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New Uses of Amino Acids as Chiral Building Blocks in Organic Synthesis

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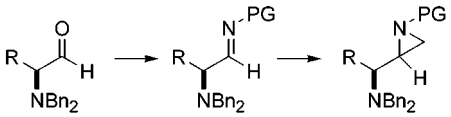
ABSTRACT



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***N,N*-Dibenzylamino aldehydes have emerged as a highly useful class of chiral building blocks in synthetic organic chemistry. We envisioned the transformation of the *N,N* -dibenzylamino aldehydes to the corresponding aldimines followed by diastereoselective methylene transfer with a sulfonium ylide to obtain α-amino aziridines in high yields.**

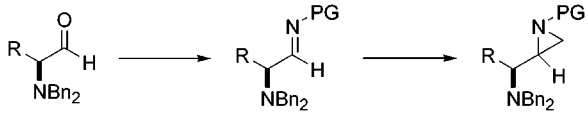
Amino acids have long been used as chiral building blocks in organic synthesis.[1] Since naturally occurring α-amino acids contain a chiral center and at least two functional groups they can be transformed to a broad range of compounds through well-designed reactions.

One of the challenges in amino acid chemistry is to prepare an α-amino aldehyde from the corresponding α-amino acid and then to form a new C−C bond in a stereoselective manner to build more complicated structures. However, α-amino aldehydes are not configurationally stable, and a suitable amino protecting group is required.

N,N-Dibenzylamino aldehydes have emerged as a highly useful class of chiral building blocks in synthetic organic chemistry.[2] We envisioned the transformation of the *N,N*-dibenzylamino aldehydes **1** to the corresponding aldimines **2** followed by diastereoselective methylene transfer to obtain α-amino aziridines **3** (Scheme 1).

The versatile utilities of chiral aziridines as chiral building blocks for the synthesis of various nitrogen-containing compounds have drawn much attention in recent years.[3] One of the most efficient methods to build the nitrogen-containing

Scheme 1



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three-membered ring system is methylene group transfer to a suitable imine counterpart. There are some literature precedents for aziridine formations by methylene transfer using sulfonium ylides. However, the participating imines were mostly derived from aromatic aldehydes.[4]

Although the C═N bond is similar to the C═O bond, there are some differences between them especially in terms of reactivity toward nucleophiles. It is well-known that the low reactivity of imines toward nucleophiles has been the most difficult problem and that it can be improved by the presence

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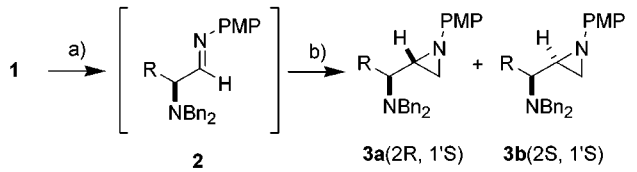
of Lewis acids, electron-withdrawing nitrogen substituents, and an aromatic group on the imine carbon.[5]

In this article we would like to report the first successful methylene transfer to the aliphatic unactivated aldimines derived from *N*,*N*-dibenzylamino aldehydes using a sulfur ylide to form α-amino aziridines stereoselectively in high yields.

The starting *N*,*N*-dibenzylamino aldehydes **1** were prepared from the corresponding α-amino acids through benzylation, reduction, and oxidation.[6] The final step is the Swern oxidation of *N*,*N*-dibenzylamino alcohol, and the reaction occurs almost quantitatively to provide the α-amino aldehyde without losing any optical integrity. The α-amino aldehydes and *p*-anisidine (*p*-methoxyaniline) were stirred in methylene chloride in the presence of molecular sieves to give the corresponding imines in high yields.[7] The *N*,*N*-dibenzyl α-amino aldimines were subjected to the coupling reaction with dimethylsulfonium methylide prepared from trimethylsulfonium iodide and *n*-BuLi. The coupling reactions proceeded smoothly to give the corresponding aziridines in high yields (Scheme 2).[8] We already reported the stereoselective addition reactions to α-*N*,*N*-dibenzylamino aldehydes **1** and expected this sulfonium ylide addition would show the same stereoselectivity where the nucleophiles approach from the *re* face of the imines by a Felkin-Ahn transition state.[2] While we were preparing this manuscript Concellón et al. reported stereoselective preparation of α-*N*,*N*-dibenzylaminoaziridines by highly stereoselective reduction of α-aminoalkyl chloromethyl ketimines prepared from *N*,*N*-dibenzylamino acid esters.[9] Though the reaction pathways are different, nucleophiles (sulfur ylide or hydride) attack the aldimines or ketimine carbon from the same side selectively to provide the major product that has opposite stereochemistry at the C-2 position in the aziridine ring. We also prepared the corresponding aziridine from the reaction of cyclohexanecarboxaldehyde in 70%. We found that the compound data of the minor product obtained from the reaction of α-*N*,*N*-dibenzylphenylalaninal aldimine with dimethylsulfonium methylide and those of the major product obtained from the reduction of the corresponding ketimine were in good agreement.

Scheme 2



a) *p*-anisidine, 4A MS, CH_2Cl_2 b) Me_3SI/*n*-BuLi,THF, -78 °C to rt

PMP = *p*-methoxyphenyl

entry	R	yield(%)	ratio (3a : 3b)
a	Benzyl	88	4:1
b	*i*-Propyl	91	5:1
c	*i*-Butyl	85	5:1
d	$TBSOCH_2$	87	7:1
e	Methyl	88	4:1*

* We obtained 69% of **3ae** aziridine and 19% of methylthiomethyl addition product to the *N*-PMP aldimine.

The above results show that the sulfonium ylide addition reactions to the α-*N*,*N*-dibenzylamino aldimines and hydride reduction of the α-*N*,*N*-dibenzylaminoalkyl chloromethyl ketimines predominantly take place on the *re* face of the C═N double bonds and that the two methodologies can be complementary for the stereoselective synthesis of functionalized chiral aziridines.

Acknowledgment. M.T.R. and W.K.L. would like to thank the Alexander von Humboldt Foundation and Korea Research Foundation (KRF-99-013-000-348) for support.

Supporting Information Available: Experimental procedure from cyclohexanecarboxaldehyde and compound data shown in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) **Representative Procedure.** Preparation of *N*-PMP-aziridine from *N*,*N*-dibenzylphenylalaninal. A mixture of the amino aldehyde (139 mg, 0.42 mmol), *p*-anisidine (57 mg, 0.47 mmol), and 1.0 g of 4 Å MS in 3 mL of methylene chloride was stirred for 12 h at room temperature. The solvent was evaporated, and the residue was dissolved in 3 mL of THF. A suspension of Me_3SI (172 mg, 0.85 mmol) in 3 mL of THF was cooled to −30 °C and treated with *n*-BuLi (1.6 M, 0.48 mL, 0.77 mmol). The mixture was stirred for 1 h and cooled to −78 °C. To the sulfonium ylide solution was added the cooled solution of the *N*-PMP-imine in 3 mL of THF slowly at −78 °C. The mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with water, and the aqueous layer was extracted with ether (5 mL × 5). The combined extract was dried over K_2CO_3, and the solvent was evaporated to give a crude product as brown oil, which was chromatographed on silica gel with 5% EtOAc/hexane to give 130 mg (69%) of the major product and 35 mg (19%) of the minor product as oil. Major product (**3aa**): (−)-(2*R*,1′*S*)-2-[1′-(dibenzylamino)-2′-(phenyl)ethyl]-1-(*p*-methoxyphenyl)aziridine; $[\alpha]^{28}_D$ +53.2 (*c*, 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 200 MHz) 7.33−7.08 (m, 15H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 3.88 (d, *J* = 13.9 Hz, 2H), 3.74 (s, 3H), 3.70 (d, *J* = 13.9 Hz, 2H), 3.18 (d, *J* = 7.6 Hz, 2H), 2.84 (q, *J* = 7.2 Hz, 1H), 2.27−2.20 (m, 2H), 2.13 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) 154.8, 147.7, 139.4, 139.3, 129.4, 128.1, 127.8, 127.7, 126.4, 125.7, 121.0, 113.9, 60.9, 55.2, 53.6, 40.2, 36.4, 34.3; MS(EI) 448 (M^+), 357, 313, 300, 253, 148, 91. Minor product (**3ba**): (−)-(2*S*,1′*S*)-2-[1′-(dibenzylamino)-2′-(phenyl)ethyl]-1-(*p*-methoxyphenyl)aziridine; R_f 0.40 (Hex/EA 15%); $[\alpha]^{27}_D$ −80.2 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.03 (15H, m), 7.00 (2H, d, *J* = 8.7 Hz), 6.80 (2H, d, *J* = 8.7 Hz), 4.02 (2H, d, *J* = 13.9 Hz), 3.87 (2H, d, *J* = 13.8 Hz), 3.76 (3H, s), 3.00−2.92 (2H, m), 2.78 (1H, dd, *J* = 5.3, 12.0 Hz), 2.32 (1H, m), 1.81 (1H, d, *J* = 6.5 Hz), 1.77 (1H, d, *J* = 3.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 154.91, 148.37, 139.92, 139.85, 129.44, 128.61, 128.08, 128.05, 126.67, 125.85, 121.45, 114.25, 61.44, 55.54, 53.97, 39.692, 35.25, 31.88; HRMS calcd for $C_{31}H_{32}N_2O$ 448.251464, found 448.251862. We proved the enantiomeric purity of the products by making the enantiomers of **3aa** and **3ba** starting from D-phenylalanine and analyzed them with chiral HPLC.

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