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Enantioselective Synthesis of Allylic Alcohols by the Sequential Aminoxylation–Olefination Reactions of Aldehydes under Ambient Conditions†

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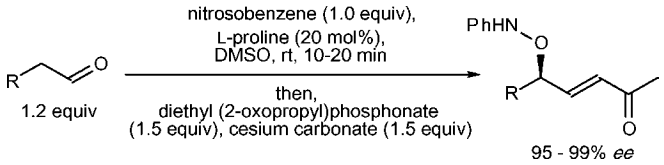
ABSTRACT



A novel, highly enantioselective synthesis of *O*-amino-substituted allylic alcohols by the sequential asymmetric α-aminoxylation/Wadsworth–Emmons–Horner olefination reactions of aldehydes is presented.

Enantiopure allylic alcohols are versatile, useful building blocks for asymmetric synthesis[1] and are prevalent in complex natural products.[2] Their utility has been largely demonstrated in a variety of organic transformations.[3] Although numerous methodologies[4] have been devised for the asymmetric synthesis of optically active allylic alcohols, the development of new, practical, synthetic processes for C−C bond formation, employing readily available substrates that do not require prior preparation, is still highly desirable. In our continuing effort in the development of mild, practical methods for catalytic asymmetric synthesis, we have studied the in situ utilization of reactive α-aminoxy aldehyde intermediates generated by the proline-catalyzed asymmetric α-aminoxylation of aldehydes.[5] In this communication, we report an extended application: a facile synthesis of highly

† Dedicated to Professor Manfred Schlosser on his 70th birthday.
‡ The Scripps Research Institute.
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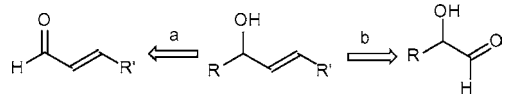
enantiopure allylic alcohols in up to 99% ee by the sequential aminoxylation−olefination of aldehydes under ambient conditions (at room temperature, air and moisture are tolerated). The process enabled reactive α-aminoxy aldehydes to be trapped in situ by Wadsworth−Emmons−Horner olefination.

Two general approaches to the preparation of optically active secondary allylic alcohols starting from aldehydes are conceivable (Scheme 1, paths a and b). One common solution

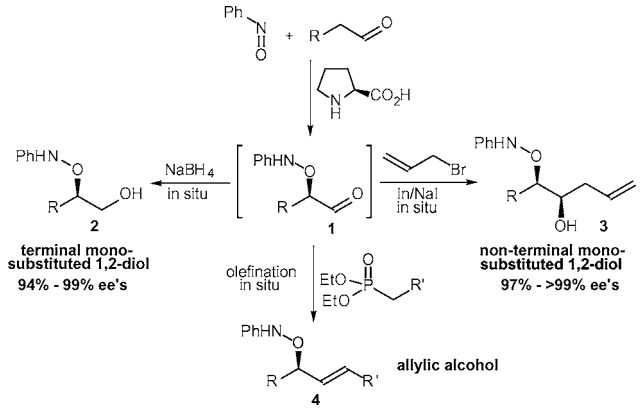
Scheme 1. Two General Approaches to the Synthesis of the Allylic Alcohols from Aldehydes



is provided through the addition of a nucleophile stereoselectively to the carbonyl group of a conjugated aldehyde (path a) to afford the allylic alcohol.[4f,6a] The second approach consists of the olefination of the chiral α-hydroxy aldehydes (path b), which is unusual since α-hydroxy aldehydes themselves are often made through the ozonolysis of the protected allylic alcohols conversely.[6]

Recently, we documented the direct catalytic asymmetric α-aminoxylation of aldehydes by using enantiopure proline as the catalyst and nitrosobenzene as the oxygen source.[5a,b] Although the α-aminoxy aldehyde monomers **1** generated in the reaction could not be isolated in good yields, they could be converted in situ by reduction or allylation to the 1,2-diol units **2** (terminal 1,2-diol)[5a] or **3** (nonterminal 1,2-diol)[5c] in good yields with excellent enantioselectivities (Scheme 2). On the basis of these discoveries, we reasoned

Scheme 2. Strategy for in Situ Trapping of the Reactive *a*-Aminoxy Aldehyde Intermediates



that such intermediates might also be utilized to synthesize optically active secondary alcohols if the reactive intermediates **1** could be trapped in situ by an olefination reaction (following path b). To test this strategy, we carried out sequential aminoxylation/Wadsworth−Emmons−Horner olefination reactions.

A preliminary study of the sequential reactions was conducted with valeraldehyde. The α-aminoxylation of valeraldehyde was subjected to our previously established conditions. A mixture of valeraldehyde (1.2 equiv), nitrosobenzene (1.0 equiv), and L-proline (20 mol %) was stirred in the solvent DMSO at room temperature for 10 min. Then, the following in situ olefination was started with addition of diethyl (2-oxopropyl)phosphonate (1.5 equiv) and lithium hydroxide (1.5 equiv). The stirring of the reaction mixture was kept at room temperature for 30 min. As a result, the corresponding amino-substituted allylic alcohol **4a** was isolated as the major product in 43% yield and with 98% ee by flash column chromatography on silica gel. The trans C=C bond of the product **4a** was created in the Wadsworth−Emmons−Horner olefination step. The excellent enantioselectivity of the sequential reactions was completely in accord with the previous results.[5a,b] The result meant that no racemization occurred in the olefination step, even with a strong base (LiOH) used for the generation of the ylide. This could be due to the different pK_a values between α-oxy aldehydes (pK_a ∼23.5 in DMSO) and (2-oxoalkyl)phosphonates (pK_a ∼17.5 in DMSO). The difference (∼6) in the pK_a values enabled the deprotonation in the second step in the sequential reactions to proceed selectively with the substrate (the phosphonate) with lower pK_a, so that the racemization of α-aminoxy aldehyde **1** at its chiral center was avoided. However, the overall yield was not satisfactory. To improve the yield, other bases (e.g., triethylamine, potassium carbonate, and cesium carbonate) were tested in the olefination step under the same sequential conditions. We obtained a good yield of 74% with cesium carbonate. In every case, the enantiomeric excess of the corresponding product **4a** was excellent (98% ee). Accordingly, cesium carbonate was employed as the base in the olefination for subsequent studies.

We explored the scope of the transformation by using various aliphatic aldehydes bearing different functionalities. It was found that the process displayed a wide substrate scope and was compatible with functionalities such as aryl, alkenyl, benzyloxy, or amido groups. Excellent enantioselectivities (with 95−99% ees) and good yields (52−81%) were achieved in all cases (Table 1). The stereochemistry of this tandem transformation was assigned according to the previously established absolute configuration of the α-aminoxy aldehyde.[5a]

Removal of the *N*-phenylamino group from product **4a** was achieved by the copper (II)-catalyzed N−O bond cleavage,[7] which gave the allylic alcohol **5** as a product in 66% yield (Scheme 3). The N−O bond cleavage reaction did not result in any loss in enantiomeric purity.

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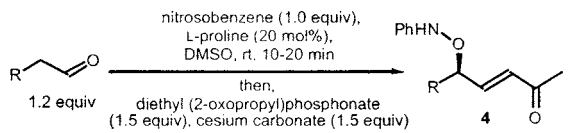
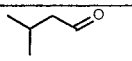
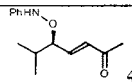
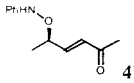
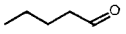
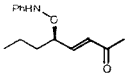
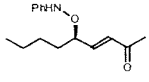
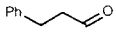
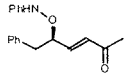
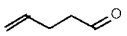
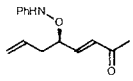
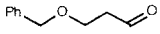
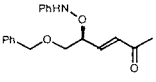
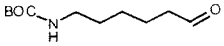
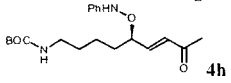
Table 1. Asymmetric Sequential Aminoxylation/ Wadsworth−Emmons−Horner Olefination of Aldehydes

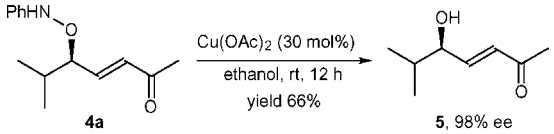


aldehyde	product	yield[a]	ee[b]
	 **4a**	74%	98%
	 **4b**	56%	98%
	 **4c**	70%	97%
	 **4d**	69%	99%
	 **4e**	81%	97%
	 **4f**	71%	98%
	 **4g**	64%	99%
	 **4h**	52%	95%

[a] All were yields of isolated products. [b] Ees were determined by chiral-phase HPLC columns.

In conclusion, we have developed a novel, practical sequential asymmetric α-aminoxylation/Wadsworth−Emmons−Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols.[8] The advantages of the sequential process include the following: (1) all starting materials are readily available; (2) the reactive aldehyde intermediates formed in the α-aminoxylation, though they cannot be isolated in good yields, and can be efficiently trapped and transformed in situ without requiring a separate preparative step; (3) the procedure is very easy to operate under the very mild conditions (at room temperature, air and moisture are tolerated); (4) both (*R*)- and (*S*)-allylic alcohols can be made since either enantiopure form of the proline is commercially available. The success in the sequential transformation also provides a clue for the development of other useful processes in which reactive intermediates can be utilized in situ.

Scheme 3



Acknowledgment. We are grateful to Dr. Lerner and The Scripps Research Institute for support.

Supporting Information Available: Spectroscopic and analytical data for **4a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038−6039. (b) Momiyama, N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2986−2988. **General Procedure for Copper(II)-Catalyzed N−O Bond Cleavage Reaction.** To a solution of **4a** (1.0 mmol) in EtOH (4 mL) was added $Cu(OAc)_2$ (0.3 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was quenched with a cold saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and condensed under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane 60/40) to afford (5*R*)-6-methyl-5-hydroxy-hept-3-en-2-one (**5**, 0.66 mmol) in 66% yield. The enantiomeric excess of the product **5** was measured by ^{1}H NMR analysis in the presence of Eu[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]$_3$, ee > 98%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, 1H, J = 16.0, 5.1 Hz, HO−CH−C**H**═), 6.28 (dd, 1H, J = 16.0, 1.6 Hz, ═C**H**COCH$_3$), 4.15−4.09 (m, 1H, C**H**-OH), 2.29 (s, 3H, COCH$_3$), 1.89−1.80 (m, 2H, OH and CH$_3$C**H** CH$_3$), 0.97 (d, 3H, J = 1.2 Hz, C**H**$_3$CH), 0.93 (d, 3H, J = 1.0 Hz, C**H**$_3$CH). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.51; H, 9.95.

(8) **General Procedure for the Sequential Asymmetric α-Aminoxylation/Wadsworth−Emmons−Horner Olefination.** To a solution of the valeraldehyde (103 mg, 1.2 mmol) and nitrosobenzene (107 mg, 1.0 mmol) in anhydrous DMSO (4 mL) was added L-proline (23 mg, 0.2 mmol). The mixture was vigorously stirred at room temperature for about 10 min. The endpoint of the reaction was monitored by its color change from green to orange. Diethyl (2-oxopropyl)phosphonate (291 mg, 1.5 mmol) and cesium carbonate (489 mg, 1.5 mmol) were then added into the reaction mixture. The stirring was continued at room temperature for 30 min. The reaction mixture was quenched with a cold saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and condensed under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane 40/60) to afford (5*R*)-6-methyl-5-(*N*-phenyl-aminoxy)-hept-3-en-2-one (**4a**, 173 mg) in 74% yield. The enantiomeric excess of the product **4a** was measured by chiral-phase HPLC using Chiralpak AS column (*i*-propanol/hexane 2/98, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 27.3 min, t_{major} = 34.1 min, ee 98%. The HPLC conditions were established by using racemic standard product, which was prepared in the same way with DL-proline as the catalyst. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 instrument: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 2H, ArH), 6.93 (m, 3H, ArH), 6.74 (dd, 1H, J = 16.2, 7.2 Hz, NHOCH−C**H**═CH−), 6.25 (d, 1H, J = 16.2 Hz, NHOCH−CH═C**H**−), 4.16 (t, 1H, J = 6.3 Hz, NHOC**H**−CH═), 2.29 (d, 3H, J = 2.1 Hz, O═C−C**H**$_3$), 2.07 (m, 1H, C**H**(CH$_3$)$_2$), 1.07 (dd, 3H, J = 6.9, 1.8 Hz, CHC**H**$_3$), 0.98 (dd, 3H, J = 6.9, 1.9 Hz, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 148.2, 144.4, 132.7, 128.9, 122.1, 114.4, 88.2, 31.6, 27.5, 18.7, 18.3. High-resolution mass spectra were recorded on an Ion Spec Fourier Transform Mass Spectrometer: HR-MS (MALDI-FTMS) calcd for $C_{14}H_{19}NNaO_2^+$ 256.1313, found 256.1316.