresponding α-amino aldehyde[32] followed by reductive amination[33] to give **21b**: IR (neat) 3309 (w) cm^{-1}; ^{1}H NMR δ 0.83–0.96 (m, 9 H), 1.31–1.50 (m, 4 H), 1.86–1.89 (m, 1 H), 2.28–2.30 (m, 1 H), 2.31 (s, 6 H), 2.32 (s, 1 H), 2.34–2.62 (m, 4 H); ^{13}C NMR δ 13.9, 19.8, 20.6, 22.3, 27.3, 32.3, 40.9 (2 C), 47.8, 49.9, 68.8.

(1*R*,2*S*)-2-(*N*,*N*-Dimethylamino)-1-phenyl-1-(*N*-phthalimidooxy)propane (22). General procedures B and D were used on 1 mmol of the N-methylephedrine. The N-phthalimido hydroxyl amine derivative was obtained in 98% yield (≥95% by NMR). Preparative TLC (R_f 0.21, 100 percent EtOAc) gave an analytically pure sample: mp 124–125 °C; IR ($CHCl_3$), 1735 (s) cm^{-1}; ^{1}H NMR δ 1.33 (d, J = 6.7 Hz, 3 H), 2.3 (s, 6 H), 3.05–3.15 (m, 1 H), 5.50 (d, J = 6.4 Hz, 1 H), 7.26–7.71 (m, 9 H); ^{13}C NMR δ 9.2, 41.1, 62.9, 89.5, 123.2, 128.0, 128.3, 128.6, 128.9, 134.2, 137.7, 163.6. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.76; H, 6.22; N, 8.64. Found: C, 68.77; H, 6.03; N, 8.48.

(1*R*,2*S*)-2-(*N*,*N*-Dimethylamino)-1-phenyl-1-(thioacetoxy)propane (23). General procedures B and D were followed on 1 mmol of N-methylephedrine. The thioester was obtained as a red oil. Bulb-to-bulb distillation, followed by column chromatography (R_f 0.43, 100% EtOAc), yielded 73% **23**: $[\alpha]^{25}_D$ –253.3 (c = 0.75, $CHCl_3$); mp 41–42 °C; IR ($CHCl_3$) 1693 (s), cm^{-1}; ^{1}H NMR δ 1.10 (d, J = 6.6 Hz, 3 H), 2.20 (s, 6 H), 2.25 (s, 3 H), 2.85–2.92 (m, 1 H), 4.81 (d, J = 7.5 Hz, 1 H), 7.20–7.32 (m, 5 H); ^{13}C NMR δ 11.3, 30.6, 41.4, 51.5, 63.4, 126.9, 128.1, 128.2, 141.6, 194.2. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.82; H, 8.02; N, 5.91. Found: C, 65.56; H, 8.12; N, 5.87.

(1*R*,2*S*)-2-(*N*,*N*-Dimethylamino)-1-phenyl-1-(propylthio)propane (24). General procedures B and D were followed. The thioether was obtained in 96% yield (≥95% by NMR). Purification by silica gel column chromatography (R_f 0.58, 100% EtOAc) gave an analytically pure sample of **24**: $[\alpha]^{25}_D$ –19.4 (c = 0.015, $CHCl_3$); ^{1}H NMR δ 0.88 (t, J = 7.3 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.45–1.48 (m, 2 H), 2.16–2.20 (m, 2 H), 2.21 (s, 6 H), 2.88 (m, 1 H), 3.90 (d, 1 H, J = 7.7 Hz) 7.30–7.33 (m, 5 H); ^{13}C NMR δ 11.2, 13.5, 22.6, 33.1, 41.2, 54.1, 64.0, 126.6, 128.1, 128.5, 142.3. Anal. Calcd for $C_{14}H_{23}NS$: C, 70.83; H, 9.77. Found: C, 70.88; H, 9.80.

(1*R*,2*S*)-[α-[1-(Dimethylamino)ethyl]benzyl]diphenylphosphine Oxide Derived from Phosphine 25. General procedures B and D were used to obtain **25** as a sticky mass which was dissolved in MeOH, and dry air was passed through it for 4 h to give the phosphine oxide. Evaporation of MeOH, followed by crystallization in EtOAc, yielded 49% of the phosphine oxide: IR ($CHCl_3$), 2980 (s), 2451 (w), 1437 (m), 1242 (s), 1189 (s), 1115 (s), 739 (s), 697 (s), 549 (m) cm^{-1}; ^{1}H NMR δ 1.51 (d, 3 H, J = 7.1 Hz), 2.60 (s, 6 H), 4.22 (m, 1 H), 4.22 (d d, 1 H, J = 9.5 Hz), 7.1–7.6 (m, 13 H), 8.10–8.20 (m, 2 H); ^{13}C NMR δ 16.4, 41.2 (2C), 47.2 (d, J_p = 63.1 Hz), 65.3, 125.8, 127.8 (4 C), 129.2 (2 C), 130.5 (2 C), 131.1 (4 C), 131.9, 132.1, 132.4, 134.1.

(2*S*)-3-Methyl-1-(*N*,*N*-dimethylamino)-3-(propylthio)butane (26). General procedure B followed by D gave the β-amino thioether in 70–80% yield: ^{1}H NMR δ 0.99 (d, 3 H, J = 6.6 Hz), 1.03 (t, 3 H, J = 7.3 Hz), 1.10 (d, 3 H, J = 6.8 Hz), 1.79 (m, 2 H), 2.11 (d sep, 1 H, J_1 = 3.2 Hz, J_2 = 6.7 Hz), 2.36 (s, 6 H), 2.59 (ABX, 2 H, J_{AX} = 5.7 Hz, J_{BX} = 8.2 Hz, J_{AB} = 13.1 Hz), 2.74 (t, 2 H, J = 7.4 Hz), 4.00 (m, 1 H); ^{13}C NMR 11.3, 13.5, 22.4, 23.3, 29.9, 30.1, 35.4, 41.4 (2 C), 55.7, 69.9.

Raney Nickel desulfurization of **26** gave **27**, which was isolated as its hydrochloride salt: ^{1}H NMR δ 0.83 (d, 6 H, J = 6.0 Hz), 1.11 (m, 2 H), 1.50 (m, 1 H), 2.6 (s, 6 H), 2.99 (m, 2 H); H); ^{13}C NMR 19.9 (2 C), 23.3, 29.9, 40.0 (2 C), 52.9.

Determination of Optical Purity by ^{31}P NMR. The triamines **6a** and the enantiomer of **6a** prepared from (1*R*,2*R*)- and (1*S*,2*S*)-pseudoephedrine showed optical rotations $[\alpha]^{25}_D$ –47.5 (c = 0.09, $CHCl_3$) and +51.8 (c = 0.11, $CHCl_3$), respectively. The optical purity was further confirmed by treating these two triamines with Johnson's reagent,[38] 2-chloro-1,3,2-oxazaphospholidine 2-sulfide derived from l-ephedrine. The resulting phosphoramides showed only one peak for each of these compounds in ^{31}P NMR [δ 80.02 for **6a** and δ 81.09 for the enantiomer of **6a**. H_3PO_4 in $CDCl_3$ was the external standard used and the spectra were recorded on JEOL FX 90Q NMR instrument].

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **6c**, **6d**, **7c**, **7d**, **14a**, **17**, **18a**, **18b**, **22**, and the phosphine oxide of **25** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Reactions of 5-Amino-1,2,3,4-thiatriazoles with Isocyanates

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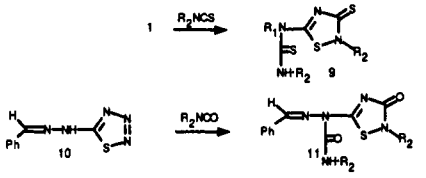
The reaction of 5-(arylamino)-1,2,3,4-thiatriazoles **1** with isocyanates initially gives 1,2,3,4-thiatriazol-5-ylureas **3** which can be isolated when the aryl group has *o*-alkyl substituents. Compounds **3** rearrange to **21** in the presence of triethylamine and then react with the second equivalent of isocyanate to give (4-aryl-2-alkyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene)ureas **12** rather than the (3-oxo-Δ^4-1,2,4-thiadiazolin-5-yl)ureas **7** which had been proposed previously.[1] The latter compounds, prepared from **8** and isocyanates, also rearrange to **12**. Mechanisms incorporating these observations are proposed (Schemes IV and VI). The structure of **12** was confirmed by single-crystal X-ray analysis of [4-(2,6-dimethylphenyl)-2-methyl-3-oxo-1,2,4-thiadiazolidin-5-ylidene]methylurea **12baa**.

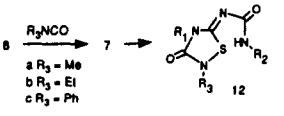
Introduction

Several years ago we reported the reaction of 5-(arylamino)-1,2,3,4-thiatriazoles **1** with isocyanates.[1] At that time the products were postulated to be (3-oxo-Δ^4-1,2,4-thiadiazolin-5-yl)ureas **7** based on ^1H and ^{13}C NMR and IR spectra, elemental analyses, and an alternate synthetic route to the same products. The proposed reaction sequences were as shown in Scheme I.

Recently the reactions of **1** with alkyl isothiocyanates were postulated to give **9**[2] and the 5-(benzylidinehydrazino)-1,2,3,4-thiatriazole **10** with isocyanates to give **11**[3] by analogy with our earlier work.



Subsequent work in our laboratory has revealed that the original[1] structure assignment as **7** was not correct due to a common pitfall in multiheteroatom cyclic systems: the unexpected and unrecognized rearrangements which occurred both during the reaction of **1** with isocyanates and also during the last step of the alternate synthesis, namely the reaction of **8** with the isocyanate. The latter reaction did not stop at **7**, but continued on to **12**. A recent review of rearrangements pertinent to this heterocyclic system has been published.[4] The present work not only establishes the correct structure as **12**, but also reveals some of the details of the reaction sequence. For compounds **3**, **7**, **8**, and **12** the letters following the number of a structure refer to R_1, R_2, and R_3 in that order.

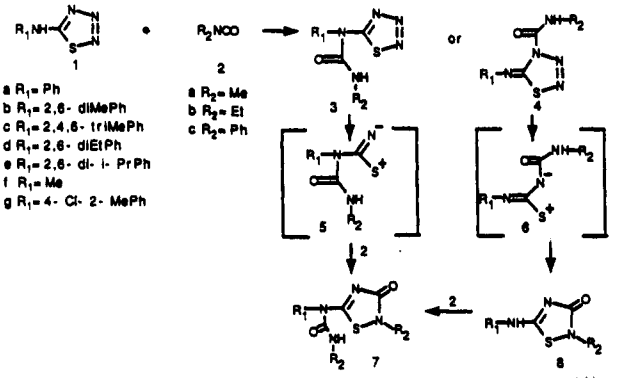


Results and Discussion

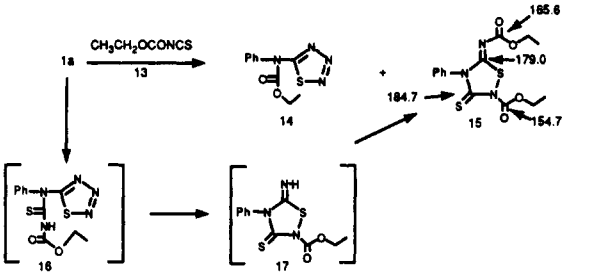
1. Reaction with Ethoxycarbonyl Isothiocyanate. The initial indication with the originally proposed structure required a revision came from the reaction of **1a** with ethoxycarbonyl isothiocyanate (**13**), which we expected to give **9** (R_1 = Ph, R_2 = $CO_2CH_2CH_3$). Instead, we obtained two products (Scheme II), whose structures were eventually determined to be **14** and **15**. The structure of **14** was proven by its synthesis from **1a** and ethyl chloroformate and by the ^{13}C NMR (C=O at δ 152.1 and C-5 at δ 170.7 as would be expected for carbamates[5] and acylated thiatriazoles[6]).

Since we had previously found that an NH was necessary in the 5-position for reactions with isocyanates,[1] we knew that **14** was not an intermediate because it was not capable of further reaction. The formation of **15** then had

Scheme I



Scheme II



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