Enantioselective radical cyclization controlled by a chiral aluminium reagent

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Free radical cyclization of cyclohexyl 8-iodonona-2,8-dienoate in the presence of a chiral aluminium reagent, prepared from (*R*)-3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol and Me_3Al, gives optically active 2-(2-methylenecyclopentyl)acetate in 63% yield and 46% ee.

Recently, remarkable progress has been made in stereochemical control in radical C–C bond formation. High diastereoselectivities have been reported in both substrate- and auxiliary-controlled reactions[1] and efforts are now being directed towards developing an enantioselective reaction.[2] We previously reported Lewis acid-promoted β-diastereoselective radical cyclization using α,β-unsaturated (−)-8-phenylmenthyl ester as a chiral radical acceptor.[3] The presence of Lewis acid is essential for both high diastereoselectivity and chemical yield. The Lewis acid appeared to control the conformation of the α,β-unsaturated ester as *s-trans* and enhance its reactivity as a radical acceptor. Since bulky Lewis acids, such as methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[4] gave especially good results, we expected that a chiral aluminium reagent, such as (*R*)-**3** or (*R*)-**4**,[5] might effect an asymmetric induction in the reaction of achiral substrates **1a** and **1b** (Scheme 1). Here we report the first example of an enantioselective radical cyclization controlled by a chiral aluminium reagent.

The cyclization of **1a** at −78 °C in the presence of 1 equiv. of (*R*)-**3**, prepared from (*R*)-binaphthol and trimethylaluminium *in situ*, gave the cyclized product (*R*)-**2a** in 89% yield and with an ee of only 2% (Table 1, run 1). A high concentration of the Lewis acid was expected to increase the enantioselectivity, however, the low solubility of (*R*)-**3** in CH_2Cl_2 prevented us from using it at a higher concentration. We hence used the chiral aluminium reagent (*R*)-**4**, which we expected to be more soluble in CH_2Cl_2 than (*R*)-**3** and may provide higher selectivity because of its bulkiness. The reaction of **1a** in the presence of 1 equiv. of (*R*)-**4** gave (*R*)-**2a** in 75% yield, and with a slightly increased ee (12%, run 2). When, **1a** was treated with a higher concentration of (*R*)-**4** (4 equiv.), a higher ee (36%) was observed, as expected (run 3).

Six-membered ring formation in this system has been shown to be inefficient at −78 °C[3] and the uncyclized product, **5** was a major product. Hence, the cyclization of **1b** was carried out at 0 °C in the presence of 4 equiv. of (*R*)-**4** to give **2b** in 63% yield and 46% ee, along with **5** (21%, run 4).

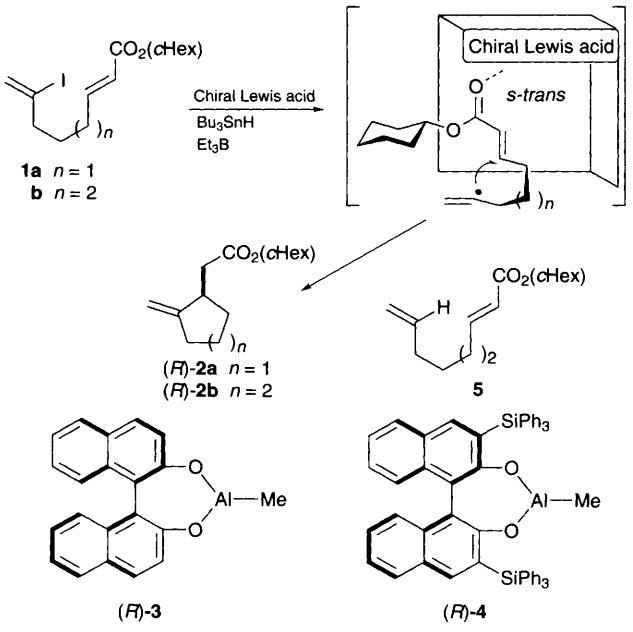
Five-membered ring formation using **6**, in which the α,β-unsaturated ester was replaced by amide, proceeded smoothly even without Lewis acid present (Scheme 2). The reaction in the presence of 4 equiv. of (*R*)-**4** at −78 °C gave (*S*)-**7** in 83% yield and 26% ee. Thus, the chirality of the product was reversed by altering the structure of the radical acceptor.

In the transition state, the α,β-unsaturated ester complexed by Lewis acid favours *s-trans* conformation. On the other hand, the

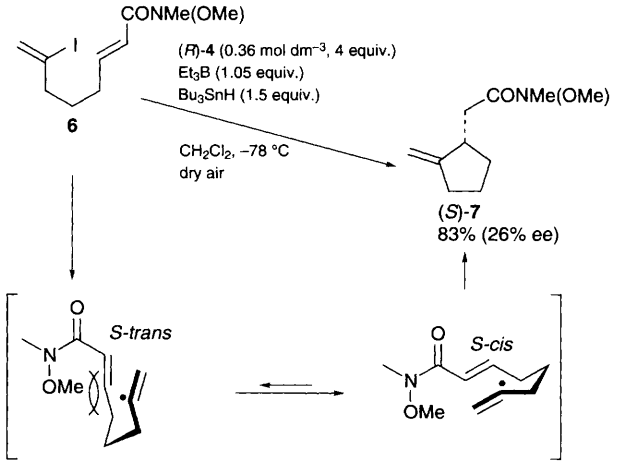
Table 1 Enantioselective radical cyclization of **1a** and **1b**[a]

Run	Starting material	Lewis acid	Concentration /mol dm^{-3}	Equiv.	Yield of **2** (%)	ee (%)
1†	**1a**	(*R*)-**3**	0.09	1	89	2
2	**1a**	(*R*)-**4**	0.09	1	75	12
3	**1a**	(*R*)-**4**	0.36	4	72	36
4	**1b**	(*R*)-**4**	0.36	4	63[b]	48

[a] The concentration of **1** was kept at 0.09 mol dm^{-3} in all of the reactions. [b] Cyclohexyl nona-2,8-dienoate **5** was obtained in 21% yield as a by-product.



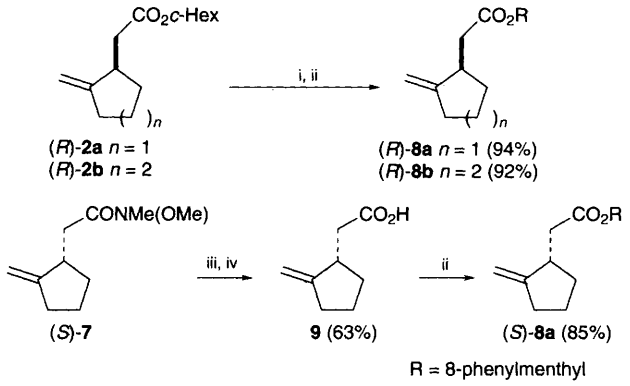
Scheme 1



Scheme 2

α,β-unsaturated amide favours the *s-cis* conformation.[1] This appeared to be the main reason for the change in the absolute configuration of the major product.

The absolute configurations of the products **2a**, **2b** and **7** were determined as follows. Hydrolysis of **2a** and **2b**, followed by condensation with (−)-8-phenylmenthol, gave (*R*)-**8a** and (*R*)-**8b** respectively. These compounds have been synthesized previously,[3a] and the de of each compound was determined by ^{1}H NMR. Compound **7** was converted to (*S*)-**8a** *via* the carboxylic acid **9** (Scheme 3).



Scheme 3 *Reagents and conditions*: i, NaOH, aq. MeOH; ii, 2,4,6-trichlorobenzoyl chloride, Et_3N, (−)-8-phenylmenthol, DMAP, toluene; iii, DIBAL-H; iv, ButOH, 2-methylbut-3-ene, $NaClO_2$, NaH_2PO_4

Footnote

† *Typical experimental procedure*: To a stirred solution of (*R*)-3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol (1.41 g, 1.76 mmol) in CH_2Cl_2 (2.64 ml) was added Me_3Al (1.0 mol dm^{-3} in hexane, 1.76 ml) at room temp. under argon. The solution was stirred for 1 h. The resulting solution of (*R*)-**4** in CH_2Cl_2 (0.4 mol dm^{-3}, 4.4 ml) was then added to **1b** (159 mg, 0.44 mmol) at room temp. under argon. To this mixture, Et_3B (1.0 mol dm^{-3} in hexane, 0.46 mmol) and Bu_3SnH were added. After stirring for 20 min, 1 mol dm^{-3} HCl was added and the aqueous layer extracted with EtOAc. The combined ether extracts were then washed with brine and then evaporated to give a residue, which was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 2 : 1, then ether : hexane = 1 : 20) to give **2b** (65 mg, 63%) and **5** (21 mg, 21%).

References

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