

Synthetic Methods

# Stereocontrolled Synthesis of *syn*- $\beta$ -Hydroxy- $\alpha$ -Amino Acids by Direct Aldolization of Pseudoephedrine Glycinamide\*\*

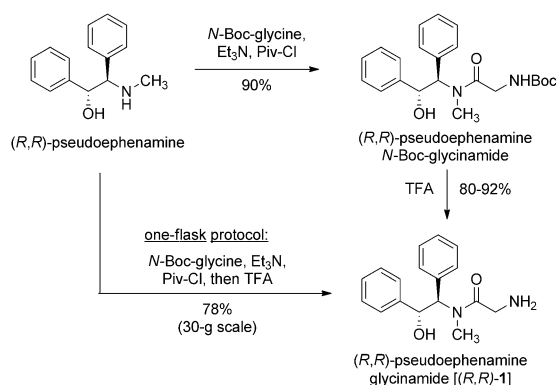
Ian B. Seiple, Jaron A. M. Mercer, Robin J. Sussman, Ziyang Zhang, and Andrew G. Myers\*

**Abstract:**  $\beta$ -Hydroxy- $\alpha$ -amino acids figure prominently as chiral building blocks in chemical synthesis and serve as precursors to numerous important medicines. Reported herein is a method for the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives by aldolization of pseudoephedrine glycinamide, which can be prepared from pseudoephedrine in a one-flask protocol. Enolization of (*R,R*)- or (*S,S*)-pseudoephedrine glycinamide with lithium hexamethyldisilazide in the presence of LiCl followed by addition of an aldehyde or ketone substrate affords aldol addition products that are stereochemically homologous with L- or D-threonine, respectively. These products, which are typically solids, can be obtained in stereoisomerically pure form in yields of 55–98%, and are readily transformed into  $\beta$ -hydroxy- $\alpha$ -amino acids by mild hydrolysis or into 2-amino-1,3-diols by reduction with sodium borohydride. This new chemistry greatly facilitates the construction of novel antibiotics of several different classes.

As part of a program to develop practical synthetic chemistry for the discovery of new antibiotics we investigated, and herein report, a two-step method for the constructive assembly of enantiomerically pure *syn*- $\beta$ -hydroxy- $\alpha$ -amino acids from simple starting materials. These products figure prominently as chemical precursors to a number of important medicines, most notably antibiotics, as evidenced by the fact that five of the compounds prepared in this study have been transformed into antibiotics from four different structural classes: amphenicols, monobactams, vancomycins, and macrolides. The chemistry we describe offers a number of practical advantages relative to existing methodology, which we discuss after presentation of our results.

The basis of the new methodology stems from the discovery that pseudoephedrine glycinamide (**1**) undergoes efficient and diastereoselective *syn* aldolization with both aldehyde and (remarkably) ketone substrates.<sup>[1]</sup> The key precursor in this transformation, **1**, is readily available in both

enantiomeric forms on multigram scale from the appropriate enantiomer of pseudoephedrine<sup>[2]</sup> and *N*-Boc glycine using either one- or two-step protocols (the yields are effectively the same; Scheme 1). The compound **1** is conveniently recrystallized from absolute ethanol and forms a free flowing,



**Scheme 1.** Synthesis of pseudoephedrine glycinamide (**1**). Boc = *tert*-butoxycarbonyl, Piv = pivaloyl, TFA = trifluoroacetic acid.

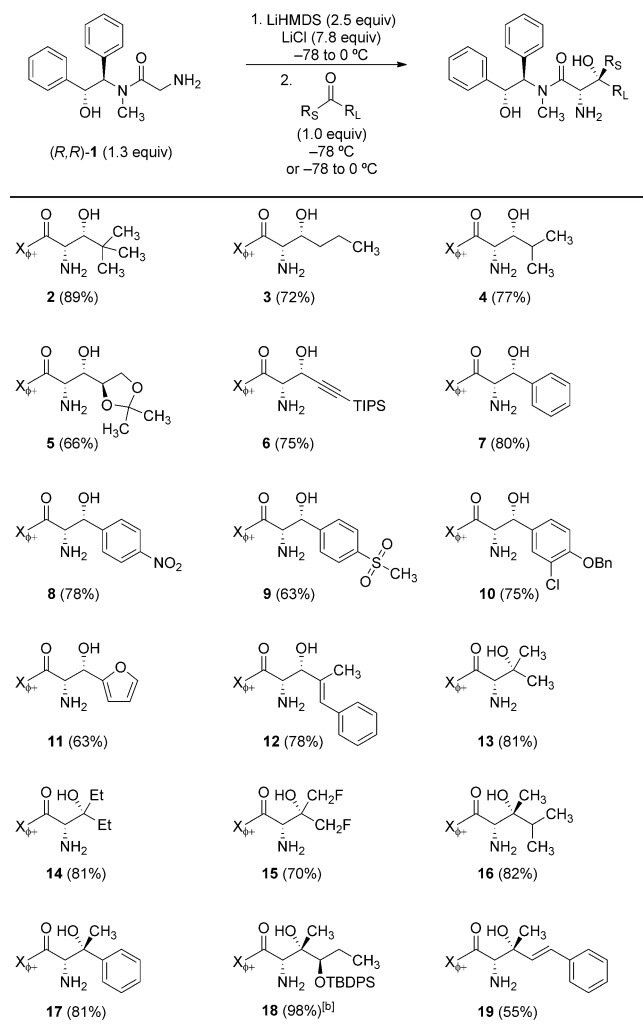
white crystalline solid (mp 168–170°C, 78% overall yield employing the one-flask protocol followed by recrystallization, 30-g scale). X-ray crystallographic analysis reveals that the crystalline lattice is free of any solvent or water molecules. Furthermore, unlike pseudoephedrine glycinamide,<sup>[3]</sup> in crystalline form **1** shows little or no propensity to hydrate upon exposure to the air and thus is easily weighed and transferred in the laboratory.

Enolization/*syn*-aldolization of **1** was readily achieved by the following general protocol. Freshly (flame) dried anhydrous lithium chloride (saturating, ca. 7.8 equiv)<sup>[4]</sup> and **1** (1.3 equiv)<sup>[5]</sup> were combined at 23°C in anhydrous THF (ca. 0.15M in **1**) and the resulting suspension was stirred at 23°C until **1** dissolved; a portion of the excess LiCl did not dissolve. The resulting suspension was cooled to –78°C whereupon a freshly prepared solution of lithium hexamethyldisilazide in THF (1M, 2.5 equiv) was added by syringe. After stirring at –78°C for 5 minutes, the reaction flask was transferred to an ice-water bath for 25 minutes, then was re-cooled to –78°C where a solution of an aldehyde or ketone substrate in THF (1M, 1 equiv) was added. The progress of the aldol addition was conveniently monitored by TLC analysis. Aldehyde reactants were typically completely consumed within 30 minutes at –78°C, whereas reactions with ketone substrates proceeded more slowly and in certain cases required warming to 0°C to achieve complete conversion (see Table 1 and the Supporting Information). In all cases

[\*] Dr. I. B. Seiple, J. A. M. Mercer, R. J. Sussman, Z. Zhang, Prof. Dr. A. G. Myers  
Department of Chemistry and Chemical Biology  
Harvard University, Cambridge, MA 02138 (USA)  
E-mail: myers@chemistry.harvard.edu

[\*\*] We gratefully acknowledge the NSF for partial financial support. We express our gratitude to Dr. Shao-Liang Zheng for his exceptional work in conducting X-Ray crystallographic analyses. J.A.M.M. acknowledges Pfizer for financial support through the ACS SURF program. I.B.S. acknowledges postdoctoral fellowship support from the National Institutes of Health (F32M099233). Z.Z. is a Howard Hughes Medical Institute International Student Research fellow.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201400928>.

**Table 1:** Aldolization of pseudoephedrine glycinamide (**1**) with aldehyde and ketone substrates.


[a]  $X_{\phi+}$  = (*R,R*)-pseudoephedrine. Reactions were run at a final concentration of 0.1 M (electrophile) and were performed on at least a 1 mmol scale. Yields of major isolated diastereomers are reported. Diastereomeric ratios can be found in the Supporting Information.

[b] Reaction was run on a 20-g scale. Enolization was conducted at 0 °C, and the final concentration of electrophile was 0.05 M. HMDS = hexamethyldisilazide, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

only one of the four possible diastereomeric aldol addition products predominated (Table 1), and this product was typically readily isolated in diastereomerically pure form by flash column chromatography (55–98% yield of purified product). The minor diastereomeric aldol addition product(s) typically constituted less than 15% of the product mixture.<sup>[6,7]</sup>

As shown in Table 1, many different aldehydes and ketones were found to be effective substrates. We observed that the majority of the purified primary aldol products were solids. In the case of the product **4** (from isobutyraldehyde) crystals suitable for X-ray analysis were obtained. The solid-state structure of **4** derived from (*R,R*)-**1** revealed it to be the *syn*-aldol product that is stereochemically homologous with L-threonine. In addition, the absolute and relative stereo-

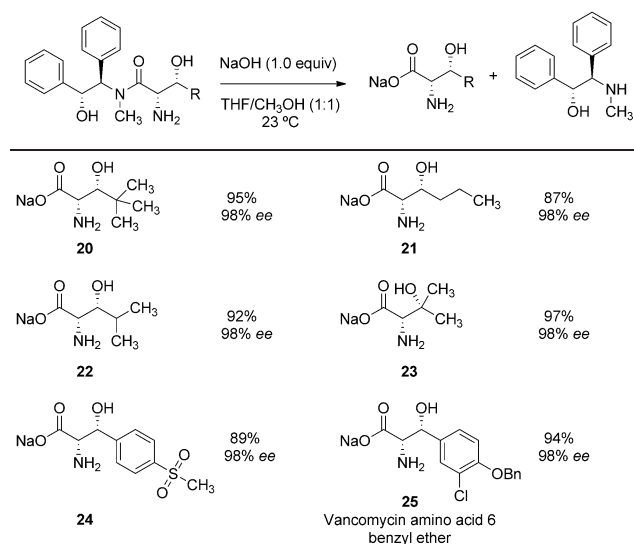
chemistries of the *syn*-aldol adducts **8** and **9** (from *para*-nitrobenzaldehyde and *para*-methanesulfonylbenzaldehyde, respectively) were rigorously established to form a homochiral series with **4** on the basis of their successful conversion into the active antibiotics chloramphenicol and thiamphenicol, respectively (see below). Stereochemical assignments of the remaining aldehyde addition products from Table 1 were made by analogy. The stereochemistry of these products conforms with the diastereofacial preferences for alkylation reactions of pseudoephedrine amide enolates, provided that a *Z* enolate (with the  $\alpha$ -amino group and enolate oxygen atom *cis*) is invoked, which seems to us to be quite reasonable.<sup>[2b]</sup> The *syn* stereochemistry presumably arises from a Zimmerman–Traxler transition structure.<sup>[8]</sup>

In addition to its general, efficient, and stereoselective reactions with aldehyde substrates (linear, branched, and  $\alpha$ -tetrasubstituted aliphatic, aromatic,  $\alpha$ -oxygenated, and  $\alpha,\beta$ -unsaturated), **1** also serves as an exceptional substrate for aldolization with ketone substrates, thus providing aldol adducts with fully substituted  $\beta$ -centers, as illustrated by the seven examples (**13–19**) in Table 1. The stereochemistry of the aldol adduct **16** (from methyl isopropyl ketone) was established unambiguously by X-ray analysis of its crystalline hydrate. Not surprisingly, it was found to be fully consistent with the stereochemistry of the aldehyde aldol adducts (the methyl group acts as the “small” group). We also rigorously established the stereochemistry of the aldol adduct **18** by X-ray analysis of a crystalline derivative, and this conformed to that of the other aldol products. This product appears to represent a case of stereochemical matching, where the diastereofacial preferences of the enolate and the chiral ketone substrate (the latter consistent with a Felkin–Anh trajectory)<sup>[9]</sup> are reinforcing, thus accounting for the extraordinarily high stereoselectivity and yield of this particular transformation. The product **19** (55% yield upon isolation), from methyl styryl ketone, was formed least efficiently, and we believe it to be a consequence of competitive conjugate addition (ca. 15%).

As a seemingly minor point, we note that careful analysis of the <sup>1</sup>H NMR spectra of the majority of the purified aldol adducts from Table 1 reveals that in addition to the two rotameric forms of the expected *syn*-aldol diastereomers, trace ( $\leq 5\%$ ) amounts of an impurity corresponding to the *N*→*O*-acyl transfer product, a  $\beta$ -amino ester, are present.<sup>[10]</sup> This data reveals that the latter constitutional isomer is only slightly higher in energy than the tertiary amide form, thus providing a rationale for the remarkable facility of the subsequent transformations of the direct aldol products, namely their hydrolysis and reduction.

In contrast to reaction conditions typical for hydrolysis of tertiary amides, hydrolysis of the aldol adducts of Table 1 proceeds under remarkably mild conditions, and are more consistent with saponification of an ester than hydrolysis of a tertiary amide (Table 2). For example, hydrolysis of **4** was complete within 4 hours at 23 °C in the presence of 1 equivalent of sodium hydroxide in 1:1 THF/methanol. Once hydrolysis was complete, pseudoephedrine was recovered by extraction with dichloromethane in quantitative yield ( $\geq 95\%$  purity), and the alkaline aqueous solution was lyophi-

**Table 2:** Mild alkaline hydrolysis of aldol adducts.<sup>[a]</sup>

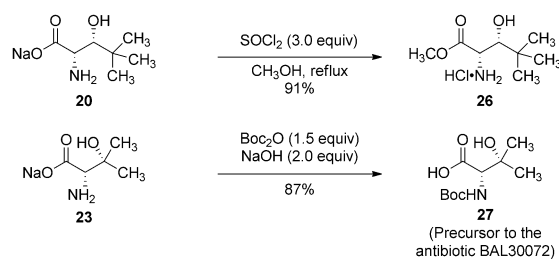


[a] (*R,R*)-Pseudoephedrine was recovered in  $\geq 90\%$  yield in each case in high purity. Yields are those of the isolated product. Enantiomeric purity was determined by  $^1\text{H}$  NMR analysis of the (*R*)- and (*S*)-MTPA amides. For experimental details, see the Supporting Information.

lized to provide the  $\beta$ -hydroxy- $\alpha$ -amino sodium carboxylate **22** in 92% yield and greater than 98% *ee* (Table 2). The inclusion of methanol was critical to avoid retroaldol fragmentation during the hydrolysis, which was otherwise facile, especially with aromatic aldol addition products. In a noteworthy example, use of the THF/methanol/sodium hydroxide protocol with substrate **10** afforded the aromatic aldolate **25** in 94% yield and greater than 98% *ee* (auxiliary recovery: 97% yield). A protected form of the latter  $\alpha$ -amino acid served as a key starting material in the synthesis of vancomycin as reported by the Nicolaou group.<sup>[11]</sup>

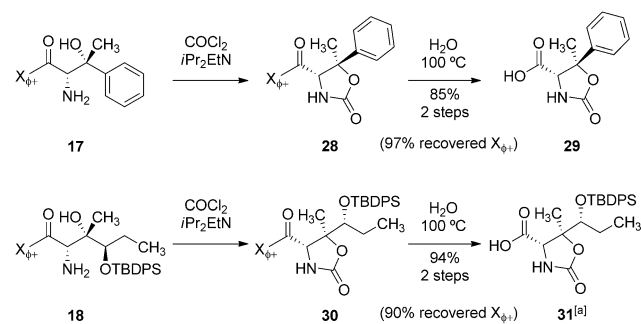
Interestingly, the present hydrolysis conditions are much milder than those required for hydrolysis of pseudoephedrine<sup>[10]</sup> and pseudoephedrine<sup>[2b]</sup> amide alkylation products, thus suggesting that the  $\beta$ -hydroxy group of the aldol adducts may facilitate  $\text{N} \rightarrow \text{O}$ -acyl transfer. In this regard, it is notable (though not surprising) that X-ray crystallographic analysis (structures **4** and **16**) reveals an internal hydrogen bond between the amide carbonyl groups and their  $\beta$ -hydroxy functions. We believe that facile hydrolysis (and reduction) of pseudoephedrine amide aldol products occurs by rapid  $\text{N} \rightarrow \text{O}$ -acyl transfer and subsequent saponification (reduction) of the resulting  $\beta$ -amino ester, as we have previously proposed for alkaline hydrolyses of pseudoephedrine amides.<sup>[10]</sup>

The  $\alpha$ -amino sodium carboxylates obtained upon alkaline hydrolysis can be converted into  $\alpha$ -amino acid methyl esters upon exposure to acidic methanol (e.g., **20**  $\rightarrow$  **26**; Scheme 2). Alternatively, treatment of the same substrates with di-*tert*-butyldicarbonate affords *N*-Boc-protected amino acids in high yield (e.g., **23**  $\rightarrow$  **27**; Scheme 2). The *N*-Boc  $\alpha$ -amino acid **27** is noteworthy for it serves as precursor to the fully synthetic monobactam antibiotic BAL30072, which is currently in phase I clinical trials as an anticipated treatment for infections caused by Gram-negative bacteria.<sup>[12]</sup>



**Scheme 2.** Esterification and *N*-Boc protection of amino carboxylates.

Alkaline hydrolysis conditions were not uniformly successful with every substrate. In certain cases retroaldol fragmentation was faster than hydrolysis, even when employing our optimal protocol. For example, treatment of the ketone aldol adduct **17** with 1 equivalent of sodium hydroxide in 1:1 methanol/water at 23 °C provided primarily three products: acetophenone, pseudoephedrine, and sodium glycinate (the latter two products presumably result from hydrolytic cleavage of **1**). None of the desired  $\beta$ -hydroxy- $\alpha$ -amino sodium carboxylate was observed.<sup>[13]</sup> We envisioned that retroaldol fragmentation would be avoided if the  $\beta$ -hydroxy substituent were shielded, and for this purpose we chose a cyclic carbamate, which can easily be introduced and removed<sup>[14]</sup> under very mild reaction conditions and has the added benefit of protecting the  $\alpha$ -amino function. Treatment of the aldol adduct **17** with phosgene (1.1 equiv) and diisopropylethylamine (3 equiv) at  $-78^\circ\text{C}$  in dichloromethane formed, within 30 minutes, the cyclic carbamate **28**, which was isolated in pure form by simple biphasic extraction (Scheme 3). Although **28** was resistant to alkaline hydrolysis

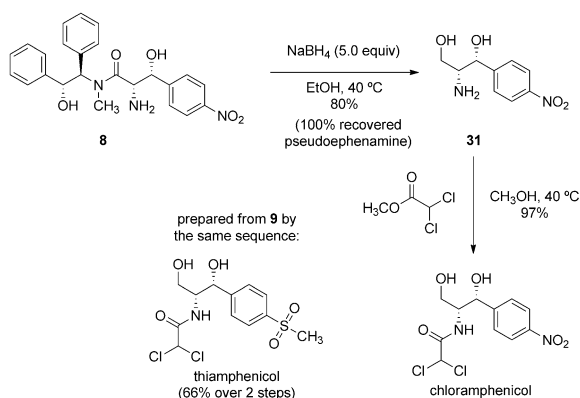


**Scheme 3.** Cyclic carbamate formation followed by hydrolysis under neutral conditions affords protected  $\alpha$ -amino acid derivatives.  $X_{\beta+\alpha}$  = (*R,R*)-pseudoephedrine. [a] Product contained  $\leq 8\%$  TBDPS-OH after aqueous extraction.

(presumably because of the acidity of the carbamate function) we found that heating a solution of **28** in a 1:1 mixture of 1,4-dioxane and pure water at reflux for 24 hours effected clean hydrolysis of the auxiliary. Straightforward acid-base extraction then provided the acid **29** in 85% yield (and, separately, pseudoephedrine in 97% yield). By an analogous sequence, treatment of **18** with phosgene provided the carbamate **30** (the stereochemistry of which was rigorously established by X-ray crystallography). This intermediate has been trans-

formed into more than 100 novel macrolide antibiotics in ongoing research in our laboratory.<sup>[15]</sup> Hydrolysis of **30** provided the acid **31** in 94% yield (90% recovered pseudoephedrine).

To apply our new aldol methodology to synthesize chloramphenicol and thiamphenicol, antibiotics which are on the essential medicine list published by the World Health Organization<sup>[16]</sup> and play critical roles in the treatment of infectious disease, especially in developing countries,<sup>[17]</sup> we investigated reductive cleavage of the auxiliary to produce 2-amino-1,3-diols. Remarkably, treatment of the aldol adduct **8** with the mild reducing agent sodium borohydride (5.0 equiv) in ethanol at 40°C provided the 2-amino-1,3-diol **32** in 80% yield (Scheme 4), and the auxiliary was recovered quantita-



**Scheme 4.** Mild reductive cleavage of aldol adducts applied to the syntheses of chloramphenicol and thiamphenicol.

tively in pure form. We are aware of only one previous report of the reduction of tertiary amides ( $\alpha$ -hydroxy morpholinamides) to the corresponding alcohols with sodium borohydride.<sup>[18]</sup> Reduction of pseudoephedrine and pseudoephedrine amides to the corresponding primary alcohols has historically been achieved using lithium amidotrihydroborate (LAB),<sup>[2b,3b,10]</sup> a much more reactive hydride donor that we introduced in 1996.<sup>[19]</sup> Again, we believe that the facile reduction with sodium borohydride we observe is due to intramolecular N $\rightarrow$ O-acyl transfer followed by reduction of the resulting  $\alpha$ -amino ester.<sup>[20]</sup> The synthesis of chloramphenicol was completed by acylation of **32** with methyl dichloroacetate (Scheme 4), thus providing the antibiotic in excellent yield in just three steps from (*R,R*)-pseudoephedrine glycinamide (**1**) and *para*-nitrobenzaldehyde. Thiamphenicol was synthesized by an identical two-step sequence from the aldol adduct **9**. In contrast to the three-step routes to chloramphenicol and thiamphenicol reported here, the commercial routes to these substances require about six linear steps, including a resolution.<sup>[21]</sup>

Commensurate with their importance in medicine, chemists have developed an extraordinarily diverse array of methods to synthesize enantiomerically enriched  $\beta$ -hydroxy- $\alpha$ -amino acids. These may be divided into two broad categories: constructive syntheses (as in the present work) and nonconstructive syntheses. The latter include the Sharp-

less asymmetric aminohydroxylation of certain alkenyl esters,<sup>[22]</sup> multistep transformations of Garner aldehyde-type intermediates,<sup>[23]</sup> asymmetric hydrogenation of 2-amino- $\beta$ -ketoesters,<sup>[24]</sup> as well as other strategies.<sup>[14f,25]</sup>

Constructive syntheses are generally more powerfully simplifying, for they enable retrosynthetic targeting of the C–C bond linking the stereogenic, heteroatom-bearing centers. The pioneering advances of the Schöllkopf group, employing bis(lactim) ethers,<sup>[26]</sup> and the Seebach group, employing masked glycine-derived heterocycles,<sup>[27]</sup> as substrates in diastereoselective aldol additions remain important enabling methodologies. To reveal the parent  $\beta$ -hydroxy- $\alpha$ -amino acids or esters, however, strongly acidic conditions are required and auxiliary-derived byproducts can complicate isolation of the products.<sup>[26e,f]</sup> Evans and Weber developed  $\alpha$ -isothiocyanato acyl oxazolidinones as substrates in their diastereoselective tin-mediated aldol chemistry,<sup>[28]</sup> and notable advances have been recorded by the groups of Willis,<sup>[29]</sup> Feng,<sup>[30]</sup> and Seidel<sup>[31]</sup> to transform this method into processes mediated by chiral catalysts. These  $\alpha$ -isothiocyanate methodologies afford thio-carbamate heterocycles as products, which conveniently serve to protect the amine and alcohol functionalities of the aldol adducts, but require a three-step procedure to reveal the embedded  $\alpha$ -amino acids. Methods employing chiral glycine enolate equivalents have also been reported by the groups of Bold,<sup>[32]</sup> Iwanowicz,<sup>[33]</sup> Caddick,<sup>[34]</sup> and Franck.<sup>[35]</sup> Hydroxymethylations of alanine equivalents to form  $\alpha$ -alkyl serine derivatives have also been reported.<sup>[36]</sup>

Another notable approach employs Schiff bases of glycine *tert*-butyl esters in aldol reactions with aldehyde substrates to provide aldol addition products which are then treated with acid to reveal the embedded  $\beta$ -hydroxy- $\alpha$ -amino esters. Advances in this area were reported by the groups of Mukaiyama,<sup>[37]</sup> Belokon,<sup>[38]</sup> Miller,<sup>[39]</sup> and Corey,<sup>[40]</sup> and subsequently several modifications have emerged and provide both *syn*<sup>[41]</sup> and *anti*<sup>[42]</sup> products. While these methods are convenient because of the facile enolization of glycine Schiff bases and the direct conversion of the aldol products into  $\beta$ -hydroxy- $\alpha$ -amino esters, they often suffer from poor diastereoselectivities, narrow substrate scope, and frequently require further functionalization to permit separation of *syn* and *anti* aldol addition products.

Ito, Hayashi, and co-workers employed  $\alpha$ -isocyno esters and amides in aldol reactions catalyzed by chiral gold(I) complexes, thus providing oxazoline-4-carboxylate products which can be converted into  $\beta$ -hydroxy- $\alpha$ -amino acids upon treatment with strong acid.<sup>[43]</sup> Oxazoline-4-carboxylates have also been constructed by the addition of 5-alkoxyoxazoles to aldehydes catalyzed by chiral aluminum catalysts, as demonstrated by Suga and Ibata<sup>[44]</sup> and the Evans group.<sup>[45]</sup> These systems were found to be highly effective only with aromatic aldehyde substrates, and conversion of the oxazoline products into  $\beta$ -hydroxy- $\alpha$ -amino acids requires three steps and harshly acidic conditions. Barbas, Tanaka, and co-workers reported a method for the aldolization of phthalimidoacetaldehyde catalyzed by proline that achieved high enantio- and diastereoselectivities, but only with  $\alpha$ -branched aldehyde substrates.<sup>[46]</sup> The Wong group has developed methodology for chemoenzymatic aldolization of glycine catalyzed by threo-



nine aldolases which, while highly stereoselective for certain aldehyde substrates, is limited in scope.<sup>[47]</sup>

Aldolization of pseudoephedrine glycinamide offers a number of advantages. Enolization of **1** proceeds under very mild conditions (LiHMDS, LiCl) without metal additives, and the *syn*-aldol products are readily obtained in stereoisomerically pure form by column chromatography. A broad selection of electrophiles, including alkyl and aryl aldehydes and ketones, undergo efficient aldolization with **1**, whereas many other glycine equivalents react efficiently only with aryl or alkyl aldehydes, and very few are reported to react efficiently with ketones.<sup>[48]</sup> With the exception of chemoenzymatic approaches,<sup>[47]</sup> the aforementioned glycine equivalents all require shielding of the  $\alpha$ -amino group, but this is not necessary with our method. Hydrolysis of the aldol adducts of **1** proceeds under unusually mild reaction conditions compared to other glycine equivalents, and both the product and the auxiliary can be isolated by straightforward biphasic extraction. Additionally, reduction of pseudoephedrine glycinamide aldol adducts to the corresponding primary alcohols can be accomplished with the mild reducing agent sodium borohydride. We believe pseudoephedrine glycinamide (**1**) is an exceedingly practical reagent for the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids and chiral 2-amino-1,3-diols, and anticipate the methods reported herein will have broad applicability in chemical synthesis.

Received: January 27, 2014  
Published online: April 1, 2014

**Keywords:** aldol reaction · amino acids · asymmetric synthesis · chiral auxiliaries · synthetic methods

- [1] Aldol addition reactions of pseudoephedrine amides (but not glycine amides) are well precedented. See: a) J. L. Vicario, D. Badía, E. Domínguez, M. Rodríguez, L. Carrillo, *J. Org. Chem.* **2000**, *65*, 3754–3760; b) J. L. Vicario, M. Rodríguez, D. Badía, L. Carrillo, E. Reyes, *Org. Lett.* **2004**, *6*, 3171–3174; c) M. Rodríguez, J. L. Vicario, D. Badía, L. Carrillo, *Org. Biomol. Chem.* **2005**, *3*, 2026–2030; d) M. Ocejo, L. Carrillo, J. S. Vicario, D. Badía, E. Reyes, *J. Org. Chem.* **2011**, *76*, 460–470; e) B. R. Kusuma, G. E. L. Brandt, B. S. J. Blagg, *Org. Lett.* **2012**, *14*, 6242–6245.
- [2] a) For practical, scalable syntheses of (*R,R*)- and (*S,S*)-pseudoephedrine, see: K. T. Mellem, A. G. Myers, *Org. Lett.* **2013**, *15*, 5594–5597; b) For the alkylation of pseudoephedrine amides, see: M. R. Morales, K. T. Mellem, A. G. Myers, *Angew. Chem.* **2012**, *124*, 4646–4649; *Angew. Chem. Int. Ed.* **2012**, *51*, 4568–4571; c) For the synthesis and alkylation of pseudoephedrine alaninamide pivaldimine, see: C. L. Hugelshofer, K. T. Mellem, A. G. Myers, *Org. Lett.* **2013**, *15*, 3134–3137.
- [3] a) A. G. Myers, J. L. Gleason, T. Yoon, *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489; b) A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656–673; c) A. G. Myers, P. Schneider, S. Kwon, D. W. Kung, *J. Org. Chem.* **1999**, *64*, 3322–3327.
- [4] Lithium chloride was essential to achieve high diastereoselectivities in aldol addition reactions. For example, addition of the lithium enolate derived from **1** (in absence of LiCl) to benzaldehyde afforded a much reduced d.r. value (53% desired:47% sum of minor isomers).
- [5] Pseudoephedrine glycinamide (**1**) can also be used as the limiting reagent, with a moderate decrease in yield: aldolization of **1** (1.0 equiv) with benzaldehyde (1.2 equiv) provided pure **7** in 65% yield (standard conditions provided the product in 80% yield).
- [6] These minor products were not readily separated and therefore were not carefully studied, with the exception of the minor adducts from symmetric ketone substrates (**13–15**). See the Supporting Information for further details.
- [7] Interestingly, we observed that aldol addition reactions of pseudoephedrine glycinamide (Ref. [3]) were inferior to those of pseudoephedrine glycinamide (**1**). For example, the yield of the isolated major *syn*-aldol adduct of pseudoephedrine glycinamide and benzaldehyde was just 57% (d.r. 72% desired:28% sum of minor isomers) whereas the parallel transformation with **1** gave an 80% yield of pure *syn*-aldol product (d.r. 85% desired:15% sum of minor isomers).
- [8] a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923; b) D. A. Evans, *Aldrichimica Acta* **1982**, *15*, 23–32.
- [9] By contrast, the mismatched combination of the enolate from (*S,S*)-**1** and the same chiral ketone that led to **18** was poorly selective, thus affording a 52:25:15:8 mixture of diastereomeric aldol adducts which was not characterized in detail.
- [10] We have previously proposed N $\rightarrow$ O-acyl transfer products as important intermediates in both acidic and alkaline hydrolyses of pseudoephedrine amides. See Ref. [3b] and the following paper: A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
- [11] K. C. Nicolaou, C. N. C. Boddy, H. Li, A. E. Koumbis, R. Hughes, S. Natarajan, N. F. Jain, J. M. Ramanjulu, S. Brase, M. E. Solomon, *Chem. Eur. J.* **1999**, *5*, 2602–2621.
- [12] M. Hornsey, L. Phee, W. Stubbings, D. W. Wareham, *Int. J. Antimicrob. Agents* **2013**, *42*, 343–346.
- [13] Attempts to hydrolyze substrate **17** with alkaline hydrogen peroxide or under acidic conditions were not successful.
- [14] a) M. E. Jung, Y. H. Jung, *Tetrahedron Lett.* **1989**, *30*, 6637–6640; b) G. M. C. Di, D. Misiti, G. Zappia, M. G. Delle, *Tetrahedron* **1993**, *49*, 11321–11328; c) L. Williams, Z. Zhang, X. Ding, M. M. Joullie, *Tetrahedron Lett.* **1995**, *36*, 7031–7034; d) M. G. Delle, G. M. C. Di, D. Misiti, G. Zappia, *Tetrahedron: Asymmetry* **1997**, *8*, 231–243; e) T. Laiß, J. Chastanet, J. Zhu, *Tetrahedron Lett.* **1997**, *38*, 1771–1772; f) C. Tomasini, A. Vecchione, *Org. Lett.* **1999**, *1*, 2153–2156.
- [15] I. B. Seiple, Z. Zhang, A. Langlois, K. Yabu, P. M. Wright, M. Condakes, F. Szczypliński, A. G. Myers, unpublished results.
- [16] World Health Organization Model List of Essential Medicines, 18th edition: <http://www.who.int/medicines/publications/essentialmedicines/en/> (Accessed December, **2013**).
- [17] M. E. Falagas, A. P. Grammatikos, A. Michalopoulos, *Expert Rev. Anti-Infect. Ther.* **2008**, *6*, 593–600.
- [18] S. R. Borkar, B. N. Manjunath, S. Balasubramaniam, I. S. Aidhen, *Carbohydr. Res.* **2012**, *358*, 30.
- [19] A. G. Myers, B. H. Yang, K. J. David, *Tetrahedron Lett.* **1996**, *37*, 3623–3626.
- [20] The reduction of  $\alpha$ -amino esters with sodium borohydride is well precedented. For an early, detailed study, see: H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada, *Chem. Pharm. Bull.* **1965**, *13*, 995–1000.
- [21] a) L. Coppi, C. Giordano, A. Longoni, S. Panossian, in *Chirality in Industry II: Developments in the Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. Sheldrake, J. Crosby), John Wiley & Sons Ltd, West Sussex, England, **1998**, pp. 353–362; b) S. V. Bhat, B. A. Nagasampagi, M. Sivakumar, *Chemistry of Natural Products*, Springer, Berlin, **2005**; c) A. A. Yunis, *Am. J. Med.* **1989**, *87*, 44N–48N.

- [22] a) B. Tao, G. Schlingloff, K. B. Sharpless, *Tetrahedron Lett.* **1998**, 39, 2507–2510; b) A. J. Morgan, C. E. Masse, J. S. Panek, *Org. Lett.* **1999**, 1, 1949–1952; c) H. Park, B. Cao, M. M. Joullie, *J. Org. Chem.* **2001**, 66, 7223–7226.
- [23] a) L. Williams, Z. Zhang, F. Shao, P. J. Carroll, M. M. Joullie, *Tetrahedron* **1996**, 52, 11673–11694; b) M. A. Blaskovich, G. Evindar, N. G. W. Rose, S. Wilkinson, Y. Luo, G. A. Lajoie, *J. Org. Chem.* **1998**, 63, 3631–3646; c) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, M. M. Zurbano, *Tetrahedron: Asymmetry* **2000**, 11, 2195–2204; d) N. Okamoto, O. Hara, K. Makino, Y. Hamada, *J. Org. Chem.* **2002**, 67, 9210–9215.
- [24] a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, et al., *J. Am. Chem. Soc.* **1989**, 111, 9134–9135; b) E. Coulon, M. Cristina, A. C. De, V. Ratovelomanana-Vidal, J.-P. Genet, *Tetrahedron Lett.* **1998**, 39, 6467–6470; c) R. Kuwano, S. Okuda, Y. Ito, *J. Org. Chem.* **1998**, 63, 3499–3503; d) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Angew. Chem.* **2004**, 116, 900–902; *Angew. Chem. Int. Ed.* **2004**, 43, 882–884; e) K. Makino, Y. Hiroki, Y. Hamada, *J. Am. Chem. Soc.* **2005**, 127, 5784–5785; f) B. Seashore-Ludlow, P. Villo, C. Hacker, P. Somfai, *Org. Lett.* **2010**, 12, 5274–5277.
- [25] a) G. Guanti, L. Banfi, E. Narisano, *Tetrahedron* **1988**, 44, 5553–5562; b) J. P. Genet, S. Juge, S. Mallart, *Tetrahedron Lett.* **1988**, 29, 6765–6768; c) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, 120, 11532–11533; d) F. A. Davis, V. Srirajan, D. L. Fanelli, P. Portonovo, *J. Org. Chem.* **2000**, 65, 7663–7666; e) K. J. Hale, S. Manaviar, V. M. Delisser, *Tetrahedron* **1994**, 50, 9181–9188; f) A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, 35, 5043–5046; g) H. Shao, M. Goodman, *J. Org. Chem.* **1996**, 61, 2582–2583; h) H. Shao, J. K. Rueter, M. Goodman, *J. Org. Chem.* **1998**, 63, 5240–5244.
- [26] a) U. Schöllkopf, U. Groth, M. R. Gull, J. Nozulak, *Liebigs Ann. Chem.* **1983**, 1133–1151; b) M. Grauert, U. Schöllkopf, *Liebigs Ann. Chem.* **1985**, 1817–1824; c) U. Schöllkopf, J. Nozulak, M. Grauert, *Synthesis* **1985**, 55–56; d) U. Schöllkopf, J. Bardenhagen, *Liebigs Ann. Chem.* **1987**, 393–397; e) U. Schöllkopf, T. Tiller, J. Bardenhagen, *Tetrahedron* **1988**, 44, 5293–5305; f) U. Groth, U. Schöllkopf, T. Tiller, *Tetrahedron* **1991**, 47, 2835–2842; g) Modifications of the Schöllkopf method have been reported. See, for example: D. Alker, G. Hamblett, L. M. Harwood, S. M. Robertson, D. J. Watkin, C. E. Williams, *Tetrahedron* **1998**, 54, 6089–6098; h) See also: F. P. Di, G. Porzi, S. Sandri, *Tetrahedron: Asymmetry* **1999**, 10, 2191–2201.
- [27] D. Seebach, E. Juaristi, D. D. Miller, C. Schickli, T. Weber, *Helv. Chim. Acta* **1987**, 70, 237–261.
- [28] a) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, 108, 6757–6761; b) D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1987**, 109, 7151–7157; c) For related methodology from the Evans group using  $\alpha$ -halo enolates, see: D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett.* **1987**, 28, 39–42.
- [29] M. C. Willis, G. A. Cutting, V. J. D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem.* **2005**, 117, 1567–1569; *Angew. Chem. Int. Ed.* **2005**, 44, 1543–1545.
- [30] X. Chen, Y. Zhu, Z. Qiao, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2010**, 16, 10124–10129.
- [31] a) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, 130, 12248–12249; b) M. K. Vecchione, L. Li, D. Seidel, *Chem. Commun.* **2010**, 46, 4604–4606.
- [32] G. Bold, R. O. Duthaler, M. Riediker, *Angew. Chem.* **1989**, 101, 491–493; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 497–498.
- [33] E. J. Iwanowicz, P. Blomgren, P. T. W. Cheng, K. Smith, W. F. Lau, Y. Y. Pan, H. H. Gu, M. F. Malley, J. Z. Gougoutas, *Synlett* **1998**, 664–666.
- [34] S. Caddick, N. J. Parr, M. C. Pritchard, *Tetrahedron Lett.* **2000**, 41, 5963–5966.
- [35] J. Patel, G. Clave, P.-Y. Renard, X. Franck, *Angew. Chem.* **2008**, 120, 4292–4295; *Angew. Chem. Int. Ed.* **2008**, 47, 4224–4227.
- [36] a) C.-B. Ji, Y.-L. Liu, Z.-Y. Cao, Y.-Y. Zhang, J. Zhou, *Tetrahedron Lett.* **2011**, 52, 6118–6121; b) S. Shirakawa, K. Ota, S. J. Terao, K. Maruoka, *Org. Biomol. Chem.* **2012**, 10, 5753–5755.
- [37] T. Nakatsuka, T. Miwa, T. Mukaiyama, *Chem. Lett.* **1981**, 279–282.
- [38] a) Y. N. Belokon, I. E. Zel'tser, V. I. Bakhmutov, M. B. Saporovskaya, M. G. Ryzhov, A. I. Yanovskii, Y. T. Struchkov, V. M. Belikov, *J. Am. Chem. Soc.* **1983**, 105, 2010–2017; b) Y. N. Belokon, K. A. Kochetkov, N. S. Ikonnikov, T. V. Strelkova, S. R. Harutyunyan, A. S. Saghiyan, *Tetrahedron: Asymmetry* **2001**, 12, 481–485.
- [39] C. M. Gasparski, M. J. Miller, *Tetrahedron* **1991**, 47, 5367–5378.
- [40] M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, 40, 3843–3846.
- [41] a) N. Yoshikawa, M. Shibusaki, *Tetrahedron* **2002**, 58, 8289–8298; b) S. Mettath, G. S. C. Srikanth, B. S. Dangerfield, S. L. Castle, *J. Org. Chem.* **2004**, 69, 6489–6492; c) B. Ma, J. L. Parkinson, S. L. Castle, *Tetrahedron Lett.* **2007**, 48, 2083–2086.
- [42] a) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, 114, 4724–4726; *Angew. Chem. Int. Ed.* **2002**, 41, 4542–4544; b) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc.* **2004**, 126, 9685–9694; c) T. Ooi, M. Taniguchi, K. Doda, K. Maruoka, *Adv. Synth. Catal.* **2004**, 346, 1073–1076; d) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, 126, 9192–9193.
- [43] a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, 108, 6405–6406; b) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron Lett.* **1988**, 29, 235–238; c) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron* **1988**, 44, 5253–5262; d) M. Sawamura, Y. Nakayama, T. Kato, Y. Ito, *J. Org. Chem.* **1995**, 60, 1727–1732.
- [44] H. Suga, K. Ikai, T. Ibata, *Tetrahedron Lett.* **1998**, 39, 869–872.
- [45] D. A. Evans, J. M. Janey, N. Magomedov, J. S. Tedrow, *Angew. Chem.* **2001**, 113, 1936–1940; *Angew. Chem. Int. Ed.* **2001**, 40, 1884–1888.
- [46] R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, 6, 3541–3544.
- [47] a) V. P. Vassilev, T. Uchiyama, T. Kajimoto, C.-H. Wong, *Tetrahedron Lett.* **1995**, 36, 4081–4084; b) T. Kimura, V. P. Vassilev, G.-J. Shen, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, 119, 11734–11742; c) For a recent review of chemoenzymatic glycine aldols, see: N. Dueckers, K. Baer, S. Simon, H. Groeger, W. Hummel, *Appl. Microbiol. Biotechnol.* **2010**, 88, 409–424.
- [48] Schöllkopf and co-workers reported successful aldol additions of their bis(lactim) ether glycine equivalent to acetone, acetophenone, and cyclohexanone (see Ref. [26a]). Seebach and co-workers reported a successful addition of their auxiliary to acetone (see Ref. [27]). Belokon et al. reported successful reaction of a glycine Schiff base Ni<sup>II</sup> complex with acetone (see Ref. [38a]). Additionally, Soloshonok et al. have described methodology for aldol addition of a chiral Schiff base of glycine complexed with Ni<sup>II</sup> to trifluoromethyl ketones: V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, *Tetrahedron: Asymmetry* **1996**, 7, 1547–1550; V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, *Tetrahedron* **1996**, 52, 12433–12442.