Enantiodivergent 1,2- and 1,3-Asymmetric Induction in α- and β-Alkoxyimines via Metal Tuning and Double Stereodifferentiation

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Enantiodivergent 1,2- and 1,3-asymmetric induction in α- and β-alkoxyimines is realized via a combination of metal tuning and double stereodifferentiation; the chelation products (5) and (11) are obtained with allyl-MgCl, -AlEt$_3$MgCl$^+$, or -ZnBr, while the non-chelation products (6) and (12) are obtained with allyl-9-borabicyclo[3.3.1]nonane.

A predominant theme in organic chemistry in recent years is the synthesis of enantiomerically pure compounds.[1] The chiral auxiliary compounds, reagents, and building blocks derived from natural products are usually available only in one enantiomeric form, and hence access to both enantiomers is highly desirable. Very high enantiodivergent 1,2- and 1,3-asymmetric induction in the aldehyde series has not yet been realized (equations 1 and 2);[2] very high to good asymmetric synthesis of (2), (3), and (8) from (1), (1), and (7), respectively, has been achieved, but the synthesis of (9) from (7) has not been proved feasible.

We report that very high enantiodivergent 1,2- and 1,3-asymmetric induction in the imine series (4) and (10)[3,4] is realized via the combination of both metal tuning and double stereodifferentiation. The results are summarized in Table 1.

In the 1,2-asymmetric induction of (4) (equation 1), allyl-MgCl, -AlEt$_3$MgCl$^+$,[5] and -ZnBr produced predominantly the chelation product (5), while allyl-Ti(OPr^i)$_3$, -B(OMe)$_2$, and -9-borabicyclo[3.3.1]nonane (9-BBN) affor-

ded preferentially the non-chelation product (6). The reagents which possess a metal or metal ion with relatively low electronegativity can co-ordinate both nitrogen and oxygen atoms, i.e. strong chelation. The boron reagents cannot chelate so efficiently and the reaction should proceed through the axial-type six-membered chair transition state[4] which gives predominantly the Cram (non-chelation) product (the axial effect). The titanium reagent is an exception; the chelation may be weak due to the presence of three OPr^i ligands.

We anticipated that the concept of double stereodifferentiation[6] could also be applied to the reaction between achiral reagents and chiral substrates with two asymmetric centres, since such a concept has been useful in the reaction between chiral reagents and chiral substrates with one stereocentre each. In comparison with the original mono-chiral imine (4b), the S,R imine (4c) was a matched pair for obtaining the chelation product, while the S,S imine (4a) was a mismatched pair. Consequently, use of the aluminium ate complex and (4c) gave (5c) in 90% diastereoselective excess (d.e.). The

Table 1. Enantiodivergent 1,2- and 1,3-asymmetric induction using $CH_2=CHCH_2M$.[a]

M	From (4)			From (10)		
	(5a):(6a)[b]	(5b):(6b)	(5c):(6c)	(11a):(12a)	(11b):(12b)	(11c):(12c)
MgCl	70:30	79:21	86:14	92: 8	85:15	38:62
$\overline{Al}Et_3MgCl^+$ [c]	89:11	93: 7	95: 5		90:10	
ZnBr	76:24	78:22	92: 8		62:38	
Ti(OPr^i)$_3$[d]	6:94	23:77	20:80		30:70	
B(OMe)$_2$[e]	10:90	7:93	10:90			
9-BBN	3:97	->99	->99	63:37	46:54	10:90

[a] To a diethyl ether solution of the allylmetal reagent (1.1 mmol), except the boron reagents in which CH_2Cl_2 was used as a solvent, the imine (1 mmol) was added at −78 °C. The reaction was quenched at 0 °C with H_2O, and the product ratio was determined by ^1H n.m.r. spectroscopy and g.l.c. [tetrahydroxyethylenediamine (THEED Wako Chem. Ind.), 10%, 3 m]. [b] The ratio of chelation: non-chelation product. The total yields were in a range of 82—95%. [c] Prepared in situ from allyl-MgCl and Et₃Al. [d] Prepared in situ from allyl-MgCl and Ti(OPr^i)$_3$Cl. [e] Prepared in situ from allyl-MgCl and BF(OMe)$_2$.

$$(1); X = O \qquad (2) \qquad (3)$$
$$(4); X = NR' \qquad (5) \qquad (6)$$

Chelation product   Non-chelation product

$$(7); X = O \qquad (8) \qquad (9)$$
$$(10); X = NR' \qquad (11) \qquad (12)$$

Chelation product   Non-chelation product
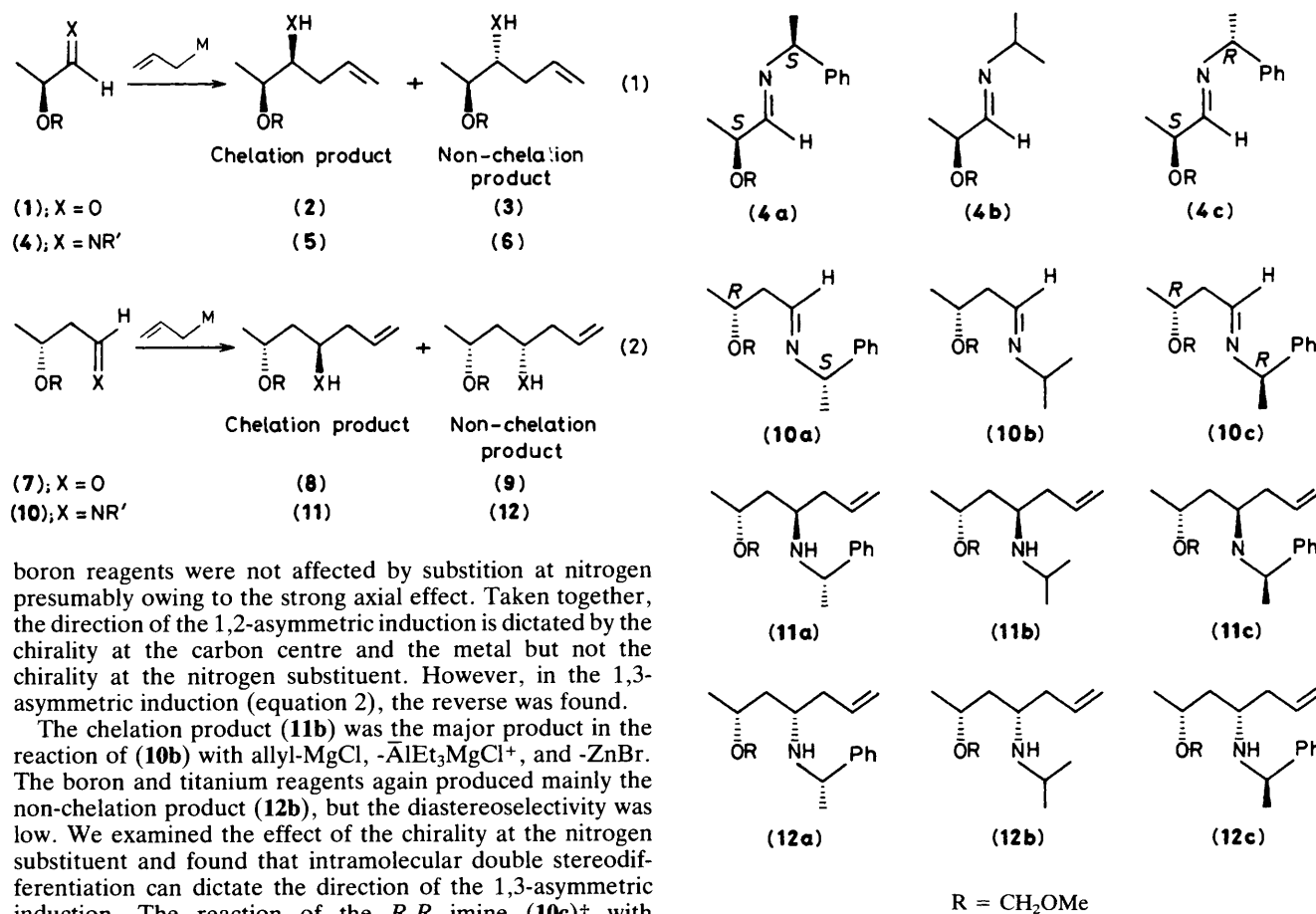
boron reagents were not affected by substition at nitrogen presumably owing to the strong axial effect. Taken together, the direction of the 1,2-asymmetric induction is dictated by the chirality at the carbon centre and the metal but not the chirality at the nitrogen substituent. However, in the 1,3-asymmetric induction (equation 2), the reverse was found.

The chelation product (11b) was the major product in the reaction of (10b) with allyl-MgCl, -$\overline{Al}Et_3MgCl^+$, and -ZnBr. The boron and titanium reagents again produced mainly the non-chelation product (12b), but the diastereoselectivity was low. We examined the effect of the chirality at the nitrogen substituent and found that intramolecular double stereodifferentiation can dictate the direction of the 1,3-asymmetric induction. The reaction of the R,R imine (10c)† with allyl-9-BBN produced (12c) in 80% d.e., and even allyl-MgCl produced (12c) predominantly. The reaction of the R,S imine (10a) with allyl-MgCl gave (11a) in 84% d.e. and even the reaction of allyl-9-BBN with (10a) produced (11a) predominantly. Therefore, the R,R combination was a matched pair for the non-chelation product, while the R,S combination was a matched pair for the chelation product.

(4a)   (4b)   (4c)

(10a)   (10b)   (10c)

(11a)   (11b)   (11c)

(12a)   (12b)   (12c)

$R = CH_2OMe$

The structures of (5), (6), (11), and (12) were determined as follows. Epoxidation of trans-hex-2-ene with m-chloroperbenzoic acid, followed by treatment with the amines at 80—100 °C produced a mixture of 2-aminohexan-3-ol and 3-aminohexan-2-ol in a ratio of ca. 1:1. The regio-isomers were separated through a silica gel column with hexane–diethyl ether (10:1) as an eluant. The reaction products [(5) and (6)] were reduced with H_2/Pd-C, and then the methoxymethyl protecting group was removed with HCl–MeOH. The authentic 3-aminohexan-2-ols were compared with the amino alcohols derived from (5) and (6). The methoxymethyl group of (11) and (12) was removed and the resulting 1,3-amino alcohols were analysed by 400 MHz ^1H n.m.r. spectroscopy. The relative stereo-

† The starting imines were prepared from the reaction of the corresponding aldehydes (1) and (7) with isopropylamine, or (S)- or (R)-α-methylbenzylamine in CH_2Cl_2 at 20 °C. Epimerization at the α-position of (4) was not observed at 25 °C. Compound (1) was prepared from ethyl (+)-lactate (Aldrich Chem. Co.) and (7) was prepared from (R)-methyl 3-hydroxybutyrate (Wako Chem. Ind.).

chemistry was assigned by the coupling constants of the vicinal protons.[7]

In conclusion, we are now in a position to prepare both chelation and non-chelation products in the imine series.‡ This is important for the enantiodivergent synthesis of amino sugars and amino acids. The combination of metal tuning and double stereodifferentiation should solve the problem of 1,n-asymmetric induction in the aldehyde series.

Received, 12th March 1985; Com. 330

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‡ We also examined the similar reaction with other protecting groups, such as methyl and 2-methoxyethoxymethyl, and obtained the same results.

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