

Enantioselective Addition of Grignard Reagents to Aldehydes

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Abstract: The addition of Grignard reagents to aldehydes in the presence of chiral aminoalcohols shows a moderate enantioselectivity. The study carried out with a series of ligands allows the correlation between the structural characteristics and their reactivity.

Introduction

The use of chiral aminoalcohol to lead asymmetrically nucleophilic additions of organometallics to carbonyl compounds is a field of great potentiality in synthesis [1]. It is based on the coordination of amines and ethers to organolithium and Grignard reagents; the efficiency of the asymmetric induction depends, among other factors, on the characteristics of the metal [2], its aggregation state [3] and on the chiral ligand structure [4].

Experimental

General Procedure

To a mixture of 1 mmol of aldehyde and the corresponding amount of chiral ligand in the reaction solvent, 1.7 mL of a 0.6M of PrMgBr in the same solvent were added at -78°C. The quenching was carried out using 1 mL of HCl 5%. The products in the reaction mixture were investigated by GC and polarimetry.

Results and Discussion

The addition of PrMgBr to 3-phenylpropanal, **1**, and benzaldehyde, **2**, was carried out in the presence of asymmetric ligands derived from 2-aminobutanol and ephedrine in different solvents and reagent:ligand:substrate ratio (see Table). Several new ligands were designed and synthesized.

Table. Reactions of PrMgBr with 3-phenylpropanal, **1**, and benzaldehyde, **2**, in the presence of chiral ligands.

Chiral Ligand ^a	Aldehyde	Reagent:Ligand: Aldehyde ratio	Solvent	Yield (%)	Absolute Configuration	% ee
3	1	1.2:0.2:1.0	toluene	77	S-(+)	5
4	1	2.0:0.5:1.0	ether	98	R-(-)	2
5	1	1.2:0.2:1.0	toluene	98	S-(+)	5
	1	1.2:0.2:1.0	ether	100	S-(+)	7
6	2	4.0:2.0:1.0	THF	98	R-(+)	3
7	1	4.0:2.0:1.0	THF	90	S-(+)	8
	1	6.0:2.0:1.0	toluene	85	S-(+)	29
	2	6.0:2.0:1.0	toluene	51	S-(-)	40
8	2	4.0:2.0:1.0	THF	60	R-(+)	9
9	1	3.0:1.0:1.0	toluene	96	R-(-)	2

^a **3** = (-)-2-dipropylaminobutanol, **4** = (-)-(1-benciloxymethylpropyl)-dipropylamine, **5** = (-)-4-ethyl-2,2-dimethyl-oxazolidine, **6** = (-)-ephedrine, **7** = (-)-pseudoephedrine, **8** = (-)-2,2,3,4-tetramethyl-5-phenyl-oxazolidine, **9** = (-)-N-propylphedrine.

Several conclusions can be extracted from this table:

- Donor solvents influence negatively the effectivity of the asymmetric catalysis, likely because these solvents compete in the coordination of the attacking reagent.
- The ligands with two asymmetric centers have higher effect in the asymmetric addition. The substitution by bigger groups in the nitrogen leads to lower selectivities.
- The use of oxazolidines does not lead to fine enantiomeric excess, probably due to the conformational rigidity.
- The asymmetric induction in the formation of aromatic secondary alcohols is more pronounced than in the aliphatic secondary alcohols.

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References and Notes

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