Tetrahedron Letters Vol. 21, pp 4175 - 4178
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0040-4039/80/1022-4175$02.00/0

EPOXIDE OPENING WITH ORGANOCUPRATES AND GRIGNARD REAGENTS IN THE PRESENCE OF CHIRAL LIGANDS

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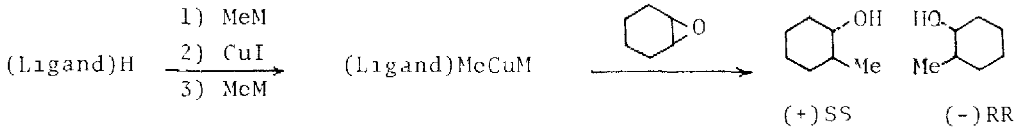
Summary The reaction of cyclohexene oxide with organocuprates and Grignard reagents in the presence of chiral ligands to give chiral β-substituted alcohols in low optical yields is described

The formation of chiral secondary alcohols by reduction of ketones with chiral hydride reagents or by reaction of aldehydes with organometallic reagents *in the presence of chiral ligands* has been highly successful in recent years[2] However, the selective opening of epoxides to give β-substituted alcohols with two asymmetric centers has remained uninvestigated[3]. Organocuprates[4] and Grignard reagents[5] readily open epoxides and it was postulated that these reactants in the presence of chiral ligands would cleave epoxides regiospecifically to yield optically active alcohols We report herein the results of the opening of cyclohexene oxide by chiral complexed nucleophiles

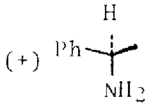
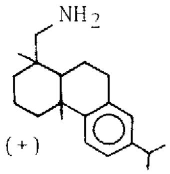
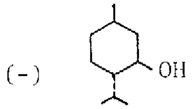
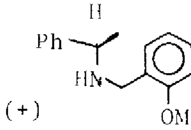
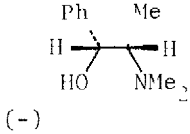
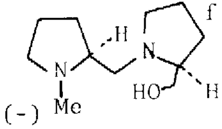


M = Li, MgBr

Initially, mixed cuprates were studied under a variety of conditions Thus, treatment of CuI with the lithium base of a chiral alcohol or amine and subsequent addition of MeLi yielded the chiral mixed cuprate (Table) Reaction with cyclohexene oxide gave trans-2-methylcyclohexanol in low optical yields Increased coordination to the cuprate (Runs 8 and 9) appeared to be detrimental to the course of the reaction[6] The use of MeMgBr for cuprate formation (Run 10) gave a significantly better isolated yield but again the optical yield was low

Table

Epoxide Opening with Chirally Complexed Nucleophiles[a]

Run	Ligand	M^+	solvent[b]	temp(°C), time	major product	optical yield %[c]	yield %
1		Li^+	Et_2O	0°, 10min, 25°, 3h	-	<1	
2		Li^+	Et_2O	0°, 10min, 25°, 3h	-	<1	
3		Li^+	Et_2O	0°, 10min, 25°, 3h	-	<1	
4	 [d]	Li^+	Et_2O	0°, 10min, 25°, 3h	-	<0.5	25
5		Li^+	Et_2O	0°, 5h	RR	3.1	25
6	 [d]	Li^+	Et_2O	0°, 5h	SS	3.4	39
7		Li^+	Et_2O	-40°, 3days	SS	3.3	30
8		Li^+	Et_2O + 1 eq TMEDA	0°, 5h	SS	1.7	39
9		Li^+	DMF:Et_2O 3:1	-15°, 18h	-	-	0
10		$MgBr^+$	THF:Me_2S, 12:1 + 1 eq MeMgBr	0°, 3h	RR	0.4	60
11[e]		$MgMe^+$	Et_2O	-15°, 16h	RR	3.6	8
12	 [f]	Li^+	Et_2O	0°, 4h, 25°, 2 days	-	-	0
13	(-)DIOP[b]	Li^+	Et_2O	0°, 5h	RR	0.8	39

Although R_2Mg in the presence of chiral ligands reacts with aldehydes to give alcohols with excellent optical yields[2], in our investigation a similiar procedure (Run 11) offered no advantage over the cuprate reagent

Finally, the cleavage of the epoxide with Me_2CuLi DIOP occurred with only slight optical induction

Recently, there have been several investigations of 1,4 conjugate addition of cuprates[7] and CuX catalyzed Grignard reagents[8] to α,β-unsaturated carbonyl compounds in the presence of chiral ligands Generally, the optical yields are similar to those observed in the present study though the reactions are mechanistically different[4]. However, Mukiayama[8b] has reported the catalyzed Grignard addition to chalcone in the presence of (S)-N-methylprolinol to give optical yields up to 68% under specific conditions (CuBr, THF solvent). Thus, while decreased complexation of the metal appears to be important for optical induction in conjugate addition reactions, it is fatal to cuprate opening of epoxides

It is not possible, from the results reported here, to propose a geometry at copper in the transition state but the stereochemistry at the metal does not appear to be of major importance in the course of the reaction

Footnotes to Table

(a) A typical procedure is as follows The chiral base (2 mmol) in 2 mL of dry ether was deprotonated with MeLi (2 mmol) at -20 to -30°C under N_2 After 5 min the solution was added to a suspension of CuI (2 mmol) in 1 mL of ether Addition of MeLi (2 mmol) to the resulting pale yellow suspension gave a homogenous yellow solution To this, cyclohexene oxide (1 mmol) in 1 5 mL of ether was added and the reaction was stirred under the conditions shown in the Table After quenching with sat aq NH_4Cl and workup, the resulting solution was concentrated and the product was isolated by preparative GLC (SE-30, 20% on Chrom W). (b) TMEDA=N,N,N',N'-tetramethylethylenediamine, DME=1,2-dimethoxyethane, (-)DIOP=(-)-O,O'-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (c) Optical yields are based on pure alcohol having a rotation of 42 9° in MeOH (see ref 9a) with an absolute configuration as in ref 9b (d) See ref 7b (e) CuI omitted (f) See ref 2

Acknowledgement One of us (S.W) wishes to thank the National Science Foundation and the Centre National de la Recherche Scientifique for a postdoctoral fellowship.

References and Notes

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(Received in France 31 July 1980)