Synthetic Methods

DOI: 10.1002/anie.201200370

Pseudoephenamine: A Practical Chiral Auxiliary for Asymmetric Synthesis**

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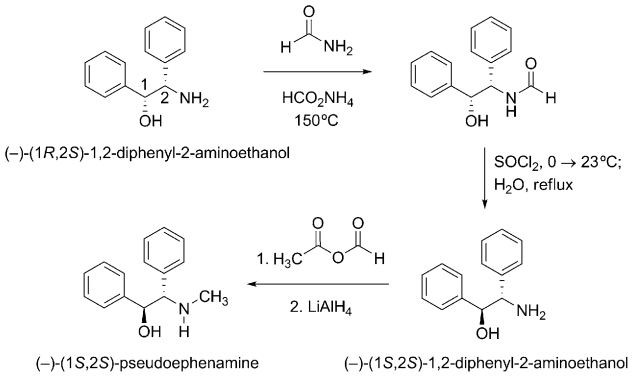
Pseudoephedrine is widely employed as a chiral auxiliary in diastereoselective alkylation reactions and provides ready access to enantiomerically enriched carboxylic acids, aldehydes, ketones, and alcohols.[1] Because pseudoephedrine can be transformed into methamphetamine and other illegal drug substances, many countries restrict or ban its sale and distribution, thus complicating its use in industrial and academic settings.[2] Herein we report that (1*S*,2*S*)- and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol (synonymously, (1*S*,2*S*)- and (1*R*,2*R*)-pseudoephenamine,[3] respectively) have a broad range of utilities in asymmetric synthesis that meet or exceed those that previously characterized the pseudoephedrine system alone, with several advantages. Specifically, 1) these auxiliaries are free from regulatory restrictions and are not known to be transformable into illicit substances, 2) asymmetric alkylation reactions that employ pseudoephenamine as a directing group proceed with equal or greater diastereoselectivities in relation to the corresponding reactions that employ pseudoephedrine, with notable improvements in the selectivities of alkylation reactions that form quaternary stereocenters, and 3) amides derived from pseudoephenamine exhibit a greater propensity to be crystalline substances compared with the corresponding pseudoephedrine derivatives and provide sharp, well-defined signals in NMR spectra.

Both enantiomeric forms of pseudoephenamine are easily prepared with well-established methods (Scheme 1). In 1951, Tishler and co-workers at Merck reported a process for the transformation of *erythro*-1,2-diphenyl-2-aminoethanol (1*R*,2*S* or 1*S*,2*R*) into the corresponding *threo* diastereomer (1*S*,2*S* or 1*R*,2*R*, respectively) by N-formylation with formamide, invertive cyclization to form the corresponding oxazoline using thionyl chloride, and hydrolytic ring-opening under acidic conditions.[4,5] By employing a small but important modification (that is, the use of formamide containing approximately 0.2 equivalents ammonium formate for N-formylation rather than pure formamide, the use of which leads to a reduced yield and yellowing of the product), we have applied the Tishler protocol for large-scale synthesis of both enantiomers of *threo*-1,2-diphenyl-2-aminoethanol from the appropriate *erythro*-diastereomer (both *erythro* diastereomers are commercially available in enantiomerically pure form and are widely used as chiral auxiliaries themselves, for example, in the Williams amino acid synthesis).[6–8] Subsequent N-methylation of *threo*-1,2-diphenyl-2-aminoethanol was achieved in 97% yield by N-formylation with acetic formic anhydride followed by reduction with lithium aluminum hydride.[9] The product was recrystallized from hot ethanol to produce large, orthorhombic, colorless crystals (m.p. 109–110 °C).[10] We have routinely prepared 20–40 g batches of (1*R*,2*R*)- or (1*S*,2*S*)-pseudoephenamine by the described four-step sequence, which proceeds in 87% yield and requires no column chromatography.[11,12] X-ray crystallographic analysis revealed that pseudoephenamine adopts a conformation identical to pseudoephedrine in the solid state, with gauche orientations between both the aminomethyl and hydroxy substituents as well as the two phenyl substituents (Figure 1).



Scheme 1. Synthesis of (−)-(1*S*,2*S*)-pseudoephenamine by a modified Tishler protocol followed by N-methylation.

Amide derivatives of pseudoephenamine were prepared from the corresponding carboxylic acid chlorides or anhydrides by routine methods and, in most cases, were crystalline solids (see the Supporting Information). Pseudoephenamine

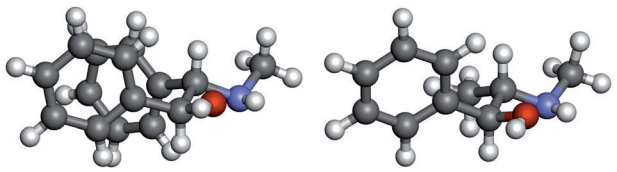


Figure 1. X-ray crystal structures of (−)-(1*S*,2*S*)-pseudoephenamine (left) and (+)-(1*S*,2*S*)-pseudoephedrine[13] (right). Thermal ellipsoids are at 50% probability.

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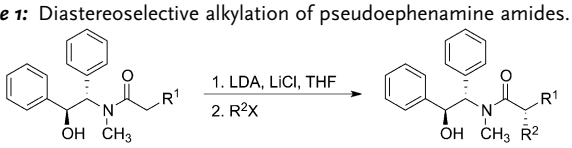
[**] We gratefully acknowledge the NSF (CHE-0749566) and the NIH (CA-047148) for financial support of this research. We also wish to thank Dr. Shao-Liang Zheng for X-ray crystallographic analyses and Dr. David Kummer for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201200370.

amide enolates were generated with lithium diisopropylamide (2.2 equiv) in tetrahydrofuran (THF) at –78 °C in the presence of a saturating amount of anhydrous lithium chloride (ca. 6 equiv), which are conditions identical to those employed for enolization of pseudoephedrine amides. Pseudoephenamine propionamide was poorly soluble in neat THF, thus precluding the use of this solvent for enolization; a 1:1 mixture of THF/pyridine proved to be a viable reaction solvent for generation of a soluble enolate in this case (also in the presence of a saturating amount of LiCl; Table 1, entries 1–3). Subsequent addition of various alkyl halides (1.5–4.0 equiv) to these enolate solutions at temperatures ranging from −78 to 0 °C led to alkylated products in 84–99 % yields (after purification by flash column chromatography or recrystallization) with uniformly high diastereoselectivities (diastereomeric ratios (d.r.) of isolated products ranged from 98:2 to ≥99:1; d.r. values of crude products are listed in Table 1). We initially measured the diastereoselectivities of these reactions by HPLC analysis of the products; however, we later determined that they could also be readily assessed by ^{1}H NMR analysis of the corresponding oxazolinium triflate derivatives, which can be obtained by invertive cyclization with triflic anhydride (see the Supporting Information for details).[14] Diastereoselectivities were uniformly high, as in the corresponding alkylation reactions of pseudoephedrine amides. The majority of the alkylation products were solids.

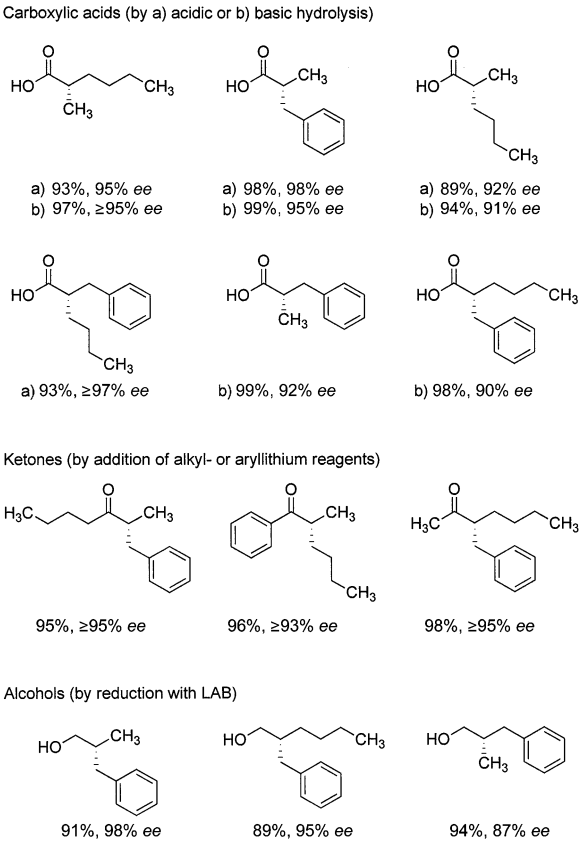
Table 1: Diastereoselective alkylation of pseudoephenamine amides.



Entry[a]	R^1	R^2	d.r. of crude product[b]	d.r. of isolated product[b]	Yield [%]	m.p. [°C]
1	Me	Bn	95:5	≥99:1	85	128–129
2	Me	*n*Bu	95:5	98:2	97	n.a.
3	Me	Et	≥94:6	98:2	96	n.a.
4	Et	Me	≥96:4	≥99:1	87	89–90
5	*n*Bu	Bn	≥98:2	≥99:1	99	112–114
6	*n*Bu	Me	95:5	98:2	84	77–79
7	Bn	Me	98:2	98:2	92	n.a.
8	Bn	*n*Bu	≥99:1	≥99:1	99	109–111

[a] Reactions in entries 1–3 were conducted in a 1:1 mixture of THF/pyridine as solvent; all other reactions were conducted in neat THF as solvent. All reactions were conducted with excess alkyl halide (1.5–4.0 equiv). [b] Diastereomeric ratios were determined by HPLC analysis; for entries 1 and 7, the corresponding trimethylsilyl ethers were analyzed by HPLC. Bn = benzyl, n.a. = not applicable.

Optically active carboxylic acids, ketones, and alcohols were obtained directly from alkylated pseudoephenamine amides by using methods paralleling those previously employed for similar transformations of pseudoephedrine amides (Scheme 2). Thus, hydrolysis of pseudoephenamine amides under both acidic and basic conditions provided carboxylic acids in high yields with little or no epimerization

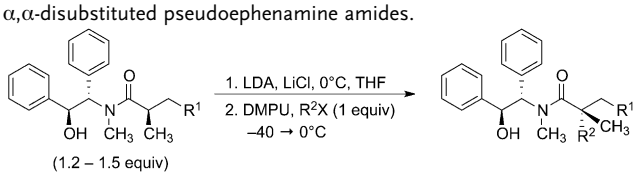


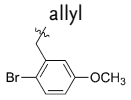
Scheme 2. Transformations of pseudoephenamine amides into enantiomerically enriched carboxylic acids, alcohols, and ketones. a) Acidic hydrolysis was achieved by heating the amide to 115 °C with 9 N sulfuric acid in dioxane. b) Basic hydrolysis was achieved by heating the amide to 95 °C with tetrabutylammonium hydroxide in a 3:1 mixture of *tert*-butyl alcohol and water.[1e]

of the α-carbon center (89–99 % yield), addition of organolithium reagents to pseudoephenamine amides afforded enantiomerically enriched ketones (95–98 % yield), and reduction of pseudoephenamine amides with lithium amidotrihydroborate (LAB)[15] gave the corresponding primary alcohols (89–94 % yield).[1e] Preliminary experiments exploring the direct transformation of pseudoephenamine amides to aldehydes with lithium triethoxyaluminum hydride as reductant have not yet provided the products in high yields (≈30–60 %).

Two methods using pseudoephenamine as a chiral auxiliary were investigated for the alkylative construction of quaternary carbon centers, and in both cases, significant enhancements in diastereoselectivities were observed compared to the corresponding transformations with pseudoephedrine. The first method involved sequential enolization–alkylation of α,α-disubstituted pseudoephenamine amides (Table 2), while the second method used a conjugate addition–alkylation protocol[16] with α-alkyl-α,β-unsaturated pseudoephenamine amides (Table 3).[17] In nearly all of the alkylation reactions, the ^{1}H NMR spectra of the crude reaction products were exceptionally clean and, indeed, in many cases the unpurified products appeared to be diastereomerically pure. The ^{1}H NMR spectra were further simpli-

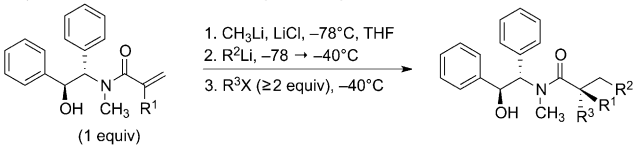
Table 2: Quaternary carbon centers formed by enolization-alkylation of α,α-disubstituted pseudoephenamine amides.



Entry	R^1	R^2	Yield [%]	d.r.[a]
1	Me	Bn	85	≥19:1 (≥19:1)
2	Me	allyl	99	≥19:1 (14:1)
3	Me		91	≥19:1 (7.3:1)
4	*n*Pr	Bn	87	≥19:1 (8.3:1)
5	Ph	allyl	82	≥19:1 (≥19:1)
6	Ph	Et	80	9.9:1[b] (6.2:1)

[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine. [b] The product diastereomers were separated by radial chromatography. The major diastereomer was isolated in 71% yield (d.r. ≥19:1), and the minor diastereomer was isolated in 6% yield (d.r. ≥19:1).

Table 3: Quaternary carbon centers formed by conjugate addition–alkylation of α,β-unsaturated pseudoephenamine amides.



Entry	R^1	R^2	R^3	Yield [%]	d.r.[a]
1	Me	*n*Bu	Bn	75	≥19:1 (10.1:1)
2	Me	*n*Bu	allyl	77	≥19:1 (11.1:1)
3	Me	Ph	allyl	80	≥19:1 (≥19:1)
4	Me	*t*Bu	allyl	85	≥19:1 (12.5:1)
5	Et	*t*Bu	Me	79	≥19:1 (9.1:1)
6	*n*-pentyl	*t*Bu	Me	76	≥19:1 (8.2:1)

[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine.

fied by the fact that the products appeared to exist in a single rotameric form; X-ray crystallographic analysis of the product of entry 1 (Table 2) showed that, in the solid state, this substance adopts the rotameric form in which the *N*-methyl group is *cis* to the quaternary center, and we believe that this is likely the case in solution as well. We confirmed that the isolated products were formed with ≥19:1 d.r. by ^{1}H NMR analysis of the corresponding oxazolinium triflate derivatives, formed with triflic anhydride. Only the example in entry 6 (Table 2) proceeded with a diastereomeric ratio <19:1 (d.r. 9.9:1), and, in this instance, the diastereomers could be separated by radial chromatography (facilitated by the UV activity of the auxiliary). As with the α,α-disubstituted pseudoephenamine amide products, the majority of pseudoephenamine amide products with α-quaternary carbon centers are solids, whereas the corresponding pseudoephedrine amide products are typically oils.

Our results suggest that, in many ways, pseudoephenamine is a superior chiral auxiliary for asymmetric synthesis compared with pseudoephedrine. Advantages include the fact that pseudoephenamine is free of regulatory restrictions, that pseudoephenamine amides have physical properties that facilitate their physical processing and spectroscopic analysis (greater crystallinity, lack of line-broadening in NMR spectra), and that alkylation reactions that form amide products with α-quaternary carbon centers proceed with notably higher diastereoselectivites.[18] To the best of our knowledge, pseudoephenamine is currently not commercially available, however, it is easily synthesized in large amounts from starting materials that are available in bulk at very low cost.

Received: January 13, 2012
Published online: March 27, 2012

Keywords: alkylation · asymmetric synthesis · chiral auxiliary · pseudoephedrine · pseudoephenamine

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[2] Pseudoephedrine is illegal in Mexico, Japan, and Colombia, and it is highly regulated by law in the United States and Australia. It is a Table 1 precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances and is a banned item on the World Anti-Doping Agency list.

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