Pergamon

Tetrahedron Letters, Vol. 38, No. 5, pp. 865-868, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02427-6

A Highly Stereoselective One-Pot Asymmetric Synthesis of Homoallylic Amines and Amino Acids From Aldehydes

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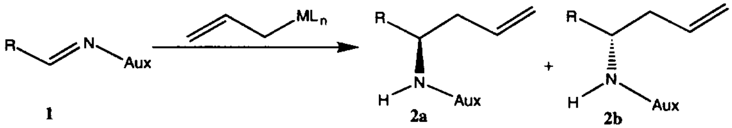
Abstract: A simple and efficient one-pot method was developed to give chiral homoallylic amines and amino acids from the respective aldehydes in high stereoselectivity.

Pharmaceutically important amino acids and β-lactam antibiotics belong to an interesting class of nitrogen-containing compounds. The precursors to such drugs can be prepared from the addition of organometallic reagents to chiral imines, prepared from condensation of aldehydes with optically pure amines, in a one-pot reaction (Scheme 1).[1] As imines are sensitive towrds hydrolysis in nature and are unstable at high temperatures, this route will provide a synthetically useful methodology for the preparation of amine derivatives.[2] Furthermore, amino acids can be directly synthesized if the addition of organometallic reagent to the glyoxylic acid derived imine can proceed without the use of protecting group on the acid functionality.

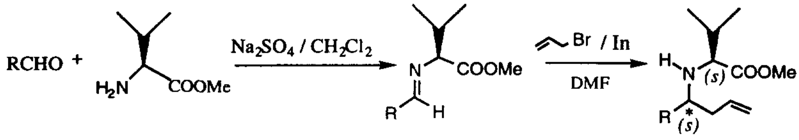
Although many different organometallic reagents that give satisfactory selectivities have been developed,[3] most of them are transmetallation processes which requires Lewis acids catalysis.[4] In this paper we describe the indium-mediated[5] allylation of one-pot imine reaction derived from L-valine methyl ester. The stereochemistry is controlled only by direct chelation of the indium species to give the respective chiral homoallylic amines and amino acids in high yields and stereoselectivities.



Scheme 1

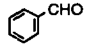
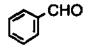
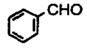
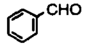
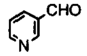
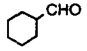
The reaction procedure is extremely simple. In the presence of a dehydrating agent (anhydrous Na_2SO_4), an aldehyde (1 equiv.) was treated with L-valine methyl ester (1.1 equiv.) in CH_2Cl_2 (5 mL) and was stirred overnight at ambient remperature. Allylic indium was prepared separately from indium (2 equiv.) and allyl bromide (3 equiv.) in DMF (1 mL) and was added to the preformed imine in the same vessel. The resultant reaction mixture was further stirred for 12 hours at ambient temperature. The respective reaction products were extracted with ether and the combined ethereal phase was washed with water, saturated brine and dried. The results are summarised in Table 1.

In all cases, excellent selectivities were observed for both aromatic and aliphatic substrates. Generally, the reactions proceeded smoothly and cleanly under mild conditions giving only the corresponding homoallylic amine in moderate to good yield. These reactions are not susceptible to side-reactions such as allylation on the ester moiety due to the functional preference of the organo-indium for the imine group.



(eq. 1)

Table 1. Diastereoselectivities of Indium-mediated Allylation of Chiral Imines [a]

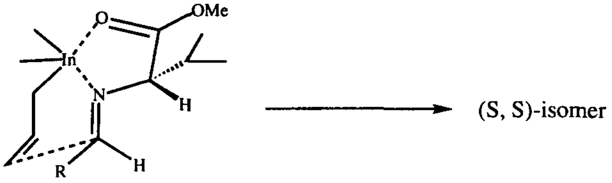
Entry	RCHO	Condition [d]	Yield % [b]	*(S, S) : (S, R)* [c]
1		20% La(OTf)$_3$	35	90:10
2		20% InCl$_3$	60	92:8
3		5% InCl$_3$	63	93:7
4		No catalyst	80	95:5
5		No catalyst	75	99:1
6		No catalyst	75	99:1
7	TMS−≡−CHO	No catalyst	80	99:1
8	HOOCCHO.H$_2$O	No catalyst	52	99:1

[a] All reactions were carried out on a 0.5 mmol scale. [b] Yield of isolated product. [c] Ratio was determined by ^{1}H NMR analyses Absolute stereochemistry confirmed by comparison with known literature data.[3a] [d] Reactions with anhydrous MgSO$_4$ as dehydrating agent were found to give lower selectivities.

Especially noteworthy is the reaction of commercially available glyoxylic acid monohydrate (Table 1, entry 8) which gives only one isomer in moderate yield. Previously, its low solubility and free acid functionality renders it very unreactive especially towards many organometallic reactions in non-protic conditions. Therefore, apart from aromatic and aliphatic substrates, this method can also be applied to the hydrated form of aldehyde which will provide one of the most straightforward syntheses of optically active amino acids.

An intriguing point is that the best selectivity was observed under which no catalyst was employed. In the presence of Lewis acid catalysts, InCl$_3$[6] or La(OTf)$_3$[7] the diastereoselectivity in fact decreased. The trend observed was that the higher the concentration of Lewis acid added, the lower the selectivity (Table 1, entries 1-4).

The excellent stereoselectivities observed may then be rationalized by the proposed transition state **A** (Figure 1). In this model, the indium species is chelated by the nitrogen and the carbonyl group of the ester. Owing to the rigid N, O-bidentate conformation, the bulky isopropyl group of the valine chiral auxillary selectively shields one face and hence allowing allylic delivery only to the *si* face. As a result, only the *(S, S)* diastereomers predominate in all cases. Experiments (Table 1, entries 1-4) lend supporting evidence for the transition model as the external Lewis acid distorts the conformation of transition state **A** thereby reducing the diastereoselectivity.



A

Figure 1

In conclusion, we have demonstrated a highly stereoselective one-pot methodology to chiral homoallylic amines and amino acids. The protocol is simple and potentially leading to versatile β-amino acid and β-lactam precursors. This method has a few noteworthy features : 1) excellent selectivities can be obtained 2) applicable to hydrated aldehydes which requires no protection of the acid functionality 3) the valine auxillary can be removed by known literature procedure[3b] and 4) great operational simplicity at ambient temperature. We are currently extending this work towards aqueous-mediated imine reactions.

We would like to acknowledge the National University of Singapore for the financial support (RP 3930657, RP 3940633, RP 3950609).

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(*Received in UK* 27 *September* 1996; *revised* 10 *December* 1996; *accepted* 13 *December* 1996)