Greatly Simplified Procedures for the Synthesis of α-Amino Acids by the Direct Alkylation of Pseudoephedrine Glycinamide Hydrate

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A modified procedure for the synthesis of highly enantiomerically enriched α-amino acids is described that involves the direct alkylation of pseudoephedrine glycinamide hydrate (**1**·H_2O) followed by hydrolysis. The modified procedure was developed to overcome several inconvenient aspects of our earlier reported procedure. Advantages of the new method include (1) a greatly simplified one-step synthesis of the alkylation substrate (**1**·H_2O) by the direct combination of glycine methyl ester hydrochloride with pseudoephedrine in the presence of lithium *tert*-butoxide, (2) the use of the weaker base lithium hexamethyldisilazide (LHMDS) in lieu of lithium diisopropylamide (LDA) for the enolization reaction, (3) a protocol for the direct alkylation of **1**·H_2O without the need for prior drying of the alkylation substrate, and (4) a one-step alkylation procedure that generates LHMDS and anhydrous lithium chloride simultaneously from the reaction of lithium metal with *n*-hexyl chloride in the presence of hexamethyldisilazane.

In prior work, a method for the asymmetric synthesis of α-amino acids was described that involved the alkylation of an enolate dianion derived from anhydrous pseudoephedrine glycinamide (**1**) followed by hydrolysis of the resulting alkylation products (**2**, Scheme 1).[1] The alkylation substrate (**1**) was prepared by the base-catalyzed condensation of glycine methyl ester with pseudoephedrine followed by crystallization of the product, pseudoephedrine glycinamide hydrate (**1**·H_2O), and drying.[2] Although the method offered several advantages over existing procedures for the alkylative assembly of α-amino acids,[1] there were aspects of the procedure that were felt to provide opportunities for improvement. These are indicated by the bold italics within Scheme 1, which also summarizes the improvements detailed in this work. Among the problematic features of the prior method were the steps to prepare the alkylation substrate **1**, which included the preparation and distillation of the free-base form of glycine methyl ester, the need to use anhydrous lithium chloride to promote the clean condensation of the latter product with pseudoephedrine, and a separate step to dry the crystalline hydrate (**1**·H_2O) to afford anhydrous **1** as a hygroscopic solid.[2] The protocol for alkylation of anhydrous **1** required the thorough drying of both **1** and lithium chloride, an additive that promotes a rapid, clean, and highly diastereoselective alkylation reaction. The procedure also demanded that the number of equivalents of the base used for enolization, lithium diisopropylamide (LDA), be measured carefully, for quantities in excess of 1.95 equiv led to partial cleavage of pseudoephedrine from the substrate **1**. In this work, we describe a modified sequence that addresses each of these concerns, providing a greatly simplified procedure for the preparation of the alkylation products **2** that is suitable for both large- and small-scale applications.

A Modified Procedure for the Preparation of Pseudoephedrine Glycinamide Hydrate (1·H_2O): Step 1. Pseudoephedrine glycinamide hydrate (**1**·H_2O) is a highly crystalline, free-flowing solid that is stable to air and moisture and is derived from two inexpensive commodity chemicals, glycine methyl ester hydrochloride and pseudoephedrine, both of which are also free-flowing, nonhygroscopic crystalline solids. The earlier procedure that was developed for the synthesis of **1**·H_2O involved the base-catalyzed condensation of pseudoephedrine with glycine methyl ester in the presence of anhydrous lithium chloride. This procedure required the initial neutralization of glycine methyl ester hydrochloride followed by distillation of the resultant liquid free base. The propensity of glycine methyl ester to polymerize upon standing led us to focus on developing a simpler synthesis of **1**·H_2O that avoided using this starting material. Attention was turned to procedures for the neutralization of glycine methyl ester hydrochloride in situ, in the presence of pseudoephedrine. This, in turn, provided an opportunity to solve another problem—the need to use anhydrous lithium chloride in the condensation reaction—by using a lithium salt for the neutralization step. In this way, lithium chloride would be formed as a byproduct of the neutralization reaction, potentially obviating the need to add this hygroscopic solid to the reaction mixture (in earlier work, lithium chloride had been shown to be a necessary additive in order to prevent the self-condensation of glycine methyl ester, as well as over-glycylation of the product **1**).[2]

An initial experiment toward this end was quite promising. Addition of 1.7 equiv of solid lithium methoxide in one portion to a stirring, ice-cooled suspension of pseudoephedrine (1 equiv) and glycine methyl ester hydrochloride (1.2 equiv) in tetrahydrofuran (THF) led to complete consumption of glycine methyl ester within 7 h at 0 °C. Approximately 20% of pseudoephedrine remained. Addition of water and recrystallization, as

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(1) (a) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656.

(2) Myers, A. G.; Yoon, T.; Gleason, J. L. *Tetrahedron Lett.* **1995**, *36*, 4555.

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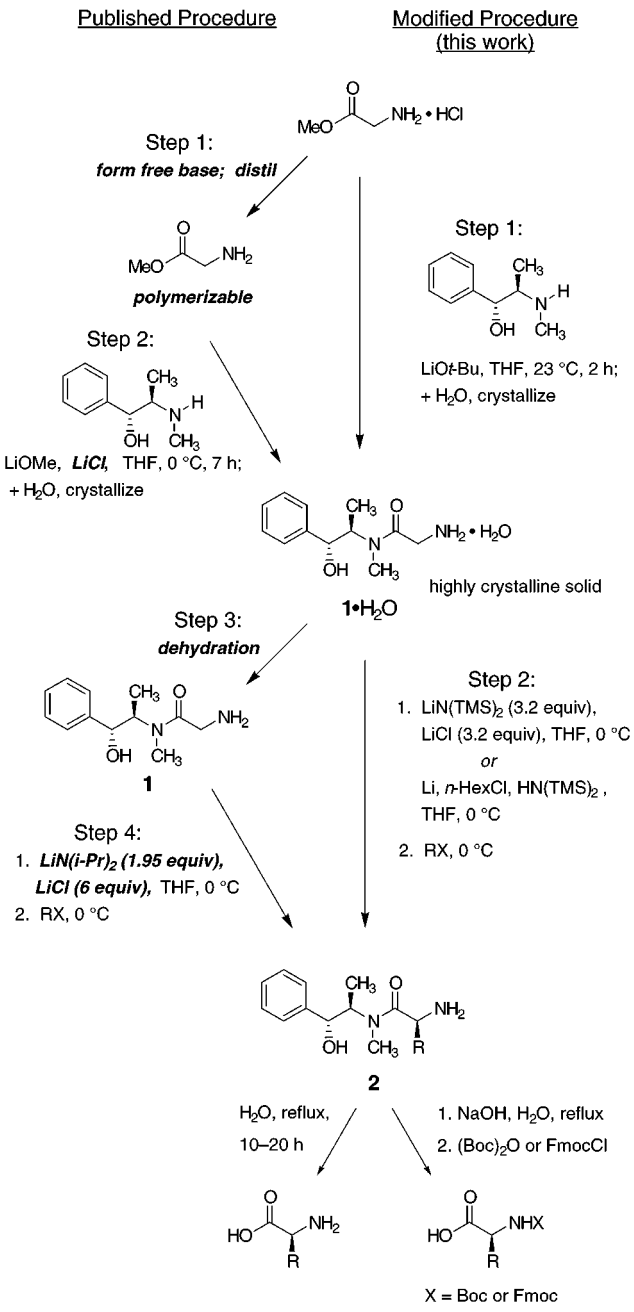
Scheme 1



before, afforded crystalline **1**·H_2O in 50−55% yield. Use of the more soluble base lithium *tert*-butoxide led to further improvement in the reaction, providing what is presently the optimum procedure.[3] Although lithium *tert*-butoxide is a hygroscopic solid, it is easily handled and is more convenient to manipulate, e.g., in benchtop weighing, than anhydrous lithium chloride (used in the prior method). The procedure entails the addition of the base to the reaction mixture in a single portion. The addition is conducted at ambient temperature and, although it produces a mild exotherm, external cooling has been found to be unnecessary, as tested thus far on scales as large as 60 g. Typically, after addition of the base, the reaction mixture clears within 15 min; ≥95% of pseudoephedrine is consumed within 1−2 h. Workup and recrystallization, as before, provides analytically pure, crystalline **1**·H_2O in 73−76% yield. For comparison, our earlier published procedure required a reaction time of ∼8 h, involved the use of 2 equiv of anhydrous lithium chloride (as well as the free-base form of glycine methyl ester), and provided **1**·H_2O in 68−76% yield.

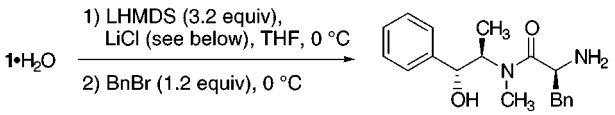
A New Enolization Protocol and a Method for the Direct Alkylation of Pseudoephedrine Glycinamide Hydrate (1·H_2O): Step 2. As stated in the introduction and summarized graphically in Scheme 1, there were several aspects of our original alkylation procedure that were targeted for modification. These included the need to ensure the dryness of both lithium chloride and pseudoephedrine glycinamide, and the need to carefully measure the number of equivalents of LDA used in the enolization reaction. The latter requirement arose because of a side reaction that occurred whenever >1.95 equiv of base was used, leading to the partial cleavage of pseudoephedrine from **1**. Through further experimentation, we have learned that it is possible to substitute the weaker base lithium hexamethyldisilazide (LHMDS) for LDA in the enolization reaction and that this base does not induce the cleavage reaction observed with the latter reagent, even when used in excess. The yield and diastereoselectivity of alkylation reactions conducted with LHMDS in lieu of LDA were not affected by the substitution. Furthermore, the presence of an excess (>2 equiv) of LHMDS in the reaction does not greatly diminish the yield of alkylation product with many alkyl halides; therefore, it is not necessary to titrate nor to accurately measure the LHMDS used in the reaction, provided that at least 2 equiv is present. LHMDS is conveniently available from commercial suppliers in several forms, both neat and in solution, and exhibits excellent shelf stability.

With an improved protocol for the enolization of **1**, efforts turned toward streamlining the entire alkylation procedure. In particular, a means of simplifying the dehydration of **1**·H_2O was sought. Although **1**·H_2O is an air-stable, free-flowing solid, anhydrous **1** is hygroscopic and must be handled with the exclusion of moisture. Furthermore, the dehydration of **1**·H_2O constitutes an additional step in the synthetic sequence. The possibility that the dehydration step might be omitted entirely was considered. Specifically, it was proposed to use the hydrate directly in the alkylation reaction with the inclusion of an extra equivalent of base to deprotonate the water of hydration. Upon investigation, we have found that the proposed protocol is not only feasible but, in many cases, represents an improved procedure as well as a one of greater convenience. Because both lithium alkoxides and lithium halides are known to influence the aggregation state and reactivity of enolates, it was deemed prudent to investigate the effect of lithium chloride under the new conditions, in which 1 equiv of lithium hydroxide is formed. The diastereoselectivity of the alkylation of **1**·H_2O using 3.2 equiv of LHMDS as base and benzyl bromide (1.2 equiv) as the electrophile was measured as a function of the concentration of added lithium chloride (Table 1). The maximum diastereoselectivity (93% de) was observed when ≥3 equiv of lithium chloride was used and was the same value as that previously obtained for this reaction using anhydrous **1**, lithium chloride, and LDA as base.

In the optimized procedure for the alkylation of **1**·H_2O, anhydrous lithium chloride (3.2 equiv) is first flame-dried

(3) This procedure is also effective for the preparation of pseudoephedrine sarcosinamide (nonhydrated), in 71% yield (from sarcosine hydrochloride) after recrystallization from toluene.

Table 1. Alkylation Diastereoselectivity as a Function of Added Lithium Chloride



2i

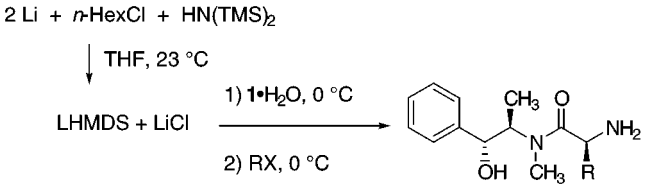
entry	enolate concn (M)	equiv LiCl	de (%)
1	0.16	0	74
2	0.16	2	88
3	0.16	3	90
4	0.16	4	93[a]
5	0.16	5	93
6	0.16	6	93
7	0.16	10	93
8	0.24	3.2	93[b]

[a] Recommended for larger-scale (≥30 mmol **1**·H_2O) experiments. [b] Recommended for smaller-scale (<30 mmol **1**·H_2O) experiments.

in vacuo in a round-bottom flask and then is allowed to cool under an inert atmosphere. Sufficient THF is added to the solid lithium chloride so as to prepare a solution that would be ~3 M in lithium chloride, were it dissolved. The resulting slurry of lithium chloride in THF is stirred at ambient temperature for at least 15 min during which time visible, but largely incomplete, solubilization occurs. At this point, **1**·H_2O (1 equiv) is added, leading to a rapid clearing of the slurry. This solubilizing effect is noteworthy, for neither LiCl nor **1**·H_2O is soluble in THF independently.[4] The clear solution of lithium chloride and **1**·H_2O has been observed to spontaneously form a thick slurry under certain circumstances. LHMDS can be added and a solution of enolate obtained in either case, but working with the thick slurry is inconvenient. Precipitation appears to occur whenever the local concentration of lithium chloride in the solution is depleted relative to the hydrate. For this reason the hydrate is never added prior to the lithium chloride, which always leads to precipitation. Rather, the hydrate is added to the prestirred slurry of lithium chloride (3 equiv) in THF. For larger-scale experiments (≥30 mmol), we recommend two additional modifications designed to minimize the precipitation of the mixture of lithium chloride and **1**·H_2O. First, the volume of THF is increased 3-fold (producing a final solution of hydrate that is ~0.33 M) and, second, the number of equivalents of lithium chloride is increased to 4, which is approximately the point of saturation of this reagent at these concentrations. In all procedures, approximately 10 min after solubilization of the mixture of lithium chloride and **1**·H_2O occurs, the reaction solution is cooled to 0 °C and, 20 min later, a commercial, 1.0 M solution of LHMDS (3.2 equiv) in THF is added rapidly to the cold solution. This addition leads to a mild exotherm. Careful monitoring has shown that the exotherm occurs primarily during the addition of the first equivalent of base, presumably involving the deprotonation of water. In the optimized procedure, 1.5 equiv of LHMDS is added carefully to the cold solution of hydrate and lithium chloride. After sufficient time has elapsed for the solution to cool once again to 0 °C, the remaining base is added very rapidly. This procedure is advisable not only for optimum temperature control during the reaction, but also because it avoids a second precipitation that can occur when approximately 2 equiv of LHMDS is added to the mixture of lithium chloride and **1**·H_2O and the resulting solution is allowed to stand. This can occur in larger-scale experiments where the addition of the base is slowed by the sheer volume that must be transferred; precipitation then occurs before the final 1.2 equiv of base can be added. This precipitation does not occur when the suggested two-stage addition protocol (1.5 equiv followed by rapid addition of 1.7 equiv, see above) is followed. It is also not observed in small scale experiments (<30 mmol), presumably because the addition of base is relatively rapid. Both protocols afford products with identical, high diastereoselectivities and yields.

The new procedure for the direct alkylation of **1**·H_2O using LHMDS as base is operationally much simpler than our earlier published procedure and reliably affords good yields of products with a wide range of alkyl halides as substrates (Table 2). An exception to this generalization may be alkyl halide substrates that are sluggish to react by nucleophilic displacement, but which undergo rapid dehydrohalogenation. Isobutyl iodide is suspected to be a case in point (entries 4 and 5, Table 2). The yield of this alkylation product using the new method is only 40−62%, whereas the earlier procedure afforded the same product in 70% yield (albeit requiring 2 d at 23 °C). The culprit here is suspected to be lithium hydroxide, but this has not been established. For most standard alkyl halide substrates, such as the remaining examples of Table 2, the modified procedure is more convenient, more reliable, and tends to proceed more cleanly and to a greater degree of completion than the earlier published procedure.

A Procedure for the Generation of LHMDS·LiCl In Situ from Lithium Metal, Hexamethyldisilazane, and Hexyl Chloride and Its Use for the Enolization−Alkylation of 1·H_2O. The only remaining unsolved problem identified within Scheme 1 is the need for anhydrous lithium chloride in the alkylation reaction mixture. As detailed above, the alkylation protocol is typically initiated by flame-drying reagent grade anhydrous lithium chloride in vacuo. Although this is easily done, we noted that the optimum number of equivalents of lithium chloride and the number of equivalents of LHMDS employed in the enolization−alkylation reaction



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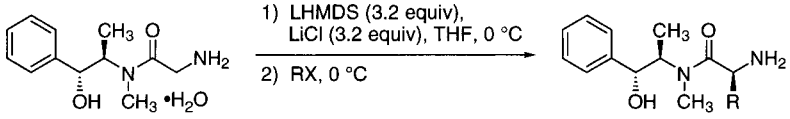
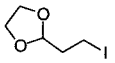
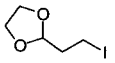
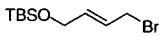
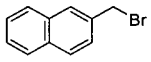
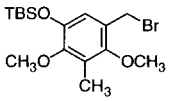
were approximately the same (~3 equiv each). Recognizing that the commercial synthesis of alkyllithium reagents is accompanied by the formation of 1 equiv of lithium chloride (typically removed during processing), we considered a scenario whereby a solution of LHMDS and lithium chloride could be formed in situ by the reaction of lithium metal with an *n*-alkyl chloride in the presence of hexamethyldisilazane. A related procedure has been described by Einhorn and Luche for the

(4) Seebach and co-workers have previously shown that lithium halides can increase the solubility of peptides in ethereal solvents by as much as 100-fold; see: Seebach, D.; Thaler, A.; Beck, A. K. *Helv. Chim. Acta* **1989**, *72*, 857.

Table 2. Diastereoselective Alkylation of Pseudoephedrine Glycinamide Hydrate (1·H_2O)



1•H_2O (0.24 M) **2a-l**

entry	RX	LHMDS[a]	equiv RX	time (h)	product	yield[b] (%)	de[c] (%)
1	CH_3I	A	1.2	1.5	**2a**	91	93
2	CH_3I	B	1.05	2	**2a**	84	93
3	CH_3CH_2I	A	1.2	1.5	**2b**	83	96
4	$(CH_3)_2CHCH_2I$	A	1.2–2.0	3–11	**2c**	40–50	89–93
5	$(CH_3)_2CHCH_2I$	A	5.0	23[g]	**2c**	62	89
6		A	1.2	3	**2d**	65	97
7		B	1.3	3	**2d**	62	96
8	$(CH_3)_3SiCH_2Br$	A	1.2	23	**2e**	56	91
9	c-$C_3H_5CH_2I$	A	1.2	2.5	**2f**	79	97
10	CH_2=$CHCH_2Br$	A	1.2	1	**2g**	86 (77)[d]	93 (>99)[f]
11	CH_2=$CHCH_2Br$	B	1.05	2	**2g**	82 (73)[d]	93 (>99)[f]
12		A	1.0	2.5	**2h**	84	92
13	$C_6H_5CH_2Br$	A	1.2	1	**2i**	89	93
14	$C_6H_5CH_2Br$	B	1.2	2	**2i**	88	93
15	3-(CH_3O)$C_6H_4CH_2Br$	A	1.0	1	**2j**	71	91
16		A	1.2	1.5	**2k**	82 (71)[d]	94 (>99)[f]
17		A	1.0	0.5	**2l**	80[d]	89[e] (97)[f]

[a] A: commercial solution (1.0 M in THF); B: generated in situ from Li, HMDS, *n*-HexCl, see text. [b] Isolated yield after chromatography. [c] Determined by capillary GC analysis after acetylation. [d] Yield of recrystallized product. [e] Determined by HPLC analysis of an *N*-benzoylated sample. [f] Diastereomeric excess (de) of recrystallized product. [g] 23 °C.

preparation of LDA.[5] The procedure envisioned was readily implemented, with great success, and was optimized using *n*-hexyl chloride so as to form the liquid byproduct hexane. In the optimized protocol, lithium wire (6.8 equiv) is washed with hexanes, cut into ~1-cm pieces, and the pieces are suspended in sufficient THF to produce a solution that is ultimately ~0.86 M in LHMDS.[6] Reagent-grade *n*-hexyl chloride (3.6 equiv) and hexamethyldisilazane (3.7 equiv) are then added at 23 °C. After a short induction period, the lithium metal begins to react, dissolving in the process. This is accompanied by a mild exotherm, which is controlled with a water or ice−water bath so as to maintain an internal reaction temperature that is below 35 °C. After 2−10 h, depending upon the quality of the lithium metal used and the reaction scale, dissolution is essentially complete and the reaction mixture is cooled in an ice bath. At this point, solid **1**·H_2O is added to the basic solution in a single portion. The ensuing reaction with the base is only mildly exothermic, and dissolution of the substrate occurs quickly forming a homogeneous enolate solution, after which time the electrophile is added. The yields and diastereoselectivities for this procedure are quite comparable to those of the procedure reported above. The method has been tested on a 50-g scale using commercial sources of anhydrous THF and HMDS, as received, and been found to be both efficient and convenient to implement.

(5) Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1987**, *52*, 4124.

(6) Einhorn and Luche recommend that lithium be added in portions in larger-scale experiments in order to control the reaction exothermicity.[5]

Experimental Section

General Experimental Procedures. All reactions were conducted under a positive pressure of argon. Lithium *tert*-butoxide can be handled and weighed in the atmosphere, but should be stored under an inert atmosphere to avoid the absorption of carbon dioxide and water from the air. Commercial alkyl halides were purified by passage through activated basic alumina (Brockman Grade 1) or were distilled from calcium hydride. Commercial solutions of lithium hexamethyldisilazide (1.0 M in THF, Aldrich) were used without titration. Reagent grade anhydrous lithium chloride was dried by heating under vacuum (150 °C, 0.5 mmHg, 12 h) and was flame-dried immediately prior to use, as described.

General Procedures for Determination of the Diastereomeric Excess of Alkylation Products. The diastereomeric excess (de) of an alkylation product was determined by acetylation followed by capillary GC analysis (Chirasil-Val column, length 25 m, inj 250 °C, det 275 °C). The procedure for acetylation of the products 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 concen-

trated in vacuo. The residue was dissolved in ethyl acetate (10 mL), and the resulting solution was analyzed by capillary GC analysis.

Improved, One-Step Synthesis of (*R*,*R*)-(−)-Pseudoephedrine Glycinamide Hydrate (1·H$_2$O). A 2-L, three-necked, round-bottom flask fitted with an inlet adapter connected to a source of vacuum and argon, a thermometer, and a glass stopper was charged with (*R*,*R*)-(−)-pseudoephedrine (60.0 g, 363 mmol, 1 equiv) and glycine methyl ester hydrochloride (59.2 g, 472 mmol, 1.30 equiv). Tetrahydrofuran (510 mL) was added to the solid mixture, and the whole was stirred at 23 °C with a magnetic stirring bar for 15 min, producing a fine suspension. The glass stopper was briefly removed and lithium *tert*-butoxide powder (40.7 g, 508 mmol, 1.40 equiv) was added to the suspension in a single portion from a weighing boat. The latter addition produced a modest exotherm (40 °C maximum internal temperature, no provision for external cooling was necessary). Within 15 min, the reaction mixture became a homogeneous, pale yellow solution. After stirring at ambient temperature for a total period of 2 h, water (450 mL) was added to the reaction solution, and the mixture was concentrated in vacuo to remove the bulk of the tetrahydrofuran. The largely aqueous concentrate was transferred to a 2-L separatory funnel and was extracted with a 1-L portion of dichloromethane. Solid sodium chloride was added to the aqueous layer to the point of saturation, and the resulting solution was extracted with four 300-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous solid potassium carbonate and then were filtered and concentrated by rotary evaporation. The liquid residue was further concentrated under high vacuum (0.5 mmHg, 10 h). The resulting syrup was dissolved in hot tetrahydrofuran (300 mL), and water (12 mL) was added to the warm solution. Upon cooling (23 °C), **1**·H$_2$O crystallized within minutes. The crystallization flask was allowed to stand overnight at 23 °C and then was cooled to −20 °C for 3 h. The crystals were collected by vacuum filtration on a 600-mL glass frit, washing with two 200-mL portions of ether. After drying in vacuo (0.5 mmHg) for 10 h, **1**·H$_2$O was obtained as a nonhygroscopic, free flowing, crystalline solid (63.9 g, 73.3%, mp 85−87 °C).[7] Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.96; H, 8.67; N, 11.75. Spectroscopic data were identical to those previously reported.[1]

Large-Scale Alkylation of (*R*,*R*)-(−)-Pseudoephedrine Glycinamide Hydrate (1·H$_2$O) Using Commercial Lithium Hexamethyldisilazide as Base. Synthesis of [1*R*(*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenethyl)-2-amino-*N*-methyl-4-pentenamide (2g). An oven-dried, 3-L, three-necked, round-bottom flask fitted with two glass stoppers and an inlet adapter connected to a source of vacuum and argon was charged with anhydrous lithium chloride (33.9 g, 800 mmol, 4.00 equiv). The flask was evacuated, and a gentle flame was applied to further dry the solid lithium chloride. After cooling to 23 °C in vacuo, the flask was flushed with argon and then was fitted with a mechanical stirrer and an oven-dried 1-L pressure-equalizing addition funnel, marked at 340 and 640 mL. Tetrahydrofuran (600 mL) was added to the flask, and the resulting suspension was stirred for 20 min at 23 °C. Solid (*R*,*R*)-(−)-pseudoephedrine glycinamide hydrate (48.1 g, 200 mmol, 1 equiv) was added to the suspension in eight portions over a period of 10 min through one of the necks by way of a powder funnel. The resulting slightly cloudy solution was cooled by immersing the reaction flask in an ice bath. The pressure-equalizing addition funnel was charged with a commercial 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran (640 mL, 640 mmol, 3.20 equiv). The argon inlet adapter was transferred from the neck of the flask to the neck of the addition funnel, and the open neck was fitted with a septum pierced with a thermocouple to monitor the internal temperature of the reaction mixture. Dropwise addition of the base was initiated when the substrate solution had cooled to 0 °C, ∼35 min after the reaction flask had been immersed in an ice bath. The rate of addition of the first 300-mL portion of base (300 mmol, 1.5 equiv, to the 340-mL mark) was modulated such that the internal reaction temperature did not exceed 3 °C (addition time ∼30 min). When the reaction mixture had again cooled to 0 °C, the stopcock of the addition funnel was opened fully to allow for rapid addition of the second portion of base (340 mL, 340 mmol, 1.70 equiv). The latter addition produced a modest exotherm (8 °C maximum internal temperature). After 20 min, allyl bromide (18.2 mL, 210 mmol, 1.05 equiv) was injected slowly into the orange enolate solution over a period of 15 min. The internal temperature did not exceed 5 °C during the addition. After the addition of allyl bromide was complete, the reaction mixture was stirred at 0 °C for 1 h. Water (500 mL) was added at this point, and the resulting biphasic mixture was carefully acidified to pH 0 by the addition of aqueous hydrochloric acid solution (6 M, 300 mL). The acidified aqueous solution was transferred to a 4-L separatory funnel and was extracted with ethyl acetate (750 mL). The organic layer was separated and extracted sequentially with single 300-mL portions of 3 M and 1 M aqueous hydrochloric acid solution, respectively. The aqueous layers were combined and cooled to an internal temperature of 5 °C by stirring in an ice−water bath. The cold solution was cautiously basified to pH 14 by the addition of 50% aqueous sodium hydroxide solution (200 mL). The temperature of the solution was maintained at or below 25 °C during basification. The basified solution was extracted sequentially with one 800-mL portion and three 250-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous solid potassium carbonate and then were filtered and concentrated in vacuo. The de of the crude reaction product was shown to be 93% by capillary GC analysis of an acetylated sample (190 °C, major t_R = 22.7 min, minor t_R = 19.6 min) as described in the general procedures. The oily, pale yellow residue solidified upon standing in vacuo (0.5 mmHg). The solid was dissolved in hot toluene (100 mL); crystallization occurred upon cooling the resulting solution to 23 °C. After standing overnight at 23 °C, the crystallization flask was cooled to −20 °C for 6 h. The crystals were collected and washed sequentially with 25 mL of cold (0 °C) toluene and four 100-mL portions of ether. The crystals were dried in vacuo (0.5 mmHg) at 23 °C for 14 h to provide 32.7 g (62.3%) of diastereomerically pure **2g**. The mother liquors were concentrated, and the liquid residue was dissolved in hot toluene (25 mL). Cooling to 23 °C and then at −20 °C (3.5 d) afforded a second crop of pure **2g** (4.4 g, 8.4%, de >99%, mp 72−73 °C). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.44; H, 8.70; N, 10.68. Spectroscopic data were identical to those previously reported.[1]

Large-Scale Alkylation of (*R*,*R*)-(−)-Pseudoephedrine Glycinamide Hydrate (1·H$_2$O) Using Lithium Hexamethyldisilazide and Lithium Chloride Generated in Situ from Lithium Metal, 1-Chlorohexane, and Hexamethyldisilazane. Synthesis of [1*R*(*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenethyl)-2-amino-*N*-methyl-4-pentenamide (2g). In this experiment, tetrahydrofuran, hexamethyldisilazane, and 1-chlorohexane were used as received from commercial suppliers, and no provisions were made to dry the reaction apparatus. A 3-L, three-necked, round-bottom flask fitted with an inlet adapter connected to a source of vacuum and argon, a magnetic stirring bar, and a thermometer was charged with tetrahydrofuran (800 mL). The flask was alternately evacuated and flushed with argon three times. Lithium wire (3.2 mm diameter, 98+%, sodium content 0.5−1%, 9.44 g, 1.36 mol, 6.80 equiv) was freed of oil by briefly rinsing in pentane and then was cut into 2−5 cm pieces, and the pieces were added to the reaction vessel under a stream of argon. Hexamethyldisilazane (156 mL, 740 mmol, 3.70 equiv) and 1-chlorohexane (99.0 mL, 720 mmol, 3.60 equiv) were added sequentially to the reaction mixture, and the reaction vessel was immersed in a water bath at 23 °C. After a few minutes, the reaction temperature increased to 35 °C and the solution became cloudy, presumably due to the precipitation of lithium chloride.[6] Ice was added to the water bath to maintain an internal temperature of ∼30 °C. Approximately 20 min after

(7) Prolonged (>1 d) drying in vacuo (0.5 mmHg) may cause partial dehydration of the product. Rehydration occurs upon exposure to the atmosphere.

the reagents had been added, cooling was discontinued, and the reaction mixture was stirred at 23 °C for 10 h, until the lithium metal appeared to have been completely consumed.[8] The resulting suspension was cooled to 0 °C in an ice−water bath, and solid (*R*,*R*)-(−)-pseudoephedrine glycinamide hydrate (48.1 g, 200 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred vigorously at 0 °C for 2.5 h to allow the crystalline hydrate to react, forming a fine, orange enolate suspension. Allyl bromide (18.2 mL, 210 mmol, 1.05 equiv) was added dropwise via syringe over a period of 10 min, so as to maintain the temperature of the reaction suspension below 8 °C. After completed addition, the resulting solution was stirred at 0 °C for 1 h. Water (500 mL) was added slowly to the reaction mixture, and the resulting biphasic mixture was carefully acidified to pH 0 by the addition of aqueous hydrochloric acid solution (6 M, 300 mL), maintaining the temperature below 10 °C. The mixture was transferred to a 4-L separatory funnel, and ethyl acetate (750 mL) was added. The organic layer was separated and subsequently extracted sequentially with 300-mL portions of 3 M and 1 M aqueous hydrochloric acid solution, respectively. The aqueous layers were combined and cooled to 5 °C by stirring in an ice−water bath. To the cold aqueous solution was added 50% aqueous sodium hydroxide solution (160 mL) at such a rate as to maintain the temperature of the solution at or below 25 °C. The basified solution (pH 14) was extracted sequentially with one 500-mL portion and three 250-mL portions of dichloromethane. The combined organic extracts were dried with anhydrous solid potassium carbonate and then were filtered and concentrated in vacuo. The de of the crude reaction product was shown to be 92% by capillary GC analysis of an acetylated sample (190 °C, major t_R = 22.2 min, minor t_R = 19.5 min), as described in the general procedures. Toluene (200 mL) was added to the cold reaction product, a pale yellow liquid, and the resulting solution was concentrated in vacuo (rotary evaporator, then at 0.5 mmHg for 2 h), affording a solid residue. The solid was dissolved in hot toluene (100 mL), and the resulting solution was allowed to cool to 23 °C. Crystallization occurred after 1 h. The crystallization flask was allowed to stand for an additional 3 h at 23 °C and then was cooled to −20 °C for 1 h. The crystals were collected and washed with three 100-mL portions of ether and then were dried in vacuo (0.5 mmHg) at 23 °C for 24 h to provide 29.4 g (56.0%) of diastereomerically pure product (**2g**). The mother liquors were concentrated and subjected to recrystallization twice, as above, to afford an additional 2.2 g of diastereomerically pure product (4.2%, de > 99%, mp 71−73 °C). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.48; H, 8.68; N, 10.76. Spectroscopic data were identical to those previously reported.[1]

(8) Small amounts of undissolved lithium metal may remain and do not influence the subsequent alkylation reaction; however, care should be exercised during the quenching of the reaction. Sonication has been reported to accelerate the rate of reaction of lithium metal with diisopropylamine.[5]

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Supporting Information Available: Experimental details and analytical data for the products of Table 2 and copies of ^{1}H and ^{13}C NMR spectra of compounds **2d** and **2j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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