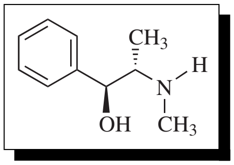
Pseudoephedrine



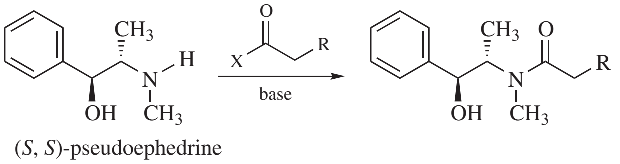
1S,2*S*-(+)
[90-82-4]
InChI = 1/C10H15NO/c1-8(11-2)10(12)9-6-4-3-5-7-9/h3-8,10-12H,1-2H3/t8-,10+/m0/s1
InChIKey = KWGRBVOPPLSCSI-WCBMZHEXBE
1*R*, 2*R*-(−)
[321-97-1] $C_{10}H_{15}ON$ (MW 165.24)
InChI = 1/C10H15NO/c1-8(11-2)10(12)9-6-4-3-5-7-9/h3-8,10-12H,1-2H3/t8-,10+/m1/s1
InChIKey = KWGRBVOPPLSCSI-SCZZXKLOBW

(reagent used as a practical chiral auxiliary for asymmetric synthesis)

Alternate Name: α-[1-(methylamino)ethyl] benzenemethanol; Ψ-ephedrine; isoephedrine.
Physical Data: mp 118–120 °C.
Solubility: sparingly soluble in water, soluble in ether, alcohol, and many other organic solvents.
Form Supplied in: white crystalline solid; widely available.
Purity: recrystallization from water.
Handling, Storage, and Precaution: stable; combustible; incompatible with strong oxidizing agents; eye, skin, and respiratory irritant; toxicity (oral) rat LD_{50}: 660 mg kg^{-1}.

Asymmetric Alkylation. *d*-Pseudoephedrine ([1*S*, 2*S*]-(+)) is a commodity chemical employed in over-the-counter medications with annual worldwide production in excess of 300 metric tons. The enantiomer, *l*-pseudoephedrine, is also readily available in bulk and is inexpensive. Pseudoephedrine has been shown to be highly effective as a chiral auxiliary in asymmetric alkylation reactions.[1,2] Treatment of either enantiomer of pseudoephedrine with carboxylic acid chlorides and anhydrides leads to efficient and selective *N*-acylation to form the corresponding tertiary amide derivatives (Table 1).[2] Typically, the only by-product in the acylation reactions is a small amount (<5%) of the *N*,*O*-diacylated product, which is easily removed by crystallization or flash column chromatography. Because intramolecular *O*→*N* acyl transfer within pseudoephedrine β-amino esters occurs rapidly, and because the *N*-acyl form is strongly favored under neutral or basic conditions,[3] products arising from (mono)acylation on oxygen rather than nitrogen are not observed.

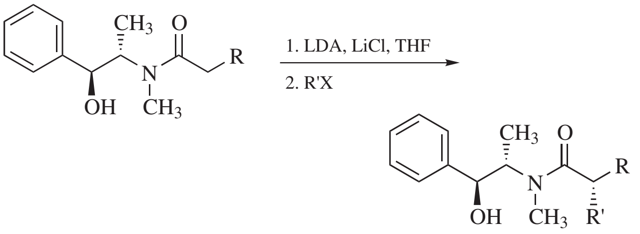
Table 1 Preparation of pseudoephedrine amides



R	X	Isolated yield (%)
CH_3	RCH_2CO_2	95
CH_3	CH_3O	89
i-Pr	Cl	92
3-Pyridyl	*t*-$BuCO_2$	72

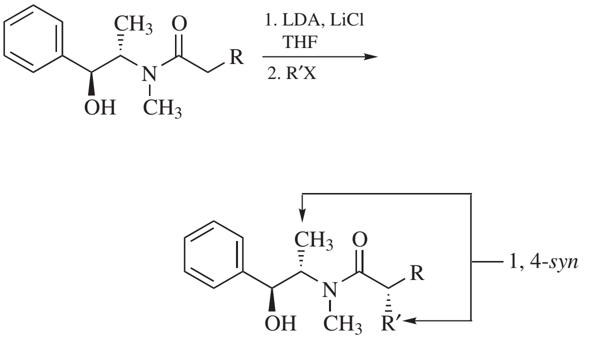
Pseudoephedrine amides undergo efficient and highly diastereoselective alkylation reactions with a wide range of alkyl halides as substrates (Table 2).[2] Alkylation of pseudoephedrine amides is accomplished by dianion formation with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) in the presence of lithium chloride (6 equiv), followed by the addition of an alkylating agent.[4] The use of lithium chloride leads to a substantial acceleration in the rate of alkylation and is essential for complete reaction. In addition, *O*-alkylation of the secondary hydroxyl group of the pseudoephedrine auxiliary is suppressed in the presence of lithium chloride. Although the specific role of lithium chloride in the reaction is not known, there is ample precedent in the literature, notably in the work of Seebach and co-workers, documenting the beneficial influence of lithium chloride in enolate alkylation reactions. These studies suggest that lithium chloride modifies the aggregation state, and thereby the reactivity of an enolate in solution.[5–8]

Table 2 Diastereoselective alkylation of pseudoephedrine amides with alkyl halides



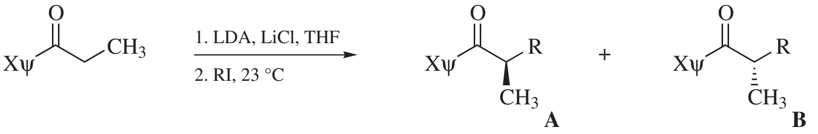
R	R'X	Isolated de (%)	Isolated yield (%)
CH_3	*n*-BuI	≥99	80
CH_3	BOMBr	98	80
t-Bu	BnBr	≥99	84
2-Thiophene	CH_3I	95	88

A useful mnemonic for deriving the preferred diastereomer formed in the alkylation reaction of pseudoephedrine amide enolates with alkyl halides is as follows: the alkyl halide enters from the same face as the methyl group of the pseudoephedrine auxiliary when the (putative) (*Z*)-enolate is drawn in a planar, extended conformation (eq 1).[1]

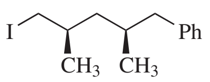
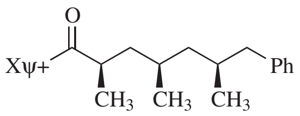
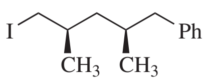
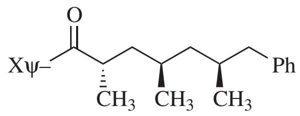
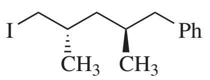
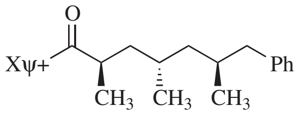
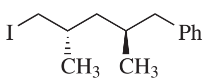
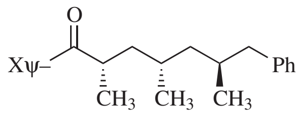


(1)

Table 3 Diastereoselcetive alkylation of pseudoephedrine amides β-branced electrophiles



Xψ = pseudoephedrine auxiliary

RI	Product	Ratio of **A**:**B**	Isolated yield (%)
		142:1 (matched)	93
		1:70 (mismatched)	96
		66:1 (mismatched)	93
		1:199 (matched)	94

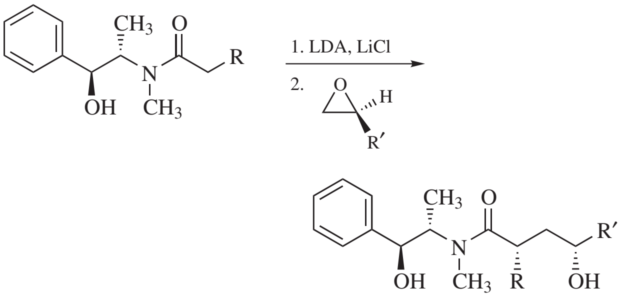
The superior nucleophilicity and excellent thermal stability of pseudoephedrine amide enolates make possible alkylation reactions with substrates that are ordinarily unreactive with the corresponding ester and imide-derived enolates, such as β-branched primary alkyl iodides.[2] Also, alkylation reactions of pseudoephedrine amide enolates with chiral β-branched primary alkyl iodides proceed with high diastereoselectivity for both the matched and mismatched cases (Table 3).[9]

Epoxides can also be used as substrates in pseudoephedrine amide enolate alkylation reactions, but react with opposite diastereofacial selectivity (suggesting a change in mechanism, proposed to involve delivery of the epoxide electrophile by coordination to a side-chain associated lithium ion), and are more limited in scope (Tables 4 and 5).[10]

A pictorial representation of the opposing diastereoselectivities of alkyl halides and epoxides is shown in Figure 1.[10] A similar electrophile dependence upon diastereoselectivity was first noted in the alkylation of prolinol amide enolates.[11]

Although alkylation reactions of pseudoephedrine amide enolates are successful with a broad range of electrophiles, a few problematic substrates have been identified. Among these are secondary alkyl halides, such as cyclohexyl bromide, and alkyl halides that are both β-branched and β-alkoxy substituted.[2] However, there is evidence that the thermal stability of pseudoephedrine amide enolates may be such that extended reaction times at ambient temperature, or even heating, may be tolerated; both approaches have led to successful alkylation reactions with problematic electrophiles (eqs 2, 3, and 4).[12,2,13]

Table 4 Diastereoselective alkylation of pseudoephedrine amides with matched epoxides



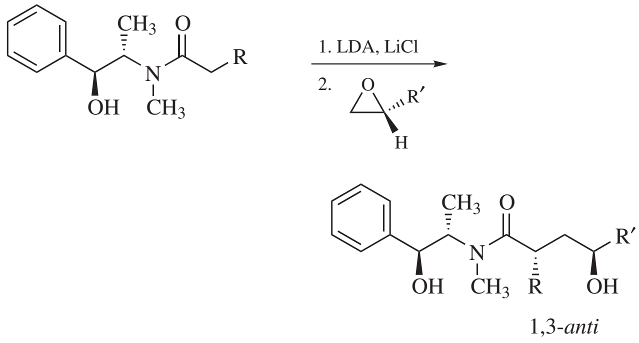
1,3-*syn*

R	R′	Isolated de (%)	Isolated yield (%)
CH_3	CH_3	93	88
CH_3	CH_2OTBS	96	84
Bn	C_6H_6	≥95	86
Bn	CH_2OBn	≥95	87

Pseudoephedrine amides with a wide variety of α-substituents, including aryl,[1] branched alkyl,[14] chloro,[1,2] fluoro (described in detail in the section Asymmetric Synthesis of Organofluorine Compounds), amino (described in detail in the section Synthesis of α-Amino Acids), and 2-pyridyl groups,[2] undergo highly diastereoselective alkylation reactions. However, to date, no general solution has emerged for the diastereoselective alkylation of pseudoephedrine amides with an α-oxygenated substituent. Enolization of pseudoephedrine α-hydroxyacetamide with 3.2 equiv of LDA furnishes a presumed trianion, with partial decomposition of the starting material. Alkylation of the resulting enolate (1.65

equiv) with benzyl bromide (limiting reagent) then produces the corresponding *C*-benzylated product with 82% de (eq 5).[2]

Table 5 Diastereoselective alkylation of pseudephedrine amides with mismatched epoxides



R	R′	Isolated de (%)	Isolated yield (%)
CH_3	CH_3	73	86
CH_3	CH_2OTBS	12	78
Bn	C_6H_6	46	72
Bn	CH_2OBn	36	80

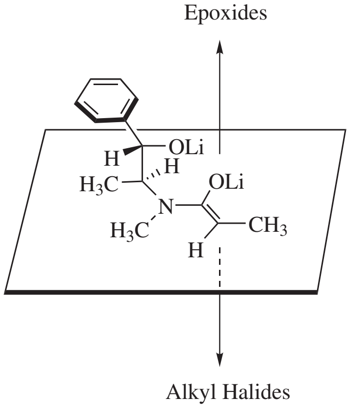
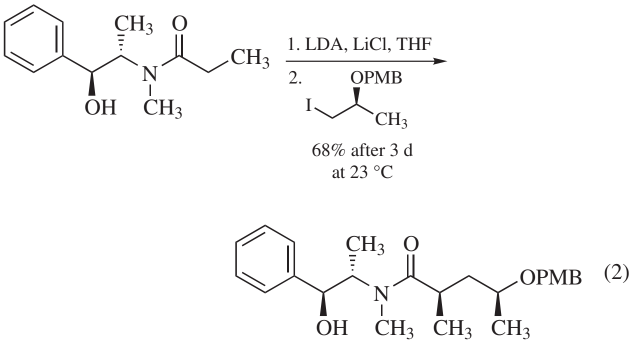


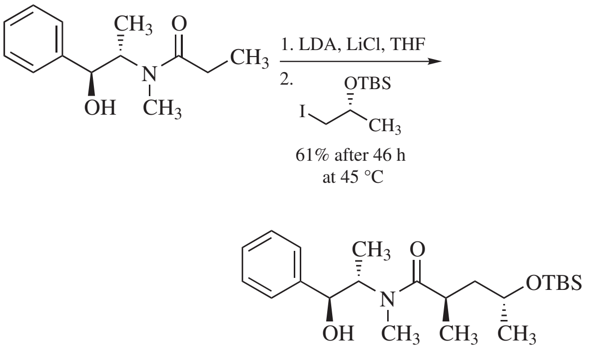
Figure 1



(2)

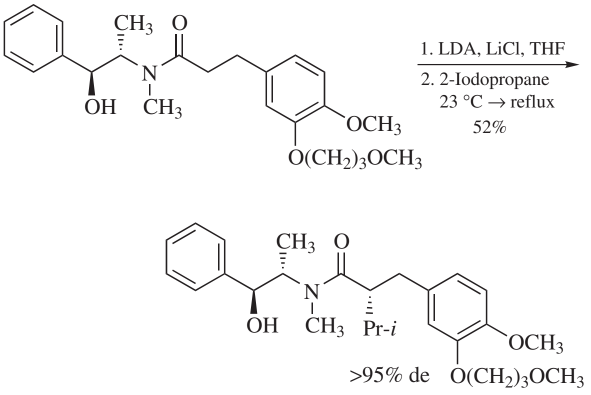
~13:1

The diastereoselectivity of the reaction is lower than that obtained in benzylations of pseudoephedrine amide enolates lacking the α-hydroxyl group. Although an extensive series of *O*-protected derivatives of α-hydroxyacetamide has been examined in a search for an alternative alkylation substrate [TBS, TBDPS, THP, Bn, BOM, Piv, and methyl(1-methoxyethyl)], none has provided satisfactory results nor offered any improvement over pseudoephedrine α-hydroxyacetamide itself.[2]



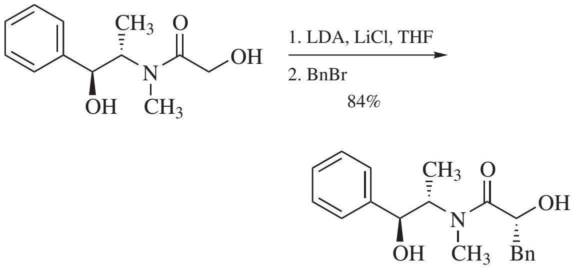
(3)

99% de



(4)

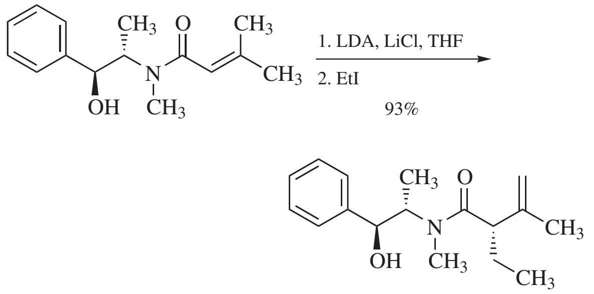
>95% de



(5)

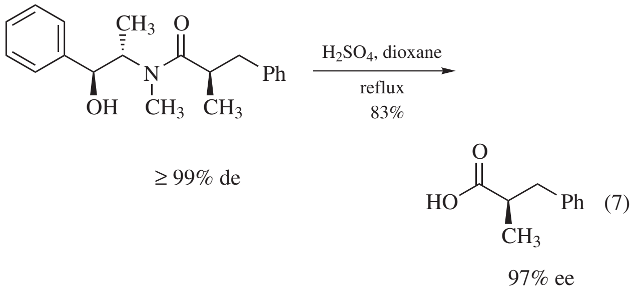
82% de

α,β-Unsaturated pseudoephedrine amides undergo γ-deprotonation when subjected to standard conditions for pseudoephedrine amide enolate formation. The resulting enolate can be α-alkylated with high diastereoselectivity to provide β,γ-unsaturated alkylated products (eq 6).[15]



(6)

Transformations of Alkylated Pseudoephedrine Amides. Alkylation products of pseudoephedrine amides are readily transformed in a single operation into highly enantiomerically enriched carboxylic acids, aldehydes, ketones, lactones or primary alcohols.[1,2] Alkylated pseudoephedrine amides can be hydrolyzed under acidic or basic conditions to form carboxylic acids. Simply heating a pseudoephedrine amide at reflux in a 1:1 mixture of sulfuric acid (9–18 N) and dioxane affords the corresponding carboxylic acid in excellent chemical yield with little or no epimerization (eq 7).[16] Under these conditions, the substrate initially undergoes a rapid *N*→*O* acyl transfer reaction followed by rate-limiting hydrolysis of the resulting *β*-ammonium ester intermediate to form the carboxylic acid.[3,17]



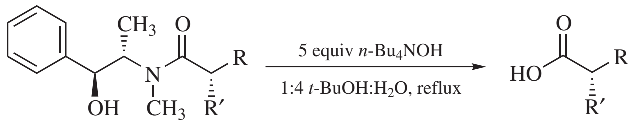
≥ 99% de

(7)

97% ee

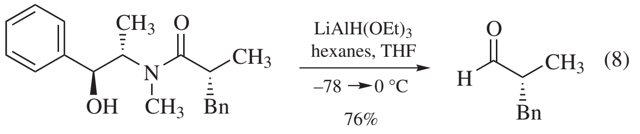
Basic conditions for the hydrolysis of pseudoephedrine amides typically involve heating the substrate with tetra-*n*-butylammonium hydroxide in a mixture of *tert*-butyl alcohol and water (Table 6).[1,2] Where the expense of tetra-*n*-butylammonium hydroxide is a consideration, or in cases where the product carboxylic acid is poorly soluble in ether (making extractive removal of tetra-*n*-butylammonium salts difficult), an alternative procedure employing sodium hydroxide in a mixture of water, methanol, and *tert*-butyl alcohol can be used. The mechanism of the base-induced hydrolysis reaction is believed to involve initial rate-limiting intramolecular *N*→*O* acyl transfer, followed by rapid saponification of the resulting *β*-amino ester.[3]

Table 6 Basic hydrolysis of pseudoephedrine amides



R	R′	Isolated ee (%)	Isolated yield (%)
CH_3	Bn	94	93
CH_3	BOM	69	92
n-Bu	CH_3	93	88
Ph	Et	64	82

Pseudoephedrine amides can be converted directly into highly enantiomerically enriched aldehydes[1,2] using Brown and Tsukamoto's lithium triethoxyaluminum hydride reagent[18] (eq 8).[19,20]

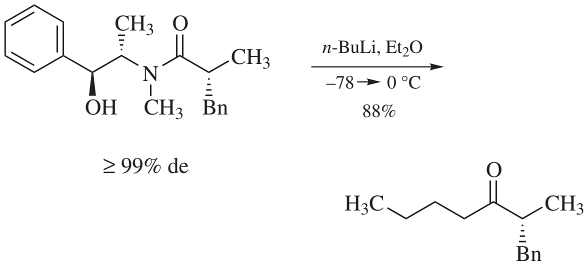


(8)

≥ 99% de

95% ee

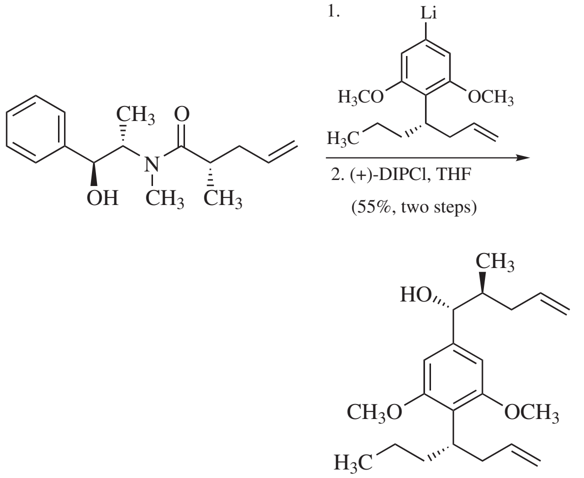
Addition of alkyllithium reagents to pseudoephedrine amides leads to the formation of enantiomerically enriched ketones[1,2,21] (eqs 9 and 10).[19,20] The protocol developed to transform alkylated pseudoephedrine amides into ketones was optimized to avoid premature breakdown of the tetrahedral intermediate generated following addition of the organolithium species to the amide.[23]



≥ 99% de

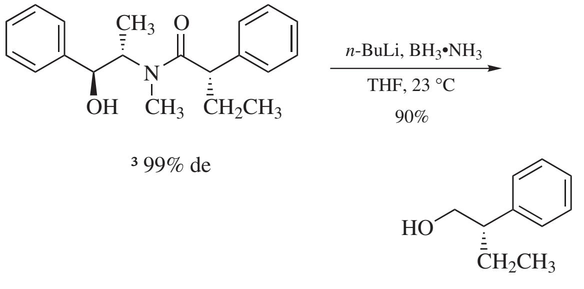
(9)

≥ 95% ee



(10)

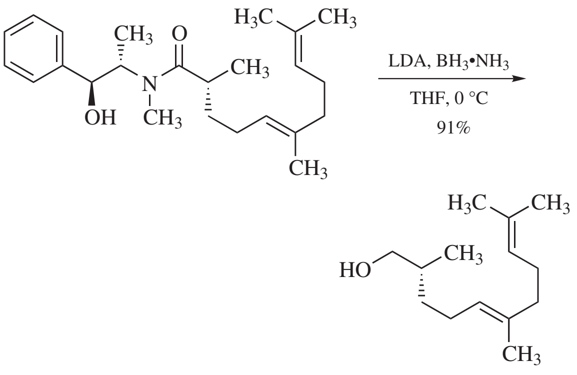
Reduction of pseudoephedrine amides with metal amide-borane complexes,[1] and lithium amidotrihydroborate (LAB) in particular,[2,24] furnishes the corresponding primary alcohols in high yield. In the initial report, LAB was prepared by deprotonation of the commercial, solid reagent borane–ammonia complex,[25] using slightly less than 1 equiv of butyllithium as base (eq 11).[24] In more recent work,[9] an improved preparation of the reagent has been developed that uses 1 equiv of LDA as base in the reaction (eq 12).[26] The greater efficiency of reductions using LDA as base is attributed to the propensity of *n*-butyllithium to form butylboron side-products in the reaction and, ultimately, butylboron alkoxide products that are difficult to hydrolyze.



^{3} 99% de

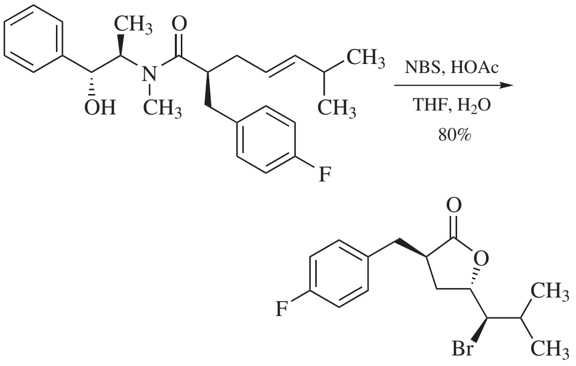
(11)

90% ee

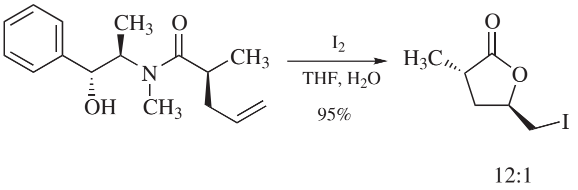


(12)

γ,δ-Unsaturated pseudoephedrine amides are efficiently converted into γ-lactones by cleavage of the auxiliary through halolactonization reactions (eqs 13 and 14).[27,28]



(13)

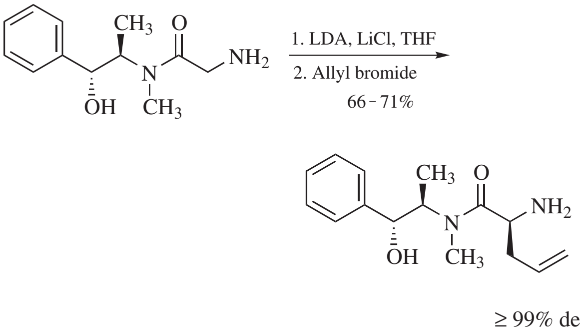


(14)

The efficiency and practicality of pseudoephedrine-based asymmetric alkylation reactions has been exploited in syntheses of several complex natural products, including cylindrocyclophane A,[22,29] fumonisin B$_2$,[30] pironetin,[15] epothilones A and B,[31] salicylihalamide A,[32] 6,7-dideoxysqualestatin H5,[33] saframycin A,[34,35] and terpestacin.[28]

Synthesis of α-Amino Acids. The diastereoselective alkylation of enolates derived from pseudoephedrine glycinamide has been shown to be an effective method for the preparation of α-amino acids of high enantiomeric purity.[36,37] Pseudoephedrine glycinamide hydrate can be easily prepared in a single step by the condensation of pseudoephedrine with the free-base form of glycine methyl ester in the presence of lithium chloride and base (*n*-butyllithium[36] or lithium methoxide[37]). The primary by-product in the reaction is the dipeptide pseudoephedrine glycylglycinamide, formed to the extent of < 10%. The crude acylation reaction mixture can be directly purified by selective crystallization of pseudoephedrine glycinamide hydrate from hot aqueous tetrahydrofuran. An improved preparation of pseudoephedrine glycinamide hydrate entails the direct treatment of glycine methyl ester hydrochloride with lithium *tert*-butoxide.[38] This procedure is advantageous because it obviates the need to use the hygroscopic reagent lithium chloride and it eliminates difficulties associated with the handling of the free-base form of glycine methyl ester, which is prone to polymerization.

Enolization of pseudoephedrine glycinamide is complicated by the presence of two other acidic sites in the molecule: the secondary hydroxyl group and the primary amino group. The enolization protocol originally reported requires the addition of a carefully measured amount of LDA to a thoroughly dried solution of pseudoephedrine glycinamide and lithium chloride.[37] The strict use of less than 2 equiv of base avoided partial cleavage of the auxiliary from pseudoephedrine glycinamide. Several practical laboratory-scale preparations of enantiomerically enriched α-amino acids, including *l*-azatyrosine[39] and *l*-allylglycine (eq 15),[40] have been executed based on this methodology.

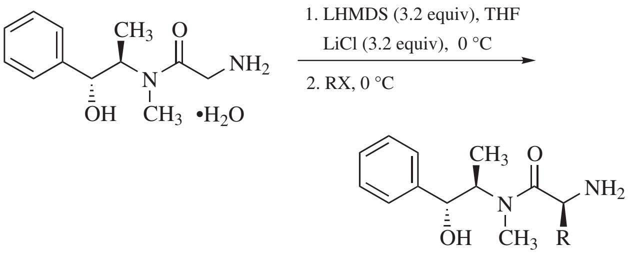


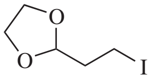
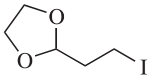
(15)

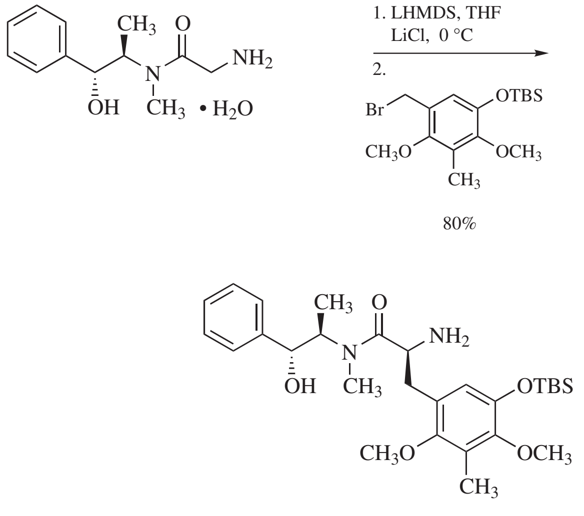
A modified procedure has since been developed that involves the direct alkylation of pseudoephedrine glycinamide hydrate.[38] In this operationally simpler procedure, excess lithium hexamethyldisilazide (LHMDS) is added to a solution of anhydrous lithium chloride and pseudoephedrine glycinamide hydrate. In situ generation of LHMDS•LiCl from lithium metal, hexamethyldisilazane (HMDS), and hexyl chloride can also been used for the enolization and subsequent alkylation of pseudoephedrine glycinamide hydrate.[38] These procedures for the alkylation of pseudoephedrine glycinamide reliably afford good yields of alkylated products (Table 7). The procedure employing commercial LHMDS has been used in the total synthesis of saframycin A (eq 16).[34,35]

Alkylation of pseudoephedrine sarcosinamide can be used to prepare enantiomerically enriched *N*-methyl-α-amino acids.[36,37] Anhydrous pseudoephedrine sarcosinamide has been prepared by the addition of sarcosine methyl ester to a mixture of pseudoephedrine, lithium chloride, and lithium methoxide. In contrast to the preparation of pseudoephedrine glycinamide, the amount of dipeptide by-product produced in the reaction is minimal, perhaps due to the increased steric hindrance of the *N*-methyl group of sarcosine. Thus, pure anhydrous pseudoephedrine sarcosinamide can be obtained from the crude acylation reaction mixture by precipitation from toluene and subsequent drying. Like anhydrous pseudoephedrine glycinamide, anhydrous pseudoephedrine sarcosinamide can be handled in the atmosphere for brief periods without consequence, but should be stored with scrupulous avoidance of moisture to prevent hydration.

Table 7 Alkylation of pseudoephedrine glycinamide hydrate

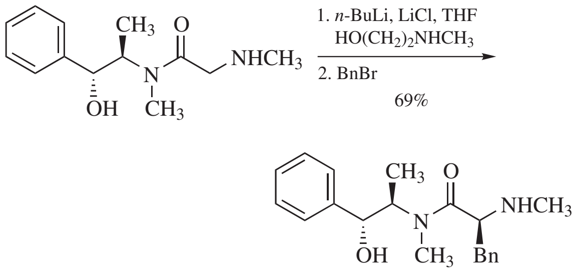


RX	LHMDS	Isolated de (%)	Isolated yield (%)
$CH_2{=}CHCH_2Br$	Commercial solution (1.0 M in THF)	93	86
$CH_2{=}CHCH_2Br$	Generated in situ (Li, HMDS, *n*-HexCl)	93	82
	Commercial solution (1.0 M in THF)	97	65
	Generated in situ (Li, HMDS, *n*-HexCl)	96	62



(16)

97% de

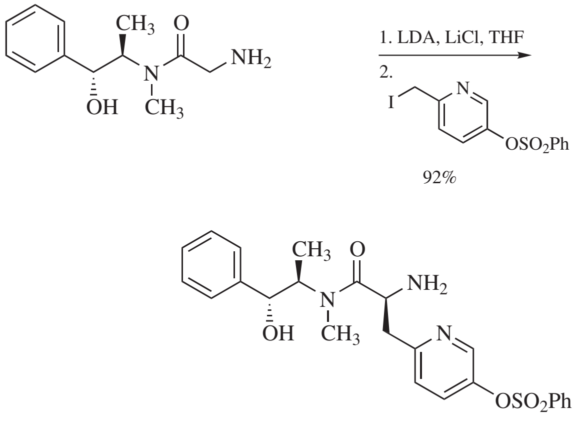


(17)

99% de

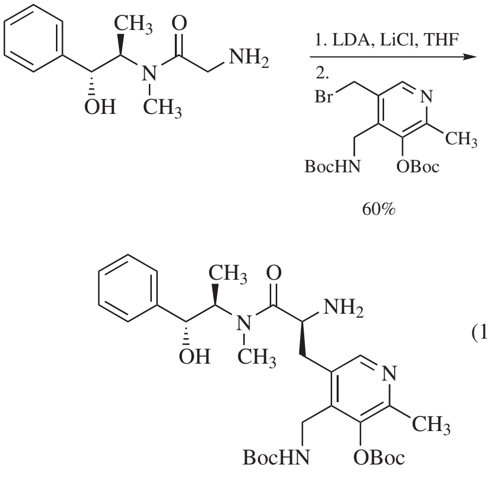
The alkylation of anhydrous pseudoephedrine sarcosinamide is similar to the alkylation of anhydrous pseudoephedrine glycinamide, with one important experimental modification, wherein the reaction is conducted in the presence of 1 equiv of *N*-methylethanolamine. The optimum conditions for alkylation of anhydrous pseudoephedrine sarcosinamide involve the addition of *n*-butyllithium or LDA (2.95 equiv) to a suspension of anhydrous pseudoephedrine sarcosinamide (1 equiv), anhydrous lithium chloride (6.00 equiv), and *N*-methylethanolamine (1.00 equiv) in THF at −78 °C, followed by warming the resulting slurry to 0 °C and the addition of an alkylating agent (1.1–1.5 equiv) (eq 17).**[37]** The presence of *N*-methylethanolamine in the alkylation reaction is necessary to achieve reproducible diastereoselectivity and may function by facilitating anionic equilibration.

Many functional groups are stable under conditions for the alkylation of pseudoephedrine glycinamide enolates, including aryl benzenesulfonate esters (eq 18),**[39]** *tert*-butyl carbamate and *tert*-butyl carbonate groups (eq 19),**[41]** *tert*-butyldimethylsilyl ethers,**[42]** benzyl ethers,**[37]** *tert*-butyl ethers,**[37]** methoxymethyl ethers,**[36]** and alkyl chlorides.**[36]** The stereochemistry of the alkylation reactions of pseudoephedrine glycinamide and pseudoephedrine sarcosinamide is the same as that observed in alkylations of simple *N*-acyl derivatives of pseudoephedrine.



(18)

90 –91% de



(19)

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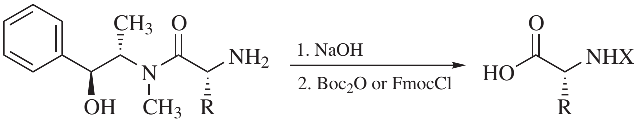
Hydrolysis reactions of alkylated pseudoephedrine glycinamides are more rapid than the hydrolysis of pseudoephedrine amides without α-amino groups. It is believed that this reflects the inductive influence of the amino group, enhancing the electrophilicity of the amide group.[37] It is significant that this rate enhancement is not accompanied by an increased rate of racemization. Typically, alkaline hydrolysis of the alkylation products occurs upon heating at reflux in aqueous sodium hydroxide solution (0.5 M, 2 equiv).[36] Upon cooling, the pseudoephedrine auxiliary is easily recovered by extraction of the aqueous product slurry with dichloromethane (typically, 96% of the pseudoephedrine auxiliary is recovered, and 83–86% after one recrystallization from water). After extraction of the auxiliary, the alkaline aqueous product solution can be treated with an acylating agent to furnish the corresponding *N*-protected α-amino acid derivative directly. *N-tert*-Butoxycarbonyl (*N*-Boc) and *N*-(9-fluorenylmethoxy)-carbonyl (*N*-Fmoc) protected α-amino acids are prepared efficiently by this method (Table 8).[37] Free α-amino acids can be obtained simply by refluxing the alkylation products in pure water. Extraction of the aqueous reaction mixture with dichloromethane, lyophilization of the aqueous layer, and trituration of the solid residue with ethanol (to remove any remaining pseudoephedrine) then provides the pure α-amino acids (Table 9).[36]

Table 8 Basic hydrolysis of pseudoephedrine amides followed by *N*-protection



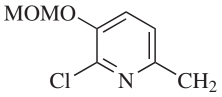
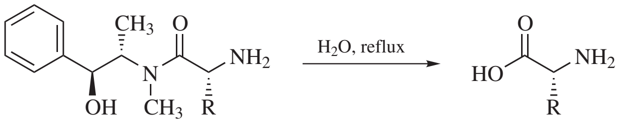
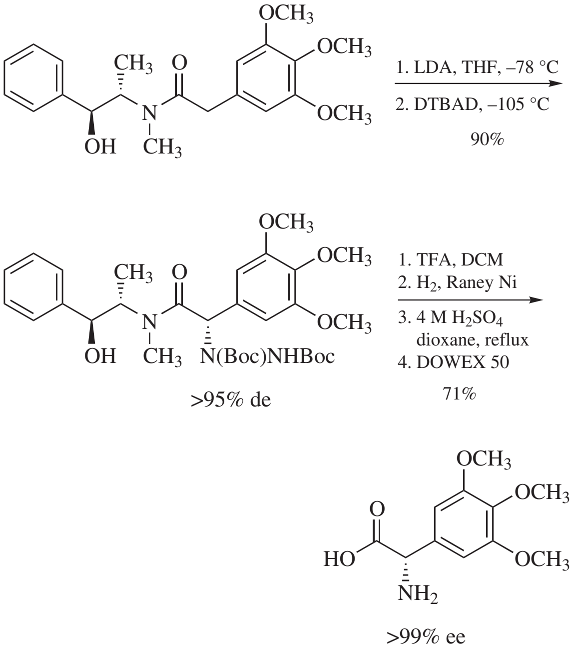
R	X	Isolated ee (%)	Isolated yield (%)
CH_3CH_2	Boc	≥99	97
CH_3CH_2	Fmoc	≥99	99
$(CH_3)_2CHCH_2$	Boc	≥99	97
	Fmoc	96	73

Table 9 Hydrolysis of pseudophedrine amides in water



R	Isolated ee (%)	Isolated yield (%)
$CH_2{=}CHCH_2$	≥99	87
c-$C_3H_5CH_2$	≥98	79
$(CH_3)_3SiCH_2$	≥99	77
2-$CH_3OC_6H_4CH_2$	≥99	71

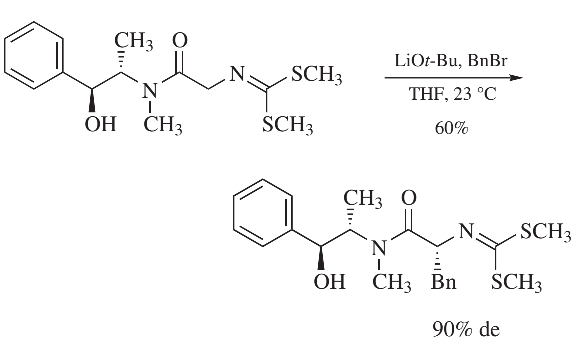
The asymmetric amination of pseudoephedrine amide enolates has been introduced as an alternative method for the synthesis of α-amino acids.[43] Lithium enolates, generated by the addition of LDA to pseudoephedrine amides, can be efficiently aminated with di-*tert*-butyl azodicarboxylate (DTBAD). The amination reaction is complete within a few minutes at low temperature and does not require the use of lithium chloride. Cleavage of the Boc groups within the adducts using trifluoroacetic acid (TFA) and hydrogenolysis of the resulting α-hydrazino derivatives then provides α-amino acids in good yield following acidic hydrolysis and ion exchange chromatography (eq 20).[43]



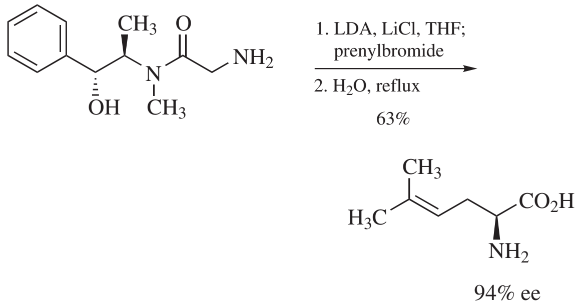
(20)

Recently, the bis(methylthio)methylene imine of pseudoephedrine glycinamide was shown to undergo diastereoselective alkylation at 23 °C with lithium *tert*-butoxide or sodium ethoxide as base and various alkyl halides as electrophiles (eq 21).[44] This procedure was used to prepare enantiomerically enriched α-amino acids.

Alkylation reactions of pseudoephedrine amides offer many practical advantages over existing procedures for the asymmetric construction of α-amino acids. These include the high crystallinity of many pseudoephedrine amides, the low cost of pseudoephedrine, the high diastereoselectivity of the alkylation reactions, a simple protocol for recovering the auxiliary, and the ease of hydrolytic, racemization-free removal of the chiral auxiliary. The methodology is also advantageous because it requires no protecting group for the α-amine. Thus, in many instances, alkylation of pseudoephedrine glycinamide has been deemed the method of choice for the preparation of enantiomerically enriched α-amino acids in quantity (eq 22).[45]

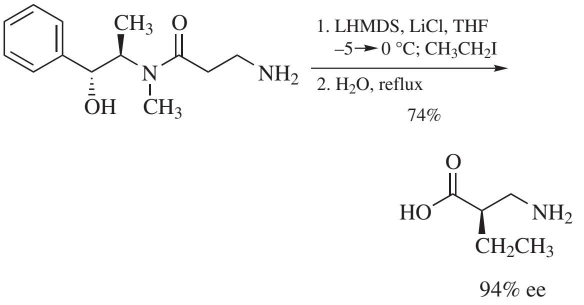


(21)



(22)

***β*-Amino Acids.** Pseudoephedrine has been used as a chiral auxiliary for the preparation of both α-substituted and α,β-disubstituted β-amino acids. Alkylation of β-alanine was shown to furnish an efficient, inexpensive, and enantioselective route to α-alkyl β-amino acids (eq 23).[46]



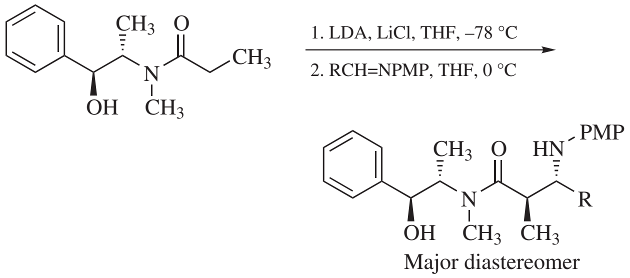
(23)

In addition, the lithium enolate derived from pseudoephedrine propionamide has been shown to undergo highly diastereoselective Mannich reactions with *p*-(methoxy)phenyl aldimines to form enantiomerically enriched α,β-disubstituted β-amino acids (Table 10).[47] As observed in alkylation reactions using alkyl halides as electrophiles, lithium chloride is necessary for the reaction of aldimines. With respect to the enolate, the stereochemistry of the alkylation reactions is the same as that observed with alkyl halides; reactions of *p*-(methoxy)phenyl aldimines are further characterized by a preference for the formation of 2,3-anti products, a unique and highly useful feature of these reactions.

Aldol Reactions. Pseudoephedrine amide enolates have been shown to undergo highly diastereoselective aldol addition reactions, providing enantiomerically enriched β-hydroxy acids, esters, ketones, and their derivatives (Table 11).[48,49] The optimized procedure for the reaction requires enolization of the pseudoephedrine amide substrate with LDA followed by transmetalation with 2 equiv of $ZrCp_2Cl_2$ at $-78\,°C$ and addition of the aldehyde electrophile at $-105\,°C$. It is noteworthy that the reaction did not require the addition of lithium chloride to favor product formation as is necessary in many other pseudoephedrine amide enolate alkylation reactions. The stereochemistry of the alkylation is the same as that observed with alkyl halides and the formation of the 2,3-*syn* aldol adduct is favored. The tendency of zirconium enolates to form *syn* aldol products has been previously reported.[50,51,52] The β-hydroxy amide products obtained can be readily transformed into the corresponding acids, esters, and ketones as reported with other alkylated pseudoephedrine amides.

An asymmetric aldol reaction between an (*S*,*S*)-(+)-pseudoephedrine-based arylacetamide and paraformaldehyde has been used to prepare enantiomerically pure isoflavanones.[53]

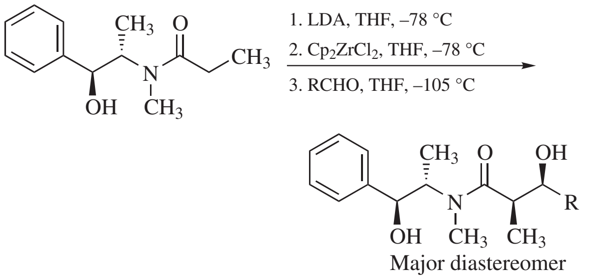
Table 10 Mannich reaction of pseudoephedrine propionamide enolate with *p*-(methoxy)phenyl aldimides



R	*anti/syn*	*anti/anti**[a]	Yield (%)
Ph	>99/1	>99/1	86
2-furyl	>99/1	>99/1	80
t-Bu	>99/1	>99/1	69

[a]Ratio of major anti diastereomer (shown) to doubly epimeric minor anti diastereomer.

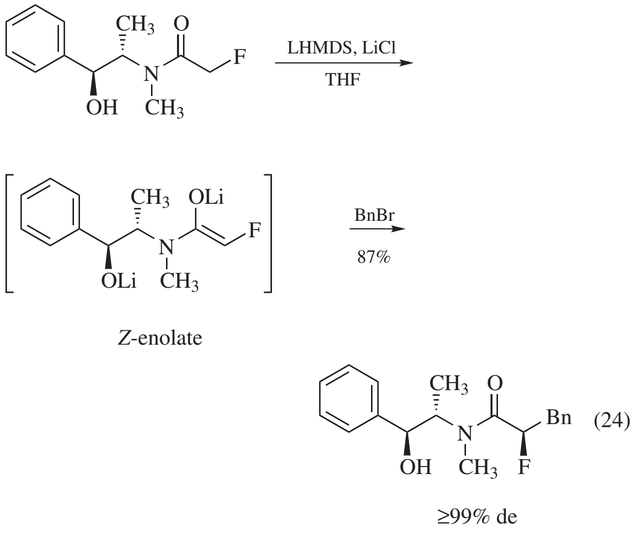
Table 11 Pseudophedrine-based asymmetric aldol reactions

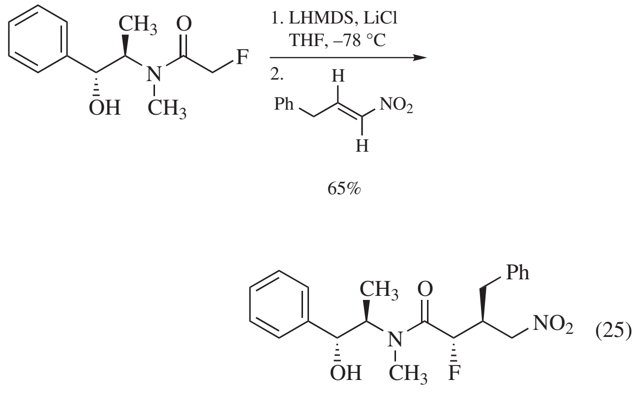


R	*syn/anti*	*syn/syn**[a]	Yield (%)
Ph	94/6	>99/1	90
Et	96/4	>99/1	90
i-Pr	>99/1	>99/1	94

[a]Ratio of major syn diastereomer (shown) to doubly epimeric minor syn diastereomer.

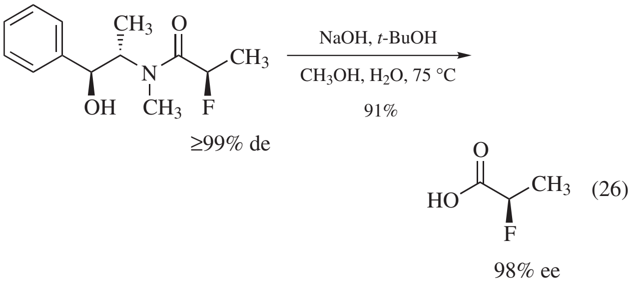
Asymmetric Synthesis of Organofluorine Compounds. Asymmetric alkylation of fluorinated pseudoephedrine amides has been employed to synthesize a variety of enantiomerically enriched α-fluoro carboxylic acid derivatives. Pseudoephedrine α-fluoroacetamide, a nonvolatile, crystalline compound, can be readily prepared by the acylation of pseudoephedrine with ethyl fluoroacetate. (CAUTION: Fluoroacetic acid and derivatives of fluoroacetic acid are exceedingly toxic, causing convulsions and ventricular fibrillation upon inhalation and should be used only under adequate supervision and in an appropriate fume hood. Although the specific toxicities of pseudoephedrine α-fluoroacetamide and other fluorinated pseudoephedrine derivatives are unknown, extreme caution in their preparation and handling is urged.) Pseudoephedrine α-fluoroacetamide can be enolized with LHMDS in the presence of anhydrous lithium chloride and the resulting enolate can be efficiently trapped with reactive electrophiles, such as benzyl bromide, to form the corresponding alkylated products with high diastereoselectivity (eq 24).[54] Interestingly, enolization of pseudoephedrine α-fluoroacetamide with LDA in the presence of anhydrous lithium chloride and subsequent trapping of the resulting enolate with reactive electrophiles resulted in the formation of alkylated products with diminished diastereoselectivity. The basis for the improved selectivity in alkylations conducted with LHMDS versus LDA is not known; however, the stereochemistry of enolate formation is proposed to be the selectivity-determining step in these reactions. Presumably, the enolization of pseudoephedrine α-fluoroacetamide with LHMDS, be it kinetically or thermodynamically controlled, exhibits a strong preference for the *Z*-configuration. The stereochemistry of the subsequent alkylation reaction is then consistent with the model proposed for the alkylation of simple *N*-acyl derivatives of pseudoephedrine. Unlike other pseudoephedrine amide enolates, the enolate derived from pseudoephedrine α-fluoroacetamide exhibits limited thermal stability above $\sim -40\,^\circ$C and, as a consequence, alkylation reactions with relatively unreactive electrophiles, such as ethyl iodide, proceed poorly. However, Michael addition with 1-nitro-3-phenyl-1-propene does occur, even at $-78\,^\circ$C, forming two of the four possible diastereomeric conjugate addition products (eq 25).[55] These products were demonstrated to be stereoisomeric at the β-carbon, and had the same configuration at the α-carbon, that expected based upon addition of simple alkyl halides to the *Z*-enolate derived from pseudoephedrine α-fluoroacetamide.



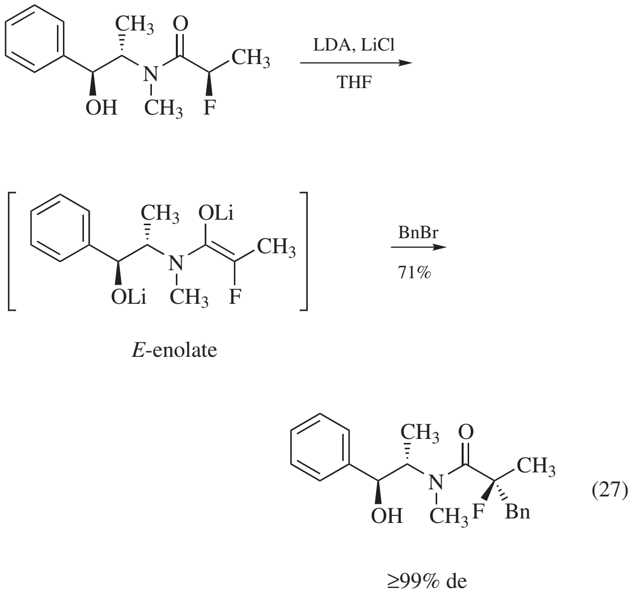


1.7:1 *anti*:*syn*

Inductive activation of the amide by the adjacent fluorine atom allows for the basic hydrolysis of the amide bond under relatively mild conditions (warming to ~75 °C in a biphasic solution of 2 N sodium hydroxide in a 2:2:1 mixture of water, *tert*-butyl alcohol, and methanol) to form carboxylic acids with high enantiomeric excess (eq 26).[54]



Alkylation of pseudoephedrine α-fluoropropionamide can be used to prepare enantiomerically enriched tertiary alkyl fluoride centers (eq 27).[56] In contrast to the alkylation of pseudoephedrine α-fluoroacetamide, alkylation of pseudoephedrine α-fluoropropionamide proceeds with high diastereoselectivity when LDA in used as the base in the reaction and low diastereoselectivity when LHMDS is used. In these reactions, deprotonation of pseudoephedrine α-fluoropropionamide with LDA, proposed to occur under kinetic control, is believed to form the corresponding *E*-enolate. Electrophilic attack by alkyl halides then occurs opposite the enolate π-face occupied by the side-chain alkoxide group, as observed with other pseudoephedrine amide enolates.



Related Reagents. Prolinol; Ephedrine; Oxazolidinones; Camphorsultams; Camphor-derived Auxiliaries; Oxazolines.

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