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Synthesis of Quaternary α-Methyl α-Amino Acids by Asymmetric Alkylation of Pseudoephenamine Alaninamide Pivaldimine

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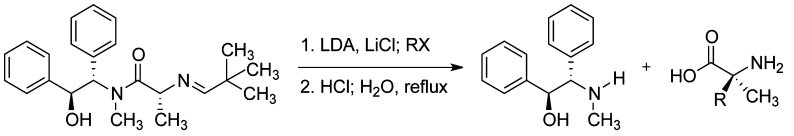
ABSTRACT



The utility of pseudoephenamine as a chiral auxiliary for the alkylative construction of quaternary α-methyl α-amino acids is demonstrated. The method is notable for the high diastereoselectivities of the alkylation reactions, for its versatility with respect to electrophilic substrate partners, and for its mild hydrolysis conditions, which provide α-amino acids without salt contaminants. Alternatively, α-amino esters can be obtained by direct alcoholysis.

(1*S*,2*S*)-Pseudoephenamine (*R*)-alaninamide pivaldimine (**1**) or its enantiomer serve as substrates in a new method for the alkylative construction of quaternary α-methyl α-amino acids. These substrates can be prepared in high yield by coupling of the appropriate stereoisomers of pseudoephenamine[1] and *N*-Boc alanine by the mixed anhydride method (pivaloyl chloride)[2] followed by *N*-Boc deprotection (HCl) and *tert*-butylimine formation (see Supporting Information). Two methods were developed to form the *N*-*tert*-butyl imine derivatives cleanly and in quantitative yield, which was essential to achieve high yields in the subsequent alkylation reactions. The first method involved adding pivaldehyde (2.0 equiv) to a stirring suspension of pseudoephenamine alaninamide (1 equiv) and activated 4 Å MS in a mixed solvent of benzene and dichloromethane at 23 °C. Evaporation of the solvents after 50 min afforded a white solid, which was held under vacuum (<1 Torr) at 35 °C overnight to remove excess pivaldehyde. The product (≥99% yield, est. ≥95% purity by ^{1}H and ^{13}C NMR) was used without further purification. A second successful protocol involved initial synthesis of pivaldehyde *N*-propyl imine as a reagent for transimination, a more facile and rapid process than imine formation from the corresponding aldehyde.[3] A mixture of pivaldehyde *N*-propyl imine (5.0 equiv) and pseudoephenamine alaninamide (1 equiv) was stirred in dry benzene at 23 °C under moderate vacuum (200 mmHg) for 30 min, during which time gas was observed to evolve from the reaction mixture (presumably *N*-propylamine). Concentration afforded a white solid, which was held under vacuum (<1 Torr) at 35 °C to remove all traces of the transimination reagent. The product, obtained in ≥99% yield (est. ≥95% purity by ^{1}H and ^{13}C NMR), was used without further purification in subsequent alkylation reactions. These methods were also effective for the preparation of (1*S*,2*S*)-pseudoephenamine (*S*)-alaninamide pivaldimine and its enantiomer, which proved to be mismatched substrates in pivaldimine alkylations (vide infra). In contrast to these successful methods for imine formation, attempts to form the *N*-*tert*-butyl imine by combining the alaninamide substrate with pivaldehyde and magnesium sulfate, or with pivaldehyde, magnesium perchlorate, and trimethylorthorformate (catalyst and stoichiometric dehydrating agent, respectively) were not satisfactory with

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(1) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568–4571.

(2) Vaughan, J. R., Jr.; Osato, R. L. *J. Am. Chem. Soc.* **1951**, *73*, 5553–5555.

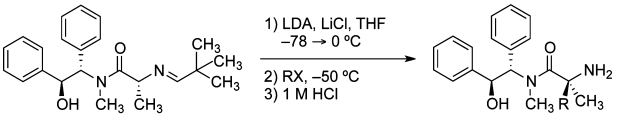
(3) (a) Smith, G. E. P., Jr.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1934**, *56*, 2095–2098. (b) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *84*, 826–831. (c) Leach, B. E.; Leussing, D. L. *J. Am. Chem. Soc.* **1971**, *93*, 3377–3384.

10.1021/ol401337p

respect to conversion and product purity, and efforts to purify samples of the imine only led to increased contamination with its hydrolysis product.

Enolization–alkylation of substrate **1** was optimally achieved by the following protocol. A solution of (1*S*,2*S*)-pseudoephenamine (*R*)-alaninamide pivaldimine (1 equiv) in dry tetrahydrofuran (THF) was transferred to a flask containing flame-dried lithium chloride (6.0 equiv), and the resulting slurry was cooled to −78 °C. A solution of lithium diisopropyl amide (LDA) in THF (2.2 equiv) was then added slowly down the side of the flask by cannula or syringe so as to allow the solution of base to cool before reaching the substrate solution. After completed addition and further stirring at −78 °C for 5 min, the reaction flask was transferred to an ice bath for 10 min before cooling to −50 °C. An electrophile (2.5 equiv) was then added to the cold reaction solution, and the ensuing alkylation reaction was monitored by TLC (reaction times typically ranged from 1.5 to 3.5 h). Upon completed reaction, a solution of 1 N hydrochloric acid was added to the reaction mixture to induce hydrolysis of the *tert*-butyl imine function within the alkylated product, which typically occurred in less than 3 h at 23 °C. Table 1 summarizes results from alkylation reactions using six different electrophiles. In all cases, diastereoselectivities equaled or exceeded 19:1, and the products, isolated in 83–95% yield by flash-column chromatography, were solids. We established that the benzylation product of entry 1 had the configuration depicted by comparison with a sample of known configuration, prepared by an independent route (see Supporting Information). The diastereoisomer that is formed arises from replacement of the α-CH bond by α-C-benzyl with retention of configuration. This alkylation product and two others whose stereochemistry was established unambiguously (shown in eq 2 of Scheme 1 and in Scheme 2 below) were found to form a homochiral series. The products of entries 2–6 of Table 1 were presumed to have formed analogously.

Table 1. Alkylation of (1*S*,2*S*)-Pseudoephenamine (*R*)-Alaninamide: Matched Case

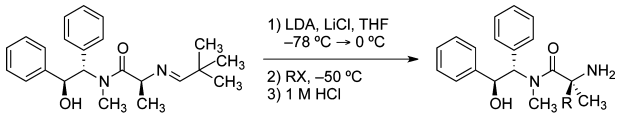


1

entry[a]	RX	crude dr[b]	isolated yield (%)
1[c]	BnBr	≥19:1	95
2	$BrCH_2CO_2tBu$	≥19:1	95
3[d]	EtI	19:1	91
4	*m*-CH_3OBnBr	≥19:1	89
5	*i*BuOTf	≥19:1	84
6	$CyCH_2OTf$	≥19:1	83

[a] 2.2 equiv of base and 2.5 equiv of electrophile were used in all cases. [b] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Conducted on a 2.1-g scale. [d] The alkylation reaction was conducted at 0 °C.

Table 2. Alkylation of (1*S*,2*S*)-Pseudoephenamine (*S*)-Alaninamide: Mismatched Case



2

entry[a]	RX	crude dr[b]	isolated yield (%)
1	BnBr	8:1	69
2	$BrCH_2CO_2tBu$	19:1	60
3[c]	EtI	13:1	72

[a] 2.2 equiv of base and 2.5 equiv of electrophile were used in all cases. [b] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] The alkylation reaction was conducted at 0 °C.

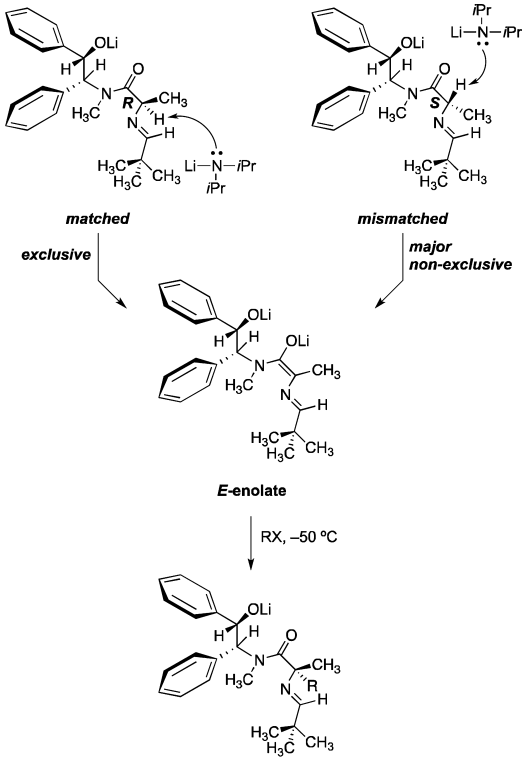


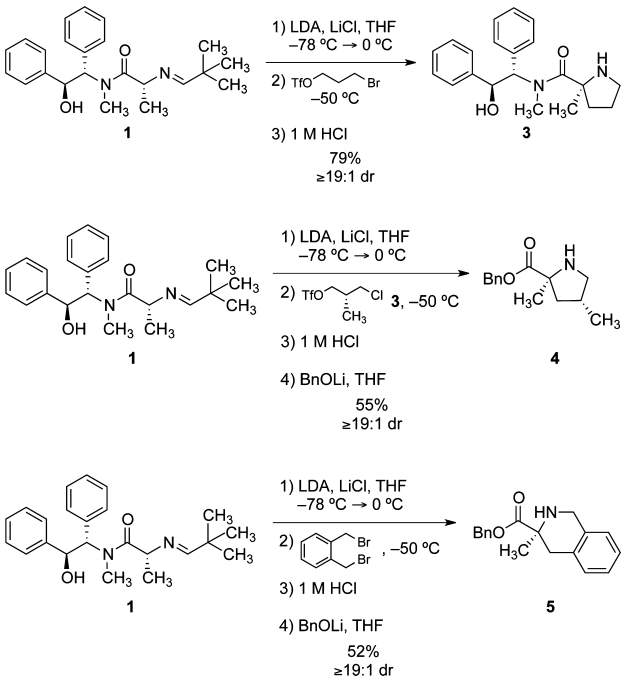
Figure 1. Proposed rationale for the stereochemical outcome of alkylations of matched and mismatched diastereomers of pseudoephenamine alaninamide pivaldimine.

Table 2 summarizes results from three parallel alkylation reactions using the diastereomeric substrate (1*S*,2*S*)-pseudoephenamine (*S*)-alaninamide (**2**), otherwise conducted as described in the paragraph above. Surprisingly, in all three cases the major product was the same as that formed using substrate **1**, although the stereoselectivities and yields were lower, making it clear that substrate **2** is mismatched.[4]

(4) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245–264.

These findings can be rationalized by arguments that extend from our earlier studies of the enolization of α,α-dialkyl pseudoephenamine and pseudoephedrine amide enolates, summarized in Figure 1.[5] Briefly, both matched

Scheme 1. Synthesis of Cyclic Amino Acid Derivatives[a]



[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude alkylation reaction mixtures.

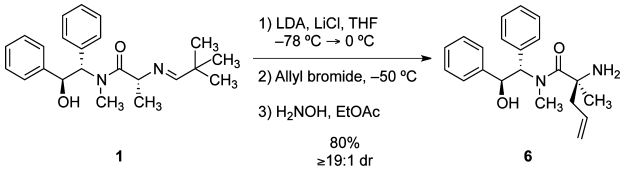
and mismatched substrates are proposed to form the same *E*-enolate intermediate (with the enoxy and α-imino groups in trans disposition), which then undergoes alkylation predominantly or exclusively in the usual sense.[6] Enolization of the mismatched substrate is believed to be less *E*-selective, however, because *E*-enolization requires approach of the base along a trajectory impeded by the auxiliary. Interestingly, if we are correct in this proposal, then formation of the *Z*-enolate from the mismatched substrate must remain a higher energy pathway in spite of the fact that it would arise from deprotonation along a more favorable trajectory. We speculate that an imporant factor may be a developing repulsive electronic interaction between the enolate oxygen atom and the α-imino lone pair in the transition state for formation of the *Z*-enolate.

As depicted in Scheme 1, it proved possible to assemble cyclic α-amino acid derivatives containing an α-quaternary center in a single operation using bis-electrophiles such as 3-bromopropyl trifluoromethanesulfonate (eq 1), (*R*)-3-chloro-2-methylpropyl trifluoromethanesulfonate

(5) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.

(6) The *E*-enolate obtained from the matched diastereomer could be trapped in the form of a cyclic siloxane whose stereochemistry was determined by NOE experiments. See Supporting Information for details.

Scheme 2. Optimized Synthesis of α-Allyl Quaternary Amide **6**



(eq 2), and α,α′-dibromo-*o*-xylene (eq 3). Due to their chromatographic instability (believed to be a consequence of facile *N*→*O* acyl transfer), products from the latter two alkylations were directly subjected to transacylation with lithium benzyloxide, a useful transformation we discuss in greater detail below.

As a concluding alkylation result, in Scheme 2 above we summarize a successful α-allylation of the matched substrate **1**, which required development of an alternative workup method (using hydroxylamine in lieu of acid to cleave the *tert*-butyl imine function of the alkylated product). Interestingly, hydrolysis of the imine function of the allylated product under the usual conditions (1 N HCl) led to a significant byproduct (Scheme 3, aminal **7**, accompanied by an unidentified minor diastereomeric aminal byproduct in a 7:1 ratio, respectively). Crystallization afforded a single crystal of pure **7** suitable for X-ray analysis (see Supporting Information). As depicted in Scheme 3, byproduct **7** presumably arises from an aza-Cope rearrangement followed by cyclization.[7]

An exceptional and highly useful feature of the present study was the finding that α-quaternary α-amino amides of pseudoephenamine undergo hydrolysis to afford α-amino acids simply upon refluxing in aqueous dioxane (salt-free conditions, Table 3), whereas treatment with lithium alkoxides affords α-amino esters (Table 4 and Scheme 1). In the former case, the pseudoephenamine auxiliary can be easily recovered in high yield by a simple extractive isolation procedure, whereas in the latter it can be isolated chromatographically.

Prior auxiliary-based methods for α-alkylation of alanine derivatives have generally achieved stereochemical control of both the enolate geometry and the nascent quaternary carbon center by incorporating the alanine

(7) This interesting transformation suggests a possible new approach to transfer aminoallylation. See, for example: Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039.

(8) For selected references describing chiral auxiliary-based methods for the asymmetric synthesis of quaternary α-methyl α-amino acids, see: (a) Schöllkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 117–119. (b) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144–154. (c) Williams, R. M.; Im, J. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286. (d) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233–1238. (e) Alonso, F.; Davies, S. G.; Elend, A. S.; Haggitt, J. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 257–264. (f) Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704–717. (g) Lu, T.; Lin, C. *J. Org. Chem.* **2011**, *76*, 1621–1633.

(9) For leading references, see: (a) Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900–4904. (b) Jew, S.; Jeong, B.; Lee, J.; Yoo, M.; Lee, Y.; Park, B.; Kim, M. G.; Park, H. *J. Org. Chem.* **2003**, *68*, 4514–4516. (c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229.

Scheme 3. Aza-Cope Rearrangement of an α-Allylation Product

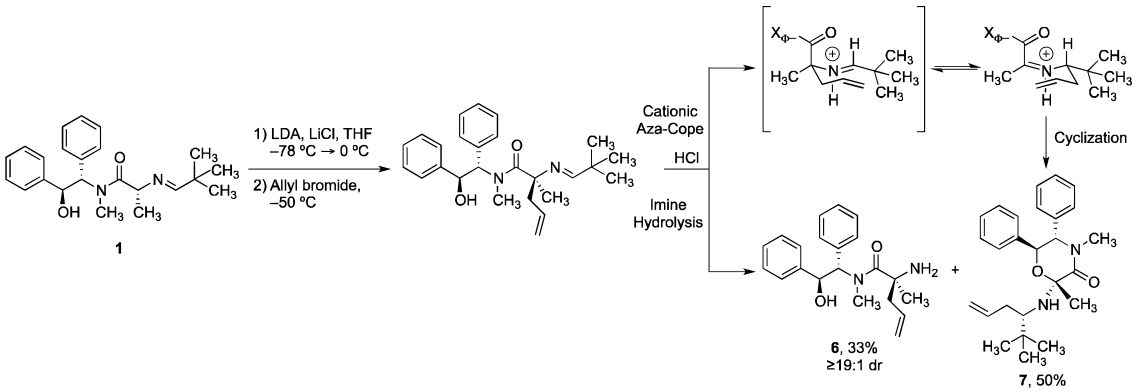
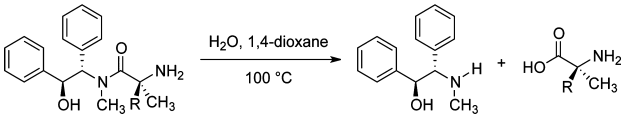


Table 3. Hydrolysis of Pseudoephenamine Amides To Form Quaternary α-Methyl α-Amino Acids

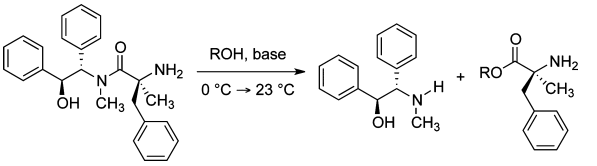


entry	R	isolated yield, α-amino acid (%)	isolated yield, auxiliary (%)
1	Bn	99[a]	99
2	Allyl	97[a]	94
3	$CyCH_2$-	99	98

[a] > 98% ee, as determined by chiral HPLC analysis.

substrate within a rigid heterocyclic framework, and liberation of the α-amino acid typically requires harsh conditions, in some cases resulting in the destruction of the auxiliary.[8] The present work differs in these respects. Advances in asymmetric phase-transfer catalysis have also achieved highly enantioselective alkylations of alanine derivatives.[9] Determination of the most appropriate methodology for a given specific application will be context-dependent, but we believe that the present work offers a potentially useful new option for the stereodefined construction of α-methyl α-amino acids.[10–12]

Table 4. Synthesis of Quaternary α-Methyl α-Amino Esters



entry	ROH	base	isolated yield, α-amino ester (%)	isolated yield, auxiliary (%)
1	CH_3OH	$NaOCH_3$	88	91
2	BnOH	*n*BuLi	84	83

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Supporting Information Available. Full experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(10) For recent reviews of the asymmetric synthesis of quaternary α-amino acids, see: (a) Cativiela, C.; Díaz-de-Villegas, M. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623. (b) Cativiela, C.; Ordoñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63.

(11) For selected references describing other methods for the asymmetric synthesis of quaternary α-methyl α-amino acids, see: (a) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256–7257. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635. (d) Smith, N. D.; Wohlrab, A. M.; Goodman, M. *Org. Lett.* **2005**, *7*, 255–258.

(12) Efforts to extend the present method to alkylate higher α-alkyl pivaldimines (replacing α-methyl with α-benzyl or α-ethyl) were not successful.