Pergamon

Tetrahedron Letters 42 (2001) 6385–6388

TETRAHEDRON LETTERS

Indium-mediated facile synthesis of chiral allylic amines†

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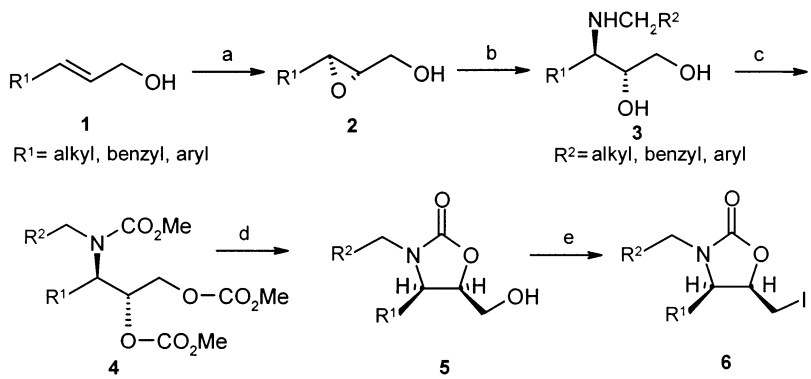
Received 8 May 2001; revised 6 July 2001; accepted 12 July 2001

Abstract—An efficient procedure for the synthesis of chiral allylic amines from 5-iodomethyl-2-oxazolidinones using indium metal in refluxing methanol is described.

The development of simple and general methods for the preparation of enantiomerically pure organic compounds from readily available, achiral substrates is one of the major challenges of organic synthesis today.[1] Allylic amines are an important class of compounds, not only for their utility as intermediates in organic synthesis, but also because of their significant physiological properties.[2] They are found in many biologically active natural products.[3] Further, the allylic amine functionality has been used as peptide mimetics, isosteres and also as β-turn promoters.[4] In addition, some allylic amines are important intermediates in the aza-Claisen rearrangement,[5] and also in ring-closing metathesis reactions.[6] The most general method for the synthesis of allylic amines involves the conversion of *N*-protected α-amino-aldehydes into allylic amine derivatives by Wittig olefination. However, α-amino-aldehydes are often susceptible to racemization at their chiral centres[7a,8] and are relatively unstable, both chemically and configurationally.[8] Other methods for the synthesis of chiral allylic amines include: asymmetric allylic amination,[9] asymmetric nucleophilic addition to carbon–nitrogen double bonds,[10] asymmetric addition to alkynes,[11] and modification of enantiomerically pure α-amino-aldehydes.[7] In addition, allylic amines have also been synthesized from 5-hydroxymethyl-2-oxazolidinone tosylates using Te^{2-}.[12]

In recent years, there has been growing interest in indium-mediated transformations[13] because of certain unique properties inherent to indium. Furthermore, indium metal is non-toxic, non-corrosive and is stable in water or air. Since indium has a close resemblance in several aspects, to magnesium and zinc it should be a reducing agent. In continuation of our work on the applications of indium for various transformations,[14] we report herein an indium-mediated facile synthesis of



Scheme 1. *Reagents and conditions*: (a) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM, –20°C (85–90%); (b) $R^2CH_2NH_2$, $Ti(O^iPr)_4$, DCM, rt (77–85%); (c) $ClCO_2Me$, K_2CO_3, THF, 0°C (88–95%); (d) KOH in 10% MeOH, rt (82–89%); (e) PPh_3, I_2, imidazole, ether:CH_3CN (3:1), rt (77–85%).

Keywords: indium; oxazolidinone; chiral allylic amine.

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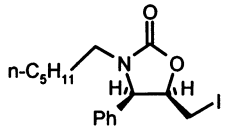
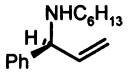
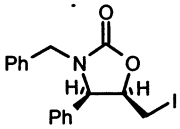
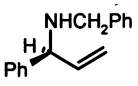
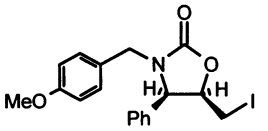
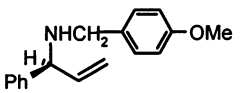
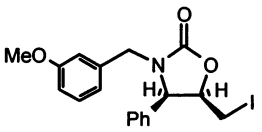
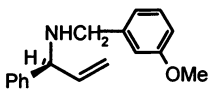
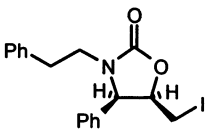
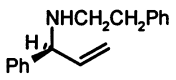
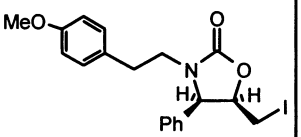
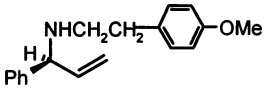
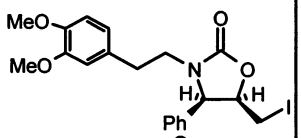
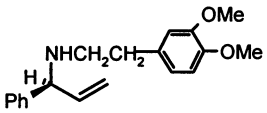
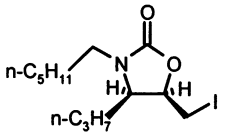
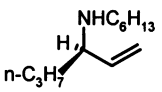
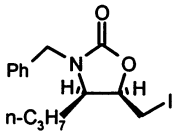
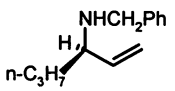
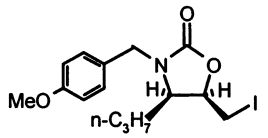
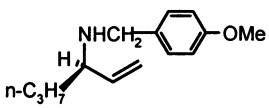
† IICT communication No. 4792.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01258-8

Table 1. Indium-mediated conversion of 5-iodomethyl-2-oxazolidinones to chiral allylic amines[a]

Entry	5-iodomethyl-2-oxazolidinone derivatives (1)	Allylic amines (2)	% Yield[b] (time, h)	$[\alpha]_D^{25}$ (c,0.5 in $CHCl_3$)[12a]
a			87 (4)	+18.5
b			92 (5)	+3.6
c			96 (5)	−8.1
d			91 (5)	+4.0
e			87 (4)	+10.3
f			93 (6)	+9.6
g			86 (6)	+5.8
h			81 (5)	−0.4
i			89 (4)	−2.0
j			85 (5)	+1.4

a) All products were characterized by ^1H, ^{13}C NMR, mass spectra, and also by comparison with authentic samples.[12a]

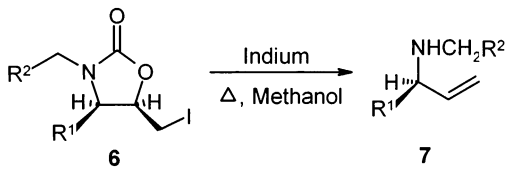
b) Isolated and unoptimized yields.

N-substituted allylic amines from 5-iodomethyl-2-oxazolidinones.

Scheme 1 illustrates the synthesis of 5-iodomethyl-2-oxazolidinones from allylic alcohols via optically active aminodiols. Allylic alcohols **1** were subjected to Sharpless asymmetric epoxidation[15] to afford epoxy alcohols **2** which, on selective ring opening with amines,[16] gave optically active aminodiols **3**. The aminodiols **3** were treated with methyl chloroformate and potassium carbonate in THF at 0°C for 6–7 h[17] to give the bis-carbonates **4**. The crude carbonates **4** were treated with 10% potassium hydroxide in methanol to afford 5-hydroxymethyl-2-oxazolidinones **5** in good yield. Treatment of **5** with triphenylphosphine, iodine and imidazole in a mixture of ether and acetonitrile[18] (3:1) gave 5-iodomethyl-2-oxazolidinones **6**. Treatment of **6** with indium metal in refluxing methanol for 4–6 h gave the corresponding chiral amines **7** in good yields (Scheme 2).

Several examples illustrating this novel and practical method for the synthesis of chiral allylic amines are listed in Table 1.[19] The experimental procedure is very simple and the products are obtained in high yields. The reaction proceeds smoothly under mild conditions. No racemization or decomposition of the products is observed under the reaction conditions as confirmed by chiral HPLC.[20] Unlike zinc or tin, indium does not require any acidic promoters or activators or anhydrous solvent to give the product. The reactions are clean and no side products are observed. Methanol appears to be the choice of solvent for this reaction. Among various metals such as indium, samarium, yttrium and tin used for this transformation, indium was found to be more effective than others in terms of yields and reaction times. For example, treatment of 3-benzyl-5-iodomethyl-4-phenyl-(4*R*,5*R*)-1,3-oxazolan-2-one (entry **1b**) with different metals such as indium, samarium, yttrium and tin for 5 h gave the corresponding chiral allylic amine (entry **2b**) in 92, 71, 52 and 65% yield, respectively, under typical reaction conditions.

In summary, we have demonstrated a novel and highly efficient protocol for the synthesis of chiral allylic amines using metallic indium. In addition to its simplicity and mild reaction conditions, the method offers high yields of products in short reaction times which makes it a useful and attractive process for the synthesis of chiral allylic amines.



6 **7**

Scheme 2.

Acknowledgements

Two of the authors (A.B./B.V.S.R.) are thankful to UGC/CSIR, New Delhi, respectively, for financial support. We are thankful to Dr. N. W. Fadnavis for HPLC analysis.

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19. **General procedure**: A mixture of 5-iodomethyl-2-oxazolidinone (2 mmol) and indium powder (4 mmol) in methanol (10 mL) was stirred under reflux for 4–6 h. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered and washed with methanol (10 mL). The combined extracts were concentrated in vacuo, purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure allylic amine. Spectral data for the products: Compound **2c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (s, 2H), 3.79 (s, 3H), 4.24 (d, $J=7.0$ Hz, 1H), 5.12 (dd, $J=10.0$, 1.0 Hz, 1H), 5.24 (dd, $J=16.0$, 1.0 Hz, 1H), 5.97 (m, 1H), 6.86 (d, $J=9.0$ Hz, 2H), 7.23 (d, $J=9.0$ Hz, 2H), 7.29–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.65, 142.87, 141.03, 132.61, 129.29, 128.49, 127.34, 127.15, 115.02, 113.81, 65.00, 55.25, 50.68; EIMS (m/z) 253 [M^+]. Compound **2g**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.73 (m, 4H), 3.79 (s, 6H), 4.17 (d, $J=7.0$ Hz, 1H), 5.16 (dd, $J=12.0$, 2.0 Hz, 1H), 5.14 (dd, $J=20.0$, 2.0 Hz, 1H), 5.89 (m, 1H), 6.67–6.76 (m, 3H), 7.19–7.27 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.21, 147.58, 142.34, 140.79, 132.61, 128.52, 128.42, 127.18, 120.62, 114.96, 112.20, 111.53, 65.86, 55.93, 55.81, 48.65, 35.76; EIMS (m/z) 297 [M^+]. Compound **2i**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, $J=7.0$ Hz, 3H), 1.26–1.54 (m, 4H), 3.03 (m, 1H), 3.63 (d, $J=9.0$ Hz, 1H), 3.82 (d, $J=9.0$ Hz, 1H), 5.09 (dd, $J=15.0$, 1.0 Hz, 1H), 5.17 (dd, $J=9.0$, 1.0 Hz, 1H), 5.62 (m, 1H), 7.19–7.12 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.21, 140.52, 128.33, 128.20, 126.81, 115.94, 60.96, 51.15, 37.86, 19.05, 14.02; EIMS (m/z) 146 [M^+–n-C_3H_7].
20. Enantiomeric purity of 1*N*-hexyl-1-phenyl-(1*S*)-2-propen-1-amine and 1*N*-benzyl-1-phenyl-(1*S*)-2-propen-1-amine (entry **2a**, 90% ee and entry **2b**, 86% ee) were determined by chiral HPLC on Chiralcel OD column (5×250 mm), Diacel Chemical Industries, Japan; mobile phase 0.025% isopropanol in hexane containing 0.05% diethylamine and 1.0% isopropanol in hexane containing 0.2% diethylamine; flow rate 0.3 mL/min. 0.5 mL/min, respectively. The enantiomeric purity of 3-hexyl-5-hydroxymethyl-4-phenyl-(4*R*,5*R*)-1,3-oxazolan-2-one and 3-benzyl-5-hydroxymethyl-4-phenyl-(4*R*,5*R*)-1,3-oxazolan-2-one (90% and 86% ee, respectively) were also determined by chiral HPLC using the same chiral column; mobile phase 20.0% isopropanol in hexane; flow rate 0.5 mL/min. This clearly indicates that the products were obtained without any racemization under the reaction conditions.