Use of Pseudoephedrine as a Practical Chiral Auxiliary for Asymmetric Synthesis

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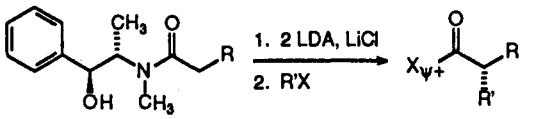
The asymmetric alkylation of the α-carbon of carboxylic acid derivatives is a fundamental and important synthetic transformation that, with few exceptions, remains within the domain of chiral auxiliary based methodology.[1] The oxazolidinone auxiliaries of Evans and co-workers have defined the standard in the field for more than a decade: they are commercially available, their imide derivatives are alkylated with predictable and high diastereoselectivity, and the latter products are readily transformed into carboxylic acids, esters, and primary alcohols.[1g] We have developed, and report herein, an exceedingly practical and versatile addition to asymmetric alkylation methodology that employs pseudoephedrine as a chiral auxiliary.

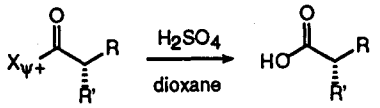
d-Pseudoephedrine ([1*S*,2*S*]-(+)) is a commodity chemical employed in over-the-counter medications with annual worldwide production in excess of 300 metric tons. *l*-Pseudoephedrine is also readily available in bulk and is inexpensive. We have found that pseudoephedrine is highly effective as a chiral auxiliary for the asymmetric alkylation of carboxamides. Treatment of either enantiomer of pseudoephedrine with carboxylic acid chlorides and anhydrides leads to efficient and selective *N*-acylation to form the corresponding tertiary amide derivatives. These amides are typically highly crystalline materials; each of the five amide substrates of Table 1 was isolated in 80–95% yield by direct recrystallization of the crude acylation reaction mixture. Alkylation of pseudoephedrine amides is accomplished by dianion formation with lithium diisopropylamide (2.25 equiv, –78 °C for 1 h, 0 °C for 15 min, and 23 °C for 5 min) in tetrahydrofuran (THF) in the presence of 6 equiv of lithium chloride, followed by the addition of an alkylating agent (Table 1). The use of lithium chloride leads to a marked acceleration in the alkylation rate and is essential for complete reaction.[2] As indicated within Table 1, these alkylation reactions are both highly efficient (80–95% yields of purified alkylation product) and diastereoselective (90–98% crude de, 96–>99% isolated de). Many of the products are crystalline materials and can be isolated in >99% diastereomeric purity by a single recrystallization. Because of the high reactivity of these enolates, the alkylation reactions often proceed at –78 °C (with a slight improvement in diastereoselectivity: **4** and **6**) and are practicable with electrophiles that do not react with imide enolates, such as *n*-alkyl iodides (see **2**, **5**, and **8**).[1g] Where crystallinity is of prime importance (e.g., process applications), the data available suggests that at least one isomer within a given diastereomeric pair is likely to be crystalline and, thus, that it may be advantageous to reverse the roles of electrophile and amide side chain using the enantiomeric pseudoephedrine auxiliary (cf. the diastereomeric pairs **2** and **6**, and **5** and **7**). The structures of alkylation products **1**, **2**, and **4** were determined by X-ray crystallographic analysis; those of the remaining entries were determined by correlation with known compounds (see supplementary material). In every case, the major product results from electrophilic attack on the putative (*Z*)-enolate (R *cis* to the enolate oxygen) from the same face as the carbon-bound methyl group of pseudoephedrine when drawn in its extended conformation.[3]

Table 1. Diastereoselective Alkylation of Pseudoephedrine Amides



R	R'X	temp (°C)	time (h)	prod.	crude de (%)	isol de (%)	yield (%)	mp (°C)
CH_3	BnBr	0	0.2	**1**	94	>99	90	136–137
CH_3	*n*-BuI	0	1.5	**2**	98	>99	80	66–67
CH_3	BOMBr	–78	1.5	**3**	98	98	80	65–66
Bn	CH_3I	0	1	**4**	94	94	99	79–81
Bn	CH_3I	–78	8	**4**	97	97	95	79–81
Bn	*n*-BuI	0	1.5	**5**	98	98	90	
n-Bu	CH_3I	0	1	**6**	94	94	94	
n-Bu	CH_3I	–78	6	**6**	96	96	89	
n-Bu	BnBr	0	0.7	**7**	98	>99	87	120–121
Ph	EtI	0	0.7	**8**	96	>99	92	65–66
Cl	BnBr	–45	1.5	**9**	90	>99	88	155–156

Table 2. Acidic Hydrolysis of Pseudoephedrine Amides



entry	substrate	R	R'	isol yield (%)	ee (%)
1	**1**	CH_3	Bn	87	97
2	**2**	CH_3	*n*-Bu	91	97
3	**7**	*n*-Bu	Bn	94	96
4	**8**	Ph	Et	96	95
5	**9**	Cl	Bn	97	95

Much of our study has been directed toward the development of methods to directly transform the amide products of Table 1 into enantiomerically enriched carboxylic acids, primary alcohols, aldehydes, and ketones. For amide products that are not acid-sensitive, the most straightforward procedure for hydrolysis of the pseudoephedrine auxiliary entails heating in the presence of strong acid. The procedure for acidic hydrolysis was optimized using the racemization-prone substrate **8** (>99% de). Hydrolysis with 1:1 18 N H_2SO_4/dioxane at reflux afforded (*S*)-2-phenylbutyric acid in 96% yield (95% ee) and proved to be generally effective for pseudoephedrine amide hydrolysis (Table 2), with the exception of substrate **3**, which decomposed under these conditions. In spite of the strongly acidic hydrolysis conditions, the method offers an exceedingly practical route to many simple, highly enantiomerically enriched carboxylic acids. Pseudoephedrine amides are also readily hydrolyzed under basic conditions, in many cases with only slight epimerization (substrates **1**, **2**, **4**, and **6**, ca. 90% yield, ≥93% ee). The standard protocol employed 5 equiv of tetra-*n*-butylammonium hydroxide in a mixture of water and *tert*-butyl alcohol (4:1, respectively) at reflux. This method offers a viable alternative for the hydrolysis of certain

(1) (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, 3961. (c) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5. (d) Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137. (e) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (f) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207. (g) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (h) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857. (i) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. For brevity, the extensive literature relating specifically to amino acid and glycolate syntheses is not cited.

(2) Reactions conducted in the presence of less than 4 equiv of lithium chloride are slower and do not proceed to completion; the diastereoselectivity of the alkylation reactions does not appear to be greatly affected by the concentration of lithium chloride. For a discussion of the influence of lithium halides upon the structure and reactivity of lithium enolates, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(3) The origins of diastereoselectivity in this system are far from clear and are a subject of current study. At present, we favor a model not involving chelation of the oxyanions.

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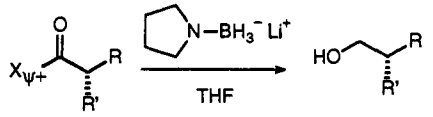
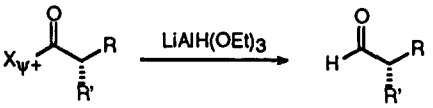
Table 3. Reduction with Borane–Lithium Pyrrolidide



entry	substrate	R	R′	isol yield (%)	ee (%)
1	1	CH_3	Bn	84	99
2	2	CH_3	*n*-Bu	81	99
3	4	Bn	CH_3	87	97
4	5	Bn	*n*-Bu	88	98
5	7	*n*-Bu	Bn	88	99
6[a]	8	Ph	Et	80	88

[a] Reduction with H_2NBH_3Li.

Table 4. Reduction with $LiAlH(OEt)_3$



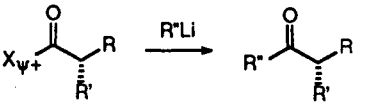
entry	substrate	R	R′	isol yield (%)	ee (%)
1	1	CH_3	Bn	77	93
2	2	CH_3	*n*-Bu	75	98
4	4	Bn	CH_3	77	94
5	5	Bn	*n*-Bu	80	97
6	7	*n*-Bu	Bn	82	97
7	8	Ph	Et	80	90

acid-sensitive substrates, but proceeds with substantial racemization in the cases of substrates **3**, **5**, **7**, and **8** (64–84% ee). In both methods of hydrolysis, as well as in the transformations outlined below, the pseudoephedrine auxiliary may be recovered in high yield, if desired, by a simple extractive isolation procedure.

Pseudoephedrine amides are readily transformed into highly enantiomerically enriched primary alcohols employing borane–lithium pyrrolidide in THF as the reducing agent.[4] For most substrates, the desired alcohol was obtained in 81–88% yield with ≥98% ee (Table 3). Reduction of the phenylacetamide derivative **8** was problematic, but could be accomplished with H_2NBH_3Li in THF (80% yield, 88% ee).

Perhaps the greatest utility of pseudoephedrine amides, and a departure from existing methodology, lies in their ability to function as direct precursors to chiral aldehydes and ketones of high enantiomeric purity (Tables 4 and 5). By using the alkoxyaluminum hydride reagent obtained from the reaction of lithium aluminum hydride with ethyl acetate,[5] pseudoephedrine amides were directly transformed into chiral aldehydes (90–98% ee, 75–82% yield, Table 4), whereas the addition of 2.2–2.4 equiv of an alkyllithium reagent to a pseudoephedrine amide in THF or ether at −78 °C and warming to 0 °C produces the corresponding ketone, typically in greater than 90% yield, with less than 2% of the corresponding tertiary alcohol (Table 5). In all cases examined, the enantiomeric purity of the aldehyde or ketone products of these reactions equaled or exceeded 90%.

Table 5. Ketones by Alkyllithium Addition



entry	substrate	R″Li	solvent	isol yield (%)	ee (%)
1	1	PhLi	THF	94	97
2	1	*n*-BuLi	Et_2O	89	97
3	2	PhLi	THF	93	99
4	3	CH_3Li	Et_2O	68	95
5	7	PhLi	Et_2O	96	97
6	7	*n*-BuLi	Et_2O	94	99
7	7	CH_3Li	Et_2O	98	99

Many of the most important and early advances in the asymmetric alkylation of carboxylate derivatives were achieved with auxiliaries derived from chiral amino alcohols.[1a–e,g,h] In the present context, it is important to note that the diastereoselective alkylation of amides derived from ephedrine, the diastereomer of pseudoephedrine, was reported more than 15 years ago.[1b,c] The use of a carcinogenic cosolvent in the latter method and reported difficulties in transforming ephedrine amides into useful products have probably limited the utility of this method. The substitution of pseudoephedrine for ephedrine leads to dramatic differences in the diastereoselectivity of the respective alkylation reactions,[6] as well as in the physical properties (crystallinity) of the substrates and products. The methods described above provide simple and inexpensive routes to a wide range of enantiomerically enriched carboxylic acids, aldehydes, alcohols, and ketones.

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Supplementary Material Available: Stereochemical assignments, ee/de determinations, representative experimental procedures, high-resolution ^{13}C NMR spectra of all pseudoephedrine amides, and structural data for compounds analyzed by X-ray crystallography (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(4) (a) Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem.* **1984**, *49*, 2438. (b) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533. (c) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1091. (d) Fuller, J. C.; Stangeland, E. L.; Jackson, T. C.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 1515. This reagent provided minimal amounts of tertiary amine, the major byproduct of amide reductions.

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

(6) The alkylation of ephedrine propionamide with butyl iodide, e.g., as described above for pseudoephedrine propionamide (using LDA and LiCl), proceeded with ca. 70% de.