Indium Mediated Efficient Conversion of 2-Iodomethyl Aziridines to Chiral Allylic Amines

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Abstract: Chiral allylic amines are synthesized in high yields by treatment of 2-iodomethyl *N*-tosyl aziridines with metallic indium in methanol at reflux.

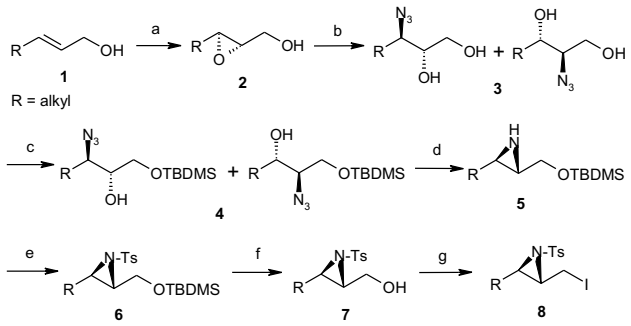
Key words: indium, *N*-tosyl aziridine, chiral allylic amine

Chiral allylic amines are versatile building blocks[1] for the synthesis of α- and β- amino acids, alkaloids and carbohydrate derivatives. The allylic amines are transformed to a range of products by functionalization, reduction or oxidation of the double bond.[2] In addition, the allylic amine core unit is found in many bioactive molecules,[3] for example (*S*)-Vigabatrin,[3j] an anti-convulsive drug, and they are also structural components of peptide isoteres, and act as β-turn promoters.[4] Thus, the synthesis of chiral allylic amines is an important industrial and synthetic goal. Consequently several procedures have been developed for the synthesis of chiral allylic amines, which include: asymmetric allylic amination,[5] asymmetric nucleophilic addition to carbon-nitrogen double bonds,[6] asymmetric addition to alkynes,[7] and modification of enantiomerically pure α-amino aldehydes.[8] However most previous synthetic transformations involve Wittig olefination on *N*-protected α-amino aldehydes, which are often susceptible to racemization of the stereogenic centers.[8a,9] Recently chiral allylic amines have also been synthesized from aziridinemethanol sulfonate esters[10a] as well as 5-hydroxymethyl-2-oxazolidinone tosylates using Te(II).[10b] However, many of these procedures have limitations in terms of yields, reaction times, selectivity, stability and availability of the reagents. Therefore there is a need to develop a convenient and potentially practical method for the synthesis of chiral allylic amines.

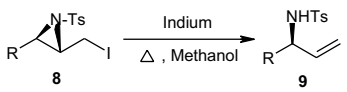
Indium mediated transformations[11] have attracted much interest because of certain unique properties possessed by indium. Indium is stable in water or air and does not require any activation or anhydrous reaction conditions. Furthermore, the first ionization potential of indium is much lower than that of zinc or tin, hence it could be a potential reducing agent.

In continuation of our interest in the use of indium metal for various transformations,[12] we herein describe a novel and highly efficient procedure for the synthesis of chiral allylic amines using indium metal. The treatment of 2-iodomethyl *N*-tosyl aziridines with indium metal in refluxing methanol afforded the corresponding chiral allylic amines (Table, entries a–e) in excellent yields. Additionally, reaction of aziridines bearing iodine at an allylic position (entries f and g) with indium metal in refluxing methanol resulted in the formation of chiral 5-amino-1,3-dienes.

Scheme 1 illustrates the synthesis of 2-iodomethyl aziridine from allylic alcohol **1**. Allylic alcohol **1** was subjected to Sharpless asymmetric epoxidation[13] to afford epoxy alcohol **2**. The chiral epoxy alcohol **2** was transformed in excellent overall yield to the "inverted" aziridino alcohol **5** by a straightforward series of operations.[14,15] The amino function was then protected as the *p*-toluenesulfonamide to give **6**. The TBDMS ether was then deprotected by TBAF in HOAc at 0 °C to give 2-hydroxymethyl aziridine **7** which on treatment with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile[16] gave 2-iodomethyl aziridine **8**. Treatment of **8** with indium metal in refluxing methanol for 4-5 h gave the corresponding chiral allylic amine **9** in excellent yield (Scheme 2).



Scheme 1 Reagents: a) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM, –20 °C. b) NaN_3, $MeO(CH_2)_2OH$, H_2O, reflux. c) TBDMSCl, imidazole, DCM, 0 °C. d) PPh_3, toluene, reflux. e) TsCl, pyridine, –20 °C. f) TBAF, HOAc, 0 °C. g) PPh_3, I_2, imidazole, ether:CH_3CN (3:1), r.t.



Scheme 2

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1437-2096,E;2001,0,10,1608,1610,ftx,en;D14801ST.pdf.

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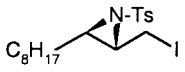
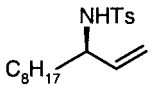
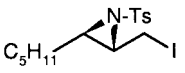
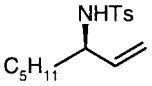
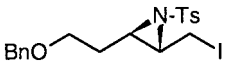
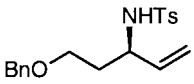
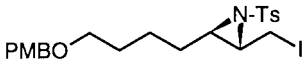
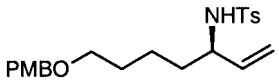
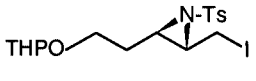
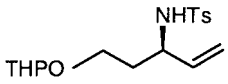
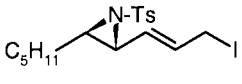
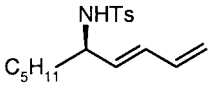
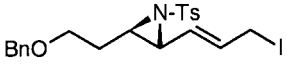
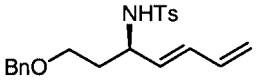
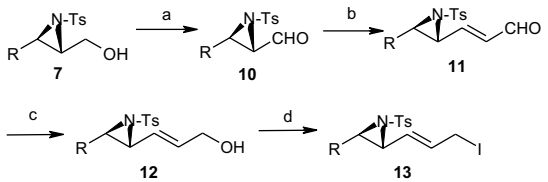
Table Indium Mediated Efficient Conversion of 2-Iodomethyl *N*-Tosyl Aziridines to Chiral Allylic Amines[a]

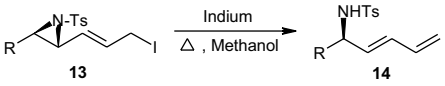
Entry	2-Iodomethyl *N*-tosyl aziridine	Allylic amines	% Yield[b] (time, h)	$[\alpha]^{20}_D$ (c, $CHCl_3$)
a			95 (4)	–15.0 (0.55)
b			96 (4)	–22.6 (0.5)
c			92 (4.5)	–14.6 (0.75)
d			90 (5)	–15.8 (1.0)
e			82 (4)	–
f			91 (4.5)	–4.7 (0.7)
g			93 (5)	+3.3 (1.1)

[a] All products are characterized by ^1H, ^{13}C NMR, mass spectra, and also by the comparison with authentic samples.
[b] Isolated and unoptimized yields.



Scheme 3 Reagents: a) SO_3·Py, Et_3N, DCM–DMSO, 0 °C. b) Ph_3P=CHCHO, benzene, r.t. c) $NaBH_4$, MeOH, 0 °C. d) PPh_3, I_2, imidazole, ether–CH_3CN, (3:1), r.t.

Scheme 3 illustrates the synthesis of compound **13** from 2-hydroxymethyl aziridine **7**. Compound **7** on oxidation with SO_3·Py gave the aldehyde **10**, which without purification, was treated with formylmethylenetriphenylphosphorane to give α,β-unsaturated aldehyde **11**. Reduction of aldehyde group with $NaBH_4$ in methanol gave **12**, which on treatment with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile gave **13**. Treatment of **13** with indium metal in refluxing methanol for 4-5 h gave the corresponding chiral amino diene **14** in excellent yield (Scheme 4).



Scheme 4

Several examples illustrating this novel and efficient protocol for the synthesis of chiral allylic amines are listed in the Table.[17] This method is very simple, more convenient and does not require any promotors or additives. Methanol appears to be the solvent of choice for this reaction. No racemization or side products are observed under the reaction conditions. Indium was found to be more effective than other metals such as zinc, samarium and yttrium for this transformation.

In summary we have demonstrated a novel and efficient protocol for the synthesis of chiral allylic amines using indium metal. In addition to its simplicity and milder reaction conditions, the method provides high yields of products with greater selectivity, which makes it a very useful and attractive process for the synthesis of chiral allylic amines.

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(17) Experimental procedure: A mixture of 2-iodomethyl *N*-tosyl aziridine (3 mmol) and indium metal (6 mmol) in methanol (10 mL) was heated under reflux for an appropriate time (Table). After completion of the reaction indicated by TLC, the solvent was removed in vacuo, diluted with water and extracted with ethyl acetate (2 × 10mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane, 1:9) to afford pure chiral allylic amine. Spectral data for the products: **2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.19 (m, 12 H), 1.47 (m, 2 H), 2.42 (s, 3 H), 3.73 (m, 1 H), 4.56 (d, *J* = 8.0 Hz, 1 H), 4.92 (dd, *J* = 10.0, 1.0 Hz, 1 H), 4.99 (dd, *J* = 16.0, 1.0 Hz, 1 H), 5.51 (m, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.98, 138.11, 137.87, 129.36, 127.13, 115.59, 56.27, 35.44, 31.76, 29.31, 29.10, 25.15, 22.56, 21.41, 14.03. EIMS (*m/z*) 210 [M^+-C_8H_{17}]. **2f:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3 H), 1.17 (m, 6 H), 1.45 (m, 2 H), 2.43 (s, 3 H), 3.81 (m, 1 H), 4.48 (d, *J* = 8.0 Hz, 1 H), 5.03 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.09 (dd, *J* = 17.5, 1.5 Hz, 1 H), 5.38 (dd, *J* = 16.0, 7.5 Hz, 1 H), 5.90 (dd, *J* = 16.0, 12.0 Hz, 1 H), 6.15 (ddd, *J* = 17.5, 10.0, 12.0 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 2 H), 7.77 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.07, 135.93, 133.11, 131.99, 129.41, 127.27, 117.42, 55.71, 35.79, 31.34, 24.98, 22.38, 21.39, 13.86. EIMS (*m/z*) 236 [M^+-C_5H_{11}].