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An Asymmetric Synthesis of α–Amino Acid Derivatives from Racemic Ethyl N-Phenylsulphonyl-α-bromoglycinate using Homochiral Aluminium Complexes.

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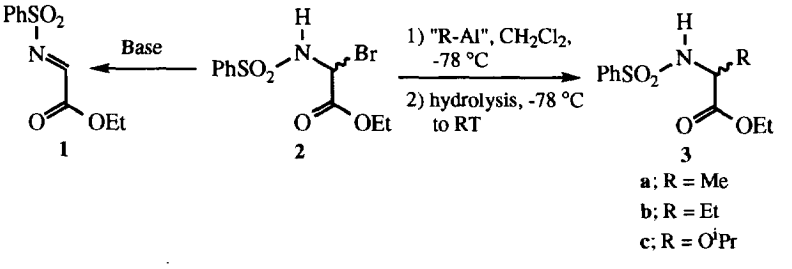
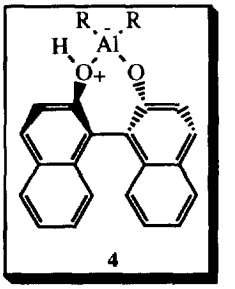
Abstract: Reactions of a racemic α-bromoglycinate **2** with readily available alkyl aluminium reagents modified by binaphthol derivatives produce α-amino acid analogues **3** in high yields and with asymmetric induction of up to 62 %.

The asymmetric synthesis of α-amino acids has been the focus of considerable synthetic endeavour for several years[1] and has relied upon methods such as an asymmetric Strecker reaction, asymmetric alkylation of glycinate derivatives, asymmetric amination of chiral enolates and asymmetric hydrogenation. During studies related to the development of new methods for asymmetric aza-Diels-Alder reactions,[2] we examined the use of various methods for the generation of imine **1** *via* elimination of HBr from α-bromoglycinate **2**[3,2b] (**Scheme 1**). These methods included the use of alkyl aluminium complexes which resulted in the generation of imine **1** under certain conditions,[4] but also resulted in the generation of α-amino acids. In this preliminary communication we report the asymmetric synthesis of α-amino acid analogues **3** from bromo glycinate **2**.

Scheme 1.





Reaction of racemic α-bromoglycinate **2** with homochiral aluminium complexes "R-Al" [readily prepared *in situ* from commercially available materials using either trimethyl, triethyl or triisopropoxyaluminium and (*R*)-binaphthol (Binol)] gave high yields and low to moderate enantiomeric excess's (e.e.'s) (**Table 1**) of the corresponding substituted amino acids **3** as shown in **Scheme 1**.

For the alanine and amino butyrate products (Entries 1-4, **Table 1**) yields of the α-amino acid derivatives were high, with asymmetric induction moderate. Perhaps surprisingly, even the iso-propoxide derivative (Entry 4) also showed asymmetric induction. It is worth noting that for all the reactions carried out, the binaphthol was recovered quantitatively and was reused.

Table 1.

Entry	Product[a] **3**	"RAl"	Temp. / °C	E.e. / %	Config.	Yield %
1	**3a**	(*R*)-Binol/Me_3Al	-78	52[b]	*S*[c]	55
2	**3b**	(*R*)-Binol/Et_3Al	RT	55[b]	*S*[e]	95
3	**3b**	(*R*)-Binol/Et_3Al	-78	62[d]	*S*[e]	90
4	**3c**	(*R*)-Binol/PrO_3Al	RT	25[f]	-	97

a; See reference 8. b; E.e. was measured by hplc of the correspondong Mosher ester, see reference 5. c; Absolute stereochemistry determined as in reference 6. d; E.e. measured by chiral hplc using a ChiralPak AD column. e; Absolute stereochemistry determined as in reference 7. f; E.e. measured by chiral hplc on a Chiracel OD column.

It is interesting to note that both **3a** and **3b** show the same sense of absolute asymmetric induction for the major product. In order to try to explain the observed induction it is necessary to understand the structure of the *in situ* generated aluminium complex "R-Al". In view of the stoichiometry of the reaction[8] it is possible that a species such as **4** could be involved. This is also supported by the fact that only 1 molar equivalent of ethane is evolved from the reaction of triethylaluminium with binaphthol. Thus, the likely complexes produced by the reaction of trialkylaluminium reagents with binaphthol would have the general structure **4**. A similar process is also likely to occur with aluminium iso-propoxide.

Once formed, aluminium complexes of type **4** have one alkyl group (or iso-propoxide) which is likely to be responsible for the generation of imine **1** by deprotonation of the sulfonamide moiety, followed by elimination of bromide ion. The resulting imine **1** would then undergo addition to the *Si*-face by the second alkyl group (or iso-propoxide) from the (*R*)-binaphthol-derived chiral aluminium complex to give (*S*)-**3** after workup. This kind of process is not dissimilar to the reactions of chiral bromo morphinones when treated with organo zinc reagents.[9]

Further studies are underway to probe the mechanism of the reaction and apply this work to a wider range of amino acid derivatives.

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References.

1. a) Harada, K.; Okawara, T.; *J. Org. Chem.*, **1973**, *38*, 707; b) Stout, D.M.; Black, L.A.; Matier, W.L.; *ibid*, **1983**, *48*, 5369; c) For a recent review see Duthaler, R.O.; *Tetrahdron*, **1994**, *50*, 1539.
2. a) McFarlane, A.K.; Thomas, G.; Whiting, A.;*Tetrahedron Lett.*, **1993**, *34*, 2379; b) *idem*, *J. Chem. Soc., Perkin Trans. I*, **1995**, 2803.
3. Maggin, M; Prato, M.; Scorrano, G.;*Tetrahedron Lett.*, **1990**, *32*, 6243
4. Morgan, P.; Whiting, A.; unpublished results.
5. Alanine analogue **3** (R=Me) was reduced with lithium aluminium hydride and converted into the (+)-Mosher ester.
6. The absolute stereochemistry of **3** (R=Me) was determined by comparison of the (+)-Mosher ester derivative prepared in reference 5, with that prepared from commercial L-alanine.
7. The absolute stereochemistry of **3** (R=Et) was determined by comparing the hplc retention times of the products from **Table 1**, with both racemic **3** (R=Et) and the N-phenylsulphonyl ethyl ester derivative of commercial (*S*)-(+)-2-aminobutyric acid.
8. General procedure for **3** (R=Et): Triethylaluminium (0.177 g, 1.552 mmol) was added to a stirred -78°C solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) under Ar in dichloromethane (15 ml), which was then added by cannula to a solution of ethyl N-phenylsulphonyl α-bromoglycinate (0.500 g, 1.552 mmol) at -78 °C in dichloromethane (50 ml). After 4 hours, the reaction was quenched with saturated ammonium chloride solution (25 ml); the organic layer was separated and the aqueous layer re-extracted with dichloromethane (3 x 20 ml); the combined organic extracts were dried ($MgSO_4$) and evaporatated to yield the crude α-substituted product **3b** as an off-white solid. Separation of the binaphthol (quantitative recovery) and **3b** by silica gel chromatography gave pure **3b** as a white solid (0.379 g, 90 %). Note: **3c** was not purified by chromatography; binaphthol was removed by selective precipitation from ether-hexane.
9. Williams, R.M.; Sinclair, P.J.; Zhai, D.; Chen, D.; *J. Am. Chem. Soc.*, **1988**, *110*, 1547.

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