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Asymmetric Grignard Addition to Aldehydes. An Example of Inverse Temperature Dependence of Enantiomeric Excess.

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Abstract : The addition of organomagnesium derivatives to aldehydes, promoted by chiral diamine **3** shows an inverse correlation between ee and temperature.

The asymmetric addition of organometallic reagents to aldehydes and ketones promoted by various chiral additives has received considerable attention over the years.[2] Although initial results were disappointing,[3] giving low enantiomeric excesses, considerable progress has been made recently.[4] The asymmetric addition of organozinc reagents to aromatic aldehydes, catalysed by chiral amino-alcohols[5a] and diols,[5b] is now a well-established technique and one of the methods of choice for the synthesis of optically active secondary alcohols.

Paradoxically, the reaction of Grignard derivatives with aldehydes has received less attention. High levels of enantioselectivity have been realised using Grignard and dialkylmagnesium reagents in conjunction with optically active amino-alcohols,[4c] Grignards modified by chiral titanium complexes,[4d, 4g] binary lithium/magnesium reagents[4f] and Grignard reagents in the presence of homochiral bis-pyrrolidine ligands.[4b] None of these reactions, however, are catalytic in the chiral additive.

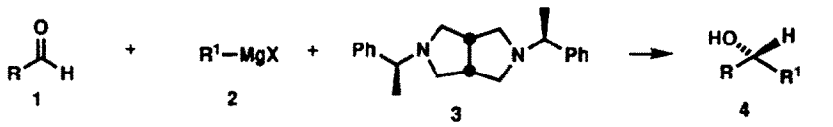
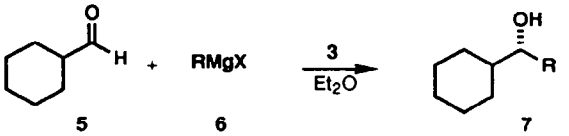


Figure 1

During some recent work aimed at delineating the potential of chiral diamines such as **3** in asymmetric synthesis,[6] we had the opportunity to study the enantioselective addition of Grignard reagents modified by **3**,[7] to aldehydes (Figure 1). In this article, we report on some interesting features displayed by this reaction, amongst which is the observation of an inverse correlation between ee and temperature.

For our initial studies, we selected cyclohexane carboxaldehyde as the substrate and varied the nature of the Grignard reagent. Some pertinent data are collected in Table 1.

Table 1. Variation of ee with the Grignard Reagent



5 6 7

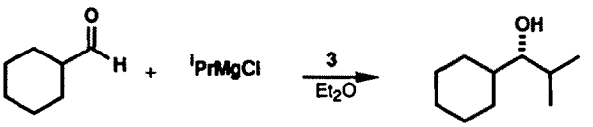
Entry	RMgX	Yield (%)[a]	ee (%)[b]
1	MeMgI	79	8
2	EtMgBr	87	14
3	^{n}PrMgCl	71	22
4	^{n}BuMgCl	73	33
5	^{n}PentMgCl	62	34
6	^{n}HexMgCl	67	35
7	^{i}PrMgCl	87	34
8	^{i}BuMgCl	63	37
9	^{t}BuMgCl	-	-

a = All yields refer to pure, isolated, material b = ee's were determined by ^{19}F NMR of the derived Mosher esters and by chiral gas chromatography The major enantiomer has the (R) absolute stereochemistry

As illustrated, increasing the chain length of the orgnomagnesium derivative results in gradual increase in the ee of the alcohol product (Entries 1-6). Branching at the β-carbon centre has little effect on the enantioselectivity of the reaction (Entries 4 and 8) whereas α-substitution improves the stereocontrol (Entries 3 and 7). Interestingly, this observation contrasts with that reported by Mukaiyama and co-workers,[4c] who found that branching had a deleterious effect on ee : (^{n}Pr, 70% ee; ^{i}Pr, 40% ee). Highly hindered Grignard reagents prove to be unreactive once coordinated to the chiral diamine ligand **3** (Entry 9).

Usually, lowering the temperature results in increase in the ee though a few cases exist showing the opposite behaviour.[8] With Grignards and dialkyl magnesium compounds, reactions mediated by chiral amino-alcohols require very low temperatures (-100°C) for high enantiocontrol Table 2 summarises the results obtained in the addition of *iso*-propyl magnesium chloride to cyclohexane carboxaldehyde.

Table 2. Variation of ee with Temperature in the Grignard Reaction

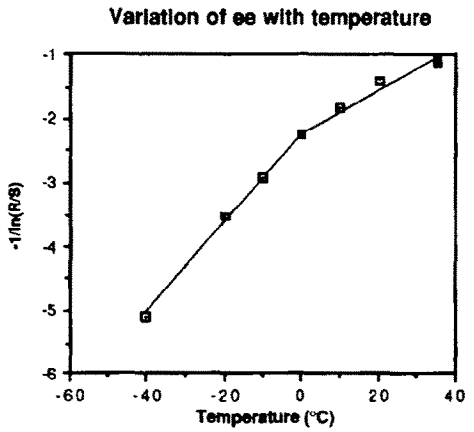


5 8 9

Entry	T (°C)	time (h)	Yield (%)	ee (%)[a]
1	- 40	48	84	9
2	- 20	48	83	14
3	- 10	48	88	17
4	0	24	86	22
5	10	16	85	27
6	20	2	87	34
7	35	1	73	42

a = ee's were determined by ^{19}F NMR of the derived Mosher esters and by chiral gas chromatography. The major enantiomer has (R) configuration.

In contrast to previous asymmetric Grignard additions, **a sharp decrease in ee is observed as the temperature is lowered.** Raising the temperature results in a steady increase in the enantiomeric excess of the product. **An increase of more than 30% ee is observed over an ~80°C temperature range.** Such an inverse ee/T correlation has been noticed in the dialkylzinc addition to aldehydes, catalysed by *cinchona* alkaloids,[9] as well as in certain asymmetric catalytic hydrogenations.[10] A plot of ee versus temperature is shown in Figure 2.



This diagram clearly shows two straight line regions connected by an inversion point. The presence of an inversion temperature suggests that the selectivity levels are weighted differently according to temperature. Several mechanistic interpretations can be put forward to rationalise this observation. However, our actual knowledge of this asymmetric reaction, which involves several discrete species in equilibrium is not sufficient to formulate an adequate explanation.

Interestingly, the asymmetric addition of di-*iso*-propyl magnesium, promoted by diamine **3**, also shows the same inverse T/ee correlation. The ee's observed for this reaction are identical (within experimental error) to those obtained in the corresponding Grignard reaction, suggesting that a dialkyl magnesium/diamine complex might be involved in this process.

Further work aimed at improving the enantioselectivity of this reaction and delineating its mechanism is currently underway in our Laboratory and the results will be reported in due course.

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8. For a stimulating review, see: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 477.
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