Pseudoephedrine as a Practical Chiral Auxiliary for the Synthesis of Highly Enantiomerically Enriched Carboxylic Acids, Alcohols, Aldehydes, and Ketones

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Abstract: The use of pseudoephedrine as a practical chiral auxiliary for asymmetric synthesis is described in full. Both enantiomers of pseudoephedrine are inexpensive commodity chemicals and can be *N*-acylated in high yields to form tertiary amides. In the presence of lithium chloride, the enolates of the corresponding pseudoephedrine amides undergo highly diastereoselective alkylations with a wide range of alkyl halides to afford α-substituted products in high yields. These products can then be transformed in a single operation into highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones.

Introduction

The asymmetric alkylation of the α-carbon of carboxylic acid derivatives is a reaction of fundamental importance in modern synthetic organic chemistry.[1] With few exceptions, this type of transformation is accomplished using chiral auxiliary-based methodology. The first practical demonstration of the use of a chiral auxiliary for the asymmetric alkylation of a carboxylic acid enolate equivalent was reported by Meyers and co-workers in 1976.[2] In this pioneering work, it was shown that oxazoline anions derived from chiral β-amino alcohols were alkylated by a range of alkyl halides with high diastereoselectivities. These alkylation products were then transformed into chiral carboxylic acids with synthetically useful optical purities (51−86% ee).

Later, Evans and Takacs[3a] and Sonnet and Heath[3b] independently demonstrated that alkylations of enolates of tertiary amides derived from the amino alcohol prolinol occurred with higher diastereoselectivities (76−94% de). Like the Meyers precedent, this work was influential not only as a practical addition to synthetic methodology, but also as a paradigm for the design of new chiral auxiliaries employing rigid cyclic platforms with well-defined conformational preferences. The C_2-symmetric bis(methoxymethoxymethyl)pyrrolidine auxiliary of Katsuki et al. exemplifies the degree to which this paradigm has evolved (alkylation de's 97 to >98%).[4] Subsequent developments in chiral auxiliary-based alkylation methodology have focused primarily on the alkylation of acyl derivatives that are more readily cleaved than amides.[5] Foremost among these are the oxazolidinone auxiliaries of Evans and co-workers,[6] which have defined the standard in this area for more than 10 years. Also noteworthy are the important camphor-derived sultam auxiliaries developed by Oppolzer and co-workers.[7] The same properties that facilitate the acyl cleavage reactions of the products of the latter reactions also serve to stabilize the intermediate enolates. As a consequence, oxazolidinone-derived enolates react efficiently only with reactive halides (e.g., allylic halides),[6] and camphor sultam-derived enolates require the presence of the reactivity-enhancing ligand hexamethylphosphoric triamide (HMPA) for efficient alkylation.[7a]

In a preliminary communication, we described the use of the readily available (in both enantiomeric forms) and inexpensive amino alcohol pseudoephedrine (Sudafed, Suphedrine, etc.) as a highly practical chiral auxiliary for asymmetric alkylation reactions.[8] Pseudoephedrine amides are easily prepared and are frequently crystalline. They undergo efficient and highly diastereoselective alkylation reactions with a wide range of alkyl halides, to include less reactive substrates such as β-branched alkyl iodides. Like the starting materials, the alkylated products are frequently crystalline and are easily enriched to ≥99% de upon recrystallization. In this work, we describe in full our findings on the use of pseudoephedrine as a chiral auxiliary in asymmetric alkylation reactions.[9] The scope of this methodology is defined, and possible factors responsible for the exceptionally high levels of diastereoselectivity observed with

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(1) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1−110. (b) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 213−274. (c) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Synthesis*; Scheffold, R., Ed.; Springer: Berlin-Heidelberg, 1986; Vol. 4, pp 125−259. (d) Crosby, J. *Tetrahedron* **1991**, *47*, 4789. (e) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 1−63.

(2) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc*. **1976**, *98*, 567.

(3) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett*. **1980**, *21*, 4233. (b) Sonnet, P.; Heath, R. R. *J. Org. Chem*. **1980**, *45*, 3137.

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

(5) For additional examples, see: (a) Davies, S. G. *Pure Appl. Chem*. **1988**, *60*, 13. (b) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. O. *Chem. Ber*. **1993**, *126*, 2663. (c) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 793.

(6) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737. (b) Mathre, D. Ph.D. Thesis, California Institute of Technology, 1985.

(7) (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (b) For a previous camphor-derived system, see: Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 207.

(8) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc*. **1994**, *116*, 9361.

(9) For the specific case of the alkylation of pseudoephedrine glycinamide and its application to the preparation of highly enantiomerically enriched α-amino acids, see: (a) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc*. **1997**, *119*, 656. (b) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc*. **1995**, *117*, 8488.

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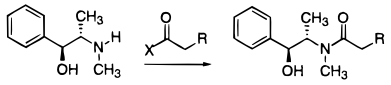
Table 1. Selective *N*-Acylation of Pseudoephedrine



entry	R	method (X)[a]	product	yield (%)	mp (°C)
1	CH_3	A	**1**	95[b]	114−115
2	CH_3	D	**1**	89[b]	114−115
3	*n*-Bu	A	**2**	91[b]	62−63
4	Bn	B	**3**	83[b]	102−104
5	Ph	B	**4**	88[b]	145−146
6	Cl	B	**5**	90	79−81
7	*i*-Pr	B	**6**	92[b]	73−74
8	*t*-Bu	B	**7**	88[b]	68−69
9	CH_2Bn	B	**8**	81[b]	100−102
10	2-thiophene	B[c]	**9**	87	110−111
11	3-pyridyl	C	**10**	97, 72[b]	117.5−118.5
12	OH	D	**11**	93	61−63

[a] Method A: Acylation with the symmetrical carboxylic acid anhydride (X = RCH_2CO_2). Method B: Acylation with the carboxylic acid chloride (X = Cl). Method C: Acylation with the mixed anhydride derived from pivaloyl chloride (X = *t*-$BuCO_2$). Method D: Acylation with the methyl ester (X = CH_3O). [b] Values for products isolated by a single recrystallization of the crude product. [c] Acylation of (1*R*,2*R*)-(−)-pseudoephedrine.

this nonconventional, acyclic auxiliary are discussed.[10] In addition, extensive developmental work on the transformation of the alkylation products into highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones is described in detail.

Results

Synthesis of Pseudoephedrine Amides. Amide bond formation is one of the most highly developed and efficient transformations in organic chemistry. Acylation reactions of the amino alcohol pseudoephedrine provide no exceptions to this generalization. As shown by the examples of Table 1, pseudoephedrine is acylated in high yield by a variety of activated carboxylic acid derivatives, to include symmetrical and mixed anhydrides and carboxylic acid chlorides.[11,12] Acylation reactions with carboxylic acid anhydrides proceed efficiently in dichloromethane or tetrahydrofuran (THF) as solvent and do not require the presence of an external base, although the reactions are much more rapid if a base such as triethylamine (1.2 equiv) is added. Acylation reactions with carboxylic acid chlorides require the presence of a slight excess of a base (e.g., Et_3N) and occur readily at 0 °C in most organic solvents. In cases where neither the anhydride nor the acid chloride derivative of a carboxylic acid is readily available, acylation using the mixed anhydride formed from the carboxylic acid, pivaloyl chloride, and triethylamine is found to be a convenient preparative method (entry 11). Each of the amide products of Table 1 is a nonhydrated, air-stable, free-flowing crystalline solid and can be isolated by direct recrystallization of the crude acylation product (entries 1−5, 7−9, and 11) or by flash column chromatography (entries 6 and 10−12). In most cases, the only byproduct in the acylation reactions is a small amount (≤5%) of the *N*,*O*-diacylated product, which is easily separated by recrystallization or flash column chromatography. Because intramolecular *O* → *N* acyl transfer within pseudoephedrine β-amino esters occurs rapidly, and because the *N*-acyl form is strongly favored under neutral or basic conditions,[11c] products arising from (mono)acylation on oxygen rather than nitrogen are not observed.

The propensity of pseudoephedrine esters to undergo rapid and efficient intramolecular *O* → *N* acyl transfer has been used to advantage in a development of great practical importance wherein pseudoephedrine amides are prepared directly from pseudoephedrine and a carboxylic acid ester in a base-catalyzed process. This transformation is believed to occur by an initial base-promoted transesterification reaction of the secondary hydroxyl group of pseudoephedrine followed by intramolecular *O* → *N* acyl transfer. A variety of bases are employed effectively in the reaction, to include sodium methoxide, lithium methoxide, and *n*-butyllithium. As an illustration, treatment of pseudoephedrine (1 equiv) with methyl propionate (2 equiv) and sodium methoxide (0.5 equiv) in THF at 23 °C for 1 h afforded pseudoephedrine propionamide (**1**) in 89% yield after recrystallization of the crude reaction product. Similar procedures have been developed for the preparation of α-hetero pseudoephedrine amides such as pseudoephedrine α-hydroxyacetamide (entry 12, Table 1) and pseudoephedrine glycinamide.[13]

Alkylation of Pseudoephedrine Amide Enolates. Two general procedures for the diastereoselective alkylation of pseudoephedrine amides have been developed. In the first, the alkylation is conducted using excess alkyl halide (procedure A, yield based on enolate), and in the second, excess enolate is used (procedure B, yield based on alkyl halide). Alkylation reactions using the alkyl halide as the limiting reagent are slightly higher yielding than those based on limiting enolate, but the difference is sufficiently minor that the primary consideration in choosing a procedure is the expense and/or availability of the alkyl halide relative to that of the pseudoephedrine amide.

In a typical protocol employing excess alkylating agent (procedure A), a suspension of anhydrous lithium chloride (6.0−7.0 equiv) in THF containing diisopropylamine (2.25 equiv) is treated at −78 °C with a solution of *n*-butyllithium in hexanes (2.1 equiv). The resulting suspension is held at −78 °C for 5 min, and the reaction flask is briefly transferred to an ice bath (5 min) and then cooled to −78 °C. A solution of the pseudoephedrine amide substrate (1 equiv) in THF is added to the cold suspension of lithium diisopropylamide−lithium chloride, and the mixture is held at −78 °C for 30−60 min, then warmed to 0 °C, and held at that temperature for 10−15 min. The enolate suspension is stirred briefly at 23 °C (3−5 min), then cooled to 0 °C, and treated with an alkylating agent (1.5−4.0 equiv). For most substrates, enolization is rapid at 0 °C, and further warming to 23 °C is probably unnecessary, although innocuous, because pseudoephedrine amide enolates generally exhibit good thermal stability at 23 °C ($t_{1/2}$ > 12 h).

Reactions employing excess enolate (procedure B) are conducted similarly, but with 1.3−1.8 equiv of enolate and 1 equiv of electrophile. It is important in these reactions that excess base (LDA) not be used, for many electrophiles are destroyed by the excess base. Typically, we employ 1.9−1.95 equiv of LDA per mole of amide substrate in reactions with excess enolate.

The presence of lithium chloride in the reaction is essential to accelerate the rate of alkylation. In addition, *O*-alkylation of the secondary hydroxyl group of the pseudoephedrine

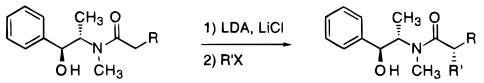
(10) For the use of the acyclic amino alcohol phenylglycinol as a chiral auxiliary, see: (a) Micouin, L.; Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J-C.; Husson, H-P. *Tetrahedron Lett.* **1994**, *35*, 7223. (b) Micouin, L.; Jullian, V.; Quirion, J-C.; Husson, H-P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839.

(11) (a) Schmidt, E.; Calliess, 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.

(12) Myers, A. G.; Yang, B. H. Submitted for publication in *Org. Synth.*

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

Table 2. Diastereoselective Alkylation of Pseudoephedrine Amides



entry	R	R′X[a]	temp (°C)	prod	crude de (%)	isol de (%)	isol yield (%)	mp (°C)
1	CH_3	BnBr	0	**12**	94	≥99[b]	90[b]	136−137
2	CH_3	*n*-BuI	0	**13**	98	≥99[b]	80[b]	66−67
3	CH_3	BOMCl	0	**14**	33	33	77	
4	CH_3	BOMBr	−78	**14**	98	98	80	65−66
5	CH_3	$C_6H_5(CH_2)_2I$	0	**15**	95	95	86	
6	CH_3	$BrCH_2CO_2$-*t*-Bu	−78	**16**	94	96	78	81−82
7	Bn	CH_3I	0	**17**	94	94	99	79−81
8	Bn	CH_3I	−78	**17**	97	97	95	79−81
9	Bn	*n*-BuI	0	**18**	98	98	90	
10	*n*-Bu	CH_3I	0	**19**	94	94	94	
11	*n*-Bu	CH_3I	−78	**19**	96	96	89	
12	*n*-Bu	BnBr	0	**20**	98	≥99[b]	87[b]	120−121
13	Ph	EtI	0	**21**	96	≥99	92	65−66
14	CH_2Bn	CH_3I	0	**22**	95	≥99[c]	92[c]	89−90
15	*i*-Pr	BnBr	0	**23**	98	≥99[b]	83[b]	118−119
16	*t*-Bu	BnBr	0	**24**	98	≥99[b]	84[b]	125−127
17	CH_3[d]	$CH_2{=}CHCH_2I$	−78	**25**	98	99	93	
18	3-pyridyl	$CH_2{=}CHCH_2I$	−78	**26**	98	98	83	109−110
19	2-thiophene[e]	CH_3I	−78	**27**	95	95	88	
20	Cl	BnBr	−45 [f]	**28**	90	≥99[c]	88[c]	155−156
21	CH_3	$I(CH_2)_2OTBS$	0	**29**[g]		97	91	
22	Bn	$I(CH_2)_2OTBS$	0	**30**[g]		≥99	90	
23[a]	CH_3	$I(CH_2)_2OTIPS$	0	**31**		97	89	

[a] All reactions were conducted with excess alkyl halide (1.5−4.0 equiv) except entry 23 where excess enolate (1.9 equiv) was employed. [b] Values for products isolated by a single recrystallization of the crude reaction mixture. [c] Two recrystallizations were conducted. [d] Alkylation of (1*R*,2*R*)-pseudoephedrine propionamide. [e] Alkylation of (1*R*,2*R*)-pseudoephedrine 2-thiopheneacetamide. [f] At temperatures higher than −45 °C, a cyclic byproduct arising from displacement of the chloride is observed. [g] Reference 22.

auxiliary is suppressed in the presence of lithium chloride. At the concentrations of a typical alkylation reaction (∼0.2 M in enolate), the solubility limit of lithium chloride is reached at approximately 5 equiv at 0 °C and 6 equiv at 23 °C. Thus, typical reactions conducted with the recommended 6.0−7.0 equiv of lithium chloride are saturated; use of more than 7 equiv of lithium chloride in the reaction produces no discernible differences in the reaction rate, yield, or diastereoselectivity. Alkylation reactions conducted in the presence of fewer than ∼4 equiv of lithium chloride are markedly slower and typically do not proceed to completion. For example, in the absence of lithium chloride, the reaction of *n*-butyl iodide with the enolate derived from pseudoephedrine propionamide proceeds to the extent of only 32% within 5 h at 0 °C, whereas in the presence of 6 equiv of lithium chloride the alkylation reaction is complete within 1.5 h at 0 °C (80% yield of recrystallized product). Trapping of the same enolate with benzyl bromide proceeds to only 60% completion in the absence of lithium chloride, but affords a 90% yield of recrystallized product in its presence (6 equiv). In neither case was the diastereoselectivity of the alkylation reaction influenced by the presence of lithium chloride in the medium.[14]

It is important to ensure that rigorously anhydrous lithium chloride is employed in the alkylation reaction, for any water of hydration will quench the strong base used in the enolization step. It is recommended that the (highly hygroscopic) anhydrous reagent be flame-dried immediately prior to use followed by cooling under an inert atmosphere at 23 °C.

The role of lithium chloride in the reaction is not known. There is ample precedent in the literature, notably in the work of Seebach and co-workers, documenting the beneficial influence of lithium chloride in enolate alkylation reactions. It has been proposed in these studies that lithium chloride may modify the aggregation state, and thereby the reactivity of an enolate in solution.[15]

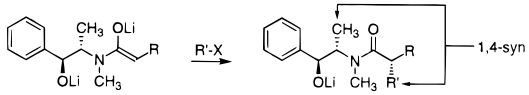


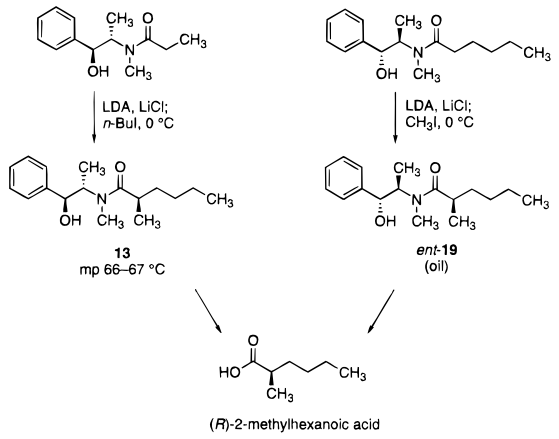
Figure 1. Mnemonic for pseudoephedrine amide enolate alkylation.

(a) Alkylation with Primary Alkyl Halides. Pseudoephedrine amide enolates react efficiently (80−99% yields of purified alkylation products) and highly diastereoselectively (90−98% crude de, 95 to ≥99% isolated de) with a wide variety of primary alkyl halides (Table 2). In every case examined to date, the major product arises from electrophilic attack on the putative (*Z*)-enolate (R syn to the enolate oxygen) from the same face (1,4-syn) as the carbon-bound methyl group of the pseudoephedrine auxiliary when the enolate is drawn in a planar, extended conformation (see Figure 1). Except for entry 23, each of the examples in Table 2 involves a readily available and/or inexpensive alkyl halide and therefore was conducted with limiting enolate (procedure A). Because pseudoephedrine amide enolates are highly nucleophilic, many primary alkyl halides react readily even at −78 °C (e.g., entries 8 and 11). Reactions conducted at −78 °C display slightly enhanced diastereoselectivities versus the same reactions conducted at 0 °C (entries 7 and 10), but reactions conducted at 0 °C are nevertheless highly diastereoselective. Notably, even poorly reactive substrates such as *n*-alkyl and *β*-oxygenated *n*-alkyl halides (entries 2, 9, and 21−23) react efficiently and highly selectively with pseu-

(14) This stands in contrast to the alkylation of the enolate derived from pseudoephedrine glycinamide (ref 9), where the selectivity of the alkylation with ethyl iodide was diminished in the absence of lithium chloride (97% de with lithium chloride versus 82% de without lithium chloride).

(15) (a) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197. (b) Miller, S. A.; Griffiths, S. L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 563. (c) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124.

Scheme 1

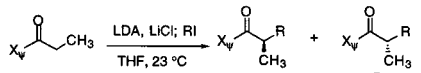


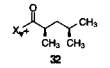
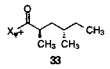
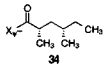
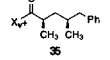
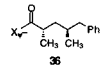
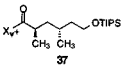
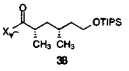
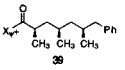
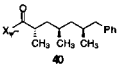
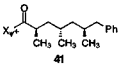
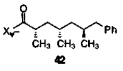
doephedrine amide enolates at 0 °C.[16] Elimination-prone substrates such as (2-iodoethyl)benzene (entry 5) also react efficiently, showing little evidence of elimination. Similarly, the potentially enolizable substrate *tert*-butyl bromoacetate (entry 6) is found to alkylate the enolate derived from pseudoephedrine propionamide in good yield. The electrophile (benzyloxy)-methyl chloride (BOM chloride, entry 3) is singular in that it is found to alkylate pseudoephedrine amide enolates with poor diastereoselectivity (33% de). This poor selectivity is thus far unique to this substrate and may reflect a change in the reaction mechanism, perhaps toward an S_N1-type transition state. The use of BOM bromide as substrate (entry 4) obviates this problem, returning the high diastereoselectivity found with all other alkyl halides used in this study.

A particularly valuable feature of pseudoephedrine as a chiral auxiliary from the standpoint of process chemistry is the crystallinity of its *N*-acyl derivatives; many of the alkylation products are crystalline materials and can be isolated in ≥99% de and >80% yield after recrystallization of the crude reaction products (entries 1−2, 12, 14−16, and 20). Typically, at least one diastereomer within a given diastereomeric pair of alkylation products is crystalline. Thus, by proper choice of the *N*-acyl group, alkyl halide, and the configuration of the pseudoephedrine auxiliary (*d* or *l*), a crystalline product can often be obtained. For example, (*R*)-2-methylhexanoic acid is obtained by the hydrolysis of either diastereomer **13** or *ent*-**19**; however, only **13** is crystalline (Scheme 1). To obtain (*R*)-2-methylhexanoic acid from a crystalline intermediate, (*S*,*S*)-pseudoephedrine propionamide is alkylated with *n*-butyl iodide, followed by acidic hydrolysis (vide infra) of the product **13**.

(b) Alkylation with β-Branched Primary Alkyl Iodides. The superior nucleophilicity and excellent thermal stability of pseudoephedrine amide enolates make possible alkylation reactions at 23 °C with ordinarily unreactive substrates such as β-branched primary alkyl iodides. This is a valuable transformation for it provides a concise route to "skipped" or 1,3-dialkyl-substituted carbon chains, found within many natural products. With chiral β-branched primary iodides, an important issue concerns the degree to which the existing stereocenter within the electrophile will influence the stereoselectivity of the alkylation reaction. In initial studies, the alkylation of both enantiomers of pseudoephedrine propionamide with (*S*)-1-iodo-2-methylbutane was examined. Each reaction was conducted using excess enolate (1.8 equiv)[17] and limiting alkyl iodide (procedure B). As shown by entries 2 and 3 of Table 3, both alkylation reactions were highly selective and efficient, although that producing the 1,3-syn product (entry 3) proceeded with slightly higher diastereoselectivity, suggesting that this represents a "matched" case. These and other findings within Table 3 represent significant advances over existing asymmetric alkylation methodology.

Table 3. Alkylation of Pseudoephedrine Amides with β-Branched Electrophiles



entry	RI[a]	time (h)	product	isol yield (%)	ratio of A : B
1		6	 **32**	89	86 : 1
2		20	 **33**	94	62 : 1
3		18	 **34**	94	1 : 89
4	 **78**	6	 **35**	97	>99 : 1
5	 **78**	7	 **36**	95	1 : 58
6	 **79**	20	 **37**	96	41 : 1
7	 **79**	20	 **38**	94	1 : 73
8	 **80**	18	 **39**	93	142 : 1
9	 **80**	18	 **40**	96	1 : 70
10	 **81**	12	 **41**	93	66 : 1
11	 **81**	18	 **42**	94	1 : 199

[a] Except in entry 1 where 4 equiv of iodide was used (yield based on pseudoephedrine amide), and the alkylation was conducted at 0 °C, all alkylations were conducted at 23 °C and used excess enolate (1.8−2.0 equiv, yield based on alkyl iodide).

As shown within Table 3, extension of the pseudoephedrine enolate methodology provides an iterative process for the synthesis of 1,3,5,*n*(odd)-polyalkyl-substituted carbon chains of any configuration.[18] Thus, treatment of the iodide **78**[19] with 1.8 equiv of the enolate derived from (*S*,*S*)-pseudoephedrine propionamide (**1**) at 23 °C for 6 h afforded the 1,3-syn alkylation product **35** with >99:1 diastereoselectivity and in 97% yield whereas use of the enolate derived from (*R*,*R*)-pseudoephedrine

(16) (a) Imide enolates, by contrast, are essentially inert toward these same substrates (ref 6b). (b) The presence of lithium chloride in the reaction medium did not alter this outcome. Thus, the lithium enolate derived from the imide *N*-propionylbenzyloxazolidinone was found not to react with *n*-butyl iodide at 0 °C in the presence of 10 equiv of lithium chloride after 16 h (Myers, A. G.; Chen, H., California Institute of Technology, unpublished results).

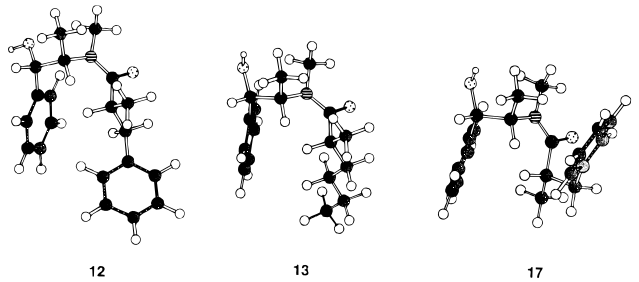
(17) Fewer equivalents of the enolate can be employed. For example, alkylation of 1.3 equiv of the enolate derived from **1** with the iodide **78** at 23 °C for 20.5 h afforded the 1,3-syn alkylation product **35** in 90% yield with 99:1 selectivity (cf. entry 4, Table 3).

(18) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5*, 457.

(19) The iodide **78** was prepared by iodination of the corresponding alcohol, prepared in ≥99% de and 90% yield by LAB reduction (see text) of the alkylation product **12**. For iodination of alcohols, see: (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. (b) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.

propionamide (*ent*-**1**) under identical conditions provided the 1,3-anti product **36** with 58:1 diastereoselectivity and in 95% yield (entries 4 and 5).[17,20] As before, the reaction producing the syn stereochemistry appears to represent a matched case while that producing the anti diastereomer represents a mismatched case, although even the mismatched alkylation reaction is highly selective. Alkylation products **35** and **36** were transformed into the corresponding alcohols by LAB reduction (vide infra), and then to the corresponding iodides in an aggregate yield in excess of 91%. Iodides **80** and **81** were felt to provide a more stringent test of secondary diastereodifferentiating effects in the alkylation reactions. Reaction of the syn iodide **80** (1 equiv) with 1.8 equiv of the enolate derived from **1** afforded the syn,syn alkylation product **39** with 142:1 selectivity and in 93% yield, whereas the enolate derived from *ent*-**1** produced the anti,syn product **40** with only slightly lower selectivity (70:1, 96% yield). Reaction of the anti iodide **81** with 1.8 equiv of the enolate derived from **1** produced the anti,-anti amide **41** with 66:1 selectivity and in 93% yield, whereas the alkylation of the enolate derived from *ent*-**1** proceeded with higher selectivity (199:1) to form the syn,anti product **42** in 94% yield. These results again support the idea that 1,3-syn products represent matched cases and demonstrate convincingly that the high diastereofacial bias of pseudoephedrine amide enolates overrides any secondary effects due to the stereocenter within the alkyl iodide. The diastereoselectivities of the alkylation reactions can be seen to increase with the steric bulk of the alkyl iodide. In addition, the results of Table 3 illustrate the exceptional efficiency of the alkylation reactions when limiting iodide is employed (procedure B), with chemical yields typically exceeding 93%.

(c) Concerning Rotamers and Diastereomeric Ratios. Like most tertiary amides, pseudoephedrine amides exhibit rotational isomerism about the N−C(O) bond and interconversion of isomers is slow on the NMR (^{1}H and ^{13}C) time scale. In one case (substrate **12**), we observed a coalescence temperature of 120 °C (^{1}H NMR at 400 MHz, DMSO) for rotamer interconversion. In solution, the ratio of rotational isomers of pseudoephedrine amides typically varies from 1:1 to 7:1. In all cases, the major rotamer in solution is assigned as that with the *N*-methyl group anti to the carbonyl group on the basis of its shielding relative to the minor isomer.[21] Interestingly, in solid state structures of three pseudoephedrine amides (**12**, **13**, and **17** below)[8] a single rotameric form is present wherein the



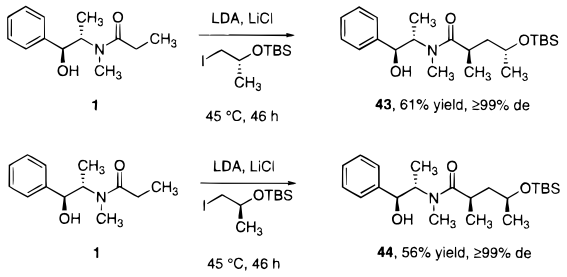
12 13 17

N-methyl group is syn to the carbonyl group, the minor isomer in solution. In a fourth structure (pseudoephedrine glycinamide monohydrate, vide infra)[13] the amide crystallized exclusively as the rotamer with the *N*-methyl group anti to the amide carbonyl. These data reveal the fine balance in energetics between isomers, and the importance of crystal packing forces on the distribution.

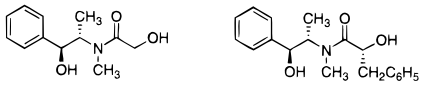
From a practical standpoint, the ^{1}H NMR spectrum of a given pseudoephedrine amide will be complicated by the presence of rotamers, and for this reason diastereomeric ratios are best assigned by capillary GC analysis. Typically, the corresponding trimethylsilyl ether or acetate ester is prepared and analyzed using a Chirasil-Val column (Alltech).

(d) Limitations of the Alkylation Methodology. In testing the limits of pseudoephedrine amide enolate alkylations, we have found that reactions with electrophiles that are both β-alkyl-branched and β-alkoxy-substituted are extremely slow, even at 45 °C. As a consequence, the chemical yields of these transformations (but not reaction diastereoselectivities) suffer (Scheme 2).[22] Similarly, the alkylation of pseudoephedrine amide enolates with secondary alkyl halides such as cyclohexyl bromide and cyclohexyl iodide is exceedingly slow and does not provide a viable route to products of this type.

Scheme 2



Another problematic case we have encountered is the alkylation of pseudoephedrine α-hydroxyacetamide (**11**) and its protected derivatives. Enolization of **11** using 3.2 equiv of LDA at −78 °C was accompanied by partial decomposition of the starting material. By using excess pseudoephedrine α-hydroxyacetamide (1.65 equiv) and limiting benzyl bromide, the *C*-alkylated product **45** was obtained in 84% yield and 82%



11 45

de. This diastereoselectivity is lower than that obtained in benzylations of other pseudoephedrine amide enolates, including the α-heterosubstituted enolates derived from pseudoephedrine glycinamide,[9] chloroacetamide,[8] and fluoroacetamide,[23] and may be related to the fact that the pseudoephedrine α-hydroxyacetamide enolate is a presumed trianion whereas the latter enolates are all dianions. Alkylation reactions of an extensive series of *O*-protected derivatives of pseudoephedrine α-hydroxyacetamide were also examined (TBS, TBDPS, THP, Bn, BOM, Piv, and methyl(1-methoxyethyl)), but none of these provided satisfactory results nor offered any improvement over pseudoephedrine α-hydroxyacetamide itself.

Transformations of Alkylated Pseudoephedrine Amides. The diastereoselective alkylation of pseudoephedrine amide enolates does not constitute a valuable addition to synthetic methodology unless the alkylation products can be transformed into useful materials. For this reason, much of our effort has

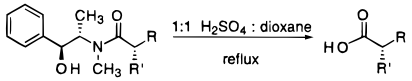
(20) In these and all subsequent alkylation reactions, care was taken to avoid adventitious diastereomeric enrichment upon purification and de values reported reflect those of the crude reaction mixtures.

(21) It has been noted previously that ^{1}H NMR resonances for protons on the *N*-methyl group anti to the carbonyl oxygen of *N*,*N*-dimethyl amides are shifted upfield of resonances corresponding to the protons of the *N*-methyl group syn to the carbonyl oxygen in benzene-d_6 as solvent: (a) Hatton, J. V.; Richards, R. E. *Mol. Phys.* **1960**, *3*, 253. (b) Hatton, J. V.; Richards, R. E. *Mol. Phys.* **1962**, *5*, 139. (c) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *5*, 517.

(22) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(23) Myers, A. G.; McKinstry, L.; Barbay, J. K. Manuscript in preparation.

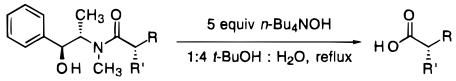
Table 4. Acidic Hydrolysis of Pseudoephedrine Amides



entry	substrate[a]	R	R′	product	isol yield (%)	isol ee or de (%)[b]
1	**12**	CH_3	Bn	**46**	95	97
2	**13**	CH_3	*n*-Bu	**47**	91	97
3	**20**	*n*-Bu	Bn	**48**	94	96
4	**21**	Ph	Et	**49**	96	95
5	**28**	Cl	Bn	**50**	97	95
6	**33**[c]			**51**	80	95
7	**34**[c]			**52**	74	93[d]

[a] The starting material was in all cases of ≥99% de except substrate **33** which was of 97% de, and substrate **34** which was of 98% de. For entry 1, 9 N H_2SO_4 was used; for all others, 18 N H_2SO_4 was employed. [b] Ee's were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amides (entries 1−5), and de's by ^{1}H NMR analysis of the carboxylic acids (entries 6 and 7). [c] See Table 3 for structures. [d] The reaction time was 2 h. If the reaction time was extended to 3 h, the de was found to be 77%.

Table 5. Basic Hydrolysis of Pseudoephedrine Amides



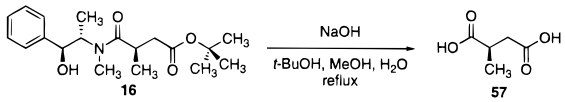
entry	substrate[a]	R	R′	product	isol yield (%)	isol ee or de (%)[b]
1	**12**	CH_3	Bn	**46**	93	94
2	**13**	CH_3	*n*-Bu	**47**	93	97
3	**14**	CH_3	BOM	**53**	92	69
4	**17**	Bn	CH_3	**54**	91	94
5	**18**	Bn	*n*-Bu	**55**	89	82
6	**19**	*n*-Bu	CH_3	**56**	88	93
7	**20**	*n*-Bu	Bn	**48**	90	84
8	**21**	Ph	Et	**49**	82	64
9	**33**[c]			**51**	86	95
10	**34**[c]			**52**	84	95

[a] Substrates **12**, **13**, **20**, and **21** were of ≥99% de, substrates **14**, **18**, and **34** were of 98% de, substrates **17** and **33** were of 97% de, and substrate **19** was of 96% de. [b] Ee's were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amides (entries 1−8), and de's by ^{1}H NMR analysis of the carboxylic acids (entries 9 and 10). [c] See Table 3 for structures.

focused on the development of methods to transform the alkylated amides of Tables 2 and 3 into useful products. Conditions have been developed to transform these alkylated pseudoephedrine amides directly into chiral carboxylic acids, alcohols, aldehydes, and ketones of high enantiomeric excess (ee).[24] Of these, the most challenging transformation was the simple hydrolysis reaction, for which acidic, basic, and slightly acidic metal-mediated conditions have been developed. The choice of a hydrolysis method will be dictated by the substrate and then by consideration of cost and convenience, as outlined below.

(a) Acidic Hydrolysis of Alkylated Pseudoephedrine Amides To Form Carboxylic Acids. For alkylation products that are not acid-sensitive, hydrolysis[11b,c] to the corresponding carboxylic acid can be effected in excellent chemical yield and with little epimerization simply by heating the amide at reflux in a 1:1 mixture of sulfuric acid (9−18 N) and dioxane (Table 4). Under these conditions, the substrate initially undergoes a rapid intramolecular *N* → *O* acyl transfer reaction followed by rate-limiting hydrolysis of the resulting ammonium ester intermediate to the carboxylic acid. Despite the harsh reaction conditions (substrate **14** undergoes decomposition rather than hydrolysis), this method provides a convenient route to a large number of highly enantiomerically enriched carboxylic acids. Even the epimerization-prone benzylic substrate of entry 4 in Table 4 affords the corresponding acid in 95% ee. The pseudoephedrine auxiliary can be recovered from these hydrolyses in excellent yield by a simple extractive workup. Lower concentrations of sulfuric acid have been employed in these hydrolyses without detectable degradation of the product yield or ee, but longer reaction times are required in these cases. Certain substrates are found to undergo detectable epimerization upon prolonged exposure to the reaction conditions (see entry 7, Table 4).

(b) Basic Hydrolysis of Alkylated Pseudoephedrine Amides To Form Carboxylic Acids. Basic conditions for the hydrolysis of pseudoephedrine amides[11b,c] were also developed. The procedure was optimized for the highly epimerizable phenylacetamide substrate **21**. Hydrolyses were conducted using a wide range of hydroxide bases in a variety of solvent systems. The hydrolysis of **21** with 5 equiv of tetra-*n*-butylammonium hydroxide in a mixture of *tert*-butyl alcohol and water (1:4, respectively) at reflux proved to be optimal with respect to reaction time, yield, and product ee. When these conditions were employed for the basic hydrolysis of other alkylated pseudoephedrine amides, results were generally far superior to those observed with the highly epimerizable substrate **21** (Table 5). A convenient workup procedure for these hydrolyses involved acidification with 3 N aqueous hydrochloric acid solution followed by extraction of the product into ether. Tetra-*n*-butylammonium salts were then readily removed by washing the ethereal product solution with water. Where the expense of tetra-*n*-butylammonium hydroxide is a consideration, or in cases where the product carboxylic acid is poorly soluble in ether (making removal of tetra-*n*-butylammonium salts difficult), a second alkaline hydrolysis procedure was developed employing sodium hydroxide (5−8 equiv) as the base in a 2:1:1 mixture of water, methanol, and *tert*-butyl alcohol at reflux. This is an excellent alternative method and was employed, for example, for the hydrolysis of the 2-methylsuccinic acid derivative **16**



16 **57**

74% yield, 94% ee

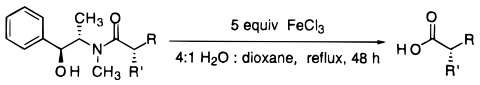
(74% yield, 94% ee), where the poor ether solubility of the product, 2-methylsuccinic acid, precluded the use of tetra-*n*-butylammonium hydroxide as base. For other substrates, this alternative hydrolysis procedure produces products of slightly lower ee as compared to the method employing tetra-*n*-butylammonium hydroxide as base. For example, hydrolysis of substrate **12** with sodium hydroxide in a 2:1:1 mixture of water, methanol, and *tert*-butyl alcohol affords the corresponding acid in 98% yield and 92% ee whereas hydrolysis of **12** with tetra-*n*-butylammonium hydroxide affords the desired acid in 93% yield and 94% ee (entry 1, Table 5).

These basic hydrolysis procedures offer viable alternatives for the hydrolysis of acid-sensitive substrates, but can lead to partial racemization in the hydrolysis of certain substrates (e.g., substrates **14**, **18**, **20**, and **21**, Table 5). In at least one case (entry 10, Table 5), basic hydrolysis proceeds with less epimerization than the acidic hydrolysis method (95% de versus 93% de, respectively).

The mechanism of the base-induced hydrolysis reaction is believed to involve initial rate-limiting intramolecular *N* → *O*

(24) Myers, A. G.; Yang, B. H.; Chen, H. Submitted for publication in *Org. Synth.*

Table 6. Hydrolysis of Pseudoephedrine Amides with $FeCl_3$ in 4:1 Aqueous Dioxane



entry	substrate[a]	R	R′	product	isol yield (%)	isol ee (%)[b]
1	**12**	CH_3	Bn	**46**	94	98
2	**13**	CH_3	*n*-Bu	**47**	85	98
3	**14**	CH_3	BOM	**53**	53	94
4	**20**	*n*-Bu	Bn	**48**	17[c]	99
5	**21**	Ph	Et	**49**	91	92

[a] The starting material was in all cases of ≥99% de except for substrate **14** which was of 98% de. [b] Ee's were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amides. [c] The hydrolysis was not complete at $t = 48$ h.

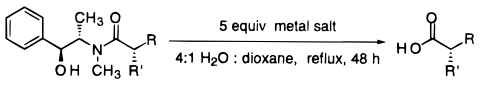
acyl transfer followed by rapid saponification of the resulting β-amino ester intermediate.[11c] As in the acidic hydrolysis protocol, the pseudoephedrine auxiliary may be recovered in high yield from basic hydrolyses, if desired, by a simple extractive isolation procedure.

(c) Efforts To Develop a Milder Hydrolysis Procedure. In an effort to develop milder conditions for the hydrolysis of pseudoephedrine amides, a wide variety of Lewis acidic metal salts was surveyed for the ability to promote the hydrolysis of the benzylated pseudoephedrine propionamide **12**. The first successful metal-promoted hydrolysis of **12** was achieved by heating **12** with 5 equiv of $ZnCl_2$ in a refluxing mixture of aqueous dioxane (1:1, pH 5) for 48 h. (*R*)-α-Methylbenzenepropionic acid was obtained in 90% yield and 83% ee. Further experimentation revealed that the use of $FeCl_3$ in refluxing dioxane (1:1, pH 1) for the hydrolysis afforded (*R*)-α-methylbenzenepropionic in 97% ee, albeit in lower yield (63%, incomplete reaction). Continued study of this system showed that, by increasing the proportion of water in the mixture (4:1 water−dioxane), the yield of the acid was increased to 94% without compromising its ee (95%). These conditions were then employed for the hydrolysis of a series of alkylated pseudoephedrine amides with generally excellent results (Table 6). The sterically hindered substrate **20** did provide an exception (entry 4); its hydrolysis was prohibitively slow under the modified conditions.

A broader survey of Lewis acidic metal salts (see the Supporting Information) failed to provide any candidate offering improved efficiency, rate, and enantioselectivity when compared to $FeCl_3$, although a surprisingly large number of metal salts examined did promote the hydrolysis of **12**. Two noteworthy alternatives revealed in this survey were the use of $ZrOCl_2$ or $Yb(OTf)_3$ (5 equiv each) in refluxing aqueous dioxane (4:1). The use of these metal salts for the hydrolysis of a series of pseudoephedrine amides is summarized in Table 7. Results were generally quite good, and particularly so in the case of the sensitive benzyl ether **14**.

The long reaction times required in these metal-mediated hydrolyses (typically 48 h) prompted us to continue our search for an alternative mild hydrolysis method. Our goal in this effort was to take advantage of the rapid $N \rightarrow O$ acyl transfer observed in the Lewis acid-promoted hydrolysis reaction while nucleophilic hydroxide was introduced for the rapid hydrolysis of the resulting ester without inducing reversion to the amide by $O \rightarrow N$ acyl transfer. The key to accomplishing this involved the in situ formation of a stable amine−borane complex by the addition of lithium borohydride to the $N \rightarrow O$ acyl transfer intermediate. The sequence of $N \rightarrow O$ acyl transfer, borane complexation, and saponification (Scheme 3) was conducted in a one-pot

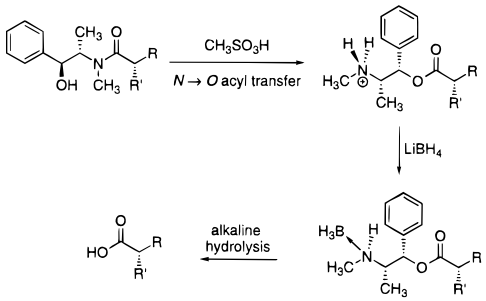
Table 7. Hydrolysis of Pseudoephedrine Amides using $Yb(OTf)_3$ or $ZrOCl_2$ in 4:1 Aqueous Dioxane



entry	substrate[a]	R	R′	metal salt	product	isol yield (%)	isol ee (%)[b]
1	**12**	CH_3	Bn	$ZrOCl_2$	**46**	92	97
2	**12**	CH_3	Bn	$Yb(OTf)_3$	**46**	91	95
3	**13**	CH_3	*n*-Bu	$ZrOCl_2$	**47**	92	99
4	**13**	CH_3	*n*-Bu	$Yb(OTf)_3$	**47**	73	98
5	**14**	CH_3	BOM	$ZrOCl_2$	**53**	72	97
6	**14**	CH_3	BOM	$Yb(OTf)_3$	**53**	92	94
7	**21**	Ph	Et	$ZrOCl_2$	**49**	90	93
8	**21**	Ph	Et	$Yb(OTf)_3$	**49**	69	82

[a] The starting material was in all cases of ≥99% de except **14** which was of 98% de. [b] Ee's were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amides.

Scheme 3

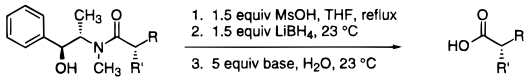


procedure, as follows. A solution of the pseudoephedrine amide substrate in THF was heated at reflux with 1.5 equiv of methanesulfonic acid until complete $N \rightarrow O$ acyl transfer had occurred, as determined by thin-layer chromatographic analysis (typically 1−3 h). The mixture was then cooled to 23.°C, and 1.5 equiv of lithium borohydride (2.0 M in THF) was added to form the amine−borane complex. The reaction mixture was diluted with an equal volume of water, and 5 equiv of sodium hydroxide or tetra-*n*-butylammonium hydroxide was added as base. The mixture was stirred at 23 °C until the hydrolysis was complete. Results for the hydrolysis of several pseudoephedrine amide substrates employing this procedure are summarized in Table 8. Although sodium hydroxide-promoted hydrolyses are slower, typically requiring 8 h versus 1 h in the tetra-*n*-butylammonium hydroxide system, the workup procedure is more convenient. On the other hand, for sterically congested substrates (e.g., substrate **20**), use of the more reactive tetra-*n*-butylammonium hydroxide base is necessary.

(d) Reduction of Pseudoephedrine Amides To Form Primary Alcohols. The transformation of pseudoephedrine amides into the corresponding primary alcohols may be considered as a special case within the broader problem of the selective reduction of tertiary amides. In general, the addition of hydride to the carbonyl group of a tertiary amide affords a tetrahedral intermediate that partitions between CN bond cleavage (leading to the primary alcohol via the aldehyde) and CO bond cleavage (leading to the formation of a tertiary amine byproduct via an imminium intermediate, Figure 2). This partitioning is highly sensitive to the reaction medium and the nature of the counterion "M". Typical metal hydride reagents such as lithium aluminum hydride[25] and diborane[26] favor the

(25) (a) Uffer, H.; Schlittler, E. *Helv. Chim. Acta* **1948**, *31*, 1397. (b) Gaylord, N. G. *Reductions with Complex Metal Hydrides*; Wiley-Interscience: New York, 1956; pp 544−592. (c) Zabicky, J., Ed. *The Chemistry of Amides*; Wiley-Interscience: New York, 1970; pp 795−801.

Table 8. Mild Hydrolysis of Pseudoephedrine Amides Involving in Situ Borane−Amine Complexation



entry	substrate[a]	R	R′	*N* → *O* acyl transfer time (h)	base[b]	product	isol yield (%)	isol ee (%)[c]
1	**12**	CH_3	Bn	1	NaOH	**46**	94	98
2	**12**	CH_3	Bn	1	*n*-Bu_4NOH	**46**	91	98
3	**13**	CH_3	*n*-Bu	1	NaOH	**47**	84	99
4	**13**	CH_3	*n*-Bu	1	*n*-Bu_4NOH	**47**	75	98
5	**14**	CH_3	BOM	1	NaOH	**53**	96	93
6	**14**	CH_3	BOM	1	*n*-Bu_4NOH	**53**	87	93
7	**20**	*n*-Bu	Bn	1.5	NaOH	**48**	—[d]	—[d]
8	**20**	*n*-Bu	Bn	1.5	*n*-Bu_4NOH	**48**	84	97
9	**21**	Ph	Et	3	NaOH	**49**	89	83
10	**21**	Ph	Et	3	*n*-Bu_4NOH	**49**	88	84

[a] The starting material was in all cases of ≥99% de except for **14** which was of 98% de. [b] Saponifications employing NaOH as base were conducted for 8 h, except in entry 3, which was conducted for 16 h, and in entry 7, which was conducted for 48 h. Saponifications employing *n*-Bu_4NOH as base were conducted for 1 h. [c] Ee's were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amides. [d] Hydrolysis was not complete even after 48 h at 23 °C.

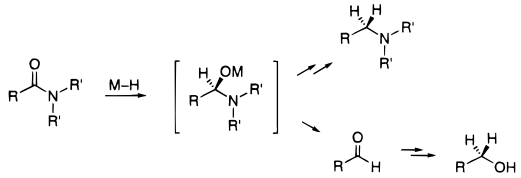
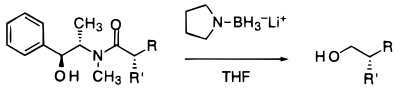


Figure 2. Divergent pathways for tertiary amide reductions.

formation of the tertiary amine byproduct. Important exceptions to this trend include the reagents lithium triethylborohydride ($LiBHEt_3$, "superhydride")[27] and 9-BBN,[28] developed by Brown and co-workers, and metal amide-borane complexes, introduced by Hutchins et al.[29] and extensively developed by Singaram and co-workers.[30] Pseudoephedrine amides were found to be inert toward superhydride and 9-BBN. As we reported in our initial communication,[8] the lithium pyrrolidide−borane reagent (lithium pyrrolididotrihydroborate, $Li(CH_2)_4NBH_3$, LPT) of Singaram et al.[30] is effective in transforming certain pseudoephedrine amides into the corresponding primary alcohols selectively and in high yield (Table 9). Subsequently, however, we have encountered difficulties with this reagent in several problematic cases (e.g., entries 3, 7, and 9 within Table 9). For example, the α-(benzyloxy)methyl-substituted amide **14** suffered partial decomposition during the reduction and the α-phenylacetamide substrate **21** provided the primary alcohol **64** in only 33% ee, with inverted configuration! In both cases, the problems encountered were attributed to base-induced epimerization (decomposition) of the intermediate aldehydes. The inverted configuration of the product **64** is believed to arise from enolization of the intermediate aldehyde by a chiral, pseudoephedrine-derived base, followed by enantioselective protonation and reduction. In addition to these examples, highly sterically hindered substrates such as **24** were found to be essentially inert to LPT. We have since reported the development of a new reagent, lithium amidotrihydroborate (LiH_2NBH_3, LAB),[31] that lacks the problematic features of LPT. In that initial report, LAB was prepared by the deprotonation of the commercial solid reagent, borane−ammonia complex,[32] using slightly less than 1 equiv of *n*-butyllithium as base at 0 °C. In more recent work, we have substantially improved the reagent preparation by the use of 1 equiv of lithium diisopropylamide (LDA) as the base in the reaction.[18] The efficiency of the reduction is greater using LDA as the base, and notably, the product is isolated with much greater facility. Difficulties encountered when *n*-butyllithium was used as base were traced to the formation of butylboron intermediates in the reaction (particularly in large-scale experiments) and, ultimately, butylboron alkoxide products that were difficult to hydrolyze. This problem could be largely circumvented by conducting the deprotonation with *n*-butyllithium at −78 °C or, preferably, could be completely avoided by deprotonation with LDA at 0 °C followed by warming to 23 °C. In the optimized procedure, solid borane−ammonia complex (4.0 equiv) is added to a solution of LDA (3.9 equiv) in THF at 0 °C, and the resulting suspension is warmed to 23 °C and held at that temperature for 15−20 min. The cloudy suspension of LAB is then cooled to 0 °C, and a solution of

Table 9. Reduction of Pseudoepedrine Amides with Borane−Lithium Pyrrolidide (LPT) to Form Primary Alcohols



entry	substrate[a]	R	R′	product	temp (°C)	time (h)	isol yield (%)	isol ee (%)[b]
1	**12**	CH_3	Bn	**58**	23	6.0	84	≥95
2	**13**	CH_3	*n*-Bu	**59**	23	10.0	81	≥95
3	**14**	CH_3	BOM	**60**	0	3.0	45	91
4	**17**	Bn	CH_3	**61**	23	10.3	87	≥95
5	**18**	Bn	*n*-Bu	**62**	23	3.1	88	≥95
6	**20**	*n*-Bu	Bn	**63**	23	5.8	89	≥95
7	**21**	Ph	Et	**64**	23	14.0	87	33[c]
8	**23**	*i*-Pr	Bn	**65**	66	11.0	80	≥95
9	**24**	*t*-Bu	Bn	**66**	66	12.0	5	—

[a] The starting material was in all cases of ≥99% de except **14** and **18** which were of 98% de, and **17** which was of 97% de. [b] Ee's were determined by ^1H NMR analysis of the corresponding Mosher ester derivatives. [c] The predominating enantiomer had inverted configuration relative to the starting material (**21**).

(26) (a) Brown, H. C.; Heim, P. *J. Am. Chem. Soc*. **1964**, *86*, 3566. (b) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441. (c) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996.

(27) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635.

(28) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem*. **1976**, *41*, 1778.

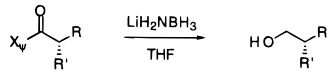
(29) Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem*. **1984**, *49*, 2438.

(30) (a) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett*. **1992**, *33*, 4533. (b) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett*. **1993**, *34*, 1091. (c) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.

(31) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett*. **1996**, *37*, 3623.

(32) (a) Andrews, G. C.; Crawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 693. (b) Andrews, G. C.; Crawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 697.

Table 10. Reduction of Pseudoephedrine Amides with Lithium Amidotrihydroborate (LAB) To Form Primary Alcohols



entry	substrate (de, %)	R	R′	product	temp (°C)	time (h)	isol yield (%)	isol ee or de (%)[a]
1	**12** (≥99)	CH_3	Bn	**58**	23	1.0	90	≥99
2	**14** (98)	CH_3	BOM	**60**	0	1.3	86	95
3	**20** (≥99)	*n*-Bu	Bn	**63**	23	2.5	92	≥95
4	**21** (≥99)	Ph	Et	**64**	23	1.9	83	92
5	**23** (≥99)	*i*-Pr	Bn	**65**	23	18	86	≥95
6	**24** (≥99)	*t*-Bu	Bn	**66**	66	10	92	≥95
7	*ent*-**31** (97)	CH_2CH_2OTIPS	CH_3	**67**	23	1	91	≥95
8	**33** (97)[b]			**68**	23	2	78[c]	97
9	**34** (98)[b]			**69**	23	2	79[c]	98
10	**35** (98)[b]			**70**	23	2	95	98
11	**36** (97)[b]			**71**	23	2	96	96
12	**37** (95)[b]			**72**	23	1	98	95
13	**38** (98)[b]			**73**	23	1	98	97
14	**39** (99)[b]			**74**	23	2	93	99
15	**40** (97)[b]			**75**	23	2	93	97
16	**41** (97)[b]			**76**	23	2	91	97
17	**42** (99)[b]			**77**	23	2	89	99

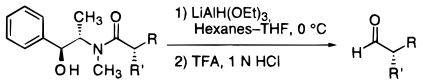
[a] The ee in entry 1 was determined by chiral HPLC (Chiralcel OD). Ee's in entries 2−7 were determined by ^{1}H NMR analysis of the corresponding Mosher ester derivatives. De's in entries 8−17 were determined by chiral capillary GC analysis of the corresponding acetate esters or trimethylsilyl ethers. [b] See Table 3 for structures. [c] The yield was lowered due to the volatility of the product.

the pseudoephedrine amide substrate (1 equiv) in THF is added. Typical reductions proceed to completion within a few hours at 23 °C, although more hindered substrates (entry 6, Table 10) may require heating to reflux (66 °C). When the reduction is complete, an acidic aqueous workup procedure provides a mixture of the desired alcohol and a (different) alkoxyboron species. Fortunately, this alkoxyboron species is exceedingly labile toward silica gel and undergoes quantitative cleavage to the alcohol during flash column chromatographic purification. Where flash column chromatography is not an acceptable means of purification (e.g., on large scale, where distillation of the alcohol might be preferable), the alkoxyboron species can be cleaved rapidly and quantitatively by treatment with 1 N aqueous sodium hydroxide solution at 23 °C for 30−60 min.

This modified LAB reduction procedure has proven to be highly effective for the synthesis of a wide variety of highly enantiomerically enriched primary alcohols from the corresponding pseudoephedrine amide precursors. As evident from the examples of Table 10, little to no epimerization of the α-stereocenter is observed. Generally, <4% of the tertiary amine byproduct is produced if care is taken to use at least 4 molar equiv of LAB in the reaction. Tertiary amine formation can be more extensive if less reductant is employed.[31] The tertiary amine generally exhibits an R_f value comparable to that of the product alcohol and is most conveniently removed by extraction with aqueous acid. When an acid wash is not desirable (for acid-sensitive substrates or for tertiary amine hydrochlorides that are not water soluble), the tertiary amine byproduct can be readily separated by flash column chromatography using triethylamine-pretreated silica gel.

Reductions of pseudoephedrine amides with LAB are much more rapid than reductions with LPT. For example, LAB reduction of substrate **12** occurs in 1 h at 23 °C (90% yield) whereas LPT reduction of **12** requires 6 h at 23 °C (84% yield). In addition, LAB appears to have a lesser tendency to effect base-induced side reactions compared to LPT. As a result, highly epimerizable aldehyde intermediates can be traversed without substantial loss of stereochemical integrity. For example, reduction of the α-(benzyloxy)methyl-substituted amide **14** (98% de) with LAB formed the corresponding alcohol in 86% yield and 95% ee and reduction of the phenylacetamide **21** (≥99% de) with LAB provided (*S*)-2-phenyl-1-butanol in 83% yield and 92% ee. In addition, LAB is found to be far superior to LPT for the reduction of sterically hindered amides. Thus, the substrate **23** was found to be inert to LPT at 23 °C but was cleanly reduced with LAB at 23 °C (entry 5, Table 10, 86% yield of alcohol, ≥95% ee). More dramatically, the highly hindered substrate **24** proved to be virtually inert toward LPT, even in refluxing THF (Table 9, entry 9, 12 h, 5% yield), but was readily reduced with LAB (Table 10, entry 6, 10 h, 66 °C, 92% yield, ≥95% ee).

Table 11. Reduction of Pseudoephedrine Amides with $LiAlH(OEt)_3$ To Form Aldehydes



entry	substrate[a]	R	R′	product	time (h)	isol yield (%)	isol ee (%)
1	**12**	CH_3	Bn	**82**	1.0	76	95
2	**13**	CH_3	*n*-Bu	**83**	1.1	75[b]	98
3	**17**	Bn	CH_3	**84**	1.2	77	94
4	**18**	Bn	*n*-Bu	**85**	0.8	80	97
5	**20**	*n*-Bu	Bn	**86**	0.8	82	97
6	**21**	Ph	Et	**87**	0.9	80	90

[a] The starting material was in all cases of ≥99% de except **17** which was of 97% de, and **18** which was of 98% de. [b] Yield was based on capillary GC analysis.

(e) Reduction of Pseudoephedrine Amides To Form Aldehydes. One of the most valuable transformations of pseudoephedrine amides is their direct conversion to highly enantiomerically enriched aldehydes using Brown and Tsukamoto's lithium triethoxyaluminum hydride reagent.[33] This reagent is produced in situ from the reaction of 1 molar equiv of lithium aluminum hydride with 1.5 molar equiv of ethyl acetate and affords aldehydes of 90−98% ee (75−82% yield, Table 11) from the corresponding pseudoephedrine amides.

In the optimum procedure, 1 equiv of a pseudoephedrine amide is added as a solution in THF to a cold (−78 °C) suspension of the lithium triethoxyaluminum hydride reagent (2.3 equiv) in hexanes. The reaction mixture is warmed to 0 °C and stirred at that temperature for 0.8−1.2 h followed by

(33) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc*. **1964**, *86*, 1089.

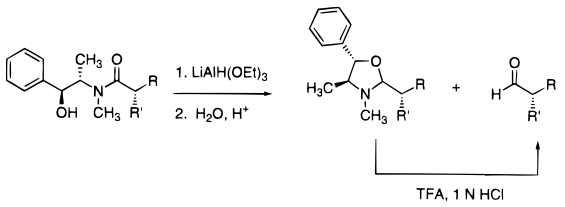


Figure 3. Generation and cleavage of pseudoephedrine aminals.

quenching. The ratio of the solvents hexanes and THF was found to be an important variable; mixtures containing less than 60% by volume of hexanes led to greater degrees of overreduction (to the primary alcohol) and tertiary amine formation. In addition, the successful generation of the alkoxyaluminum hydride reagent was found to be quite sensitive to the quality of the lithium aluminum hydride reagent. According to the reaction stoichiometry, a 10% underestimation of the content of lithium aluminum hydride results in a 40% decrease in the amount of active hydride produced. Commercial stock solutions of lithium aluminum hydride proved to be unreliable for the preparation of lithium triethoxyaluminum hydride. Optimal results were achieved when anhydrous ethyl acetate was added slowly (ca. 1−2 h) to an ice-cooled suspension of solid lithium aluminum hydride (stored and transferred under nitrogen) in anhydrous hexanes.

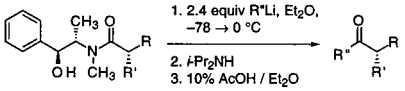
Quenching of the reaction mixture with a dilute solution of aqueous acid (e.g., 0.5 N aqueous hydrochloric acid solution) afforded a mixture of the desired aldehyde and a pseudoephedrine aminal byproduct in a ratio ranging from 1:1 to 5:1, respectively, depending upon the substrate (Figure 3).[34] By quenching the reaction with stronger acid (10 equiv of trifluoroacetic acid in 1 N aqueous hydrochloric acid solution), complete conversion of the aminal byproduct to the desired aldehyde was achieved. Only in rare instances did trace amounts of aminal (1−2%) remain after this workup procedure. Although inappropriate for acid-sensitive substrates, this protocol was nevertheless quite effective for the preparation of a number of highly enantiomerically enriched aldehydes. Ee's of 94−98% are possible, and even the highly racemization-prone aldehyde **87** was isolated in 90% ee.

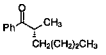
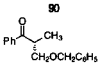
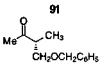
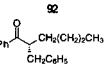
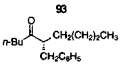
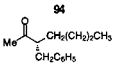
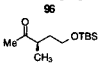
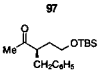
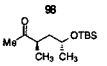
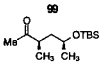
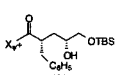
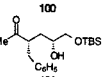
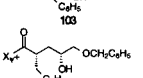
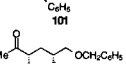
(f) Addition of Alkyllithium Reagents to Pseudoephedrine Amides To Form Enantiomerically Enriched Ketones. It has long been known that tertiary carboxamides can be transformed into ketones in one step by the addition of an organolithium reagent followed by an aqueous workup.[35] The success of this reaction relies upon the formation of a stable tetrahedral intermediate which breaks down upon workup to release the ketone. If breakdown of this intermediate occurs prior to workup, the liberated ketone can further react to give a tertiary alcohol byproduct. The protocol developed to transform alkylated pseudoephedrine amides into ketones was optimized to avoid premature breakdown of the tetrahedral intermediate.

In a typical procedure, 2.4 equiv of an organolithium reagent is added to an ethereal solution (or suspension) of the amide at −78 °C followed by warming of the reaction mixture to 0 °C. Addition of the organolithium reagent to the carbonyl group does not occur until the mixture is warmed. By conducting the initial addition at −78 °C, however, complete deprotonation of the secondary hydroxyl group of the pseudoephedrine auxiliary is ensured, thus preventing premature breakdown of the tetrahedral intermediate. Typically, the addition reaction is complete within a few minutes of warming to 0 °C. To quench the reaction, excess alkyllithium is first scavenged by the addition of diisopropylamine, and then the tetrahedral intermediate is decomposed by the addition of a solution of acetic acid in ether (10% v/v).

As shown by the results of Table 12, the ketone products are generally obtained in excellent yields and with little to no epimerization of the α-stereocenter. In the case of substrate **14** (entries 4 and 5), competing β-elimination of benzyl alcohol attenuated the product yield somewhat, and in the case of substrate **21** (entry 9), the kinetic acidity of the benzylic proton lowered both the yield and ee of the product due to competing enolization.

Table 12. Reaction of Pseudoephedrine Amides with Organolithium Reagents To Form Ketones



entry[a]	substrate	R"	product	isol yield (%)	isol ee or de (%)[b]
1	**12**	Ph	 **88**	94	≥95
2	**12**	*n*-Bu	 **89**	89	≥95
3	**13**	Ph	 **90**	93	≥95
4	**14**	Ph	 **91**	64	≥95
5	**14**	Me	 **92**	68	95
6	**20**	Ph	 **93**	96	≥95
7	**20**	*n*-Bu	 **94**	94	≥95
8	**20**	Me	 **95**	98	≥95
9	**21**	Me	 **96**	54	88
10[c]	**29**	Me	 **97**	89[d]	≥95[d]
11[c]	**30**	Me	 **98**	92[d]	≥95[d]
12[c]	**43**[e]	Me	 **99**	92	97
13[c]	**44**[e]	Me	 **100**	90	96
14[c]	 **103**	Me	 **101**	97[d]	≥95[d]
15[c]	 **104**	Me	 **102**	90[d]	≥95[d]

[a] The starting material was in all cases of ≥99% de except **14** which was of 98% de and **29** which was of 97% de. [b] Ee's were determined by ^{1}H NMR analysis of the Mosher ester derivatives of the corresponding secondary alcohols (entries 1−9) or desilylated ketones (entries 10 and 11). De's in entries 12 and 13 were determined by chiral capillary GC analysis of the acetate esters of the desilylated ketones. [c] 2.5 equiv of MeLi was used in entries 10 and 11, 3.5 equiv in entries 12 and 13, 5.0 equiv in entry 14, and 4.0 equiv in entry 15. [d] Reference 22. [e] See Scheme 2 for structures.

(34) In all cases, the pseudoephedrine aminal was found to be a single diastereomer, of undetermined stereochemistry.

(35) (a) Evans, E. A. *J. Chem. Soc.* **1956**, 4691. (b) Evans, E. A. *Chem. Ind. (London)* **1957**, 1596. (c) Izzo, P. T.; Safir, S. R. *J. Org. Chem.* **1959**, *24*, 701.

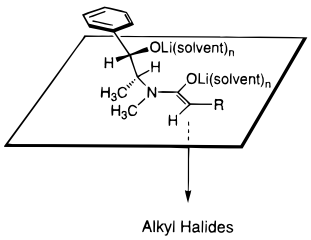


Figure 4. Proposed reactive conformation of pseudoephedrine amide enolates.

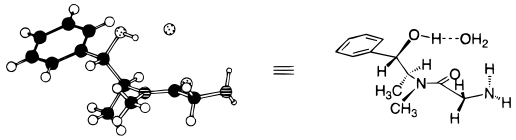


Figure 5. Crystal structure of pseudoephedrine glycinamide monohydrate.

Basis for Selectivity in Pseudoephedrine Amide Enolate Alkylations. Our efforts to discern the basis for the high diastereoselectivities in the alkylation of pseudoephedrine amide enolates have been limited by a paucity of physical data concerning the conformations of these enolates in solution or in the solid state. In spite of the generally high crystallinity of pseudoephedrine amides, in no case have we been successful in crystallizing a pseudoephedrine amide enolate, despite extensive effort. Similarly, attempts to gain solution structural information by NMR spectroscopy of pseudoephedrine amide enolates have been complicated by poor line shape and highly complex spectra. The structural similarity between pseudoephedrine amides and prolinol amides (both are amides of 2-amino alcohols) and the observation that, in both systems, alkyl halides and epoxides exhibit opposite diastereoselectivity in alkylation reactions[22,36] suggest that the origin of selectivity in the two systems may be similar. Askin et al. have suggested that the alkoxy group of prolinol amide enolates may direct the alkylation reaction in the case of epoxide electrophiles, and provide a steric blockade in reactions with alkyl halides.[36] A similar rationale may explain the selectivity of pseudoephedrine amide enolate alkylations if a reactive conformer such as that shown in Figure 4 is invoked. In this conformation, the lithium alkoxide and, perhaps more importantly, the solvent molecules (tetrahydrofuran and possibly diisopropylamine) associated with the lithium cation are proposed to block the β-face of the (*Z*)-enolate, forcing the alkylation to occur from the α-face. 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.[37] The positioning of the secondary alkoxide on the β-face of the enolate may also benefit from extended coordination of the oxyanions with one or more lithium cations. The feasibility of such a staggered conformer is supported by the X-ray crystal structure of pseudoephedrine glycinamide hydrate (Figure 5),[13] wherein allylic and torsional strain is minimized, and the secondary hydroxyl group is disposed on the β-face of the plane defined by the amide bond linkage. Although the proposed model provides a rationale for the observed selectivity, it should be noted that several important features of the actual transition structure of the enolate have been neglected such as its aggregation state, rotameric distribution, state of ionization, and the degree of pyramidalization of nitrogen, as well as the bond-breaking and bond-forming trajectories.

In the context of this discussion of the diastereoselectivity of pseudoephedrine amide enolate alkylations, it is interesting to note that the use of ephedrine, the diastereomer of pseudoephedrine, as a chiral auxiliary in amide enolate alkylations proves markedly inferior from a number of standpoints. The use of ephedrine as a chiral auxiliary was described more than 15 years ago and, as outlined in that work, entailed the use of the carcinogenic cosolvent HMPA in the alkylation reactions.[38] In addition, difficulties in transforming the alkylated ephedrine amides into useful products were reported. We have reinvestigated the alkylation of ephedrine amides using the protocol described above for pseudoephedrine amide enolate alkylations (employing lithium chloride as an additive) and have found these alkylations to exhibit only modest diastereoselectivity.[39] In addition, ephedrine amides lack the desirable process features of pseudoephedrine amides; they are typically oils.

Conclusion

Pseudoephedrine has been documented to be a highly practical chiral auxiliary for asymmetric alkylation reactions. The enolates of pseudoephedrine amides undergo efficient and highly diastereoselective alkylation reactions with a wide variety of alkyl halides, and a broad range of cleavage reactions allow for the conversion of the alkylated products into highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones. In addition, the low cost of the auxiliary, the crystallinity of many of the starting materials and products, and the fact that carcinogenic cosolvents are not required make the reported procedures amenable to large-scale and process applications.

Experimental Section

General Procedures. All nonaqueous reactions were performed under a positive pressure of argon, unless otherwise noted. Flash column chromatography was performed as described by Still et al.[40] employing 230−400 mesh silica gel.

Materials. Tetrahydrofuran and ether were distilled under nitrogen from sodium−benzophenone ketyl. Dichloromethane, diisopropylamine, triethylamine, chlorotrimethylsilane, acetonitrile, pyrrolidine, and toluene were distilled under nitrogen from calcium hydride. Lithium chloride was dried under vacuum at 150 °C for 24 h and then stored under a nitrogen atmosphere or alternatively flame-dried under vacuum immediately prior to use. Benzyl bromide, iodomethane, isobutyl iodide, and (2-iodoethyl)benzene were passed through basic alumina immediately prior to use. Allyl iodide and ethyl iodide were washed with aqueous sodium thiosulfate solution, dried over potassium carbonate, and passed through basic alumina immediately prior to use. The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[41] Ethyl acetate and hexanes used in the generation of lithium triethoxyaluminum hydride were distilled from calcium hydride at atmospheric pressure. Sodium methoxide, borane−ammonia complex, and lithium aluminum hydride were stored and transferred under nitrogen.

BOMBr and BOMCl were prepared according to the literature procedure.[42] 2-Iodo-[(1-triisopropylsilyl)oxy]ethanol was prepared by

(36) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245.

(37) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(38) (a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, 3961. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5.

(39) For example, enolization of ephedrine propionamide (1 equiv) with LDA (2.1 equiv) in the presence of lithium chloride (6 equiv), as described for pseudoephedrine propionamide, and addition of *n*-butyl iodide at 0 °C afforded a diastereomeric mixture of alkylation products (70% de, configuration not determined) in 90% yield after purification by flash column chromatography.

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(41) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(42) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Syntheses*; Collect. Vol. VI, Wiley: New York, 1988; p 101.

silylation[43] of 2-iodoethanol with triisopropylsilyl chloride (1.3 equiv), imidazole (2.6 equiv), and 4-(dimethylamino)pyridine (0.5 equiv) in dichloromethane at 23 °C for 4.3 h.

Instrumentation. Chiral capillary gas chromatography (GC) analysis was carried out using a 25 m × 0.25 mm i.d. Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi.

Determination of Absolute Stereochemistry of Alkylation Products. The structures of alkylation products **12**, **13**, and **17** were determined by X-ray crystallographic analysis. Product **14** was transformed by LAB to the known (*S*)-2-methyl-1,3-propanediol benzyl ether.[6b] Both (*R*)- and (*S*)-Mosher ester derivatives[44] of this alcohol were prepared and were identified conclusively by comparison with ^{1}H NMR data from authentic materials.[6b] Products **18** and **20** form a diastereomeric pair. Their hydrolysis produces enantiomeric acids whose configuration was established by comparison of the respective optical rotations to literature values of the known (*R*)-2-benzylhexanoic acid.[45] Products **13** and **19** form a diastereomeric pair; because the configuration of **13** was secured by X-ray analysis, that of **19** is defined unambiguously. Acidic hydrolysis of amide **21** produces 2-phenylbutyric acid, which was coupled with (*R*)-(α-methylbenzyl)amine as described below for acid **46**. The resulting (*R*)-α-methylbenzyl amide was shown to be identical to the (*R*)-α-methylbenzyl amide of commercially available (*S*)-2-phenylbutyric acid by chiral capillary GC analysis. Treatment of α-chloride **28** with sodium azide (1.1 equiv) in *N*,*N*-dimethylformamide at 0 °C, followed by reduction with triphenylphosphine (2 equiv) in THF at 23 °C, formed a phenylalanine derivative (with inversion) which was hydrolyzed (sulfuric acid, dioxane, reflux) to form L-phenylalanine. Comparisons with the authentic antipodes of phenylalanine were made by HPLC using a Crownpak CR (+) column. In each of these cases, the major pseudoephedrine alkylation product results from electrophilic attack on the putative (*Z*)-enolate (R syn to the enolate oxygen) from the same face as the carbon-bound methyl group of pseudoephedrine when it is drawn in its extended conformation. The remaining alkylation reactions were assumed to proceed analogously.

Synthesis of Pseudoephedrine Amides: (*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide (1). (a) Acylation with Propionic Anhydride. A 1-L flask was charged with (+)-pseudoephedrine (21.0 g, 127 mmol, 1 equiv), triethylamine (21.3 mL, 153 mmol, 1.20 equiv), and dichloromethane (250 mL). The flask was placed in a water bath at 23 °C, and propionic anhydride (17.4 mL, 136 mmol, 1.07 equiv) was added to the solution in 1-mL portions over several minutes. The reaction mixture was stirred for 30 min at 23 °C, and then excess anhydride was quenched by the addition of water (40 mL). The organic layer was separated and extracted with half-saturated aqueous sodium bicarbonate solution (2 × 40 mL) and 1 N aqueous hydrochloric acid solution (2 × 40 mL). The organic extract was dried over sodium sulfate and concentrated to furnish a white solid. Recrystallization of the product from hot toluene (110 °C, 85 mL) furnished amide **1** as a white crystalline solid (26.9 g, 95%): mp 114−115 °C; ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, C_6D_6) δ 6.95−7.45 (m, 5H), 4.83 (br, 1H), 4.51 (t, 1H, J = 7.2 Hz), 4.1 (m, 1H), 3.68* (m, 1H), 2.77* (s, 3H), 2.40* (m, 2H), 2.06 (s, 3H), 1.73 (m, 2H), 1.22* (t, 3H, J = 7.3 Hz), 0.9−1.1 (m, 6H), 0.53* (d, 3H, J = 6.7 Hz); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 175.8, 174.8*, 142.2, 141.5*, 128.3*, 128.1, 127.9*, 127.4, 126.7*, 126.3, 76.1, 75.0*, 58.1, 57.7*, 32.1, 27.3, 26.6*, 15.2*, 14.2, 9.4*, 9.0; FTIR (neat, cm^{-1}) 3380 (br, m, OH), 1621 (s, C═O); HRMS (FAB) calcd for $C_{13}H_{20}NO_2$ $(MH)^+$ 222.1495, found 222.1490. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.62; H, 8.36; N, 6.34.

(b) Acylation with Methyl Propionate. A 250-mL round-bottomed flask was charged with sodium methoxide (2.7 g, 50 mmol, 0.50 equiv), (+)-pseudoephedrine (16.5 g, 100 mmol, 1 equiv), and tetrahydrofuran (100 mL). This mixture was stirred at 23 °C until the solids had dissolved to give a slightly cloudy, pale yellow solution (ca. 10 min). Methyl propionate (19.2 mL, 200 mmol, 2.00 equiv) was then added, and the resulting mixture was stirred for 1 h at 23 °C. The mixture was partitioned between 1 N aqueous hydrochloric acid solution (150 mL) and dichloromethane (150 mL), and the aqueous layer was separated and extracted with dichloromethane (150 mL). The combined organic layers were washed with water (150 mL), then dried over sodium sulfate, and concentrated to furnish an off-white solid. Recrystallization of the product from hot toluene (110 °C, 30 mL) furnished amide **1** as a white crystalline solid (19.7 g, 89%) with spectroscopic data identical to those reported above. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.32; H, 8.65; N, 6.33. Found: C, 70.32; H, 8.29; N, 6.06.

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylhexanamide (2). A 1-L flask was charged with (+)-pseudoephedrine (40.0 g, 242 mmol, 1 equiv) and tetrahydrofuran (500 mL). The flask was placed in a water bath at 23 °C, and hexanoic anhydride (55.5 g, 259 mmol, 1.07 equiv) was added to the solution via cannula over 10 min. The reaction mixture was stirred for 25 min at 23 °C, and then the hexanoic acid was quenched by the cautious addition of saturated aqueous sodium bicarbonate solution (300 mL). Tetrahydrofuran was removed under reduced pressure, and the resulting aqueous solution was partitioned between water (500 mL) and ethyl acetate (250 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were dried over sodium sulfate and concentrated. Recrystallization of the crude reaction product from a 1:1 mixture of ether and hexanes (40 °C, 200 mL) furnished amide **2** as a white crystalline solid (58.2 g, 91%): mp 62−63 °C; ^{1}H NMR (7:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, C_6D_6) δ 7.0−7.4 (m, 5H), 4.9 (br, 1H), 4.52 (d, 1H, J = 6.9 Hz), 4.14 (m, 2H), 3.77* (m, 1H), 2.79* (s, 3H), 2.42* (m, 2H), 2.13 (s, 3H), 1.83 (m, 2H), 1.59 (qn, 2H, J = 7.6 Hz), 1.1−1.4 (m, 4H), 0.99 (d, 3H, J = 7.0 Hz), 0.86 (t, 3H, J = 7.0 Hz), 0.59* (d, 3H, J = 6.8 Hz); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 175.2, 174.2*, 142.3, 141.6*, 128.3*, 128.0, 127.8*, 127.3, 126.7*, 126.2, 76.1, 75.1*, 58.2, 57.0*, 34.1, 33.4*, 32.4*, 31.5*, 31.3, 26.6, 24.9*, 24.5, 22.31*, 22.29, 15.2*, 14.2, 13.82*, 13.79; FTIR (neat, cm^{-1}) 3378 (br, m, OH), 1618 (s, C═O); HRMS (FAB) calcd for $C_{16}H_{26}NO_2$ $(MH)^+$ 264.1965, found 264.1966. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.40; H, 9.71; N, 5.11.

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylbenzenepropionamide (3). A solution of hydrocinnamoyl chloride (24.4 g, 145 mmol, 1.15 equiv) in tetrahydrofuran (50 mL) was added via cannula over 10 min to an ice-cooled solution of (+)-pseudoephedrine (20.8 g, 126 mmol, 1 equiv) and triethylamine (22.8 mL, 164 mmol, 1.30 equiv) in tetrahydrofuran (300 mL). After 10 min, excess acid chloride was quenched by the addition of water (10 mL). The product mixture was partitioned between ethyl acetate (500 mL) and brine (40 mL), and the organic layer was separated and extracted with brine (2 × 40 mL). The organic layer was dried over sodium sulfate and concentrated. Recrystallization of the crude reaction product from hot toluene (110 °C, 125 mL) furnished amide **3** as a white crystalline solid (31.2 g, 83%): mp 102−104 °C; ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, C_6D_6) δ 7.0−7.4 (m, 10H), 4.59 (br, 1H), 4.48 (t, 1H, J = 7.1 Hz), 4.20 (m, 1H), 4.01* (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 3.66* (m, 1H), 3.15* (m, 2H), 2.93 (t, 2H, J = 7.7 Hz), 2.79* (s, 3H), 2.49* (m, 2H), 2.13 (m, 2H), 2.02 (s, 3H), 0.92 (d, 3H, J = 7.0 Hz), 0.49* (d, 3H, J = 6.8 Hz); ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 174.3, 173.2*, 142.2, 141.5*, 141.3*, 141.1, 128.6*, 128.39, 128.36, 128.31, 128.29, 128.2*, 127.6*, 126.8*, 126.4, 126.1, 125.9*, 76.3, 75.3*, 58.2, 58.0*, 36.1, 35.4*, 32.3*, 31.5*, 31.1, 26.9, 15.2*, 14.3; FTIR (neat, cm^{-1}) 3374 (br, m, OH), 1621 (s, C═O); HRMS (FAB) calcd for $C_{19}H_{24}NO_2$ $(MH)^+$ 298.1808, found 298.1806. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.45; H, 8.00; N, 4.40.

(*S*,*S*)-α-Chloro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide (5). A solution of (+)-pseudoephedrine (5.69 g, 33.3 mmol, 1.10 equiv) and triethylamine (4.64 mL, 33.3 mmol, 1 equiv) in dichloromethane (55 mL) was added via cannula to an ice-cooled solution of chloroacetic anhydride (5.00 g, 33.3 mmol, 1 equiv) in dichloromethane (60 mL). The resulting mixture was stirred for 1 h

(43) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41.
(44) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(45) Watson, M. B.; Youngson, G. W. *J. Chem. Soc. C* **1968**, 258.

at 0 °C and then partitioned between saturated aqueous sodium bicarbonate solution (100 mL) and dichloromethane (200 mL). The aqueous layer was separated and extracted with dichloromethane (100 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate−hexanes (25 → 75%) afforded amide **5** as an oil which crystallized upon standing (6.60 g, 90%): mp 79−81 °C; ^{1}H NMR (1:1 rotamer ratio, 300 MHz, $CDCl_3$) δ 7.28−7.41 (m, 5H), 4.54−4.63 (m, 3H), 4.35 (d, 1H, J = 12.4 Hz), 4.07 (d, 1H, J = 12.3 Hz), 4.07 (s, 2H), 3.98 (m, 1H), 3.74 (br, d, 1H, J = 4.7 Hz), 3.30 (d, 1H, J = 3.2 Hz), 2.94 (s, 3H), 1.05 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 6.8 Hz); ^{13}C NMR (1:1 rotamer ratio, 75 MHz, $CDCl_3$) δ 168.2, 168.0, 141.6, 141.1, 128.7, 128.4, 127.9, 126.7, 126.5, 75.8, 75.1, 59.1, 57.7, 42.0, 41.7, 32.0, 27.4, 15.3, 14.0; FTIR (neat, cm^{-1}) 3392 (br, m, OH), 1638 (s, C═O).

Amide **5** could also be purified by crystallization of the crude acylation product. After aqueous workup and concentration as above, the oily product residue was dissolved in ether (to ca. 1.4 M), and the resulting solution was cooled to −20 °C and seeded with authentic amide **5**. After 24 h, the product was collected by filtration to afford a first crop yield of 46%. The mother liquor was concentrated, and the oily residue was dissolved in a smaller volume of ether (to ca. 2.5 M). The solution was cooled to −20 °C and seeded with authentic amide **5**. After 24 h, a second crop was collected by filtration to afford amide **5** in 32% yield (total 78% yield). Spectroscopic data were identical to those listed above: mp 79−81 °C. Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.61; H, 6.66; N, 5.76.

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylbenzenebutanamide (8). A solution of 4-phenylbutyric acid (4.57 g, 29.1 mmol, 1.20 equiv) in dichloromethane (15 mL) was charged sequentially with oxalyl chloride (2.53 mL, 29.1 mmol, 1.20 equiv) and *N*,*N*-dimethylformamide (10 μL, 0.13 mmol, 0.005 equiv), and the resulting solution was stirred at 23 °C for 1 h, during which time the bubbling ceased. Amide **8** was prepared according to the procedure detailed above for the acylation product **3**, using (+)-pseudoephedrine (4.00 g, 24.2 mmol, 1 equiv), triethylamine (4.72 mL, 33.9 mmol, 1.40 equiv), and the 4-phenylbutyryl chloride prepared above. The crude reaction product was recrystallized from hot toluene (110 °C, 15 mL), furnishing the amide **8** as a white crystalline solid (6.08 g, 81%): mp 100−102 °C; ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 7.1−7.4 (m, 10H), 4.60 (m, 1H), 4.53* (m, 1H), 4.45 (m, 1H), 4.32 (br, 1H), 3.90* (m, 1H), 2.92* (s, 3H), 2.75 (s, 3H), 2.69 (m, 2H), 2.35 (m, 2H), 2.00 (m, 2H), 1.10 (d, 3H, J = 6.9 Hz), 0.95* (d, 3H, J = 6.8 Hz); ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 175.0, 174.0*, 142.4, 141.9*, 141.6, 141.2*, 128.6*, 128.5, 128.3, 127.6, 126.8*, 126.4, 125.9*, 76.5, 75.5*, 58.5, 58.2*, 35.4*, 35.1, 33.3, 32.8*, 26.8*, 26.3, 15.3*, 14.4; FTIR (neat, cm^{-1}) 3374 (br, m, OH), 1620 (s, C═O); HRMS (FAB) calcd for $C_{20}H_{26}NO_2$ $(MH)^+$ 312.1964, found 312.1974. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.06; H, 7.94; N, 4.62.

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-3-pyridylacetamide (10). Triethylamine (3.34 mL, 24.0 mmol, 3.00 equiv) was added to a suspension of 3-pyridylacetic acid hydrochloride (2.08 g, 12.0 mmol, 1.50 equiv) in acetonitrile (60 mL). The resulting suspension was stirred at 23 °C for 10 min and then cooled to 0 °C. Pivaloyl chloride (1.48 mL, 12.0 mmol, 1.50 equiv) was added followed by tetrahydrofuran (10 mL) to improve stirring of the thick suspension. A solution of (+)-pseudoephedrine (1.32 g, 7.99 mmol, 1 equiv) and triethylamine (1.11 mL, 7.99 mmol, 1 equiv) in tetrahydrofuran (20 mL, followed by a 3-mL rinse) was added rapidly via cannula. The mixture was warmed slowly to 15 °C over 1 h, and excess anhydride was quenched by the addition of water (10 mL). Volatile solvents were removed under reduced pressure, and the resulting aqueous residue was partitioned between 0.5 N aqueous sodium hydroxide solution and 10% methanol−dichloromethane (50 mL). The aqueous layer was separated and extracted further with 10% methanol−dichloromethane (4 × 50 mL). The combined organic layers were washed with 1 N aqueous sodium hydroxide solution (15 mL), then dried over sodium sulfate, and concentrated. Purification of the product by flash column chromatography eluting with a gradient of ethyl acetate−methanol−triethylamine [90:8:2 → 88:10:2] afforded amide **10** as a white crystalline solid (2.21 g, 93%): mp 117.5−118.5 °C; ^{1}H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 8.2−8.6 (m, 2H), 7.6−7.7 (m, 1H), 7.1−7.4 (m, 6H), 4.4−4.7 (m, 2H), 4.0−4.3* (m, 2H), 3.80* (d, 2H, J = 1.8 Hz), 3.67 (s, 2H), 2.96* (s, 3H), 2.89 (s, 3H), 1.13 (d, 3H, J = 6.8 Hz), 0.93* (d, 3H, J = 6.8 Hz); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 171.0, 170.8*, 149.8*, 149.6, 147.4, 147.2*, 142.1, 142.0*, 136.9*, 136.6, 131.5*, 130.6, 128.3*, 128.0, 127.7*, 127.3, 126.5*, 126.3, 123.2, 123.0*, 75.3, 74.8*, 58.4, 56.5*, 38.0, 37.4*, 31.8*, 27.1, 15.2*, 14.0; FTIR (neat, cm^{-1}) 3385 (br, m, OH), 1626 (s, C═O); HRMS (FAB) calcd for $C_{17}H_{21}N_2O_2$ $(MH)^+$ 285.1603, found 285.1596; Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.77; H, 7.08; N, 9.81.

Amide **10** could also be purified by recrystallization. Following a procedure similar to that described above, using (+)-pseudoephedrine (1.49 g, 8.99 mmol, 1 equiv), triethylamine (3.38 mL, 24.3 mmol, 3.00 equiv), 3-pyridylacetic acid hydrochloride (2.11 g, 12.1 mmol, 1.35 equiv), and pivaloyl chloride (1.50 mL, 12.1 mmol, 1.35 equiv), the crude reaction product was recrystallized from hot toluene (110 °C, 8 mL), furnishing the amide **10** as a crystalline solid (1.83 g, 72%). Spectroscopic data were identical to those listed above: mp 117.5−118.5 °C. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.60; H, 7.18; N, 9.73.

(*S*,*S*)-α-Hydroxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide (11). A solution of *n*-butyllithium in hexanes (2.37 M, 5.62 mL, 13.3 mmol, 0.500 equiv) was added to an ice-cooled suspension of lithium chloride (3.39 g, 79.9 mmol, 3.00 equiv) and (+)-pseudoephedrine (4.40 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (200 mL), and the suspension was stirred at 0 °C for 30 min. Methyl glycolate (4.11 mL, 53.3 mmol, 2.00 equiv) was added via syringe over 5 min, and the mixture was warmed to 23 °C and stirred at that temperature for 3 h. A solution of 0.5 N aqueous sodium hydroxide (100 mL) was added, and the biphasic mixture was stirred at 23 °C for 1 h. Volatile organic solvents were removed under reduced pressure, and the resulting aqueous residue was extracted with five 50-mL portions of 10% methanol−dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the product by flash column chromatography eluting with a gradient of methanol−dichloromethane (6 → 10%) afforded amide **11** as a colorless oil which slowly solidified (5.55 g, 93%): mp 61−63 °C; ^{1}H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 7.20−7.45 (m, 5H), 4.60 (m, 2H), 4.36* (m, 2H), 4.15 (m, 2H), 3.75* (br, 1H), 3.65 (br, 1H), 3.60* (m, 2H), 3.20 (br, 1H), 3.01* (s, 3H), 2.75 (s, 3H), 2.40* (br, 1H), 1.08 (d, 3H, J = 6.6 Hz), 0.99* (d, 3H, J = 6.8 Hz); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 172.9, 172.6*, 141.6, 141.1*, 128.7*, 128.4, 127.9*, 126.7, 126.5, 75.6, 74.9*, 60.1, 60.0*, 57.3*, 56.7, 29.0, 27.1*, 15.0*, 14.0; FTIR (neat, cm^{-1}) 3390 (br, s, OH), 1634 (s, C═O); HRMS (EI) calcd for $C_{12}H_{18}NO_3$ $(MH)^+$ 224.1287, found 224.1289. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.53; H, 7.58; N, 6.20.

Alkylation Reactions Using Procedure A (Excess Alkyl Halide). [1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethylbenzenepropionamide (12). A three-necked, 2-L flask equipped with a mechanical stirrer was charged with lithium chloride (25.0 g, 596 mmol, 6.00 equiv), diisopropylamine (31.3 mL, 224 mmol, 2.25 equiv), and tetrahydrofuran (120 mL). The resulting suspension was cooled to −78 °C, and a solution of *n*-butyllithium in hexanes (2.43 M, 85.1 mL, 207 mmol, 2.08 equiv) was added via cannula. The suspension was warmed briefly to 0 °C and then cooled to −78 °C. An ice-cooled solution of amide **1** (22.0 g, 99.4 mmol, 1 equiv) in a minimal amount of tetrahydrofuran (300 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min and finally cooled to 0 °C, whereupon benzyl bromide (17.7 mL, 149 mmol, 1.50 equiv) was added. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (800 mL) and ethyl acetate (500 mL), and the aqueous layer was separated and extracted with two 150-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and

concentrated to afford a yellow solid. Recrystallization of the product from hot toluene (110 °C, 100 mL) furnished amide **12** as a white crystalline solid (27.8 g, 90%). Amide **12** (30 mg, 0.096 mmol, 1 equiv) was silylated with chlorotrimethylsilane (34 μL, 0.27 mmol, 2.8 equiv) and triethylamine (49 μL, 0.35 mmol, 3.6 equiv) in dichloromethane (1 mL) at 23 °C for 10 min, and chiral capillary GC analysis[46] of the resulting trimethylsilyl ether established that amide **12** was of ≥99% de: mp 136−137 °C; ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, C_6D_6) δ 6.9−7.4 (m, 10 H), 4.45 (m, 1H), 4.25 (br, 1H), 3.96* (m, 1H), 3.80* (m, 1H), 3.36* (dd, 1H, J = 13.1 Hz, 6.92 Hz), 3.01 (m, 1H), 2.75* (m, 2H), 2.70* (s, 3H), 2.52 (m, 2H), 2.08 (s, 3H), 1.05* (d, 3H, J = 7.0 Hz), 1.02 (d, 3H, J = 6.5 Hz), 0.83 (d, 3H, J = 7.0 Hz), 0.59* (d, 3H, J = 6.8 Hz); ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$) δ 178.2, 177.2*, 142.3, 141.1*, 140.5*, 139.9, 129.2*, 128.9, 128.6*, 128.31*, 128.26, 127.5*, 126.8*, 126.4, 126.2, 76.4, 75.2*, 58.0, 40.3, 40.0*, 38.9, 38.1*, 32.3, 27.1*, 17.7*, 17.4, 15.5*, 14.3; FTIR (neat, cm^{-1}) 3384 (br, m, OH), 1617 (s, C═O); HRMS (FAB) calcd for $C_{20}H_{26}NO_2$ $(MH)^+$ 312.1965, found 312.1972. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.87; H, 8.06; N, 4.50.

A General Procedure for Alkylation Reactions Using Procedure B (Excess Enolate). [1*S*(R),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl-4-[(triisopropylsilyl)oxy]butanamide (31). A solution of *n*-butyllithium in hexanes (2.55 M, 27.4 mL, 69.9 mmol, 4.00 equiv) was added via cannula to a suspension of lithium chloride (9.39 g, 222 mmol, 12.7 equiv) and diisopropylamine (10.6 mL, 75.3 mmol, 4.31 equiv) in THF (50 mL) at −78 °C. The resulting suspension was warmed to 0 °C briefly and then was cooled to −78 °C. An ice-cooled solution of amide **1** (8.12 g, 36.7 mmol, 2.10 equiv) in THF (110 mL, followed by a 4-mL rinse) was added via cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min. The mixture was cooled to 0 °C, and 2-iodo-1-[(triisopropylsilyl)oxy]ethanol (5.73 g, 17.5 mmol, 1 equiv) was added neat to the reaction via cannula. After being stirred for 18.5 h at 0 °C, the reaction mixture was treated with half-saturated aqueous ammonium chloride solution (180 mL), and the resulting mixture was extracted with ethyl acetate (4 × 110 mL). The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (65% ether−hexanes) afforded amide **31** as a highly viscous, yellow oil (6.57 g, 89%). Chiral capillary GC analysis[46] of the corresponding trimethylsilyl ether, prepared as described above for amide **12**, established that amide **31** was of 97% de: ^{1}H NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, C_6D_6) δ 7.31 (d, 2H, J = 7.4 Hz), 7.25* (d, 2H, J = 7.4 Hz), 7.03−7.22 (m, 3H), 4.55 (t, 1H, J = 7.3 Hz), 4.14−4.38 (br, m, 1H), 4.02* (m, 1H), 3.78* (t, 2H, J = 5.8 Hz), 3.52 (m, 2H), 2.86 (m, 1H), 2.79* (s, 3H), 2.47 (s, 3H), 1.96 (m, 1H), 1.50 (m, 1H), 1.07 (m, 27H), 0.63* (d, 3H, J = 6.6 Hz); ^{13}C NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$), δ 179.1, 177.7*, 142.6, 141.4*, 128.7*, 128.6*, 128.4, 127.6, 127.1*, 126.4, 76.5, 75.5*, 61.3*, 60.7, 58.5, 58.0*, 37.2, 36.9*, 32.7 (br), 32.5, 32.2*, 27.0*, 18.1, 17.6*, 17.0, 15.6*, 14.5, 12.3*, 12.1; FTIR (neat, cm^{-1}) 3383 (br, m, OH), 1621 (s, C═O); HRMS (FAB) calcd for $C_{24}H_{44}O_3NSi$ $(MH)^+$ 422.3090, found 422.3086. Anal. Calcd for $C_{24}H_{43}O_3NSi$: C, 68.36; H, 10.28; N, 3.32. Found: C, 68.32; H, 10.26; N, 3.35.

Hydrolysis of Pseudoephedrine Amides with H_2SO_4 in 1:1 Aqueous Dioxane. (*R*)-α-Methylbenzenepropionic Acid (46). A 250-mL round-bottomed flask was charged with amide **12** (10.0 g, 32.1 mmol, 1 equiv), dioxane (50 mL), and 9 N aqueous sulfuric acid solution (50 mL). The biphasic mixture was heated at reflux for 6 h and then cooled to 0 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 50% (w/w) aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (100 mL) and dichloromethane (200 mL). The aqueous layer was separated and extracted with dichloromethane (200 mL). The aqueous layer was acidified to pH ≤ 2 by the slow addition of 6 N aqueous sulfuric acid solution and then extracted with dichloromethane (3 × 200 mL). The latter organic extracts were combined and concentrated to a volume of ca. 50 mL, and the concentrate was then washed with 1 N aqueous hydrochloric acid solution to remove residual dioxane. The resulting organic layer was dried over sodium sulfate and concentrated to afford acid **46** as a clear liquid (5.07 g, 95%). Coupling of acid **46** (25 mg, 0.15 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (24 μL, 0.19 mmol, 1.2 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol, 1.5 equiv), 1-hydroxybenzotriazole hydrate (31 mg, 0.23 mmol, 1.5 equiv), and triethylamine (86 μL, 0.62 mmol, 4.0 equiv) in *N*,*N*-dimethylformamide (0.5 mL) at 23 °C for 20 h gave the corresponding (*R*)-α-methylbenzyl amide[47] which was analyzed by chiral capillary GC to establish an ee of 97% for acid **46**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 3.09 (dd, 1H, J_1 = 13.1 Hz, J_2 = 6.1 Hz), 2.75 (m, 2H), 1.18 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.5, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.5; FTIR (neat, cm^{-1}) 2976 (br, s, OH), 1707 (s, C═O); HRMS (FAB) calcd for $C_{10}H_{12}O_2$ $(M)^+$ 164.0838, found 164.0832. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.30.

The carboxylic acids of entries 2−7 (Table 4) were prepared analogously except that 18 N H_2SO_4 was employed and the reaction time was reduced to 1−2 h at reflux.

Hydrolysis of Pseudoephedrine Amides with *n*-Bu_4NOH in 4:1 Aqueous *tert*-Butyl Alcohol. (*R*)-α-Methylbenzenepropionic Acid (46). A 100-mL round-bottomed flask was charged with amide **12** (0.500 g, 1.61 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 5.21 g, 8.03 mmol, 5.00 equiv), *tert*-butyl alcohol (5 mL), and water (15 mL), and the biphasic mixture was heated at reflux for 24 h. The mixture was cooled to 23 °C and then partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (25 mL). The aqueous layer was separated and extracted with two 25-mL portions of ether and then brought to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The acidified solution was saturated with sodium chloride and extracted with three 35-mL portions of ether. The combined ether extracts were washed with water (10 mL), then dried over sodium sulfate, and concentrated to afford acid **46** as a clear liquid (0.245 g, 93%) with spectroscopic data identical to those obtained from **46** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[47] prepared as described above, established that **46** prepared by this method was of 94% ee. The purity of **46** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

Hydrolysis of Pseudoephedrine Amides with NaOH in 2:1:1 Water−*tert*-Butyl Alcohol−Methanol. (*R*)-α-Methylbenzenepropionic Acid (46). A 250-mL round-bottomed flask was charged with amide **12** (10.0 g, 32.1 mmol, 1 equiv), *tert*-butyl alcohol (25 mL), methanol (25 mL), and 3.22 N aqueous sodium hydroxide solution (50 mL, 161 mmol, 5.01 equiv). The mixture was heated at reflux for 24 h and then cooled to 23 °C. The mixture was concentrated to remove the organic solvents, and the resulting aqueous solution was partitioned between water (200 mL) and dichloromethane (200 mL). The aqueous layer was separated, extracted with dichloromethane (200 mL), and then acidified to pH ≤ 2 by the slow addition of 6 N aqueous sulfuric acid solution. The acidified aqueous solution was extracted with dichloromethane (3 × 200 mL), and the combined organic extracts were dried over sodium sulfate and concentrated to afford acid **46** as a clear liquid (5.18 g, 98%) with spectroscopic data identical to those obtained from **46** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[47] prepared as described above, established that **46** prepared by this method was of 92% ee. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.79; H, 7.09.

(46) In each case, an authentic sample of the minor diastereomeric alkylation product was prepared for comparative analysis (chiral capillary GC analysis of the corresponding trimethylsilyl ether or acetate ester). In the case of amides **16**, **21**, **26**, **27**, and **29**−**31**, diastereomeric mixtures of α-epimers were obtained by epimerization with LDA (5 equiv) or lithium 2,2,6,6-tetramethylpiperidide (5 equiv) in THF for 5 h at 23 °C followed by quenching with aqueous ammonium chloride solution. Amide **28** was epimerized by stirring with lithium chloride (5 equiv) in *N*,*N*-dimethylformamide at 23 °C for 12 h. Each of the remaining alkylation products in Tables 2 and 3 was epimerized by stirring the substrate with trifluoroacetic acid (10 equiv) in THF at reflux for 1 h (effecting $N \rightarrow O$ acyl transfer as well as α-epimerization), followed by neutralization with aqueous sodium bicarbonate solution at 23 °C for 24 h (causing $O \rightarrow N$ acyl transfer).

(47) In each case, an authentic sample of the minor diastereomeric (*R*)-α-methylbenzyl amide was prepared for comparative analysis.

Hydrolysis of Pseudoephedrine Amides with $FeCl_3$ in 4:1 Aqueous Dioxane. (*R*)-α-Methylbenzenepropionic acid (46). A 10-mL round-bottomed flask was charged with amide **12** (157 mg, 0.505 mmol, 1 equiv), iron(III) chloride hexahydrate (676 mg, 2.50 mmol, 4.95 equiv), water (4 mL), and dioxane (1 mL). The biphasic mixture was heated at reflux for 48 h and then cooled to 23 °C. The pH of the mixture was adjusted to ≥10 by the dropwise addition of 50% (w/w) aqueous sodium hydroxide solution, and the resulting mixture was partitioned beween water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated, extracted with dichloromethane (10 mL), and then acidified to pH ≤ 2 by the dropwise addition of 6 N aqueous sulfuric acid solution. The resulting aqueous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate and concentrated to afford acid **46** as a clear liquid (78.2 mg, 94%) with spectroscopic data identical to those obtained from **46** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[47] prepared as described above, established that **46** prepared by this method was of 98% ee. The purity of **46** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

Hydrolysis of Pseudoephedrine Amides Using $Yb(OTf)_3$ or $ZrOCl_2$ in 4:1 Aqueous Dioxane. (*R*)-α-Methylbenzenepropionic Acid (46). These hydrolyses were performed in a manner analogous to the hydrolysis with $FeCl_3$, substituting zirconyl chloride or ytterbium triflate (5 equiv) for iron(III) chloride.

Hydrolysis of Pseudoephedrine Amides Involving in Situ Borane−Amine Complexation (Sodium Hydroxide). (*R*)-α-Methylbenzenepropionic Acid (46). A 10-mL round-bottomed flask was charged with amide **12** (160 mg, 0.513 mmol, 1 equiv), tetrahydrofuran (2.0 mL), and methanesulfonic acid (48 μL, 0.74 mmol, 1.44 equiv). This mixture was heated at reflux for 1 h and then cooled to 23 °C. A solution of lithium borohydride (2.0 M, 0.38 mL, 0.76 mmol, 1.5 equiv) in tetrahydrofuran was cautiously added to the mixture, leading to significant gas evolution. A solution of aqueous sodium hydroxide (1.25 N, 2.0 mL, 2.5 mmol, 4.9 equiv) was then cautiously added, and the resulting mixture was stirred for 8 h at 23 °C. The reaction mixture was partitioned between water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated and extracted with dichloromethane (10 mL) and then acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution. The resulting acidified solution was extracted with dichloromethane (3 × 10 mL). The latter extracts were combined, dried over sodium sulfate, and concentrated to afford acid **46** as a clear liquid (79.5 mg, 94%) with spectroscopic data identical to those obtained from **46** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[47] prepared as described above, established that **46** prepared by this method was of 98% ee. The purity of **46** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

Hydrolysis of Pseudoephedrine Amides Involving in Situ Borane−Amine Complexation (*n*-Bu_4NOH). (*R*)-α-Methylbenzenepropionic Acid (46). A flame-dried 10-mL round-bottomed flask was charged with amide **12** (158 mg, 0.508 mmol, 1 equiv), tetrahydrofuran (2.0 mL), and methanesulfonic acid (48 μL, 0.74 mmol, 1.46 equiv). The mixture was heated at reflux for 1 h and then cooled to 23 °C. A solution of lithium borohydride (2.0 M, 0.38 mL, 0.76 mmol, 1.5 equiv) in tetrahydrofuran was cautiously added to the mixture, leading to significant gas evolution. Water (1.0 mL) and an aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 1.62 g, 2.50 mmol, 4.92 equiv) were then cautiously added, and the mixture was stirred at 23 °C for 1 h. The reaction mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (50 mL) and ether (10 mL). The aqueous phase was separated, extracted with ether (2 × 10 mL) and acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution, and with ether (3 × 10 mL). The latter organic extracts were combined and washed sequentially with 1 N aqueous hydrochloric acid solution (10 mL) and brine (10 mL) to remove residual tetra-*n*-butylammonium salts, then dried over sodium sulfate, and concentrated to afford acid **46** as a clear liquid (75.4 mg, 91%) with spectroscopic data identical to those obtained from **46** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[47] prepared as described above, established that **46** prepared by this method was of 94% ee. The purity of **46** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

(*R*)-α-Methylbutanedioic Acid (57). A 25-mL round-bottomed flask was charged with amide **16** (563 mg, 1.76 mmol, 1 equiv), *tert*-butyl alcohol (3 mL), methanol (3 mL), and 1 N aqueous sodium hydroxide solution (12 mL, 12 mmol, 6.8 equiv). The mixture was heated at reflux for 24 h and then cooled to 23 °C. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (100 mL) and dichloromethane (10 mL). The aqueous layer was separated, extracted with dichloromethane (2 × 10 mL), and then acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution. The acidified aqueous layer was saturated with sodium chloride and then extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried over sodium sulfate and concentrated to afford diacid **57** as a white solid (173 mg, 74%). Diacid **57** was reduced with lithium aluminum hydride (3 equiv) in THF at 0 °C to the corresponding diol, and ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding bis-(Mosher esters)[44] derived from both (*R*)- and (*S*)-Mosher acid established that diacid **57** was of 94% ee: mp 104−106 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 5.03 (br, 2H), 2.82 (m, 1H), 2.65 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.3 Hz), 2.38 (dd, 1H, J_1 = 16.7 Hz, J_2 = 5.8 Hz), 1.20 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 179.2, 175.6, 38.5, 37.0, 17.4; FTIR (neat, cm^{-1}) 2700−3300 (br, m, OH), 1694 (s, C=O); HRMS (EI) calcd for $C_5H_9O_4$ $(MH)^+$ 133.0501, found 133.0504. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10; N, 0. Found: C, 45.86; H, 5.93; N, 0.14.

Reduction of Pseudoephedrine Amides with Lithium Amidotrihydroborate (LAB) To Form Primary Alcohols. (2*R*,4*S*)-2,4-Dimethyl-5-phenylpentanol (70). A solution of *n*-butyllithium in hexanes (2.33 M, 20.0 mL, 46.5 mmol, 3.90 equiv) was added to a solution of diisopropylamine (7.02 mL, 50.1 mmol, 4.20 equiv) in tetrahydrofuran (50 mL) at −78 °C. The resulting solution was stirred at −78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane−ammonia complex (90%, 1.64 g, 47.7 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **35** (4.22 g, 11.9 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C, held at that temperature for 2 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (120 mL). The mixture was stirred for 30 min at 0 °C and then extracted with four 45-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (20 mL), 2 N aqueous sodium hydroxide solution (20 mL), and brine (20 mL). The ether extracts were dried over magnesium sulfate and concentrated. Purification of the residue by flash column chromatography (35% ether−petroleum ether) afforded alcohol **70** as a colorless liquid (2.18 g, 95% yield). Acetylation of alcohol **70** (6.3 mg, 0.033 mmol, 1 equiv) with acetic anhydride (9.0 μL, 0.10 mmol, 3.0 equiv) and 4-(dimethylamino)-pyridine (16 mg, 0.13 mmol, 4 equiv) in dichloromethane (0.5 mL) at 23 °C for 1 h and chiral capillary GC analysis[48] of the resulting acetate ester established that alcohol **70** was of 98% de: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1−7.4 (m, 5H), 3.52 (dd, 1H, J_1 = 10.5 Hz, J_2 = 5.1 Hz), 3.38 (dd, 1H, J_1 = 10.5 Hz, J_2 = 6.6 Hz), 2.68 (dd, 1H, J_1 = 13.3 Hz, J_2 = 5.4 Hz), 2.28 (dd, 1H, J_1 = 13.3 Hz, J_2 = 8.6 Hz), 1.80 (m, 2H), 1.37 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.8 Hz), 1.03 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.3 Hz), 0.96 (d, 3H, J = 6.7 Hz), 0.86 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 129.2, 128.2, 125.8, 68.2, 43.4, 40.8, 33.3, 32.5, 20.2, 17.4; FTIR (neat, cm^{-1}) 3346 (br, m, OH). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48; N, 0. Found: C, 80.93; H, 10.43; N, <0.05.

Reaction of Primary Alcohols with Triphenylphosphine and Iodine To Form Iodides. (*R*)-1-Iodo-2-methyl-3-phenylpropane (78). Imidazole (6.86 g, 101 mmol, 1.50 equiv) and iodine (23.0 g, 90.7 mmol, 1.35 equiv) were added sequentially to a solution of triphenylphosphine (21.1 g, 80.6 mmol, 1.20 equiv) in dichloromethane (250 mL) at 23 °C. A solution of alcohol **58** (10.1 g, 67.2 mmol, 1

(48) Acetate esters of the diastereomeric alcohol pairs **68** and **69**, **70** and **71**, **72** and **73**, **74** and **75**, and **76** and **77** were separated with baseline resolution when assayed by chiral capillary GC analysis.

equiv) in dichloromethane (30 mL) was added to the resulting fine suspension via cannula. After 2 h, dichloromethane was removed in vacuo. The solid residue was suspended in a minimal amount of dichloromethane (30 mL), and the suspension was loaded onto a column of silica gel eluting with 10% ether−petroleum ether to afford the iodide **78** as a colorless liquid (17.1 g, 98%): ^{1}H NMR (400 MHz, C_6D_6) δ 6.9−7.2 (m, 5H), 2.73 (dd, 1H, J_1 = 9.7 Hz, J_2 = 4.9 Hz), 2.70 (dd, 1H, J_1 = 9.7 Hz, J_2 = 5.5 Hz), 2.43 (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.0 Hz), 2.18 (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.1 Hz), 1.33 (m, 1H), 0.72 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 129.0, 128.3, 126.2, 42.5, 36.7, 20.7, 17.0; FTIR (neat, cm^{-1}) 2958 (s), 1494 (s), 1453 (s), 1194 (s); HRMS (EI) calcd for $C_{10}H_{13}I$ $(M)^+$ 260.0062, found 260.0057. Anal. Calcd for $C_{10}H_{13}I$: C, 46.18; H, 5.04. Found: C, 46.34, H, 5.20.

Reduction of Pseudoephedrine Amides with LiAlH(OEt)$_3$ To Form Aldehydes. (*R*)-α-Methylbenzenepropanal (82). A 1-L round-bottomed flask was charged with solid lithium aluminum hydride (95%, 2.95 g, 73.9 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (170 mL), and the flask was cooled to 0 °C. Ethyl acetate (10.7 mL, 110 mmol, 3.41 equiv) was added by addition funnel over a period of 1.5 h, and the resulting suspension of lithium triethoxyaluminum hydride was cooled to −78 °C. A solution of amide **12** (10.0 g, 32.1 mmol, 1 equiv) in tetrahydrofuran (110 mL) was added via cannula over 5 min, and the reaction mixture was warmed to 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (25 mL, 325 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (400 mL), and the transfer was quantitated with an additional portion of tetrahydrofuran (10 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min and then diluted with 1 N aqueous hydrochloric acid solution (700 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (250 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7−8) was separated and extracted with ethyl acetate (100 mL). The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (7.5% ethyl acetate−hexanes) afforded the aldehyde **82** as a colorless liquid (3.64 g, 76%). Aldehyde **82** was oxidized[49] to the corresponding carboxylic acid **46**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described above for acid **46**, established that aldehyde **82** was of 95% ee: ^{1}H NMR (300 MHz, C_6D_6) δ 9.29 (d, 1H, J = 1.2 Hz), 6.8−7.1 (m, 5H), 2.72 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.4 Hz), 2.10 (m, 2H), 0.69 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 138.7, 128.9, 128.4, 126.3, 48.0, 36.5, 13.1; FTIR (neat, cm^{-1}) 1723 (s, C═O); HRMS (FAB) calcd for $C_{10}H_{13}O$ $(MH)^+$ 149.0966, found 149.0965.

Reaction of Pseudoephedrine Amides with Organolithium Reagents To Form Ketones. (*R*)-2-Methyl-1,3-diphenyl-1-propanone (88). Amide **12** (261 mg, 0.839 mmol, 1 equiv) was suspended in toluene (5 mL) in a 25-mL rounded-bottomed flask. The suspension was warmed to 70 °C to dissolve the amide, and the resulting solution was cooled to 23 °C and then concentrated under reduced pressure. The reaction flask was flushed with dry argon, tetrahydrofuran (10 mL) was added, and the resulting slurry was cooled to −78 °C. A solution of phenyllithium in 70% cyclohexane−ether (1.94 M, 1.04 mL, 2.02 mmol, 2.41 equiv) was added via syringe, and the mixture was then warmed to 0 °C and held at that temperature for 5 min. Excess phenyllithium was quenched at 0 °C by the addition of diisopropylamine (0.12 mL, 0.84 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL), and the organic phase was separated and extracted with saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL). The organic phase was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate−hexanes (3 → 10%) afforded ketone **88** as a clear liquid (176 mg, 94% yield). High-resolution ^{1}H NMR analysis (300 MHz, C_6D_6) of the Mosher ester derivatives,[50] prepared as described for alcohol **58**, of the diastereomeric alcohol mixture obtained by the reduction of ketone **88** with lithium aluminum hydride (as described for ketone **89** below) established that ketone **88** was of ≥95% ee: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1−7.8 (m, 10H), 3.79 (sx, 1H, J = 6.9 Hz), 3.22 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.3 Hz), 2.74 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.9 Hz), 1.25 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 139.9, 136.4, 132.9, 129.1, 128.6, 128.3, 128.2, 126.2, 42.7, 39.3, 17.4; FTIR (neat, cm^{-1}) 1679 (s, C═O); HRMS (EI) calcd for $C_{16}H_{16}O$, $(M)^+$ 224.1201 found 224.1201.

(*R*)-2-Methyl-1-phenyl-3-heptanone (89). Amide **12** (10.0 g, 32.1 mmol, 1 equiv) was suspended in toluene (50 mL) in a 500-mL round-bottomed flask. The suspension was warmed to 70 °C to dissolve the amide, and the resulting solution was cooled to 23 °C and then concentrated under reduced pressure. The reaction flask was then flushed with dry argon, ether (250 mL) was added, and the resulting slurry was cooled to −78 °C. A solution of *n*-butyllithium in hexanes (2.39 M, 32.3 mL, 77.2 mmol, 2.40 equiv) was added via syringe, and the mixture was then warmed to 0 °C and held at that temperature for 15 min. Excess *n*-butyllithium was quenched at 0 °C by the addition of diisopropylamine (4.5 mL, 32 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (20% v/v, 100 mL) was added. The mixture was partitioned between ethyl acetate (300 mL) and water (300 mL), and the aqueous phase was separated and extracted with dichloromethane (2 × 300 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate−hexanes (2 → 5%) afforded ketone **89** as a clear liquid (5.80 g, 88% yield). A solution of lithium aluminum hydride in ether (1.0 M, 0.75 mL, 0.75 mmol, 1.5 equiv) was added to a solution of ketone **89** (102 mg, 0.50 mmol, 1 equiv) in ether (1 mL) at 0 °C to afford a mixture of diastereomeric alcohols. High-resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the corresponding Mosher ester derivatives,[50] prepared as described for alcohol **58**, of this mixture of diastereomeric alcohols established that ketone **89** was of ≥95% ee: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 5H), 2.97 (dd, 1H, J_1 = 13.2 Hz, J_2 = 7.1 Hz), 2.83 (sx, 1H, J = 7.0 Hz), 2.55 (dd, 1H, J_1 = 13.2 Hz, J_2 = 7.3 Hz), 2.39 (dt, 1H, J_1 = 16.9 Hz, J_2 = 7.3 Hz), 2.25 (dt, 1H, J_1 = 16.9 Hz, J_2 = 7.3 Hz), 1.45 (m, 2H), 1.23 (sx, 2H, J = 7.4 Hz), 1.07 (d, 3H, J = 6.9 Hz), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 139.8, 128.9, 128.3, 126.2, 48.1, 41.7, 39.1, 25.6, 22.3, 16.5, 13.9; FTIR (neat, cm^{-1}) 1712 (s, C═O); HRMS (EI) calcd for $C_{14}H_{20}O$ $(M)^+$ 204.1514, found 204.1517.

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Supporting Information Available: Tabular results from a study of the effect of metal salts in the hydrolysis of amide **12** and experimental procedures, spectroscopic data, and proof of composition for compounds **4**, **6**, **7**, **9**, **13**−**28**, **32**−**45**, **47**−**56**, **58**−**69**, **71**−**77**, **79**−**81**, **83**−**87**, and **90**−**100** (49 pages). See any current masthead page for ordering and Internet access instructions.

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(50) Both (*R*)- and (*S*)-Mosher ester derivatives were prepared for comparative analysis.