Highly Practical Methodology for the Synthesis of D- and L-α-Amino Acids, *N*-Protected α-Amino Acids, and *N*-Methyl-α-amino Acids

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Abstract: Full details are provided for an exceedingly practical method to synthesize D- and L-α-amino acids, *N*-protected α-amino acids, and *N*-methyl-α-amino acids, employing as a key step the asymmetric alkylation of pseudoephedrine glycinamide (**1**) or pseudoephedrine sarcosinamide (**2**). Practical procedures for the synthesis of **1** and **2** from pseudoephedrine and glycine methyl ester or sarcosine methyl ester, respectively, are presented. Optimum protocols for the enolization and subsequent alkylation of **1** and **2** are described. Alkylation reactions of **1** and **2** are found to be quite efficient with a wide range of alkyl halide substrates, and the products are formed with high diastereoselectivity. The products of these alkylation reactions are hydrolyzed efficiently and with little to no racemization simply by heating in water or water−dioxane mixtures. This protocol provides an exceedingly practical method for the preparation of salt-free α-amino acids of high enantiomeric purity. Alternatively, the alkylation products may be hydrolyzed in high yield and with little to no racemization by heating with aqueous sodium hydroxide. The alkaline hydrolyzate can then be treated with an acylating reagent to provide directly highly enantiomerically enriched *N*-protected derivatives such as *N*-Boc and *N*-Fmoc. Key features necessary for the successful execution of these experimental procedures are identified.

As the defining subunit of peptides and proteins, α-amino acids play a central role in chemistry and biology. Their availability is critical in basic research applications, as well as in industry. In addition to the need for large-scale production of the 20 common proteinogenic α-amino acids, there is an ever increasing demand for the much rarer nonproteinogenic α-amino acids. These may be natural products or wholly synthetic, non-natural materials. Fueled by advances in the biochemical sciences, nonproteinogenic α-amino acids are now incorporated into designed peptides and proteins, both in vitro[1] and in vivo.[2] In addition, non-natural α-amino acids often appear within the increasingly sophisticated structures of novel pharmaceutical agents.

These factors have stimulated the development of a wealth of methodology for the synthesis of α-amino acids, both by the modification of available residues[3] and, of greater generality and concern in the present context, by the use of stereoselective, de-novo constructive synthetic reactions. The latter subject has been thoroughly reviewed, most recently in the excellent texts of Williams and Duthaler.[4] Many powerful methods have emerged for the asymmetric synthesis of α-amino acids. Conceptually, one of the most direct and general methods for the preparation of α-amino acids is the alkylation of the

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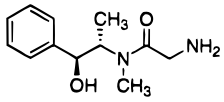
α-carbon of an enolate derivative of glycine. Many variants of this reaction that involve the diastereoselective alkylation of chiral glycine enolate derivatives have been developed.[5] The use of chiral electrophilic glycine equivalents for the asymmetric synthesis of α-amino acids has also been reported.[6] In addition, impressive advances in the asymmetric alkylation (∼50−70% ee) of achiral glycine derivatives using chiral phase-transfer catalysts have been described in a series of papers from O'Donnell and co-workers.[7]

Recently, we reported a new method for the asymmetric synthesis of α-amino acids that is based on the diastereoselective alkylation of pseudoephedrine glycinamide (**1**).[8] As a process that employs stoichiometric quantities of a chiral auxiliary, this method might initially appear to be noncompetitive with an asymmetric catalytic procedure, especially in light of the truly spectacular recent achievements in the asymmetric hydrogenation of α,β-didehydro-α-amino acids.[9] However, the latter advances must be weighed considering the availability of the α,β-didehydro-α-amino acid precursors.[10] These are frequently prepared by multistep methods (one of which typically involves an alkylative construction reaction), and invariably require that the amino group be protected. We believe that, in many cases, the methodology described herein offers practical advantages over existing procedures for the asymmetric construction of α-amino acids. These include the low cost and availability in bulk of both enantiomeric forms of pseudoephedrine, the tendency of many pseudoephedrine amides to be crystalline, the high diastereoselectivity of the alkylation reactions, and the facility of and lack of racemization in the hydrolytic removal of the chiral auxiliary. The method is also distinguished by the fact that each of the synthetic manipulations may be executed without the use of protective groups on the amino group of glycine. These and other features lend practicality to the methodology, be it for the preparation of large or small quantities of highly enantiomerically enriched D- or L-α-amino acids.

Presented herein are complete details of the preparation and alkylation of pseudoephedrine glycinamide (**1**) and pseudoephedrine sarcosinamide (**2**), as well as for the transformation of the alkylation products into free and/or *N*-protected α-amino acids of high enantiomeric purity.



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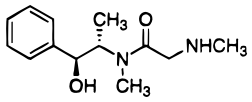
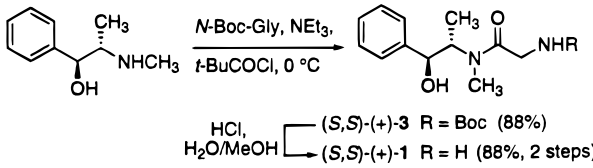


2

Initial Studies

Preparation of the Alkylation Substrates Pseudoephedrine Glycinamide (1) and Pseudoephedrine Sarcosinamide (2). This project was initiated by the finding that the simple chiral amino alcohol pseudoephedrine serves as a valuable chiral auxiliary for the asymmetric alkylation of a wide range of its *N*-acyl derivatives.[11] The goal here was to extend this chemistry to prepare α-amino acids by the alkylation of a pseudoephedrine glycinamide derivative. Initial considerations focused primarily on the choice of an appropriate protective group for the amino group of glycine. While several groups were examined, and successfully so (vide infra), these experiments were superseded with the finding that the optimum pseudoephedrine glycinamide derivative was the simplest possible, i.e., structure **1** (or, for the preparation of *N*-methyl-α-amino acids, the sarcosinamide **2**), in which no protective group at all was employed.

Pseudoephedrine glycinamide (**1**) was initially prepared by the selective *N*-acylation of pseudoephedrine (1.0 equiv) with the mixed anhydride derived from *N*-Boc-glycine (1.0 equiv) and trimethylacetyl chloride (1.0 equiv) in the presence of triethylamine (2.2 equiv) in dichloromethane at 0 °C, affording *N*-Boc-pseudoephedrine glycinamide (**3**) as a viscous oil (88%



yield).[12,13] Treatment of **3** with trifluoroacetic acid and anisole (3:1) in dichloromethane at 23 °C or with mixtures of aqueous hydrochloric acid (3 M) and methanol at 23 °C cleanly cleaved the *N*-Boc group to provide **1**. After thorough dehydration of a solution of **1** in dichloromethane (drying with potassium carbonate), the product was precipitated from toluene solution, and the isolated solid was further dried in vacuo at 50−65 °C for 12 h to afford anhydrous, solid pseudoephedrine glycinamide (**1**) in 80−90% yield. This two-step acylation/deprotection sequence for the preparation of **1** could be conducted in a single reaction flask. Thus, after addition of pseudoephedrine to the mixed anhydride derived from *N*-Boc-glycine and trimethylacetyl chloride, as described above, removal of the solvent and addition of methanol and aqueous hydrochloric acid solution, and isolation, as outlined above, anhydrous pseudoephedrine glycinamide (**1**) was obtained in 88% yield.

After initial alkylation studies established the value of **1** for the preparation of α-amino acids, a more economical, single-step method for the preparation of **1** from pseudoephedrine was developed.[12] This procedure effects a direct condensation between pseudoephedrine and glycine methyl ester under basic conditions. The reaction is noteworthy in that the secondary amino group of pseudoephedrine is amidated by the glycine carboxylic ester without significant competition from the amino group of glycine, thus obviating the need for protection of this functionality. The initial protocol developed for this condensation involved deprotonation of the hydroxyl group of pseudoephedrine (1 equiv) with *n*-butyllithium (10 M solution in hexanes,[14] 0.2−0.9 equiv) in the presence of anhydrous lithium chloride[15] (2.0 equiv) in tetrahydrofuran at 0 °C. Subsequent addition of a solution of glycine methyl ester (1.25 equiv) in

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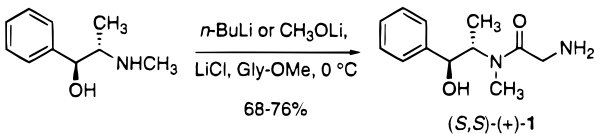
(13) It was shown more than 80 years ago that pseudoephedrine undergoes selective *N*-acylation with both carboxylic acid chlorides and anhydrides. See: (a) Schmidt, E.; Calliesz, F. W. *Arch. Pharm.* **1912**, *250*, 154. (b) Mitchell, W. *J. Chem. Soc.* **1940**, 1153. (c) Welsh, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 128.

(14) Minimizing the volume of hexanes was found to be beneficial for the reaction.

(15) For a discussion of the role of lithium chloride in this reaction, see ref 12.

tetrahydrofuran and stirring the resulting mixture for 1 h at 0 °C afforded **1** as the major reaction product. The primary

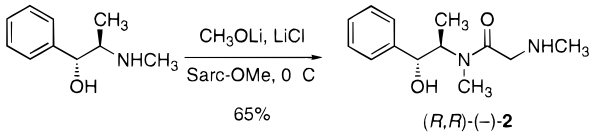


byproduct in the reaction was the dipeptide pseudoephedrine glycylglycinamide (structure **8** below), formed to the extent of <10%. This and any other impurities were readily removed in a convenient procedure for the purification of **1** that capitalized upon the fact that **1** forms a highly crystalline monohydrate. Direct crystallization of the crude acylation reaction mixtures from hot aqueous tetrahydrofuran afforded the pure monohydrate in 76% yield.

This one-step synthesis of pseudoephedrine glycinamide (**1**) is believed to proceed by the initial transesterification of glycine methyl ester with the secondary hydroxyl group of pseudoephedrine,[16] followed by rapid intramolecular *O*→*N*-acyl transfer.[13c] The fact that the acylation reaction proceeded to completion with substoichiometric amounts of *n*-butyllithium suggested that lithium methoxide liberated during the reaction was capable of acting as a catalyst for the transesterification step. This supposition was confirmed and beneficially exploited in a refinement wherein lithium methoxide (0.5 equiv) was substituted for *n*-butyllithium in the acylation reaction, with no discernible difference in the yield of **1**.[17]

The attainment of high yields in alkylation reactions of **1** (vide infra) is possible only when rigorously anhydrous **1** is used. Failure to properly dehydrate **1** leads to a stoichiometric consumption of the strong base that would otherwise enolize **1** (*n*-butyllithium or lithium diisopropylamide; see below) and therefore to incomplete conversion of **1** in the alkylation reaction. For this reason, it is essential that the recommended protocol for the drying of **1** be followed punctiliously. The highly crystalline monohydrate is ideal for the purification of **1** where significant contaminants exist (vide supra), but it cannot be dehydrated efficiently by simply heating in vacuo. Dehydration of the crystalline monohydrate is achieved by dissolution of the solid in dichloromethane and drying of the resulting solution over potassium carbonate, followed by precipitation from toluene and drying in vacuo, as outlined above. An alternative dehydration protocol was also developed wherein the monohydrate is dissolved in acetonitrile and the resulting solution is concentrated in vacuo (azeotropic removal of water) to afford anhydrous **1**, which is subsequently precipitated from toluene solution and dried in vacuo, as described above. In the anhydrous state, pseudoephedrine glycinamide (**1**) is a stable, colorless solid. It may be handled in the atmosphere for brief periods without consequence, but should be stored with scrupulous avoidance of moisture to prevent hydration. If the material becomes partially hydrated, as evidenced by incomplete conversions in the alkylation reaction, it should be redried by heating in vacuo at 50−65 °C for 12 h.

The single-step procedure described for the synthesis of **1** was easily adapted for the preparation of pseudoephedrine sarcosinamide (**2**), a precursor for the synthesis of *N*-methyl-α-amino acids. Thus, addition of sarcosine methyl ester (1.15 equiv) to a mixture of pseudoephedrine (1 equiv), lithium chloride (2 equiv), and lithium methoxide (0.5 equiv) in tetrahydrofuran at 0 °C, followed by stirring the resulting suspension for 12 h at 23 °C, produced pseudoephedrine sarcosinamide (**2**). After thorough dehydration of a solution



of **2** in dichloromethane (drying with potassium carbonate), the product was precipitated from toluene solution, and the isolated solid was further dried in vacuo at 50 °C for 12 h to afford pure, anhydrous pseudoephedrine sarcosinamide (**2**) in 65% yield. A noteworthy observation in the preparation of **2** is that very little dipeptide byproduct is produced in the reaction (presumably a consequence of the increased steric hindrance of the *N*-methyl group of sarcosine), thus simplifying the purification of **2**. In the anhydrous state, pseudoephedrine sarcosinamide (**2**) is a stable, colorless solid. Like **1**, it may be handled in the atmosphere for brief periods without consequence, but should be stored with scrupulous avoidance of moisture to prevent hydration. If the material becomes partially hydrated, as evidenced by incomplete conversions in the alkylation reaction, it should be redried by heating in vacuo at 50−65 °C for 12 h.

Enolization of Pseudoephedrine Glycinamide. One of the unique features of the use of **1** as a chiral glycine enolate precursor is the fact that the primary amino group of **1** is not protected.[18] This introduces a potential complication in the enolization of **1** in that three different acidic functional groups are present in the molecule (listed in order of decreasing thermodynamic acidity): the secondary hydroxyl group, the glycine α-carbon, and the primary amino group. It was anticipated that the (*Z*)-enolate **4** would be the thermodynamic product from the reaction of 2 equiv of strong base with **1**, but it was recognized, and later confirmed experimentally, that **4** might not be the kinetic product of the reaction.

All evidence to date suggests that the addition of slightly less than 2 equiv of strong base (lithium diisopropylamide or *n*-butyllithium, 1.95 equiv) to a solution of **1** (1 equiv) in tetrahydrofuran at −78 °C in the presence of anhydrous lithium chloride (6.00 equiv) leads to kinetic deprotonation of the hydroxyl and amino groups of **1** to generate the *O*,*N*-dianion **5** (Scheme 1). Evidence for the intermediacy of **5** and for anionic equilibration in the reaction is provided by the observation that the *N*,*N*-diallylated compound **6** is formed as a reaction product (30%) when allyl iodide is added to a mixture of **1** (1 equiv), lithium chloride (6.00 equiv), and lithium diisopropylamide (1.95 equiv) at −78 °C (20 min incubation at −78 °C prior to and immediately after the addition of **1**, −78 °C quench).[19] If the reaction mixture is allowed to warm to 0 °C prior to the addition of allyl iodide, equilibration to the thermodynamically more stable enolate **4** must occur, for addition of allyl iodide (at 0 °C) affords the *C*-alkylated product **7** exclusively (77−83% yield); no products arising from *N*-alkylation are observed.[20]

The use of 1.95 equiv of base (*n*-butyllithium or lithium diisopropylamide) in the enolization of **1** is essential to obtain

(16) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.

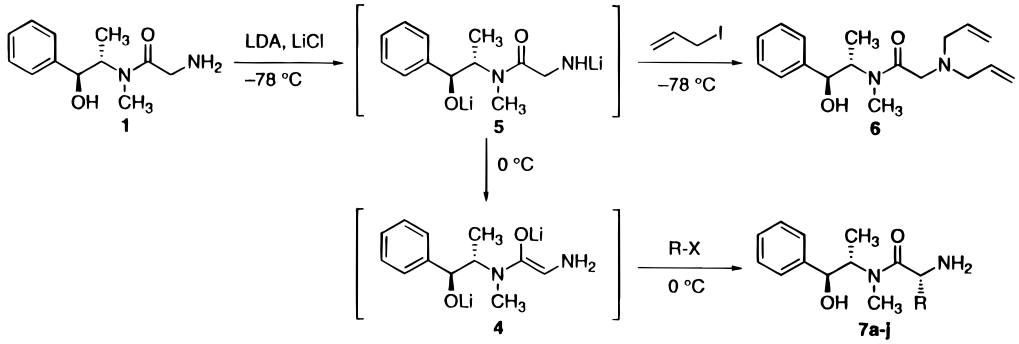
(17) Myers, A. G.; Gleason, J. L. *Org. Synth.*, submitted for publication.

(18) Tsunoda et al. have also described the enolization (and subsequent Claisen rearrangement) of a glycinamide bearing a free amino group. See: Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 3297.

(19) The *N*,*N*-diallylated product **6** is accompanied by some *C*-allylated product **7c** (13%) and recovered **1** (32%).

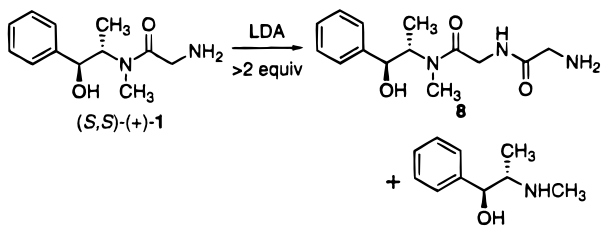
(20) Care must be exercised when reactions employing an excess of alkylating agent are worked up, for both **1** and its *C*-alkylation products will undergo *N*-alkylation when concentrated at ambient temperature in the presence of an alkyl halide. The desired *C*-alkylation product can be separated from excess alkylating agent by acid/base extraction (see the Experimental Section), thereby avoiding *N*-alkylation entirely.

Scheme 1. Enolization and Alkylation of Pseudoephedrine Glycinamide (**1**)

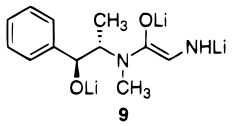


high yields of alkylated product. The use of slightly less than 2 equiv of base (1.95 equiv is recommended) ensures a vehicle for anionic equilibration (**1** monoalkoxide), but, moreover, avoids the onset of a deleterious side reaction that occurs when >2 equiv of base is used in the deprotonation reaction. This decomposition is evidenced by the liberation of free pseudoephedrine in the reaction and, in the case of lithium diisopropylamide-mediated deprotonation, produces a distinct orange color which contrasts with the normal yellow color of the enolate suspensions prepared with 1.95 equiv of base.[21] Because of the need for precise control of the amount of base in the deprotonation reaction, it is imperative that the solutions of *n*-butyllithium used in the reaction be accurately titrated. We highly recommend an adaptation of the procedure of Watson and Eastham for the titration of *n*-butyllithium (see the Experimental Section).[22] Also, because the base (lithium diisopropylamide or *n*-butyllithium) is the limiting reagent in the alkylation reaction, it is critical to ensure that both the lithium chloride and pseudoephedrine glycinamide (**1**) are thoroughly dried in order to achieve good conversions to product. Reagent-grade anhydrous lithium chloride is exceedingly hygroscopic, and as a precaution, we further dry it immediately prior to use by heating with a flame in vacuo, followed by cooling under an inert atmosphere. It has been our experience that one of these three factors (incorrect titer of *n*-butyllithium, improperly dried **1**, and/or improperly dried lithium chloride) is invariably responsible when less than optimum results are obtained in an alkylation reaction.

The decomposition reactions that occur when **1** is treated with excess base (>2 equiv) vary with the base used. When an excess of *n*-butyllithium is used, not surprisingly, products resulting from the addition of *n*-butyllithium to the amide carbonyl are observed. Deprotonation of **1** with excess lithium diisopropylamide (2.20 equiv) also leads to decomposition of the amide; however, in this case the products are pseudoephedrine glycylglycinamide (**8**; 12% yield) and pseudoephedrine (15% yield).[23] The mechanism of the latter base-induced



glycine transfer reaction is of interest.[24] The reaction occurs when the solution of lithium diisopropylamide and **1** is warmed from −78 to 0 °C. Because solutions of the enolate (**4**) exhibit good thermal stability ($t_{1/2}$ > 1 h at 23 °C) once generated, mechanisms involving the unimolecular decomposition of **4** (e.g., to form reactive ketene or α-lactam intermediates) appear unlikely. The amount of byproduct formation increases when 2.5 equiv of lithium diisopropylamide is used in the deprotonation reaction (18% dipeptide **8**, 34% pseudoephedrine), but not when 3.0 equiv of lithium diisopropylamide is used (9% dipeptide **8**, 16% pseudoephedrine). These data suggest that mechanisms invoking the unimolecular decomposition of an intermediate trianion (e.g., **9**) are also unlikely. The data support



the idea that the dipeptide **8** and pseudoephedrine arise from a bimolecular decomposition pathway, perhaps by the combination of two molecules of the *O*,*N*-dianion **5** in a nucleophilic cleavage of the amide bond, or, similarly, by nucleophilic attack of the putative trianion **9** on the *O*,*N*-dianion **5**.[25] We emphasize that these decomposition reactions can be almost entirely avoided simply by using 1.95 equiv of base in the deprotonation reaction (<5% free pseudoephedrine is observed), presumably because the equilibration of dianions **5** and **4** is faster than the proposed bimolecular decomposition reaction(s).

There are three protocols that we have used for the deprotonation of **1** which differ in the type of base used and in the order of addition of reagents: (method A) slow, dropwise addition of a solution of lithium diisopropylamide (1.95 equiv) in tetrahydrofuran to a slurry of **1** (1 equiv) and anhydrous lithium chloride (6.00 equiv) in tetrahydrofuran at 0 °C;[26] (method B) addition of a solution of **1** (1 equiv) in tetrahydrofuran to a

(21) The distinct orange color dissipates immediately upon addition of alkylating agents, producing a bright yellow suspension.

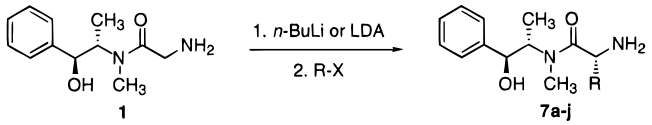
(22) (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Gall, M.; House, H. O. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 121. We have also successfully employed diphenylacetic acid as an indicator for the titration of *n*-butyllithium (Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879). However, we are aware of two instances where titration with diphenylacetic acid failed to give an accurate titer of *n*-butyllithium in other laboratories, whereas the titration method of Watson and Eastham was successful. The reasons for the erroneous titrations with diphenylacetic acid were not identified.

(23) Yields of the decomposition products were determined by reversed-phase HPLC analysis (mobile phase 15% acetonitrile, 0.1% trifluoroacetic acid; 25 cm × 4.6 μm C_{18} column; 220 nm detection). Response factors were determined by the injection of standard solutions of authentic **1**, **8**, and pseudoephedrine.

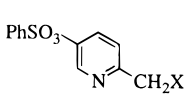
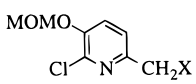
(24) The mechanism is complicated by the presence of two amide rotamers of **1**, essentially nonequilibrating at −78 °C.

(25) In support of a nucleophilic cleavage mechanism, we find that when a crossover experiment is conducted with a mixture of **1** (0.5 equiv) and **2** (0.5 equiv) using excess LDA (2.5 equiv), products of both sarcosine and glycine transfer to the glycinamide **1**, but not the sarcosinamide **2**, are observed. This result suggests that the transfer reaction is sensitive to the steric bulk of the amino group, consistent with a nucleophilic addition mechanism.

Table 1. Diastereoselective Alkylation of Pseudoephedrine Glycinamide (**1**)



1 **7a-j**

entry	RX	method of enolization	temp (°C)	time (h)	product	yield[a] (%)	de[b] (%)	mp (°C)
1	CH_3I	B	0	1	**7a**	75[c]	82	
2	CH_3I	B	−45	3	**7a**	73[d]	85	
3	CH_3I	C	−78	5	**7a**	61[d]	94	
4	CH_3CH_2I	C	0	1.5	**7b**	80 (76)	97 (≥99)	92−97
5	CH_3CH_2Br	B	0	27	**7b**	82[d]	96	
6	$CH_2{=}CHCH_2Br$	B	0	0.3	**7c**	80 (69)	93 (≥99)	79−83
7	$CH_2{=}CHCH_2I$	C	0	0.5	**7c**	77−83	90−92	
8	$(CH_3)_2CHCH_2I$	C	0	48	**7d**	55	97	
9	$(CH_3)_2CHCH_2I$	C	23	24	**7d**	66 (43)	94 (≥99)	86−88
10	$(CH_3)_2CHCH_2I$	C	23	8[e]	**7d**	73	95	
11	$(CH_3)_2CHCH_2OSO_2CH_3$	C	0	24		NR		
12	$(CH_3)_2CHCH_2OSO_2CF_3$	C	0	1.3	**7d**	50	97	
13	c-$C_3H_5CH_2I$	C	0	10	**7e**	82 (66)[f]	98 (≥99)	82−84
14	$C_6H_5CH_2Cl$	B	0	5	**7f**	80[d]	75	
15	$C_6H_5CH_2Br$	A	0	1	**7f**	79 (65)	91 (≥99)	131.5−133
16	$C_6H_5CH_2Br$	C	−78	12	**7f**	73[d]	91−93	
17	$C_6H_5CH_2I$	B	0	0.8	**7f**	70	94	
18	2-(CH_3O)-$C_6H_4CH_2Br$	C	0	2	**7g**	83	91	
19	$(CH_3)_3SiCH_2Br$	A	23	22	**7h**	89 (57)	91 (≥99)	92−94
20	 X = I	A	0	0.3	**7i**	80[g]	89[h]	
21	X = I	A	−78 → −45	3, 3	**7i**	92[g]	90−91[h]	
22	X = I	A	−78	6−8	**7i**	57−96[g]	94−95[h]	
23	X = Br	A	0	0.8	**7i**	89[g]	85[h]	
24	 X = I	C	0	0.25	**7j**	72[g]	88[h]	
25	X = I	C	−78	5	**7j**	89[g]	93[h]	
26	X = Br	C	0	0.25	**7j**	70−85[g]	85[h]	
27	X = Cl	C	0	0.5	**7j**	66[g]	70[h]	

[a] Values in parentheses are for products isolated by recrystallization. [b] Selectivity determined by capillary GC analysis. [c] Product isolated as the diacetate. [d] Yield determined by capillary GC analysis of the corresponding diacetates. [e] Reaction used 5 equiv of isobutyl iodide. [f] Approximately 7% of the homoallylic isomer (S_N2' product) was also isolated in this reaction. The isolated product was contaminated with ca. 1% of this byproduct. [g] Yield based upon consumed iodide (1.4−2 equiv of **1** used). [h] Selectivity determined by HPLC analysis of the amino acid produced by hydrolysis of the crude alkylation product.

slurry of lithium diisopropylamide (1.95 equiv) and anhydrous lithium chloride (6.00 equiv) in tetrahydrofuran at −78 °C, followed by warming of the resulting suspension to 0 °C; (method C) slow addition of a solution of *n*-butyllithium in hexanes (1.95 equiv) to a slurry of **1** and anhydrous lithium chloride (6.00 equiv) in tetrahydrofuran at −78 °C, followed by warming of the resulting suspension to 0 °C.[27]

Method A is recommended as the most versatile and convenient procedure for enolate formation, especially for large-scale applications. Method B was developed initially for enolization of **1**, but has been largely supplanted in our laboratory by the greater convenience of method A. In addition, more concentrated solutions of enolate **4** can be prepared by method A than by method B, because the addition of **1** to solutions of lithium diisopropylamide at −78 °C leads to the formation of gels if the final substrate concentration is greater than 0.25 M. Moreover, method A is more tolerant of slight errors in the titer of base than method B. Method C represents a convenient alternative for smaller scale reactions (≤5 mmol), but is problematic on a larger scale due to difficulties in controlling the reaction temperature during the deprotonation step which, as a consequence, leads to the partial decomposition of **1**.

Alkylation of Pseudoephedrine Glycinamide. A wide range of alkyl halides are found to react efficiently and diastereoselectively with the enolate **4** (Table 1). Activated alkyl halides such as methyl iodide and benzyl bromide react even at −78 °C, whereas substrates such as ethyl iodide react conveniently at 0 °C. Because **4** exhibits the high nucleophilicity and thermal stability generally associated with amide enolates, by conducting the alkylation reactions at 23 °C, even poorly reactive substrates such as isobutyl iodide and (trimethylsilyl)methyl bromide[28] can be made to react. For readily available alkyl halide substrates, an excess of alkylating agent (1.1−1.25 equiv) is used in the reaction.[20] For valuable alkyl halides, where it is desirable that they be the limiting reagent, excess enolate is employed in the reaction (typically 1.3−2.0 equiv). It is important to note that reactions employing excess enolate exhibit higher yields (based on 1 equiv of alkyl halide) than reactions employing excess alkyl halide (yield based on 1 equiv of **1**). Many functional groups are found to be stable to the alkylation reaction conditions, including aryl benzenesulfonate esters,[29] *tert*-butyl carbamate and *tert*-butyl carbonate

(26) In large-scale alkylation reactions, the rate of addition of lithium diisopropylamide should be modulated to maintain an internal reaction temperature of ≤5 °C to avoid decomposition.

(27) When solutions of *n*-butyllithium are added to solutions containing **1**, the alkyllithium solution should be added to the inside edge of the flask, such that it runs down the side of the flask before mixing with the bulk solution (or slurry), allowing the reagent to cool to −78 °C before mixing. Adding warm (23 °C) solutions of *n*-butyllithium directly into the middle of a solution containing **1** at −78 °C will result in significant decomposition.

(28) (Trimethylsilyl)methyl chloride was found to be unreactive toward enolate **4**. Alkylation of **1** with (trimethylsilyl)methyl iodide resulted in decomposition.

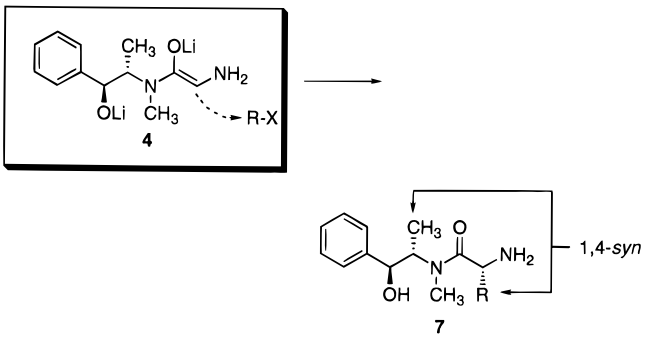


Figure 1. Mnemonic for enolate alkylation.

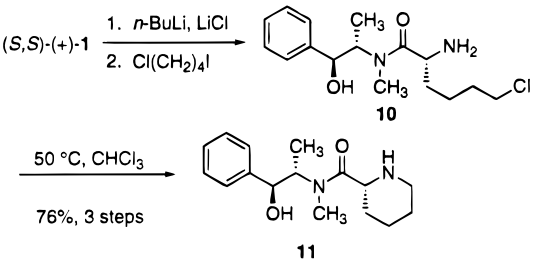
groups[30] *tert*-butyldimethylsilyl ethers,[31] benzyl ethers, *tert*-butyl ethers, methoxymethyl ethers, and alkyl chlorides.

In every case examined thus far, the sense of stereochemical induction in the alkylation reaction is that shown in the equation of Table 1. This stereochemical outcome is the same as that observed in the alkylations of simple *N*-acyl derivatives of pseudoephedrine.[11] Thus, both simple and glycine-derived pseudoephedrine amide enolates exhibit the same diastereofacial selectivity in alkylation reactions, if both enolates possess the same stereochemistry (presumed *Z*).[32] This result suggests that the glycine-derived primary amino group of **4** may not play a primary role in determining the facial selectivity of the alkylation reaction. A useful mnemonic for deriving the sense of induction in the alkylation reaction is as follows: the electrophile enters from the same face as the methyl group of the pseudoephedrine residue when the (putative) (*Z*)-enolate **4** is drawn in a planar, extended conformation (see Figure 1). Thus, the alkylation of (*S*,*S*)-(+)-**1** provides D-α-amino acid derivatives, and its enantiomer, (*R*,*R*)-(−)-**1**, provides the corresponding L-α-amino acid derivatives. Proof of the stereochemistry of the alkylation products was obtained by their conversion to and comparison with α-amino acids of known configuration using optical rotation and chiral HPLC analysis (vide infra). In a few cases (**8g**,**j**), the absolute stereochemistry of the products was inferred from the order of elution of major and minor enantiomers in the chiral HPLC analysis.[33]

A hallmark of alkylation reactions of the enolate **4** is their high diastereoselectivity.[34] Activated alkyl halides (e.g., benzyl bromide and allyl bromide) afford products with diastereomeric excesses between 90% and 94% in alkylations conducted at 0 °C. Reactions with less reactive alkyl halides (e.g., ethyl iodide, cyclopropylmethyl iodide, and isobutyl iodide) are found to be even more highly diastereoselective (95−98% de, 0 °C). The diastereoselectivity of the alkylation reactions is found to vary slightly with the reaction temperature. For example, alkylation of **4** with benzyl bromide proceeds in 91−93% de at −78 °C and 90−91% de at 0 °C. Similarly, α-(halomethyl)pyridines (see entries 19−26, Table 1) react with 4−6% greater de values (93−95%) when the temperature of the alkylation reactions is reduced to −78 °C from 0 °C.[29] The diastereoselectivity of the reaction of **4** with iodomethane shows the greatest sensitivity to reaction temperature. Alkylation of **4** with iodomethane at 0 °C proceeds with 82% de, whereas the diastereomeric excess at −78 °C is 94%. The advantage of achieving improved diastereoselectivity by conducting an alkylation reaction at a lower temperature must be weighed against the decrease in reaction rate that will result from the lower reaction temperature. For example, the latter alkylation (with iodomethane) was incomplete after 5 h at −78 °C (61% yield of product). Because few alkylation reactions benefit significantly from a lower temperature, we recommend 0 °C as a typical operating temperature. Even reactions conducted at 23 °C (necessary for hindered alkyl halides) are found to be highly diastereoselective. For example, the reaction of **4** with isobutyl iodide (1.25 equiv) at 23 °C proceeds in 94% de (24 h). The same reaction conducted at 0 °C proceeds in 97% de but requires 2 days for completion.

In certain cases, the diastereoselectivity of an alkylation reaction is affected by the nature of the leaving group. In general, alkyl iodides provide the highest selectivities and alkyl chlorides the lowest. For example, alkylations of **4** at 0 °C with the series benzyl chloride, bromide, and iodide proceed with de values of 75%, 91%, and 94%, respectively. This trend is followed with other benzylic halides as well, e.g., α-(halomethyl)pyridines (see entries 24−27, Table 1).[29] Allylic and *n*-alkyl halides do not display significant differences in diastereoselectivity between bromide and iodide leaving groups, but unactivated bromides react appreciably more slowly than the iodides (cf. entries 4 and 5, Table 1). *n*-Alkyl chlorides are found to be completely unreactive toward **4**, and benzylic chlorides react slowly. In two cases examined, methanesulfonate esters (isobutyl mesylate and (trimethylsilyl)methyl mesylate) were found to be unreactive. In only one case have we employed an alkyl triflate as substrate. The alkylation of **4** with isobutyl triflate proceeded rapidly at 0 °C and with high diastereoselectivity (97%). The yield of this reaction was lower than the yield observed for alkylation of **4** with isobutyl iodide (optimum ∼73%), perhaps reflecting a greater degree of elimination with the triflate.

An important extension of the alkylation methodology is achieved by employing 1,*n*-dihalides in the reaction, giving rise to cyclic α-amino acid derivatives. For example, alkylation of **4** with 1-chloro-4-iodobutane proceeds rapidly at 0 °C to afford the amino chloride **10**. This product is stable under the initial alkylation conditions and to aqueous workup, but cyclizes when heated in chloroform at 50 °C for 5 h. In this manner, the pipecolic acid derivative **11** was obtained in 76% yield (96% de).



Many of the alkylation products are crystalline solids and are readily purified by recrystallization. Recrystallization frequently leads to an enhancement in the de of the isolated product, often to ≥99% de (see the values in parentheses in

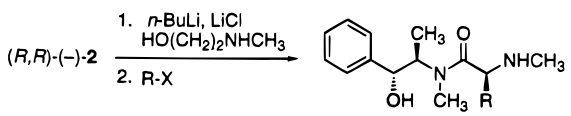
(29) Myers, A. G.; Gleason, J. L. *J. Org. Chem.* **1996**, *61*, 813.
(30) SinhaRoy, R.; Imperiali, B. *Tetrahedron Lett.* **1996**, *37*, 2129.
(31) Kearney, P. C.; Nowak, M. W.; Zhong, W.; Silverman, S. K.; Lester, H. A.; Dougherty, D. A. *Mol. Pharm.*, submitted for publication.
(32) It is generally assumed that the enolization of tertiary amides produces the (*Z*)-isomer. See: (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (b) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (c) Evans, D. A.; Tacaks, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.
(33) The more rapid elution of D-α-amino acids, relative to their L-antipodes, with Crownpak CR(+) chiral HPLC columns is documented (*Instruction Manual*, Crownpak CR(+) column, Daicel Chemical Industries).
(34) In all cases, the diastereoselectivity of the alkylation reactions was determined by capillary GC analysis (except as noted). ^{1}H NMR determination of diastereomeric ratios is complicated by the presence of amide rotamers in solution. Diastereomeric pairs of alkylation products exist with different ratios of rotamers, thus requiring the correct identification and integration of all four possible reasonances for a given proton within a pair of diastereomers.

Table 1). In cases where the alkylation products are not crystalline, they may be purified by chromatography on silica gel using a methanol−triethylamine−dichloromethane solvent system for elution. Resolution of the diastereomeric alkylation products is sometimes possible by chromatography, particularly in the case of benzylic halides, for which the minor diastereomers tend to elute faster than the major diastereomeric products.

As we observed in the alkylation of pseudoephedrine amides derived from simple aliphatic carboxylic acids,[11] the presence of anhydrous lithium chloride in the reaction is required to accelerate the rate of enolate alkylation. The marked influence of lithium halide salts on enolate alkylation reactions is well precedented, most notably in the work of Seebach et al.[35] In the alkylation of **4** with ethyl iodide, the reaction is complete within 1 h at 0 °C in the presence of anhydrous lithium chloride (6 equiv), but is less than 80% complete after 3 h in the absence of anhydrous lithium chloride. Reaction solutions containing 6 equiv of lithium chloride are essentially saturated; use of greater amounts of lithium chloride produces no discernible advantage in diastereoselectivity or reaction rate. Importantly, the exclusion of lithium chloride from the alkylation of **4** with ethyl iodide diminishes the diastereoselectivity of the reaction (82% de versus 97% de in the presence of lithium chloride). Such a marked decrease in de was not observed in alkylations of simple *N*-acyl derivatives of pseudoephedrine conducted in the absence of lithium chloride.[11] The use of lithium bromide (6 equiv) as an additive also accelerates alkylation reactions of **4** (reaction with ethyl iodide at 0 °C is complete within 1 h); however, lower levels of diastereoselectivity (91−93% de for ethyl iodide) are observed.

The diastereoselectivity of the reaction of the enolate **4** with isobutyl iodide was analyzed as a function of time in order to detect nonlinear effects and/or evidence of epimerization in the reaction. This particular reaction was chosen because it proceeded sufficiently slowly at 23 °C as to make the analysis convenient. Aliquots from a reaction conducted at 23 °C and employing 5 equiv of isobutyl iodide and 1 equiv of **4** at 23 °C were withdrawn and quenched at several time points within a 7-h period. The aliquots withdrawn were subjected to standard workup procedures, and the products were acetylated for analysis by capillary gas chromatography. Over the 7-h period of the reaction, the ratio of diastereomeric products was constant (97.6:2.4, 95.2% de). Thus, no obvious nonlinear effects were observed, nor was their evidence of epimerization in the reaction.

Alkylation of Pseudoephedrine Sarcosinamide. The alkylation of pseudoephedrine sarcosinamide (**2**) is similar to the alkylation of the glycinamide **1**, 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 **2** involve the addition of *n*-butyllithium or lithium diisopropylamide (2.95 equiv) to a suspension of **2** (1 equiv), anhydrous lithium chloride (6.00 equiv), and *N*-methylethanolamine (1.00 equiv) in tetrahydrofuran at −78 °C, followed by warming the resulting slurry to 0 °C and the addition of an alkylating agent (1.1−1.5 equiv). Under these conditions, the alkylation of **2** with benzyl bromide affords the *N*-methylphenylalanine derivative **12f** in 88% de and 93% yield.

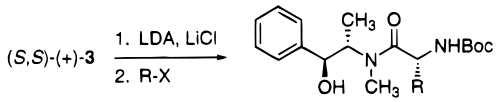


12b R = Et (77%)
12f R = Bn (93%, 69% recryst.)

The product is a crystalline solid, and may be recrystallized to 99% de in 69% yield. Alkylation of **2** with ethyl iodide under similar conditions provides the *N*-methyl-2-aminobutyramide derivative **12b** in 77% yield (94% de) after purification by column chromatography.

The presence of *N*-methylethanolamine in the alkylation reaction is necessary to achieve reproducible diastereoselectivity and may function by facilitating anionic equilibration. Reactions conducted in its absence are much more sensitive to variations in the reaction conditions, particularly in the amount of base employed. For example, utilizing the standard enolization conditions for the alkylation of **1** (e.g., 1.95 equiv of *n*-butyllithium), the reaction of **2** with benzyl bromide afforded **12f** in 81−82% de, while the use of slightly less *n*-butyllithium (1.85 equiv) resulted in a much improved diastereoselectivity (86% de, 72% yield, capillary GC analysis).

Alkylation of *N*-Protected Derivatives of Pseudoephedrine Glycinamide. Prior to the discovery of conditions for the alkylation of pseudoephedrine glycinamide (**1**), alkylation reactions of various *N*-protected derivatives of **1** were explored. Among these, we examined the use of Knapp's *N*,*N*-dialkyltriazone methodology for the protection of **1**.[36] Unfortunately, the low solubility and reactivity of the derived enolates thwarted these efforts. We also examined the use of carbamate protective groups, and although success was achieved in the alkylation of CBz-protected **1**, the limited stability of the CBz group to either alkaline or acidic hydrolysis conditions prevented further development of this methodology. A more successful approach utilized the more robust (toward alkaline hydrolysis conditions) *N*-Boc protective group. *N*-Boc-pseudoephedrine glycinamide (**3**) was transformed into a presumed enolate trianion by treatment with lithium diisopropylamide (3.10 equiv) in the presence of anhydrous lithium chloride (6.00 equiv) in tetrahydrofuran at −78 °C, followed by warming the resulting mixture to 0 °C. Addition of benzyl bromide to the enolate solution at 0 °C resulted in selective *C*-alkylation, affording the *N*-Boc-phenylalanine derivative **13f** in 79% yield and 87% de.



13b R = Et (79%)
13f R = Bn (79%)

Similarly, alkylation of **3** with ethyl iodide at 0 °C afforded **13b** in 79% yield and 93% de. In contrast to the enolization of **1**, the enolization of the *N*-protected amide **3** was not sensitive to the presence of excess lithium diisopropylamide in the reaction mixture. Although the *N*-Boc derivatives generally do not display the desirable property of crystallinity, the products of alkylation reactions of **3** are advantageous in that they may be directly transformed into *N*-Boc-protected α-amino ketones through the addition of alkyllithium and alkylmagnesium reagents.[37]

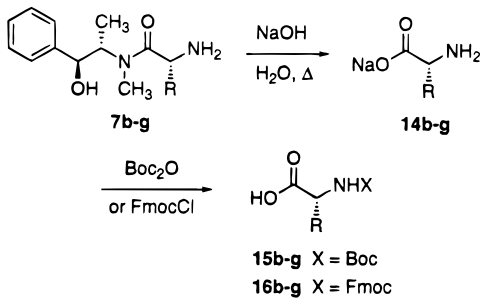
Hydrolysis of Pseudoephedrine Amides. We have found that the products of alkylation of pseudoephedrine glycinamide (**1**) are hydrolyzed with exceptional facility and efficiency

(35) See ref 5j and (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Seebach, D.; Bossler, H.; Grundler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197.

(36) (a) Knapp, S.; Hale, J. J.; Bastos, B.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109. (b) Knapp, S.; Hale, J. J.; Bastos, B.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239.

(37) *N*-Boc-pseudoephedrine amides have been used in the preparation of *N*-Boc-α-amino ketone derivatives. Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429.

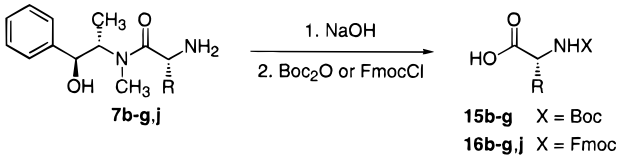
simply by heating in an alkaline aqueous medium. The mild conditions of this alkaline hydrolysis reaction (vide infra) stand in marked contrast to the harsh conditions necessary for the basic hydrolysis of simple tertiary amides. The use of secondary amines as chiral auxiliaries for the asymmetric alkylation of carboxylate derivatives (tertiary amides) has been hampered by the harsh conditions typically required to hydrolyze the amide bond in the products. In one of the earliest practical auxiliary-based asymmetric alkylation procedures, Evans and Takacs showed that tertiary amides derived from prolinol underwent acidic hydrolysis more readily than amides derived from simple dialkylamines by virtue of an intramolecular *N*→*O*-acyl transfer mechanism.[32c,38] It has long been known that pseudoephedrine amides also undergo a facile intramolecular *N*→*O*-acyl transfer reaction under acidic conditions.[13c] It is reasonable to propose that such an intramolecular *N*→*O*-acyl transfer reaction might also occur under the basic conditions of our optimum hydrolysis protocol. Although it is expected that the product of the acyl transfer reaction, a *β*-amino alcohol ester, would be thermodynamically unstable under the reaction conditions, this intermediate should partition favorably between hydrolysis to product and reversion to starting material, thereby accounting for the overall rate enhancement observed.[39,40] These hydrolysis reactions are more rapid than those of simple pseudoephedrine amides (e.g., alkylation products of pseudoephedrine propionamide).[11] It is believed that this reflects the inductive influence of the amino group and its enhancement of the electrophilicity of the amide carbonyl group. It is significant that this rate enhancement is not accompanied by a correspondingly increased rate of racemization. Conversely, less racemization is observed for the hydrolysis of pseudoephedrine glycinamide alkylation products than for the simple alkyl amides.

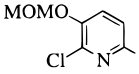


Typical conditions for the hydrolysis of the alkylation products involve heating at reflux for 1.5−5 h in aqueous sodium hydroxide solution (0.5 M, 2 equiv).[41] Upon cooling, an aqueous suspension is obtained that contains the precipitated pseudoephedrine auxiliary and the (soluble) sodium salt of the product α-amino acid. The auxiliary is easily recovered, quantitatively, by extracting the aqueous product slurry with dichloromethane (96% recovery of pseudoephedrine, 83−86% yield after recrystallization from water). The alkaline aqueous product solution obtained after extraction of the auxiliary can be treated directly with an acylating agent to afford the corresponding *N*-protected α-amino acid derivative. Thus, *N*-*tert*-butoxycarbonyl (*N*-Boc) and *N*-(9-fluorenylmethyloxy)-carbonyl (*N*-Fmoc) protected α-amino acids are obtained by treatment of an aqueous solution of the α-amino acid salt with di-*tert*-butyl dicarbonate or 9-fluorenylmethyl chloroformate, respectively. For the preparation of *N*-Fmoc-α-amino acids, it is necessary to quench the excess of sodium hydroxide in solution with sodium bicarbonate prior to the addition of 9-fluorenylmethyl chloroformate; otherwise cleavage of the *N*-Fmoc group occurs. As a general practice, the addition of sufficient sodium bicarbonate to quench excess sodium hydroxide is recommended for all direct acylation reactions of the basic hydrolysis mixtures. As illustrated by the examples in Table 2, this two-step hydrolysis/acylation method typically proceeds in very high yield. Furthermore, the reaction products are formed with a high degree of purity. For example, in the case of *N*-Boc-protected α-amino acids, the crude products are typically found to be analytically pure. In the case of *N*-Fmoc-protected α-amino acids, analytically pure products are usually obtained after a single recrystallization. Occasionally, the preparation of *N*-Fmoc-α-amino acids can be complicated by the formation of dipeptide byproducts when 9-fluorenylmethyl chloroformate is used as the acylating agent.[42] In these cases, use of the milder acylating agent *N*-(9-fluorenylmethyloxycarbonyloxy)succinimide often circumvents this side reaction.[43]

A critical aspect of the basic hydrolysis protocol is the fact that the products are formed with little to no racemization. This may be attributed to the low kinetic acidity of the α-C−H bond of the amide starting materials and the product carboxylate ions. Hydrolysis of alkylation products of ≥99% de typically affords α-amino acid derivatives of ≥99% ee. Occasionally, kinetic enrichment in the hydrolysis reaction was observed. For

Table 2. Basic Hydrolysis of Pseudoephedrine Amides Followed by *N*-Protection



			15b−g		16b−g,j	
7[a]	R	time (h)	yield (%)	ee[b] (%)	yield (%)	ee[b] (%)
b	CH_3CN_2-	1.5	97	≥99	99[c]	≥99
c	$CH_2{=}CHCH_2-$	1.5	91	≥99	75	≥99
d	$(CH_3)_2CHCH-$	1.5	97	≥99	81	≥99
e	c-$C_3H_5CH_2-$	2	93[d]	≥98	84[c]	≥99
f	$C_6H_5CH_2-$	3	88	≥99	90	≥99
g[e]	2-$CH_3OC_6H_4CH_2Br$	4−5	86	96	81[c]	98
j[f]		3			73[g]	96

[a] All starting materials were of ≥99% de except as noted. [b] Enantiomeric excesses (ee's) were determined by HPLC analysis. [c] Reaction performed using Fmoc-*N*-hydroxysuccinimide. [d] Isolated product contains ca. 1% of the 2-amino-5-hexenoic acid derivative. [e] Starting material was 91% de. Hydrolysis afforded amino acid of 94% ee; additional ee enrichment of **15g** and **16g** due to recrystallization. [f] Starting material de not determined directly. [g] Yield includes removal of the methoxymethyl protecting group (TFA, THF/H_2O).

(38) For the first practical demonstration of an asymmetric alkylation reaction of a carboxylate derivative (employing a chiral amino alcohol as an auxiliary) see: (a) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268. (b) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1974**, *98*, 567.

(39) The hydrolysis of *N*-acetylpseudoephedrine under alkaline conditions was reported by Mitchell. See ref 13b.

(40) A related observation was made earlier by Meyers and Temple concerning the hydrolysis of 2-oxazolines, wherein the hydrolysis of *β*-amino alcohol ester hydrochlorides (resulting from the acid-catalyzed ring opening of 2-oxazolines) occurred under both acidic and basic reaction conditions. See: Meyers, A. I.; Temple, D. L. *J. Am. Chem. Soc.* **1970**, *92*, 6646.

(41) If required for solubility, methanol or dioxane may be added as a cosolvent.

(42) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 1987. (b) Atherton, E.; Scheppard, R. C. In *The Peptides*; Udenfriend, S., Meienhofer, J., Eds.; Academic Press: Orlando, 1987; Vol. 9, p 1.

(43) Paquet, A. *Can. J. Chem.* **1982**, *60*, 976.

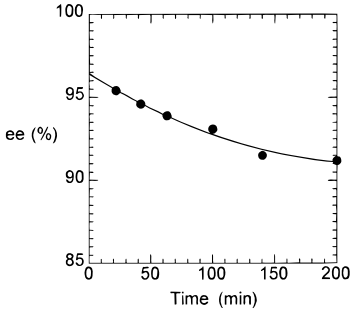
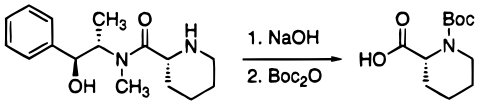


Figure 2. Hydrolysis of **7g**: kinetic resolution.

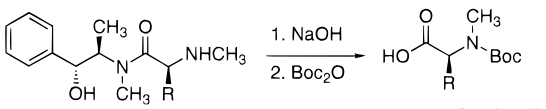
example, alkaline hydrolysis of amide **7g** of 91% de afforded an enriched product of 94% ee. Further evidence for kinetic resolution during this hydrolysis reaction was obtained by withdrawing small aliquots from a reaction mixture employing **7g** of 84% de (2 equiv of NaOH, 4:1 MeOH:H_2O, reflux), followed by HPLC analysis. As shown in Figure 2, the enantiomeric excess of the product is found to diminish with time, from an initial high of ≥95% ee to a value approaching the diastereomeric excess of the starting amide. After 3.3 h at reflux, the reaction was approximately 90% complete and the enantiomeric excess of the product was 91%. The small amount of amide **7g** recovered (8%) was found to be greatly reduced in diastereomeric purity (41% de).

N-Alkylpseudoephedrine amides are also efficiently hydrolyzed in base with little to no racemization. For example, heating the pipecolic acid derivative **11** (96% de) at reflux in aqueous sodium hydroxide solution (0.5 M, 2 equiv) for 3 h followed by cooling and acylation with di-*tert*-butyl dicarbonate, as described above, afforded *N*-Boc-pipecolic acid (**17**) in 77%



11 **17**

yield and 96% ee. Hydrolysis of the products from the alkylation of pseudoephedrine sarcosinamide (**2**) is slower. For example, hydrolysis of the *N*-methylphenylalaninamide **12f** (≥99% de) with sodium hydroxide solution (0.5 M, 2 equiv) required 18 h at reflux for complete consumption of the starting material. Direct *N*-acylation of the crude sodium salt of the α-amino acid with di-*tert*-butyl dicarbonate provided *N*-Boc-*N*-methyl-L-phenylalanine (**18f**) in 85% yield and 95% ee. Hydrolysis of the ethylated product **12b** (94% de) required 10 h and proceeded with kinetic enrichment to provide, after *N*-acylation, *N*-Boc-*N*-methyl-L-2-aminobutyric acid (**18b**) in 89% yield and 98% ee.

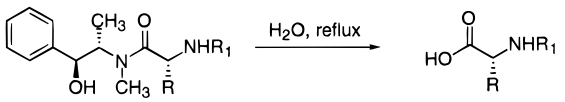


12b,f

18b R = Et (89%)
18f R = Bn (81%)

A second cleavage protocol was developed that was made possible by the fact that most products from the alkylation of **1** display at least partial solubility in water and, owing to the presence of a free amino group within these substrates, the resulting aqueous solutions (or suspensions) are moderately alkaline (pH ≈ 10). These factors help to rationalize the remarkable finding, of tremendous practical importance, that heating at reflux (10−20 h) of a solution (suspension) of an alkylation product in pure water alone leads to quantitative

Table 3. Hydrolysis of Pseudoephedrine Amides in Water



7b-h R_1 = H
12f R_1 = CH_3

19b-h R_1 = H
20f R_1 = CH_3

amide[a]	R	time (h)	yield (%)	crude ee[b] (%)	isol ee[c] (%)
7b	CH_3CH_2−	10	88	≥99	≥99
7c	CH_2=$CHCH_2$−	10	87	98	≥99
7d	$(CH_3)_2CHCH_2$−	10	86	≥99	≥99
7e	c-$C_3H_5CH_2$−	12	79[d]	≥97	≥98
7f	$C_6H_5CH_2$−	18	77	98	≥99
7g[e]	2-$CH_3OC_6H_4CH_2$−	22	71	98	≥99
7h	$(CH_3)_3SiCH_2$−	20	77	ND	≥99
12f	$C_6H_5CH_2$−	96[f]	70	96	98

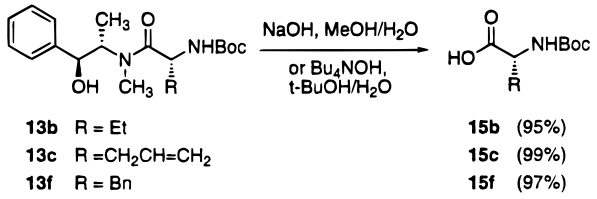
[a] All starting materials were of ≥99% de except as noted. Enantiomeric excesses (ee's) were determined by HPLC analysis. [b] Prior to trituration with EtOH. [c] Subsequent to trituration with EtOH. [d] Isolated product was contaminated with ca. 1% 2-amino-5-hexenoic acid. [e] Starting material was 91% de. This reaction was conducted in a 4:1 mixture of water and *p*-dioxane. [f] This reaction was conducted in water for 48 h, and then in 2:1 water−dioxane for 48 h.

hydrolysis to produce the α-amino acid and the free pseudoephedrine auxiliary (Table 3).[44] Again, little to no epimerization (typically <2%) occurs during the hydrolysis reaction. An important advantage of this hydrolysis protocol is the total absence of salts, or any exogenous reagents, in the reaction mixture. This enormously facilitates the isolation of salt-free α-amino acids (alternative methods for the synthesis of α-amino acids typically require a desalting procedure, such as ion exchange chromatography). Recovery of the chiral auxiliary from the hydrolysis mixture is accomplished by extraction of the aqueous product solution with dichloromethane. Lyophilization of the aqueous product solution then affords the free α-amino acid directly, typically as a solid. Trituration of the solid product with an alcoholic solvent (usually ethanol) serves to remove any residual pseudoephedrine and often leads to enantiomeric enrichment of the isolated α-amino acid as well. As with the sodium hydroxide-promoted hydrolysis protocol, kinetic resolution has been observed in hydrolyses in pure water as well. For example, hydrolysis of the amide **7g** (91% de) in dioxane−water (1:5) for 22 h afforded the α-amino acid **19g** in 98% ee (99% ee after trituration with ethanol) and in 71% yield.

Hydrolyses of *N*-Boc- and *N*-Fmoc-Protected Amides. Prior to the development of the above procedures, the hydrolysis of *N*-Boc- and *N*-Fmoc-protected pseudoephedrine amides was investigated as a method for the preparation of *N*-Boc- and *N*-Fmoc-α-amino acids. *N*-Boc-pseudoephedrine amides **13b**, **13c**, and **13f** were prepared either by the direct alkylation of **3** (vide supra) or by acylation of products of the alkylation of **1** with di-*tert*-butyl dicarbonate or 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile. Hydrolysis of *N*-Boc-pseudoephedrine amides is readily achieved by heating in the presence of sodium hydroxide (5 equiv) in methanol−water mixtures, or with tetrabutylammonium hydroxide (5 equiv) in 2-methyl-2-propanol−water mixtures. Epimerization occurs to a greater extent in these hydrolyses than with the alkaline hydrolysis of the glycinamide alkylation products **7b**−**h** described above, but is nevertheless minimal. For example, hydrolysis of the *N*-Boc-phenylalaninamide **13f** (≥99% de) with tetrabutylammonium hydroxide (5 equiv) in 2-methyl-2-propanol−water (4:1) at

(44) For substrates with extremely low water solubility, dioxane−water mixtures may be used in the hydrolysis reaction.

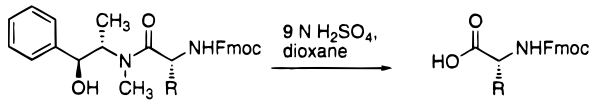
reflux for 2.5 h afforded *N*-Boc-D-phenylalanine (**15f**) in 97%



13b R = Et **15b** (95%)
13c R = $CH_2CH{=}CH_2$ **15c** (99%)
13f R = Bn **15f** (97%)

yield and 94% ee. Similarly, hydrolysis of the *N*-Boc-2-aminobutyramide derivative **13b** (≥99% de) afforded *N*-Boc-D-2-aminobutyric acid (**15b**) in 99% yield (96% ee), and hydrolysis of the *N*-Boc-D-allylglycinamide derivative **13c** (99% de) afforded *N*-Boc-allylglycine (**15c**) in 99% yield and 90% ee. The milder hydrolysis conditions and lesser degree of racemization in the hydrolyses of the unprotected pseudoephedrine amides have led us to favor that method, followed by *N*-acylation of the hydrolysis products, for the preparation of *N*-Boc-α-amino acids.

The alkylation products **7b** and **7f** were also readily acylated with 9-fluorenylmethyl chloroformate (1.10 equiv) in mixtures of dioxane and saturated aqueous sodium bicarbonate solution to provide the corresponding *N*-Fmoc derivatives **21b** and **21f**. These *N*-Fmoc derivatives were readily hydrolyzed under acidic conditions. For example, heating a solution of the *N*-Fmoc-phenylalaninamide **21f** (≥99% de) in a mixture of dioxane and 9 N aqueous sulfuric acid (1:1) at reflux for 8 h afforded *N*-Fmoc-D-phenylalanine (**16f**) in 96% yield. Cleavage of the



21b R = Et **16b** (83%)
21f R = Bn **16f** (96%)

N-Fmoc group (0.5 M NaOH, MeOH) and analysis of the resulting free α-amino acid showed that no racemization (≥99% ee) had occurred during the hydrolysis step. Similarly, acidic hydrolysis of the *N*-Fmoc-2-aminobutyramide derivative **21b** provided the *N*-Fmoc-D-2-aminobutyric acid (**16b**) in 83% yield and ≥99% ee. This hydrolysis protocol is effective for the preparation of *N*-Fmoc-α-amino acid derivatives that are stable to strong acid, and thus complements the base-catalyzed hydrolyses of the unprotected pseudoephedrine amides described above.

Discussion

The diastereoselectivities observed in alkylations of enolates of pseudoephedrine amides are exceptionally high for a chiral auxiliary that lacks the apparent organizational features of, e.g., a C-2 symmetric, cyclic auxiliary.[45] The basis for this high diastereoselectivity is not obvious. Predicting the solution structure(s) of the enolate **4** is a daunting task given the number of potentially coordinating residues in the molecule and is further compounded by questions of aggregation and solvation, particularly so, with the presence of lithium chloride in solution. Furthermore, the extrapolation of any predicted ground state structure to a transition state structure is clearly even more tenuous. Nevertheless, it is useful for the design of future experiments to develop working models of the alkylation reaction. The challenge in this exercise is to find any conformation of the pseudoephedrine side chain within the enolate **4** that effectively blocks the appropriate enolate π-face,

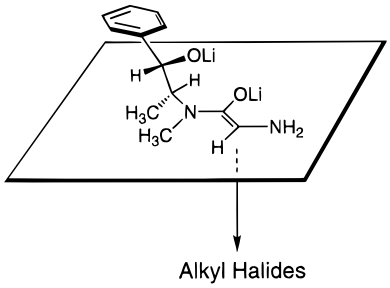


Figure 3. Proposed reactive conformation of enolate **4**.

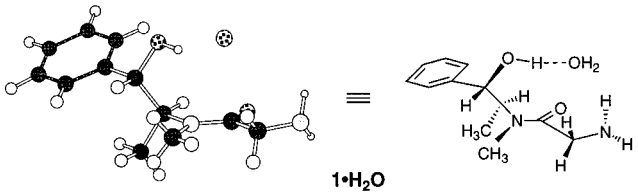


Figure 4. Crystal structure of pseudoephedrine glycinamide monohydrate.

thereby accounting for the extraordinarily high diastereoselectivities observed in the alkylation reactions. Simply linking the two oxy anions by a lithium cation in a seven-membered ring, the somewhat classical rendering of a "chelation control" mechanism, hardly accounts for such a bias. Our preferred working model is depicted in Figure 3 and invokes the blocking of the enolate π-face by the secondary lithium alkoxide and, perhaps more importantly, the solvent (tetrahydrofuran) molecules associated with this lithium cation.[46] We note that in this model the pseudoephedrine side chain adopts a staggered conformation in which the C−H bond α to nitrogen lies in-plane with the enolate oxygen, in accord with predictions based on allylic strain arguments.[47] The oxy anions may share one or more lithium cations in this model, but this would be a different type of chelate structure than that alluded to above.[48]

It is interesting to compare the working model of Figure 3 with the crystal structure of pseudoephedrine glycinamide monohydrate (**1**·H_2O, Figure 4). Many of the structural features of the proposed reactive conformation of enolate **4** are reflected in the crystal structure of **1**·H_2O, including minimized allylic and dihedral strain and positioning of the secondary hydroxyl group above one plane of the amide residue. Although **1**·H_2O is admittedly a poor model of the enolate **4**, the same structural features that cause **1**·H_2O to adopt the conformation shown may play a role in the solution conformation of the enolate **4** as well.

Although the origin of diastereoselectivity in alkylation reactions of **4** may be open to interpretation, there can be little doubt that the reaction is of general utility and that the diastereoselectivities are uniformly high. The method has been employed in our laboratory, as well as others, for the preparation of a wide range of nonproteinogenic α-amino acids.[29−31] The alkylation reaction is reliable and easy to conduct, provided that certain simple precautionary measures are followed. The

(45) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857.

(46) For evidence of the blocking of an enolate π-face by a metal alkoxide (and the influence of different metal ions on that blocking) see: Meyers, A. I.; Wunsch, T. *J. Org. Chem.* **1990**, *55*, 4233.

(47) For a recent review of $A_{1,3}$ strain as a controlling factor in stereoselective transformations, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(48) Quirion et al. have investigated the diastereoselective alkylation of amide enolates derived from *N*-methylphenylglycinol. The sense of diastereoselectivity they observe corresponds with that of pseudoephedrine amide enolate alkylations, but their proposed transition structure is different: Micouin, L.; Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 7223. See also: Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529.

amount of base (1.95 equiv) must be accurately measured; solutions of *n*-butyllithium used in the reaction must be accurately titrated. Pseudoephedrine glycinamide (**1**) must be properly dehydrated, as described above, by precipitation of the anhydrous solid from toluene and drying the solid by heating in vacuo. Lithium chloride employed in the reaction must also be thoroughly dried, preferably by flame-drying the anhydrous reagent in vacuo immediately prior to use. The importance of careful attention to these experimental details cannot be emphasized too strongly, as they are crucial for the successful implementation of this methodology.

Several features of the methodology described establish a uniquely practical method for the asymmetric synthesis of α-amino acids. The advantages of pseudoephedrine as a chiral auxiliary have been outlined above. An exceedingly practical single-step method for the preparation of the solid reagent pseudoephedrine glycinamide (**1**) from pseudoephedrine and glycine methyl ester was described. Deprotonation of **1** under equilibrating conditions produces an enolate derivative with the desirable properties of high reactivity, thermal stability, and diastereoselectivity in its alkylation reactions. The intrinsic ability of pseudoephedrine amides to undergo facile intramolecular *N*→*O*-acyl transfer reactions is believed to account for the remarkably facile hydrolytic cleavage of the auxiliary from the alkylation products observed under alkaline conditions. The hydrolysis reaction typically proceeds with less than 2% racemization. A further advantage of the method is the fact that no protection of the glycine amino group is required. These features combine to define a practical procedure for the preparation of α-amino acids on both large and small scales.

Experimental Section

General Experimental Procedures. Commercial alkyl halides were either filtered through activated basic alumina (Brockman Grade 1) or distilled from calcium hydride immediately prior to use. Reagent grade anhydrous lithium chloride was further dried by heating under vacuum (150 °C, 1 mmHg, 12 h) and was flame-dried under vacuum in the reaction flask immediately prior to use. Solutions for alkylation reactions were deoxygenated by alternate evacuation and flushing of the reaction flask with argon (three iterations). All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by immersion in a staining solution (ninhydrin) followed by heating on a hot plate.

Synthesis of (*S,S*)-(+)-Pseudoephedrine Glycinamide [(*S,S*)-(+)-1]. From *N*-Boc-glycine. Trimethylacetyl chloride (14.1 mL, 0.114 mol, 1.00 equiv) was added dropwise to a vigorously stirred solution of *N*-(*tert*-butoxycarbonyl)glycine (20.0 g, 0.114 mol, 1.00 equiv) and triethylamine (19.1 mL, 0.137 mol, 1.20 equiv) in dichloromethane (400 mL) at 0 °C. After 5 min, a fine white solid precipitated from the reaction mixture. After 30 min, a second portion of triethylamine (19.1 mL, 0.137 mol, 1.20 equiv) and solid (*S,S*)-(+)-pseudoephedrine (18.9 g, 0.114 mol, 1 equiv) were added sequentially to the cold reaction mixture. The reaction mixture was stirred for 45 min at 0 °C. Volatiles were removed in vacuo, and the resulting slurry was dissolved in 1:1 methanol−water (400 mL). The resulting solution was cooled in an ice bath, and concentrated hydrochloric acid (150 mL) was added carefully to the cold solution. Vigorous gas evolution was observed during and immediately following the addition. After stirring for 3 h at 0 °C, the reaction mixture was freed of methanol by concentration in vacuo at 23 °C. The aqueous concentrate was cooled in ice while the pH was adjusted to 14 by the slow addition of 50% aqueous sodium hydroxide solution (*caution! exotherm*). The addition rate was moderated so as to maintain a solution temperature of ≤45 °C. The basic aqueous solution was extracted with four 250-mL portions of dichloromethane. The combined organic extracts were dried over solid anhydrous potassium carbonate, and the dried solution was filtered through a pad of Celite on Whatman no. 1 filter paper (note: the use of other drying agents, such as sodium sulfate, is not recommended as they may lead to incomplete dehydration of the product solution). The filtrate was concentrated in vacuo, producing an oily residue. The residue was dissolved in toluene (ca. 200 mL), and the resulting solution was concentrated in vacuo. The oily residue obtained upon concentration was dissolved in toluene (80 mL; warming with a heat gun may facilitate this process), and the resulting solution was seeded with anhydrous (*S,S*)-(+)-pseudoephedrine glycinamide. When precipitation of the product appeared to be complete (ca. 2 h), the flask was cooled to 0 °C and was held at that temperature for 1 h. The solid product was collected and reserved. The mother liquors were concentrated, and the residue was dissolved in toluene (40 mL). The resulting solution was cooled to 0 °C and seeded. After 12 h, the crystals that formed were collected and combined with the first crop. The solid product was dried in vacuo (0.2 mmHg) at 55 °C for 12 h to afford 22.22 g of anhydrous **1**: mp 78−80 °C; TLC $R_f = 0.18$ (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (1:1 ratio of rotamers, $CDCl_3$) (*J* in hertz) δ 7.29−7.40 (m, 5H), 4.53−4.63 (m, 1.5H), 3.88 (m, 0.5H), 3.72 (d, 0.5H, $J = 15.5$), 3.46 (d_{app}, 1H, $J = 16.6$), 3.37 (d, 0.5H, $J = 17.1$), 2.97 (s, 1.5H), 2.79 (s, 1.5H), 2.11 (s (br), 3H), 1.09 (d, 1.5H, $J = 6.7$), 0.99 (d, 1.5H, $J = 6.7$); ^{13}C NMR ($CDCl_3$) δ 174.1, 173.5, 142.3, 142.1, 128.7, 128.5, 128.2, 127.9, 126.9, 126.7, 75.8, 74.9, 57.5, 57.2, 43.7, 43.4, 30.1, 27.1, 15.3, 14.4. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.54; H, 7.93; N, 12.46. $[\alpha]_D^{20} = +102.0°$ ($c = 1.1$, CH_3OH). For (*R,R*)-(−)-**1**, $[\alpha]_D^{20} = -101.2°$ ($c = 1.2$, CH_3OH).

From *N*-Boc-pseudoephedrine Glycinamide (3). Aqueous hydrochloric acid solution (3 M, 100 mL) was added to a solution of **3** (8.27 g, 25.7 mmol, 1 equiv) in methanol (100 mL) at 0 °C. After stirring for 3 h at 0 °C, the reaction mixture was freed of methanol by concentration in vacuo at 23 °C. The aqueous concentrate was cooled in ice while the pH was adjusted to 14 by the slow addition of 50% aqueous sodium hydroxide solution (*caution! exotherm*). The addition rate was moderated so as to maintain a solution temperature of ≤45 °C. The basic aqueous solution was extracted with one 300-mL and three 100-mL portions of dichloromethane. The combined organic extracts were dried over solid anhydrous potassium carbonate, and the dried solution was filtered through a pad of Celite on Whatman no. 1 filter paper (note: the use of other drying agents, such as sodium sulfate, is not recommended as they may lead to incomplete dehydration of the product solution). The filtrate was concentrated in vacuo, producing an oily residue. The residue was dissolved in toluene (ca. 100 mL), and the resulting solution was concentrated in vacuo. The oily residue obtained upon concentration was dissolved in warm toluene (20 mL, 80 °C), and the resulting solution was seeded with anhydrous (*S,S*)-(+)-pseudoephedrine glycinamide. When precipitation of the product appeared to be complete (2 h), the flask was cooled to 0 °C and was held at that temperature for 1 h. The solid product was collected and was dried in vacuo (0.2 mmHg) at 60 °C for 12 h to afford 4.77 g (84%) of anhydrous **1**. The isolated product was identical to that obtained from the procedure described above.

From Glycine Methyl Ester with *n*-Butyllithium as Catalyst. A solution of *n*-butyllithium (25.0 mL, 10 M in hexane, 0.250 mol, 0.830 equiv) was added dropwise to an ice-cold solution of (*S,S*)-(+)-pseudoephedrine (50.0 g, 0.300 mol, 1 equiv) and anhydrous lithium chloride (25.0 g, 0.590 mol, 1.97 equiv) in tetrahydrofuran (500 mL). After 10 min, a solution of glycine methyl ester[49] (32.0 g, 0.360 mol, 1.20 equiv) in tetrahydrofuran (50 mL) was added dropwise to the reaction mixture over a 1.5-h period. After completed addition, the mixture was stirred at 0 °C for 1 h. Water (50 mL) was added, and the reaction mixture was concentrated in vacuo to remove tetrahydrofuran. The liquid residue was diluted with 1 N aqueous sodium hydroxide solution (200 mL), and the product was extracted with three 200-mL portions of a 10:1 mixture of dichloromethane−2-propanol. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in hot tetrahydrofuran (120 mL), water was added (6 mL), and the solution was allowed to cool, whereupon extensive crystallization of the product

(49) (a) Frankel, M.; Katchalski, E. *J. Am. Chem. Soc.* **1942**, *64*, 2264. (b) Almeida, J. G.; Anaya, J.; Martin, N.; Grande, M.; Caballero, M. C. *Tetrahedron: Asymmetry* **1992**, *3*, 1431.

occurred. Crystallization was completed by allowing the flask to stand for 24 h at −20 °C. The crystals were collected and air-dried to give 53.0 g of (*S*,*S*)-(+)-**1**·H_2O (73%, mp 84−86 °C). Further crystallization from the mother liquors provided an additional 2.20 g of product (3%). The spectral data (^{1}H NMR and IR) are identical to those listed above for anhydrous **1**: $[\alpha]_D^{20} = +96.6°$ (c = 2.0, CH_3OH). Anal. Calcd for $C_{12}H_{20}NO_3$: C, 59.93; H, 8.32; N, 11.66. Found: C, 59.85; H, 8.58; N, 11.58.

From Glycine Methyl Ester with Lithium Methoxide as Catalyst (Described for (*R*,*R*)-(−)-1). Solid, anhydrous lithium methoxide (6.89 g, 0.182 mol, 0.500 equiv) was added in one portion to an ice-cold solution of (*R*,*R*)-(−)-pseudoephedrine (60.0 g, 0.363 mol, 1 equiv) and anhydrous lithium chloride (30.8 g, 0.726 mol, 2.00 equiv) in tetrahydrofuran (500 mL). After 10 min, a solution of glycine methyl ester[49] (40.4 g, 0.454 mol, 1.25 equiv) in tetrahydrofuran (100 mL) was added dropwise to the reaction mixture over a 1-h period. After completed addition, the mixture was stirred at 0 °C for 7 h. Water (500 mL) was added, and the reaction mixture was concentrated in vacuo to remove tetrahydrofuran. The liquid residue was diluted with water (250 mL), and the product was extracted with one 500-mL and four 250-mL portions of dichloromethane. The combined organics were dried with anhydrous potassium carbonate, filtered, and concentrated. The residue was dissolved in hot tetrahydrofuran (300 mL), water was added (10 mL), and the solution was allowed to cool, whereupon extensive crystallization of the product occurred. Crystallization was completed by allowing the flask to stand for 2 h at −20 °C. The crystals were collected and dried in vacuo (0.5 mmHg) at 23 °C to afford 62.8 g of (*R*,*R*)-(−)-**1**·H_2O (72%) which was identical in all respects (with the exception of displaying the opposite optical rotation) to the material obtained using the procedure described above.

Dehydration of 1·H_2O. Method A. A suspension of **1**·H_2O (62.8 g) in dichloromethane (1.2 L) was stirred vigorously for 1 h, to break up all large lumps of solid. Anhydrous potassium carbonate (60 g) was added to the suspension (note: the use of other drying agents, such as sodium sulfate, is not recommended as they may lead to incomplete dehydration of the product solution). After stirring for 10 min, the resulting translucent solution was filtered through 40 g of Celite on Whatman no. 1 filter paper, and the resulting clear filtrate was concentrated in vacuo. The oily residue was dissolved in toluene (200 mL), and the resulting solution was concentrated to remove residual dichloromethane. The resulting oily residue was dissolved in hot toluene (175 mL). Upon cooling to 23 °C, anhydrous **1** precipitated from solution. The solid was collected by filtration, was rinsed with 200 mL of ether, and was dried in vacuo (0.5 mmHg) at 23 °C for 1 h and at 60 °C for 12 h to afford 53.8 g of anhydrous **1** (93%, mp 78−80 °C). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.65; H, 8.25; N, 12.53.

Dehydration of 1·H_2O. Method B. A solution of **1**·H_2O (50.3 g) in warm acetonitrile (ca. 200 mL) was concentrated in vacuo. The residue was dissolved in toluene (250 mL), and the resulting solution was concentrated. Anhydrous **1** was obtained by precipitation of the residue from toluene and was dried as in method A to give 45.7 g of anhydrous **1** (98%). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.13; N, 12.57.

(*R*,*R*)-(−)-Pseudoephedrine *N*-Methylglycinamide (2). Solid, anhydrous lithium methoxide (1.19 g, 31.3 mmol, 0.50 equiv) was added to a slurry of (*R*,*R*)-(−)-pseudoephedrine (10.33 g, 62.5 mmol, 1 equiv) and anhydrous lithium chloride (5.57 g, 131 mmol, 2.10 equiv) in tetrahydrofuran (110 mL) at 0 °C. After 10 min, a solution of sarcosine methyl ester (7.42 g, 72.0 mmol, 1.15 equiv) in tetrahydrofuran (15 mL) was added dropwise to the reaction mixture over a 45-min period. After completed addition, the resulting slurry was stirred at 0 °C for 1.5 h and at 23 °C for 12 h. Water (15 mL) was added, and the mixture was concentrated in vacuo to remove tetrahydrofuran. The liquid residue was diluted with 1 N aqueous sodium hydroxide solution (100 mL), and the resulting solution was extracted with one 125-mL portion and three 100-mL portions of dichloromethane. The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated to afford a slightly yellow oil (note: the use of other drying agents, such as sodium sulfate, is not recommended as they may lead to incomplete dehydration of the product solution). The oily residue was dissolved in, and concentrated from, two 100-mL portions of toluene. The resulting oily residue was dissolved in toluene (22 mL). Crystallization was induced by scratching the inside of the crystallization flask with a metal spatula. After standing under an atmosphere of argon at 23 °C for 9 h, the white crystals were collected and dried in vacuo (0.2 mmHg) at 50 °C for 12 h to afford (*R*,*R*)-(−)-**2** (10.82 g, 73%). TLC R_f = 0.08 (5% MeOH, 1% NEt_3, 94% CH_2Cl_2); mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 1:1.1 mixture of rotamers) (J in hertz) δ 7.39−7.25 (m, 5H), 4.61 (d, 0.5H, J = 7.9), 4.49 (d, 0.5H, J = 9.3), 3.94−3.88 (m, 1H), 3.61 (d, 0.5H, J = 13.7), 3.36 (d, 0.5H, J = 13.7), 3.34 (d, 0.5H, J = 16.2), 3.28 (d, 0.5H, J = 16.2), 2.95 (s, 1.5H), 2.78 (s, 1.5H), 2.51 (s, 1.5H), 2.41 (s, 1.5H), 1.11 (d, 1.5H, J = 6.8), 0.98 (d, 0.5H, J = 6.7); ^{13}C NMR ($CDCl_3$, 1:1.1 mixture of rotamers) δ 172.5, 171.3, 142.5, 142.4, 128.5, 128.2, 127.9, 127.6, 126.7, 126.5, 75.9, 75.0, 58.0, 57.5, 52.9, 52.7, 36.3, 30.8, 26.7, 15.6, 14.1; $[\alpha]_D^{20} = -117.6°$ (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.06; H, 8.54; N, 11.86. Found: C, 66.22; H, 8.21; N, 11.83.

(*S*,*S*)-(+)-*N*-Boc-pseudoephedrine Glycinamide (3). Trimethylacetyl chloride (5.62 mL, 45.7 mmol, 1.00 equiv) was added slowly to a solution of *N*-Boc-glycine (8.00 g, 45.7 mmol, 1.00 equiv) and triethylamine (7.04 mL, 50.2 mmol, 1.10 equiv) in dichloromethane (150 mL) at 0 °C, producing a colorless suspension. After stirring at 0 °C for 30 min, a second portion of triethylamine (7.04 mL, 50.2 mmol, 1.10 equiv) was added, followed by the addition of solid (*S*,*S*)-(+)-pseudoephedrine (7.55 g, 45.7 mmol, 1 equiv). After stirring for 1 h at 0 °C, the reaction mixture was diluted with 1 M aqueous hydrochloric acid solution (150 mL), saturated aqueous sodium chloride solution (100 mL), and ethyl acetate. The layers were separated, and the aqueous layer was extracted with a second portion of ethyl acetate (100 mL). The combined organic layers were washed with saturated aqueous potassium carbonate solution (200 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (40% → 60%) to afford 13.0 g (88%) of amide **3** as a viscous oil. ^{1}H NMR (1:1 rotamer ratio, $CDCl_3$) (J in hertz) δ 7.25−7.33 (m, 5H), 5.62 (m, 1H), 4.50−4.62 (m, 1.5H), 4.13 (dd, 0.5H, J = 16.5, 3.5), 3.98 (dd, 0.5H, J = 16.6, 5.0), 3.86 (d, 1H, J = 4.2), 3.81 (m, 0.5H), 2.91 (s, 1.5H), 2.84 (s, 1.5H), 1.43 (s, 9H), 0.99 (d, 1.5H, J = 6.6), 0.93 (d, 1.5H, J = 6.7); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.4, 155.8, 155.7, 141.6, 141.2, 128.5, 128.3, 128.2, 127.8, 126.8, 126.5, 79.4, 79.3, 75.6, 74.9, 57.4, 56.8, 42.7, 42.4, 29.9, 28.2, 26.8, 15.0, 14.1; $[\alpha]_D^{20} = +80.6$ (c = 1.09, CH_2Cl_2). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.20; H, 7.85; N, 8.58.

Titration of *n*-Butyllithium.[22] A solution of *n*-butyllithium in hexanes (∼2.5 M, 5−10 drops) was added to a solution of 2,2′-dipyridyl (2 mg) in ether (25 mL) at 23 °C until a dark red solution was obtained. A solution of *sec*-butanol in toluene (1.00 M) was added by drops to the solution until the red color was discharged. The solution of *n*-butyllithium in hexanes was then added dropwise to the resulting yellow solution until a single drop turned the solution red. An accurately measured aliquot of the solution of *sec*-butanol in toluene (1.00 M, 2.5 mL) was then added to the solution. The solution of *n*-butyllithium in hexanes was added slowly to the indicator solution until a single drop turned the solution red, taking care to note the exact volume added. Two to three iterations were conducted using the same indicator solution to determine an averaged value for the concentration of the *n*-butyllithium solution.

General Procedures for Determination of Diastereomeric Excesses of Alkylation Products. Diastereomeric ratios for the alkylation products were determined by acetylation of the products, followed by capillary GC analysis. The procedure for acetylation is as follows. Acetic anhydride (1 mL) and 4-(dimethylamino)pyridine (ca. 2 mg) were added to a solution of the alkylation product (10−20 mg) in pyridine (1 mL). The resulting solution was stirred at 23 °C for 1 h and then was diluted with water (20 mL). The aqueous solution was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL) and the resulting solution was analyzed by capillary GC analysis using a Chirasil-Val column.

The minor diastereomers were identified by epimerization of the alkylation products, conducted as follows (for **7h**). *n*-Butyllithium (2.60

M in hexanes, 117 μL, 0.305 mmol, 1.5 equiv) was added to a solution of **7h** (57 mg, 0.203 mmol, 1 equiv) in tetrahydrofuran (3 mL) at −78 °C. After stirring for 15 min at −78 °C, the yellow solution was warmed to 0 °C. After stirring at 0 °C for 30 min, water (15 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The oily residue was acetylated and analyzed by capillary GC as described above.

Analysis of *N*-Boc-protected alkylation products was effected by cleavage of the Boc protecting group (1:1 3 M aqueous hydrochloric acid solution−methanol, 30 min) followed by concentration, acetylation (as described above), and analysis by capillary GC. Analysis of *N*-methylated alkylation products was carried out by acetylation as described above, with the exception that the acetylation reaction was conducted at 50 °C for 1 h.

Alkylation of (*S*,*S*)-(+)-Pseudoephedrine Glycinamide (1) Using Lithium Diisopropylamide as Base (Method A). (*S*,*S*)-Pseudoephedrine D-Phenylalanamide (7f). A solution of *n*-butyllithium in hexanes (2.69 M, 1.63 mL, 4.39 mmol, 1.95 equiv) was added to a solution of diisopropylamine (630 μL, 4.50 mmol, 2.00 equiv) in tetrahydrofuran (4 mL) at 0 °C. After 10 min, the resulting solution of lithium diisopropylamide was transferred via cannula over 5 min to a stirred slurry of anhydrous (*S*,*S*)-(+)-**1** (500 mg, 2.25 mmol, 1 equiv) and flame-dried lithium chloride (572 mg, 13.5 mmol, 6.00 equiv) in tetrahydrofuran (6 mL) at 0 °C. After stirring at 0 °C for 20 min, benzyl bromide (281 μL, 2.36 mmol, 1.05 equiv) was added dropwise to the bright yellow suspension. After 1 h, aqueous hydrochloric acid solution (1 M, 25 mL) was added to the reaction mixture, followed by ethyl acetate (50 mL). The organic layer was separated and extracted with a second portion of aqueous hydrochloric acid solution (1 M, 25 mL). The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and carefully basified to pH 14 by addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with three 40-mL portions of dichloromethane. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated in vacuo to provide a solid residue. The solid was recrystallized from hot (90 °C) toluene (ca. 5 mL). Upon cooling to 23 °C, the product crystallized rapidly. The recrystallization flask was cooled to 0 °C and was held at that temperature for 1 h, at which time the crystals were isolated by filtration, washed with a small amount of ether (10 mL), and dried in vacuo (0.5 mmHg) to afford 459 mg (65%) of **7f**. The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (230 °C, major R_t = 22.8 min, minor R_t = 17.9 min). The crude product was shown to be 90% de, and the recrystallized product was shown to be ≥99% de: mp 131.5−133 °C; TLC R_f = 0.53 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (5:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.18−7.34 (m, 10H), 4.49−4.57 (m, 2H), 4.15* (m, 1H), 3.96* (dd, 1H, *J* = 8.7, 4.2), 3.86 (t, 1H, *J* = 7.1), 3.28* (dd, 1H, *J* = 13.6, 4.3), 2.95* (s, 3H), 2.82 (dd, 1H, *J* = 13.3, 7.0), 2.72 (dd, 1H, *J* = 13.2, 7.2), 2.64 (s, 3H), 1.72 (s (br), 3H), 0.99* (d, 3H, *J* = 6.7), 0.88 (d, 3H, *J* = 6.2); ^{13}C NMR ($CDCl_3$) δ 176.5, 175.3*, 142.0, 141.6*, 138.5*, 137.6, 129.4*, 129.2, 128.7*, 128.5, 128.4, 128.3, 127.7, 126.8*, 126.6, 126.4, 75.8, 75.2*, 57.9*, 57.2, 53.5, 53.3*, 42.4, 42.1*, 30.9, 27.1*, 15.6*, 14.2. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.02; H, 7.80; N, 8.88.

Alkylation of (*S*,*S*)-(+)-Pseudoephedrine Glycinamide (1) Using Lithium Diisopropylamide as Base (Method B). (*S*,*S*)-Pseudoephedrine D-Allylglycinamide (7c). A solution of *n*-butyllithium in hexanes (2.85 M, 15.0 mL, 42.6 mmol, 1.95 equiv) was added to a slurry of anhydrous lithium chloride (5.56 g, 131 mmol, 6.00 equiv) and diisopropylamine (6.13 mL, 43.7 mmol, 2.00 equiv) in tetrahydrofuran (60 mL) at −78 °C. After 10 min, a solution of (*S*,*S*)-(+)-**1** (4.86 g, 21.9 mmol, 1 equiv) in tetrahydrofuran (30 mL with a 10-mL wash) was added via cannula to the lithium diisopropylamide slurry over a 5-min period. After 20 min, the dark yellow suspension was transferred to an ice bath. After 20 min at 0 °C, allyl bromide (2.08 mL, 24.1 mmol, 1.10 equiv) was added to the bright yellow, opaque suspension. The yellow color was observed to dissipate within 15 min. Aqueous hydrochloric acid solution (1 M, 150 mL) was added *at this point*, followed by ethyl acetate (200 mL). The organic layer was separated and extracted with a second portion of aqueous hydrochloric acid solution (1 M, 150 mL). The combined aqueous layers were cooled in an ice bath and carefully basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was then extracted with four 150-mL portions of dichloromethane. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated in vacuo to give an oil which crystallized slowly upon standing. The solid product was dissolved in hot toluene (20 mL), and the resulting solution was seeded with authentic **7c** and then was cooled to −20 °C. After crystallization was complete, the product was collected by filtration and was washed with ether to give 3.18 g of **7c** (55%). The mother liquors were concentrated in vacuo, and the residue was purified by chromatography on silica gel eluting with a mixture of 4% methanol, 4% triethylamine, and 92% dichloromethane to provide an additional 1.70 g of product as an oil. The oil was dissolved in hot toluene (15 mL), and the resulting solution was cooled to −20 °C and was seeded as before. The crystals that formed were collected and washed with ether to give an additional 0.80 g of product (14%). The total yield of **7c** was 3.98 g (69%, 73% of theoretical based on 0.95 equiv of dianion). The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (190 °C, major R_t = 18.7 min, minor R_t = 14.7 min). The crude product was shown to be 93% de, and the recrystallized product was shown to be ≥99% de: mp 79−83 °C; TLC R_f = 0.59 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (3:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.23−7.38 (m, 5H), 5.64−5.85 (m, 1H), 5.07−5.14 (m, 2H), 4.55−4.59 (m, 2H), 4.03*(m, 1H), 3.69* (m, 1H), 3.65 (dd, 1H, *J* = 7.5, 5.3), 2.93* (s, 3H), 2.87 (s, 3H), 2.61−2.66* (m, 2H), 2.23 (m, 1H), 2.13 (m, 1H), 1.03 (d, 3H, *J* = 6.4), 0.96* (d, 3H, *J* = 6.7); ^{13}C NMR ($CDCl_3$) δ 176.1, 175.1*, 142.1, 141.8*, 134.7*, 133.7, 128.5*, 128.2, 128.1*, 127.6, 126.8*, 126.5, 118.1, 117.9*, 75.5, 74.9*, 57.6, 51.2, 51.0*, 39.8*, 39.6, 31.4, 27.0*, 15.5*, 13.4. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.55; H, 8.55; N, 10.72.

Small-Scale Alkylation of (*S*,*S*)-(+)-Pseudoephedrine Glycinamide (1) Using *n*-Butyllithium as Base (Method C). (*S*,*S*)-Pseudoephedrine D-2-Aminobutyramide (7b). A solution of (*S*,*S*)-(+)-**1** (339 mg, 1.53 mmol, 1 equiv) in tetrahydrofuran (4 mL with a 4-mL wash) was transferred via cannula to a flask containing anhydrous lithium chloride (388 mg, 9.15 mmol, 6.00 equiv). The resulting suspension was cooled to −78 °C. A solution of *n*-butyllithium in hexanes (2.67 M, 1.11 mL, 2.97 mmol, 1.95 equiv) was added slowly to the inner edge of the reaction flask such that the solution was cooled before mixing with the reaction suspension. After 20 min, the dark yellow slurry was transferred to an ice bath. After 20 min at 0 °C, iodoethane (159 μL, 1.98 mmol, 1.30 equiv) was added to the bright yellow reaction suspension. After 90 min, aqueous hydrochloric acid solution (1 M, 25 mL) was added to the reaction mixture, followed by ethyl acetate (60 mL). The organic layer was separated and extracted with a second portion of aqueous hydrochloric acid solution (1 M, 25 mL). The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and carefully basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with four 40-mL portions of dichloromethane. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a mixture of 4% methanol, 4% triethylamine, and 92% dichloromethane to give the product **7b** (304 mg, 80%, 84% of theory based on 0.95 equiv of dianion) as an oil which crystallized upon standing. The product was recrystallized by dissolving in hot toluene (8 mL) and cooling the resulting solution to −20 °C. The crystals that formed were collected and washed with ether to afford 273 mg of **7b** (72%, 75% of theory based on 0.95 equiv of dianion). The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (200 °C, major R_t = 9.7 min, minor R_t = 8.0 min). The crude product was shown to be 97% de, and the recrystallized product was shown to be ≥99% de: mp 92−97 °C; TLC R_f = 0.54 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (5:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.21−7.36 (m, 5H), 4.65 (m, 1H), 4.52 (d, 1H, *J* = 8.4), 3.93* (m, 1H), 3.46 (dd, 1H, *J* = 6.9, 5.9), 2.89* (s, 3H), 2.84 (s, 3H), 2.6−3.2 (s (br), 3H), 1.87* (m, 1H), 1.52 (m, 1H),

1.39 (m, 1H), 0.97 (d, 3H, J = 6.8), 0.91−0.99* (m, 6H), 0.87 (t, 3H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 176.3, 175.5*, 142.2*, 142.1, 128.2*, 128.0, 127.7*, 127.3, 126.6*, 126.4, 75.0, 74.4*, 57.3*, 56.4, 52.6*, 52.4, 30.6, 27.8*, 27.7, 26.8, 15.3*, 14.2, 10.0*, 9.8. Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.80; H, 8.77; N, 11.19.

Pseudoephedrine D-β-[6-Chloro-5-[(methoxymethyl)oxy]-2-pyridyl]alaninamide (7j). A solution of *n*-butyllithium in hexanes (2.60 M, 1.47 mL, 3.83 mmol, 2.73 equiv) was added slowly to the inner edge of a flask containing a slurry of anhydrous (*S*,*S*)-(+)-**1** (437 mg, 1.96 mmol, 1.40 equiv) and flame-dried lithium chloride (500 mg, 11.8 mmol, 8.43 mmol) in tetrahydrofuran (12 mL) at −78 °C. After stirring for 20 min at −78 °C, the reaction flask was transferred to an ice bath. After stirring for 20 min at 0 °C, the reaction flask was cooled to −78 °C. After stirring for 5 min at −78 °C, a precooled (−78 °C) solution of 2-chloro-3-[(methoxymethyl)oxy]-6-(iodomethyl)pyridine (440 mg, 1.40 mmol, 1 equiv) in tetrahydrofuran (3 mL, with a 3 mL wash) was added to the pale yellow suspension. After stirring for 5 h at −78 °C, the reaction was terminated by the addition of 1 M aqueous hydrochloric acid solution (30 mL). The resulting mixture was warmed to 23 °C and extracted with ethyl acetate (50 mL). The organic layer was washed with a second portion of 1 M aqueous hydrochloric acid solution (30 mL). The combined aqueous extracts were cooled in an ice bath and basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The resulting alkaline aqueous solution was extracted with four 25-mL portions of dichloromethane. The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated. A small amount (34 mg) of the crude residue was reserved for chiral HPLC analysis, and the remaining crude residue (607 mg) was purified by chromatography on silica gel eluting with 4% methanol, 4% triethylamine, and 92% dichloromethane to afford 480 mg (89%) of the alkylation product as an oil. The diastereomeric excess of the crude product was estimated by hydrolysis (2 mL of 0.5 M aqueous sodium hydroxide solution, reflux 4 h), followed by extraction of the aqueous mixture with dichloromethane (3 × 10 mL), and acidification of the aqueous layer to pH 1 with concentrated perchloric acid followed by chiral HPLC analysis (pH 2.0 $HClO_4$, 0.8 mL/min, 220 nm, major R_t = 7.0 min, minor R_t = 10.4 min), indicating a de of 93%: TLC R_f = 0.51 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (1.2:1 rotamer ratio, $CDCl_3$) (J in hertz) δ 7.50 (d, 0.5H, J = 7.1), 7.22−7.42 (m, 5.5H), 7.10 (d, 0.5H, J = 8.2), 7.04 (d, 0.5H, J = 8.2), 5.22 (s, 1H), 5.20 (s, 1H), 4.62 (d, 0.5H, J = 9.2), 4.52−4.57 (m, 1H), 4.29 (m, 0.5H), 4.13 (m, 1H), 3.49 (s, 1.5H) 3.48 (s, 1.5H), 3.40 (dd, 0.5H, J = 14.0, 3.0), 2.94 (s, 1.5H), 2.92 (s, 1.5H), 2.88−2.94 (m, 1H), 2.77 (dd, 0.5H, J = 14.0, 7.4), 0.94 (d, 1.5H, J = 6.7), 0.91 (d, 1.5H, J = 6.2); ^{13}C NMR ($CDCl_3$) δ 175.7, 174.7, 151.3, 150.8, 147.7, 147.6, 142.0, 141.4, 140.3, 128.5, 128.2, 128.1, 127.5, 127.2, 126.5, 124.1, 124.0, 123.5, 123.4, 95.0, 94.9, 75.3, 57.7, 56.3, 51.7, 51.4, 42.2, 42.1, 31.3, 26.7, 15.5, 14.2; HRMS calcd for $C_{20}H_{27}ClN_3O_4$ (M + H) 408.1690, found 408.1682.

(*R*,*R*)-Pseudoephedrine L-(Trimethylsilyl)alaninamide (7h). 7h was prepared by alkylation of (*R*,*R*)-(−)-**1** (10.6 g, 47.9 mmol, 1 equiv) with (bromomethyl)trimethylsilane (10.0 g, 59.8 mmol, 1.25 equiv) following the procedure outlined for **7f** (alkylation time 22 h at 23 °C). The product was purified by chromatography on silica gel eluting with 4% methanol, 4% triethylamine, and 92% dichloromethane to afford 13.12 g of **7h** as an oil which crystallized upon standing. The product was recrystallized from butyl acetate (15 mL)−hexanes (15 mL) at −20 °C to afford 4.87 g of analytically pure **7h**. Three additional crops of product afforded an additional 3.72 g of product (total 8.59 g, 57%). The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (220 °C, major R_t = 11.6 min, minor R_t = 9.6 min). The chromatographed product was 90% de (the de of the crude product could not be determined because the minor diastereomer and the starting material coeluted), and the recrystallized product was ≥99% de: ^{1}H NMR (3:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (J in hertz) δ 7.24−7.36 (m, 5H), 4.62 (m, 1H), 4.52 (m, 1H), 3.97* (m, 1H), 3.77* (dd, 1H, J = 10.3, 3.9), 3.63 (dd, 1H, J = 9.0, 5.0), 2.90* (s, 3H), 2.81 (s, 3H), 1.20* (dd, 1H, J = 15.0, 3.8), 0.98 (d, 3H, J = 6.7), 0.93* (d, 3H, J = 6.7), 0.85* (d, 1H, J = 15.0, 10.3), 0.78 (dd, 1H, J = 14.9, 4.8), 0.66 (dd, 1H, J = 14.7, 9.2), 0.09* (s, 9H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 177.9, 177.2*, 142.2*, 142.1, 128.3, 128.0, 127.8*, 127.3, 126.6, 126.4, 75.3, 74.7*, 57.4*, 56.5, 48.9*, 48.6, 30.6, 26.9*, 23.2*, 22.9, 15.4*, 14.0, −0.9*, −1.0. Anal. Calcd for $C_{16}H_{28}N_2O_2Si$: C, 62.29; H, 9.15; N, 9.08. Found: C, 62.64; H, 8.75; N, 9.08.

(*S*,*S*)-Pseudoephedrine D-Pipecolinamide (11). A solution of (*S*,*S*)-(+)-**1** (511 mg, 2.30 mmol, 1 equiv) in tetrahydrofuran (10 mL with a 8-mL wash) was transferred via cannula to a flask containing anhydrous lithium chloride (585 mg, 13.8 mmol, 6.00 equiv). The resulting slurry was cooled to −78 °C. A solution of *n*-butyllithium in hexanes (2.85 M, 1.57 mL, 4.48 mmol, 1.95 equiv) was added slowly to the inner edge of the flask such that it was cooled before mixing with the reaction slurry. After 20 min, the dark yellow suspension was transferred to an ice bath. After stirring for 20 min at 0 °C, 1-chloro-3-iodopropane (404 μL, 3.22 mmol, 1.40 equiv) was added to the bright yellow reaction suspension. After 100 min, 1 M aqueous hydrochloric acid solution (30 mL) was added to the reaction mixture, followed by ethyl acetate (75 mL). The organic layer was separated and extracted with a second portion of aqueous hydrochloric acid solution (1 M, 30 mL). The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and was carefully basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with four 40-mL portions of dichloromethane. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated in vacuo to provide an oily residue. The residue was dissolved in chloroform (20 mL), and the resulting solution was warmed to 48 °C. After stirring at 48 °C for 5 h, the solution was cooled and diluted with 0.5 M aqueous sodium hydroxide solution (25 mL) and the layers were separated. The aqueous layer was extracted with two 30-mL portions of dichloromethane, and the combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 4% methanol, 4% triethylamine, and 92% dichloromethane to afford the product **11** (457 mg, 76%) as an oil. The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (220 °C, major R_t = 14.6 min, minor R_t = 16.9 min). The product was found to be 96% de: TLC R_f = 0.45 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (4:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (J in hertz) δ 7.22−7.36 (m, 5H), 4.61 (d, 1H, J = 8.0), 4.53* (d, 1H, J = 8.7); 4.40 (m, 1H), 4.12* (m, 1H), 3.68 (dd, 1H, J = 10.9, 2.2), 3.11 (d, 1H, J = 12.1), 2.90* (s, 3H), 2.84 (s, 3H), 2.64 (m, 1H), 1.87 (m, 1H), 1.29−1.60 (m, 5H), 1.07 (d, 3H, J = 6.9), 0.95* (d, 3H, J = 6.5); ^{13}C NMR ($CDCl_3$) δ 173.8*, 173.6, 142.0, 128.3*, 128.0, 127.7*, 127.3, 126.7*, 126.6, 75.4*, 74.8, 57.7*, 57.0, 56.5, 45.6*, 44.5, 31.0, 29.6*, 28.4, 26.4*, 25.4, 24.1*, 23.5, 15.3*, 14.2; HRMS calcd for $C_{16}H_{25}N_2O_2$ (M + H) 277.1916, found 277.1907.

(*R*,*R*)-Pseudoephedrine *N*-Methyl-L-phenylalaninamide (12f). A solution of *n*-butyllithium in hexanes (2.60 M, 1.20 mL, 3.12 mmol, 2.95 equiv) was added slowly to the inner edge of a flask containing a slurry of anhydrous (*R*,*R*)-**2** (250 mg, 1.06 mmol, 1 equiv), *N*-methylethanolamine (85 μL, 1.06 mmol, 1.00 equiv), and anhydrous lithium chloride (269 mg, 6.35 mmol, 6.00 equiv) in tetrahydrofuran (10 mL) at −78 °C. The resulting yellow suspension was stirred at −78 °C for 20 min, at which time the reaction flask was warmed to 0 °C. After stirring at 0 °C for 20 min, benzyl bromide (139 μL, 1.16 mmol, 1.1 equiv) was added to the colorless slurry. After stirring for 1 h at 0 °C, aqueous hydrochloric acid solution (1 M, 30 mL) was added to the colorless solution, followed by ethyl acetate (50 mL). The organic layer was separated and extracted with two 25-mL portions of 1 M aqueous hydrochloric acid solution. The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and carefully basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with three 40-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to provide 372 mg of the crude alkylation product as an oily residue. A small portion of the residue (37 mg) was reserved for analysis, and the remaining residue (335 mg) was purified by chromatography on silica gel eluting with 4% methanol, 4% triethylamine, and 92% dichloromethane to afford 289 mg (93%) of **12f** as an oil which rapidly crystallized upon standing. The solid was recrystal-

lized by dissolution in hot (80 °C) toluene (2 mL) and allowing the resulting solution to cool to 23 °C, whereupon the product crystallized rapidly. The recrystallization flask was cooled in an ice bath for 30 min, and the product was isolated by filtration. The solids were washed with two portions of cold (0 °C) toluene (2 × 2 mL) and one portion of cold (0 °C) ether (5 mL) and were dried in vacuo to afford 178 mg (57%) of **12f**. The mother liquors were concentrated in vacuo, the residue was dissolved in toluene (1.5 mL), and the resulting solution was cooled to −20 °C and seeded with authentic **12f**. After 12 h, the crystals which had formed were collected by filtration and were rinsed with cold toluene (2 mL, 0 °C) and ether (4 mL, 0 °C) to afford 48 mg of **12f** (total 226 mg, 69% yield). The isolated product was determined to be a monohydrate by ^{1}H NMR and elemental analysis. The diastereomeric excess of the product was determined by capillary GC analysis as described in the general procedures (230 °C, major R_t = 14.5 min, minor R_t = 15.7 min). The crude product was 88% de, and the recrystallized product was ≥99% de: mp 119−120 °C; TLC R_f = 0.55 (5% MeOH, 5% NEt_3, 90% CH_2Cl_2); ^{1}H NMR (5:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.17−7.35 (m, 10H), 4.67 (m, 1H), 4.48 (d, 1H, *J* = 8.3), 4.07* (m, 1H), 3.81* (t_{app}, 1H, *J* = 7.2), 3.72 (dd, 1H, *J* = 9.0, 5.7), 3.14* (dd, 1H, *J* = 5.6, 13.4), 3.00 (dd, 1H, *J* = 13.0, 5.5), 2.96* (s, 3H), 2.77 (dd, 1H, *J* = 12.9, 9.2), 2.50 (s, 3H), 3.32 (s, 3H), 1.8−2.3 (s (br), 4H), 0.96* (d, 3H, *J* = 6.7), 0.78 (d, 3H, *J* = 6.8); ^{13}C NMR ($CDCl_3$) δ 176.1, 142.0, 137.5, 129.3*, 129.1, 128.6*, 128.4*, 128.3, 128.2, 127.7, 126.8*, 126.5, 76.5, 75.7*, 61.7, 56.4, 40.3, 34.5*, 34.3, 30.4, 15.7*, 14.0. Anal. Calcd for $C_{20}H_{26}N_2O_2 + H_2O$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.60; H, 8.54; N, 7.90.

(*S*,*S*)-Pseudoephedrine *N*-Boc-D-2-aminobutyramide (13b). A solution of *n*-butyllithium in hexanes (2.71 M, 791 μL, 2.14 mmol, 3.10 equiv) was added slowly to a slurry of anhydrous lithium chloride (176 mg, 4.15 mmol, 6.00 equiv) and diisopropylamine (310 μL, 2.21 mmol, 3.20 equiv) in tetrahydrofuran (4 mL) at −78 °C. After stirring at −78 °C for 10 min, a solution of (*S*,*S*)-(+)-**3** (223 mg, 0.692 mmol, 1 equiv) in tetrahydrofuran (4 mL + 2 mL wash) was added via cannula to the lithium diisopropylamide slurry. After stirring for 20 min at −78 °C, the reaction suspension was warmed to 0 °C. After stirring for 20 min at 0 °C, iodoethane (66 μL, 0.830 mmol, 1.20 equiv) was added to the pale yellow suspension. After stirring for 1 h at 0 °C, the reaction was terminated by the addition of 1 M aqueous hydrochloric acid solution (30 mL). The biphasic mixture was extracted with two portions of ethyl acetate (50 and 40 mL). The organic layers were combined, and the resulting solution was washed with saturated aqueous sodium bicarbonate solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. A small amount of the crude residue (27 mg) was reserved for GC analysis. The remaining crude residue (201 mg) was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (40% → 50%) to afford 169 mg (79%) of **13b** as an oil. The diastereomeric excess of the product was determined by capillary GC analysis, as outlined above, to be 93% (see **7b** for retention times): ^{1}H NMR (2:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.22−7.39 (m, 5H), 5.42 (d, 1H, *J* = 8.2), 5.38* (d, 1H, *J* = 9.7), 4.41−4.62 (m, 3H), 4.28 (s (br), 1H), 4.16* (m, 1H), 2.93 (s, 3H), 2.32* (s (br), 1H), 1.86* (m, 1H), 1.37−1.66 (m, 2H), 1.43 (s, 9H), 1.41* (s, 9H), 1.05 (d, 3H, *J* = 6.7), 0.98* (d, 3H, *J* = 6.7), 0.93* (t, 3H, *J* = 7.4), 0.88 (t, 3H, *J* = 7.4); ^{13}C NMR ($CDCl_3$) δ 174.1, 173.0*, 155.7, 155.4*, 141.7, 141.3*, 128.6, 128.2, 128.0, 127.8, 126.9, 126.4, 79.6, 79.2*, 75.5, 75.2*, 58.3, 57.8*, 52.0, 51.4*, 32.0, 28.2, 27.0*, 26.1*, 25.8, 15.4*, 14.3, 9.8*, 9.6. Anal. Calcd for $C_{19}H_{30}NO_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.06; H, 8.49; N, 7.89.

General Procedures for the Determination of the Enantiomeric Excesses of α-Amino Acids. Primary α-amino acids were analyzed by HPLC using a Crownpak CR(+) column, except as noted. Secondary α-amino acids were analyzed by HPLC with a Chiralpak WH column. Baseline separation was achieved in all cases. The minor enantiomers were identified by comparison with authentic materials (either racemic mixtures or the optically pure antipodes). Racemates for noncommercial α-amino acids were identified by epimerization of the alkylation products (as described above for **7h**) and subsequent hydrolysis of the residue obtained (2 mL of 0.5 M aqueous sodium hydroxide solution, reflux, 5 h), followed by extraction of the hydrolysis mixture with dichloromethane (2 × 20 mL), acidification of the aqueous layer with concentrated perchloric acid solution, and analysis of the resulting solution by HPLC. The enantiomeric excesses of *N*-Boc-α-amino acids were determined by hydrolysis of the *N*-Boc protective group (1:1 3 M aqueous hydrochloric acid solution−methanol, 23 °C, 30 min) followed by concentration *and* chiral HPLC analysis of the cleavage reaction mixture. The enantiomeric excesses of *N*-Fmoc-α-amino acids were determined by cleavage of the protective group (1:1 0.5 M aqueous sodium hydroxide solution−methanol, 30 min) followed by 4-fold dilution with water and filtration of the resulting solution through Celite, concentration of the filtrate in vacuo, dilution of the residue in pH 1 aqueous perchloric acid solution, and chiral HPLC analysis of the resulting solution.

Hydrolysis and *N*-Boc Protection of Alkylation Products. *N*-Boc-D-2-aminobutyric Acid (15b). An aqueous solution of sodium hydroxide (1 M, 2.78 mL, 2.78 mmol, 2.00 equiv) was added to a solution of (*S*,*S*)-pseudoephedrine (*R*)-2-aminobutyramide (**7b**) (348 mg, 1.39 mmol, 1 equiv) in water (2.8 mL). The resulting solution was heated at reflux for 90 min. Upon cooling to 23 °C, pseudoephedrine was observed to crystallize from the reaction mixture. Water (15 mL) was added, and the aqueous mixture was extracted with two 30-mL portions of dichloromethane. The combined organic layers were washed with a second portion of water (20 mL), and the aqueous layer was extracted with dichloromethane (15 mL). All aqueous layers were combined, and the resulting solution was concentrated in vacuo to a volume of approximately 10 mL. Analysis of a small aliquot (50 μL) of the combined aqueous layers showed that the α-amino acid was formed with ≥99% ee. Solid sodium bicarbonate (234 mg, 2.78 mmol, 2.00 equiv) and *p*-dioxane (10 mL) were added sequentially to the alkaline solution. The resulting solution was cooled in an ice bath, and di-*tert*-butyl dicarbonate (364 mg, 1.67 mmol, 1.20 equiv) was added to the reaction mixture at 0 °C. After stirring for 1 h, the reaction mixture was allowed to warm to 23 °C, and was stirred at that temperature for 30 min. Water (30 mL) was added, and the aqueous product solution was extracted with ethyl acetate (60 mL). The organic layer was washed with 2% aqueous sodium bicarbonate solution (20 mL). The aqueous layers were combined, and the resulting solution was carefully acidified to pH 3.5 by the addition of saturated aqueous citric acid solution. The acidified solution was extracted with three 25-mL portions of ethyl acetate. The combined organic layers were washed with two 25-mL portions of water and then were dried over sodium sulfate, filtered, and concentrated in vacuo to give the carboxylic acid **15b** as an oil (278 mg, 97%) which was pure by spectroscopic and elemental analysis. (Note: Omitting the final aqueous extractions will result in contamination of the product with citric acid. Aqueous hydrochloric acid solution (1 M) may be used in lieu of saturated aqueous citric acid solution (see the procedure below for the preparation of **15f**), provided that the basic, aqueous product solution is cooled during the acidification and the addition of acid is terminated at pH 2.) The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 $HClO_4$ mobile phase, 0.4 mL/min, 200 nm, major R_t = 4.1 min, minor R_t = 5.2 min). The product was shown to be ≥99% ee: ^{1}H NMR (2:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 9.64 (s (br), 1H), 6.50* (s (br), 1H), 5.09 (d, 1H, *J* = 7.5), 4.29 (m, 1H), 4.10* (m, 1H), 1.90 (m, 1H), 1.75 (m, 1H), 1.45 (s, 9H), 0.98 (t, 3H, *J* = 7.0); ^{13}C NMR ($CDCl_3$) δ 177.3, 156.9*, 155.6, 81.6*, 80.1, 55.8*, 54.4, 28.3, 25.6*, 9.7*, 9.5. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.12; H, 8.43; N, 6.89. Found: C, 53.26; H, 8.54; N, 6.98.

Hydrolysis and *N*-Boc Protection of Alkylation Products Including Recovery of Pseudoephedrine. *N*-Boc-D-phenylalaninine (15f). An aqueous solution of sodium hydroxide (1 M, 2.12 mL, 2.12 mmol, 2.00 equiv) was added to a solution of (*S*,*S*)-pseudoephedrine (*R*)-phenylalaninamide (**7f**) (316 mg, 1.01 mmol, 1 equiv) in water (2.1 mL). The resulting solution was heated at reflux for 2 h. Upon cooling to 23 °C, pseudoephedrine was observed to crystallize from the reaction mixture. Water (15 mL) was added, and the aqueous mixture was extracted with two 30-mL portions of dichloromethane. The combined organic layers were washed with a second portion of water (20 mL), and the aqueous layer was extracted with dichloromethane (15 mL). All aqueous layers were combined, the resulting solution was concentrated in vacuo to a volume of approximately 10 mL, and the resulting

solution was reserved. Analysis of a small aliquot (50 μL) of the combined aqueous layers showed that the α-amino acid was formed with ≥99% ee. The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to afford a solid. The solid was dried in vacuo to afford 161 mg (96%) of recovered pseudoephedrine.[50]

p-Dioxane (10 mL) was added to the reserved alkaline, aqueous product solution. The resulting solution was cooled in an ice bath, and di-*tert*-butyl dicarbonate (364 mg, 1.67 mmol, 1.20 equiv) was added. After stirring for 1 h, water (30 mL) was added and the aqueous product solution was extracted with ethyl acetate (60 mL). The organic layer was washed with 0.5 M aqueous sodium hydroxide solution (15 mL). The aqueous layers were combined, and the resulting solution was cooled in an ice bath and carefully acidified to pH 2 by the slow, cautious addition of 1 M aqueous hydrochloric acid solution. The acidified solution was extracted with three 25-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give the carboxylic acid **15f** as an oil (237 mg, 88%) which was pure by spectroscopic and elemental analysis. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 $HClO_4$ mobile phase, 0.8 mL/min, 200 nm, major $R_t = 9.5$ min, minor $R_t = 12.7$ min). The product was shown to be ≥99% ee: ^{1}H NMR (2:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 9.23 (s (br), 1H), 7.21−7.34 (m, 5H), 6.54* (d, 1H, *J* = 7.3), 5.05 (d, 1H, *J* = 7.9), 4.63 (m, 1H), 4.41* (m, 1H), 2.91−3.25 (m, 2H), 1.43 (s, 9H), 1.30* (s, 9H); ^{13}C NMR ($CDCl_3$) δ 175.9, 175.7*, 156.5*, 155.4, 136.4*, 135.9, 129.3, 128.4, 126.9, 81.5*, 80.2, 56.0*, 54.2, 38.9*, 37.7, 28.2, 27.9*. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.41; H, 7.31; N, 5.21.

Hydrolysis and *N*-Fmoc Protection of Alkylation Products. *N*-Fmoc-D-allylglycine (16c). An aqueous solution of sodium hydroxide (1 M, 633 μL, 633 μmol, 2.00 equiv) was added to a solution of (*S*,*S*)-pseudoephedrine (*R*)-allylglycinamide (**7c**) (83 mg, 316 μmol, 1 equiv) in water (2.53 mL). The resulting solution was heated at reflux for 90 min. Upon cooling to 23 °C, pseudoephedrine was observed to crystallize from the reaction mixture. Water (10 mL) was added, and the aqueous mixture was extracted with two 15-mL portions of dichloromethane. The combined organic layers were washed with a second portion of water (20 mL), and the aqueous layer was extracted with dichloromethane (15 mL). All aqueous layers were combined, and the resulting solution was concentrated in vacuo to a volume of approximately 5 mL. Analysis of a small aliquot (50 μL) of the combined aqueous layers showed that the α-amino acid was ≥99% ee. Solid sodium bicarbonate (53 mg, 633 μmol, 2.00 equiv) and *p*-dioxane (10 mL) were added sequentially to the alkaline product solution. The resulting solution was cooled in an ice bath, and 9-fluorenylmethyl chloroformate (90 mg, 348 μmol, 1.10 equiv) was added. After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to 23 °C and was stirred at that temperature for 2 h. Water (15 mL) was added, and the aqueous product solution was extracted with a 1:1 mixture of ether and ethyl acetate (30 mL). The organic layer was washed with 2% aqueous sodium bicarbonate solution (15 mL). The aqueous layers were combined, and the resulting solution was acidified to pH 1 by the addition of 1 M aqueous hydrochloric acid solution. The acidified solution was extracted with two 30-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Residual solvents were removed by dissolving the residue in toluene (50 mL) and concentrating in vacuo, followed by dissolving in chloroform (2 × 25 mL) and concentrating in vacuo. The product was obtained as a white crystalline solid (102 mg, 96%). A small amount of the product (5 mg) was reserved for analysis, and the remainder was recrystallized from ethyl acetate−hexanes (4 mL, 1:3) to afford 76 mg (75%) of analytically pure **16c**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 $HClO_4$ mobile phase, 0.4 mL/min, 200 nm, major $R_t = 4.8$ min, minor $R_t = 5.8$ min). The product was shown to be ≥99% ee: mp 134.5−136 °C; ^{1}H NMR (9:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 10.85 (s (br), 1H), 7.74 (d, 2H, *J* = 7.4), 7.56 (m, 2H), 7.38 (t, 2H, *J* = 7.3), 7.29 (t, 2H, *J* = 7.3), 6.32* (d, 1H, *J* = 5.6), 5.65−5.76 (m, 1H), 5.38 (d, 1H, *J* = 8.0), 5.07−5.19 (m, 2H), 4.50 (m, 1H), 4.40 (d, 2H, *J* = 7.0), 4.21 (t, 1H, *J* = 6.9), 4.15* (m, 1H), 2.57 (m, 2H), 2.40* (m, 2H); ^{13}C NMR ($CDCl_3$) δ 176.5, 155.9, 143.7, 143.6, 143.5, 141.2, 131.7, 131.5*, 127.7, 127.0, 126.7, 125.0, 124.6*, 120.0, 119.7, 119.5, 67.6*, 67.2, 53.7*, 53.1, 47.0, 36.3. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.12; H, 5.63; N, 4.19.

***N*-Fmoc-D-2-aminobutyric Acid (16b). 16b** was prepared by the hydrolysis of **7b** (405 mg, 1.62 mmol, 1 equiv) following the procedure described for **16c** (hydrolysis time 90 min) with the exception that *N*-(9-fluorenylmethylcarbonyloxy)succinimide (600 mg, 1.78 mmol, 1.1 equiv) was used in the acylation step in place of 9-fluorenylmethyl chloroformate. The product was purified by recrystallization in two crops from ethyl acetate−hexanes (1:2, 9-mL first crop, 3-mL second crop) to afford 525 mg (99%) of analytically pure **16b**. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 1.5 $HClO_4$ mobile phase, 0.4 mL/min, 200 nm, major $R_t = 4.1$ min, minor $R_t = 5.2$ min). The product was shown to be ≥99% ee: mp 155−158 °C; ^{1}H NMR (3:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 11.11 (s (br), 1H), 7.79 (d, 2H, *J* = 7.4), 7.62 (m, 2H), 7.42 (t, 2H, *J* = 7.4), 7.33 (t, 2H, *J* = 7.3), 6.52* (d, 1H, *J* = 6.4), 5.44 (d, 1H, *J* = 8.0), 4.38−4.54 (m, 3H), 4.25 (t, 1H, *J* = 6.9), 4.09* (m, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.00 (t, 3H, *J* = 7.3), 0.92* (t, 1H, *J* = 6.8); ^{13}C NMR ($CDCl_3$) δ 177.2, 156.1, 143.8, 143.6, 141.3, 127.7, 127.0, 125.0, 124.7*, 120.0, 67.6*, 67.1, 54.9, 47.1, 25.5, 9.5. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.01; H, 5.87; N, 4.28.

***N*-Fmoc-D-β-(6-chloro-5-hydroxy-2-pyridyl)alanine (16j).** A suspension of amide **7j** (480 mg, 1.18 mmol, 1 equiv) in 0.5 M aqueous sodium hydroxide solution (4.70 mL, 2.35 mmol, 2.00 equiv) was heated at reflux for 3 h. The resulting homogenous mixture was cooled, diluted with water (20 mL), and extracted with dichloromethane (2 × 30 mL). The organic layers were extracted with a second portion of water (15 mL). The aqueous extracts were combined, and the volume of the resulting solution was reduced to ca. 10 mL by concentration in vacuo. Dioxane (10 mL) and solid sodium bicarbonate (198 mg, 2.35 mmol, 2 equiv) were added to the alkaline product mixture, and the resulting solution was cooled in an ice bath. *N*-(9-Fluorenylmethylcarbonyloxy)succinimide (476 mg, 1.41 mmol, 1.2 equiv) was added to the cooled solution. After stirring at 0 °C for 1.5 h, the ice bath was removed and the reaction suspension was allowed to warm to 23 °C. After stirring for 2.5 h at 23 °C, 1 M aqueous hydrochloric acid solution (15 mL) was added to the suspension and the resulting mixture was extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with water, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to provide an oily residue.

The oily residue was dissolved in tetrahydrofuran (6 mL) and water (4 mL), the resulting solution was cooled to 0 °C, and trifluoroacetic acid (8 mL) was added. The resulting solution was stirred for 1 h at 0 °C, at which time the cooling bath was removed and the solution was allowed to warm to 23 °C. After stirring for 2 h at 23 °C, the solvents were removed by concentration in vacuo. The residue was dissolved in a mixture of ethyl acetate (25 mL) and ether (25 mL), and the resulting solution was extracted with saturated aqueous sodium bicarbonate solution (ca. 15 mL), taking any solids present into the aqueous layer. The organic layer was washed with 2% aqueous sodium bicarbonate solution (2 × 15 mL, until no solids remained in the organic layer). The aqueous extracts were combined with ethyl acetate (50 mL), and the resulting biphasic mixture was acidified by the slow, cautious addition of 6 M aqueous hydrochloric acid solution until the aqueous layer was acidic (pH 1). The layers were separated, and the organic layer was washed with water (30 mL). The aqueous washings were extracted with a second portion of ethyl acetate (25 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The waxy solid residue was dissolved in warm chloroform (15 mL, 50 °C). After the resulting

(50) The recovered pseudoephedrine is typically found to be pure by ^{1}H NMR analysis. If desired, the recovered solid can be recrystallized from water and dried in vacuo to afford analytically pure material (typical recovery 83−85%). See: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergammon Press: Oxford, 1988; p 266.

solution had cooled to 23 °C, hexanes (10 mL) were added slowly. The precipitate which formed was isolated by filtration and was dried in vacuo to afford 378 mg (73%) of analytically pure **16j**. The enantiomeric excess of the isolated product was determined by cleavage of the Fmoc protective group as described above, followed by chiral HPLC analysis (pH 2.0 $HClO_4$, 0.8 mL/min, 220 nm, major R_t = 7.0 min, minor R_t = 10.4 min) which revealed that the product was 96% ee: mp 185−187 °C; ^{1}H NMR (>10:1 rotamer ratio, minor rotamer peaks not reported, CD_3OD) (*J* in hertz) δ 7.76 (d, 2H, *J* = 7.5), 7.56 (m, 2H), 7.36 (t, 2H, *J* = 7.3), 7.27 (d, 2H, *J* = 7.5), 7.17 (d, 1H, *J* = 8.1), 7.07 (d, 1H, *J* = 8.1), 4.53 (dd, 1H, *J* = 9.6, 4.6), 4.24 (t, 2H, *J* = 7.7), 4.16 (q_{app}, 1H, *J* = 6.8), 3.23 (dd, 1H, *J* = 14.1, 4.6), 2.99 (dd, 1H, *J* = 14.0, 9.8); ^{13}C NMR (CD_3OD) δ 174.8, 158.3, 149.9, 149.2, 145.2, 145.1, 142.5, 128.7, 128.1, 126.2, 125.7, 124.9, 120.9, 68.0, 55.4, 48.3, 38.9. Anal. Calcd for $C_{23}H_{19}ClN_2O_5$: C, 62.95; H, 4.36; N, 6.38. Found: C, 62.91; H, 4.25; N, 6.23.

Aqueous Hydrolysis of Alkylation Products. Isolation of Free α-Amino Acids. D-Allylglycine (19c). A suspension of (*S*,*S*)-pseudoephedrine D-allylglycinamide (**7c**) (697 mg, 2.59 mmol) in water (5.20 mL) was heated at reflux for 9 h. The reaction mixture was cooled to 23 °C and was diluted with water (25 mL). The aqueous product solution was extracted with two 25-mL portions of dichloromethane. The combined organic extracts were extracted with water (25 mL). Analysis of a small aliquot (50 μL) of the combined aqueous extracts showed that the α-amino acid had been formed with 98% ee. The aqueous layers were combined, and the resulting solution was concentrated in vacuo to afford a white crystalline solid. The solid was triturated with ethanol to remove residual pseudoephedrine. The crystalline product was dried under vacuum (0.2 mmHg) to give 258 mg (87%) of D-allylglycine (**19c**). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to afford 331 mg (78%) of (*S*,*S*)-(+)-pseudoephedrine The enantiomeric excess of the product **19c** was determined by chiral HPLC analysis as described above (pH 1.5 $HClO_4$ mobile phase, 0.4 mL/min, 200 nm, major R_t = 4.8 min, minor R_t = 5.8 min). The product was shown to be ≥99% ee: $[\alpha]_D^{20}$ = +37.5° (*c* = 4.09, H_2O), lit.[51] $[\alpha]_D^{20}$ +37.8° (*c* = 4, H_2O); ^{1}H NMR (D_2O) (*J* in hertz) δ 5.64 (m, 1H), 5.14 (d, 1H, *J* = 18.6), 5.13 (d, 1H, *J* = 10.0), 3.67 (dd, 1H, *J* = 7.0, 5.1), 2.50 (m, 2H). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.10; H, 7.74; N, 12.19.

D-2-Methoxyphenylalanine (19g). 19g was prepared by the hydrolysis of **7g** (810 mg, 2.36 mmol, 1 equiv) in water (20 mL) following the procedure outlined for **19c**. After an initial 12 h at reflux, 4 mL of dioxane was added and reflux was continued for 10 h. After workup as described for **19c**, 328 mg (71%) of **19g** was isolated as a hemihydrate. The enantiomeric excess of the product was determined by chiral HPLC analysis as described above (pH 2.0 $HClO_4$, 5% MeOH mobile phase, 0.7 mL/min, 200 nm, major R_t = 17.3 min, minor R_t = 24.6 min). The crude hydrolyzate was shown to be 98% ee, and the isolated product was 99% ee: ^{1}H NMR (D_2O) (*J* in hertz) δ 7.33 (t, 1 H, *J* = 7.5 Hz), 7.19 (d, 1 H, *J* = 7.3 Hz), 7.03 (d, 1, *J* = 8.2 Hz H), 6.96 (t, 1 H, *J* = 7.4 Hz), 3.97 (dd, 1 H, *J* = 8.0, 4.7 Hz), 3.83 (s, 3 H), 3.32 (dd, 1 H, *J* = 14.3, 4.7 Hz), 3.00 (dd, 1 H, *J* = 14.3, 8.0 Hz). Anal. Calcd for $C_{10}H_{13}NO_3 \cdot {}^1/_2H_2O$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.64; H, 6.99; N, 6.75.

L-(Trimethylsilyl)alanine (19h). 19h was prepared by the hydrolysis of **7h** (1.09 g, 3.89 mmol, 1 equiv) in water (15 mL) following the procedure outlined for **19c** (hydrolysis time 20 h) to afford 468 mg (82%) of L-(trimethylsilyl)alanine. The enantiomeric excess of the product was determined by the method of Marfey[52] (chiral HPLC analysis of the Marfey derivative: 25 cm × 4.6 μm C_{18} column, 1 mL/min, 0.1% TFA/40−60% MeCN gradient over 20 min, major R_t = 13.7 min, minor R_t = 17.2 min). The isolated product was shown to be ≥99% ee: $[\alpha]_D^{20}$ = +33.3° (*c* = 0.526, 4 M HCl), lit.[5c] $[\alpha]_D^{20}$ +31° (*c* = 0.51, 4 M HCl); ^{1}H NMR (D_2O) (*J* in hertz) δ 3.61 (dd, 1H, *J* = 9.6, 5.9), 1.00 (m, 2H), −0.04 (s, 9H). Anal. Calcd for $C_6H_{15}NO_2Si$: C, 44.69; H, 9.38; N, 8.69. Found: C, 44.85; H, 9.32; N, 8.80.

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***N*-Methyl-D-phenylalanine (20f).** A suspension of (*S*,*S*)-pseudoephedrine *N*-methyl-D-phenylalaninamide (**ent-12f**, prepared from the alkylation of (*S*,*S*)-(+)-**2**) (850 mg, 2.60 mmol, 1 equiv) in water (10 mL) was heated at reflux for 48 h, at which time some solids remained. Dioxane (6 mL) was added, and the resulting solution was heated at reflux for an additional 48 h and then was cooled to 23 °C. The cooled mixture was diluted with water (25 mL) and was extracted with dichloromethane (3 × 30 mL). The organic layers were extracted with two additional 25-mL portions of water. The combined aqueous layers were concentrated in vacuo to provide a solid residue. The solid was triturated with ethanol (20 mL) and dried in vacuo to afford 324 mg (70%) of **20f**. The product was shown to be ≥99% ee by chiral HPLC analysis (see **18f** for conditions): $[\alpha]_D^{20}$ = −18.6° (*c* = 0.97, 1 M HCl), lit.[51] $[\alpha]_D^{20}$ −24.7° (*c* = 1.6, 1 M HCl); ^{1}H NMR (D_2O) (*J* in hertz) δ 7.25−7.39 (m, 5H), 3.80 (t, 1H, *J* = 6.2), 3.18 (d, 2H, *J* = 6.2), 2.63 (s, 3H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.59; H, 7.28; N, 7.82.

Preparation of *N*-Boc-Protected Pseudoephedrine Amides from Pseudoephedrine Glycinamide Alkylation Products. (*S*,*S*)-Pseudoephedrine *N*-Boc-D-allylglycinamide (13c). Di-*tert*-butyl dicarbonate (203 mg, 0.929 mmol, 1.2 equiv) was added to a biphasic mixture of **7c** (203 mg, 0.774 mmol, 1 equiv) in dioxane (2 mL) and saturated aqueous sodium bicarbonate solution (1 mL). After stirring the resulting mixture vigorously for 1 h at 23 °C, water (10 mL) and ether (25 mL) were added and the layers were separated. The aqueous layer was extracted with a second portion of ether (10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (40% → 45%) to afford 278 mg (99%) of **13c**: ^{1}H NMR (2:1 rotamer ratio, the asterisk denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.25−7.36 (m, 5H), 5.81* (m, 1H), 5.68 (m, 1H), 5.37 (d, 1H, *J* = 8.2), 5.32* (d, 1H), 5.06−5.18 (m, 2H), 4.71* (m, 1H), 4.49−4.63 (m, 3H), 4.19* (m, 1H), 4.03* (s (br), 1H), 2.95 (s, 3H), 2.60* (m, 1H), 2.46* (m, 1H), 2.20−2.39 (m, 2H), 1.43 (s, 9H), 1.40* (s, 9H), 1.05 (d, 3H, *J* = 6.7), 0.99* (d, 3H, *J* = 6.7); ^{13}C NMR ($CDCl_3$) δ 173.5, 172.4*, 155.5, 155.2*, 141.7, 141.2*, 133.7*, 132.6, 128.7, 128.4*, 128.3, 127.8, 126.9*, 126.5, 118.6, 118.0*, 79.8, 79.4*, 75.6, 75.3*, 58.4, 58.0*, 50.6, 49.9*, 37.3*, 37.1, 32.1, 28.3, 27.1*, 15.5*, 14.4; HRMS calcd for $C_{20}H_{31}N_2O_4$ (M + H) 363.2283, found 363.2286.

Hydrolysis of *N*-Boc-pseudoephedrine Amides. *N*-Boc-D-allylglycine (15c). A solution of **13c** (181 mg, 0.499 mmol, 1 equiv) and 1 M aqueous sodium hydroxide solution (2.50 mL, 2.50 mmol, 5.00 equiv) in methanol (10 mL) was heated to reflux. After heating at reflux for 3.5 h, the solution was cooled and methanol was removed by concentration in vacuo. The resulting aqueous product mixture was diluted with water (10 mL) and extracted with ether (25 mL). The organic layer was washed with 0.5 M aqueous sodium hydroxide solution (10 mL). The combined aqueous layers were cooled in an ice bath and acidified to pH 1 by the slow, cautious addition of 1 M aqueous hydrochloric acid solution. The acidified aqueous solution was extracted with two 50-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 107 mg (99%) of *N*-Boc-allylglycine (**15c**) which was identical with material prepared by the hydrolysis of **7c**. The product was shown to be 90% ee by chiral HPLC analysis (see **15c** above).

Preparation of *N*-Fmoc-pseudoephedrine Amides from Pseudoephedrine Glycinamide Alkylation Products. (*S*,*S*)-Pseudoephedrine *N*-Fmoc-D-2-aminobutyramide (21b). 9-Fluorenylmethyl chloroformate (119 mg, 0.460 mmol, 1.20 equiv) was added to a biphasic mixture of **7b** (96 mg, 0.383 mmol, 1 equiv) in dioxane (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL). After stirring vigorously for 2 h at 23 °C, saturated aqueous sodium bicarbonate solution (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes (30% → 50%) to afford 180 mg (99%) of **21b** as a viscous oil: ^{1}H NMR (2:1 rotamer ratio, the denotes minor rotamer peaks, $CDCl_3$) (*J* in hertz) δ 7.76 (d, 2H, *J* = 7.4), 7.62* (d, 2H, *J* = 6.7), 7.60 (d, 2H, *J* = 5.1), 7.27−7.42 (m, 9H), 5.70* (d,

1H, $J = 8.1$), 5.68 (d, 1H, $J = 8.1$), 4.47−4.67 (m, 3H), 4.30−4.42 (m, 2H), 4.22 (t, 1H, $J = 6.9$), 3.97 (s (br), 1H), 2.97*, (s, 3H), 2.95 (s, 3H), 2.04 (s (br), 1H), 1.97* (m, 1H), 1.47−1.78 (m, 2H), 1.10 (d, 3H, $J = 6.9$), 0.98* (m, 6H), 0.89 (t, 3H, $J = 7.4$); ^{13}C NMR ($CDCl_3$) δ 173.5, 172.7*, 156.1, 156.0*, 143.9, 143.8*, 143.7, 141.8, 141.2, 128.3, 127.7*, 127.6, 127.0, 126.8*, 126.4, 125.1, 119.9, 75.6, 75.2*, 66.9, 66.8*, 58.0, 52.5, 52.1*, 47.1, 32.1, 27.0, 26.1*, 25.8, 15.5, 14.4, 9.8*, 9.5; HRMS calcd for $C_{29}H_{33}N_2O_4$ (M + H) 473.2440, found 473.2442.

Hydrolysis of *N*-Fmoc-pseudoephedrine Amides. *N*-Fmoc-D-phenylalanine (16f). A solution of **21b** (151 mg, 0.282 mmol, 1 equiv) in a mixture of dioxane (2 mL), water (1.5 mL) and concentrated sulfuric acid (0.5 mL) was heated to reflux. After heating at reflux for 8 h, the solution was cooled, water (20 mL) was added, and the resulting solution was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with water (10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford 105 mg (96%) of **16f** which was identical with the product prepared by the hydrolysis of **7f**. The product was shown to be 99% ee by chiral HPLC analysis (see **16f** above).

***N*-Fmoc-D-2-aminobutyric Acid (16b). 16b** was prepared by the hydrolysis of **21b** (105 mg, 0.222 mmol, 1 equiv) following the procedure outlined for **16f**. Upon initial isolation, ^{1}H NMR analysis of the crude reaction product indicated that it contained a minor byproduct, tentatively identified (on the basis of its reversion to **21b** upon neutralization with base) as the sulfate salt of the *N*→*O*-acyl transfer product. The crude product was dissolved in a mixture of ethyl acetate and hexanes (20 mL, 1:1), and the resulting solution was extracted with saturated aqueous sodium bicarbonate solution (6 × 15 mL, until no solids were observed in the aqueous layer). The aqueous extracts were combined, and the resulting solution was cooled in an ice bath and was acidified to pH 1 by the slow, careful addition of 6 M aqueous hydrochloric acid solution. The resulting acidified solution was extracted with ethyl acetate (2 × 25 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 60 mg (83%) of **16b**, which was identical with material prepared by the hydrolysis of **7b**. The product was shown to be 99% ee by chiral HPLC analysis (see **16b** above).

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Supporting Information Available: Experimental details for the preparation, purification, and characterization of all compounds not included in the main Experimental Section and all IR fingerprint data (27 pages). See any current masthead page for ordering and Internet access instructions.

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