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SYNTHESIS VIA OXAZOLINES. VIII. ASYMMETRIC ADDITION OF GRIGNARD REAGENTS TO CARBONYL COMPOUNDS IN THE PRESENCE OF A CHIRAL OXAZOLINE

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In the two previous reports[1,2] the use of chiral oxazolines 1 and 2 in asymmetric syntheses were described. We have now extended our studies to include chiral complexes of Grignard reagents (3 and 4) which lead to secondary and tertiary alcohols 5 (R'=H and R'=alkyl, respectively) in 12-25% optical purity. The asymmetric Grignard addition was studied both in the presence of the alkoxymagnesium halide 3, formed by initially treating 1 with an equivalent of RMgBr, and in the

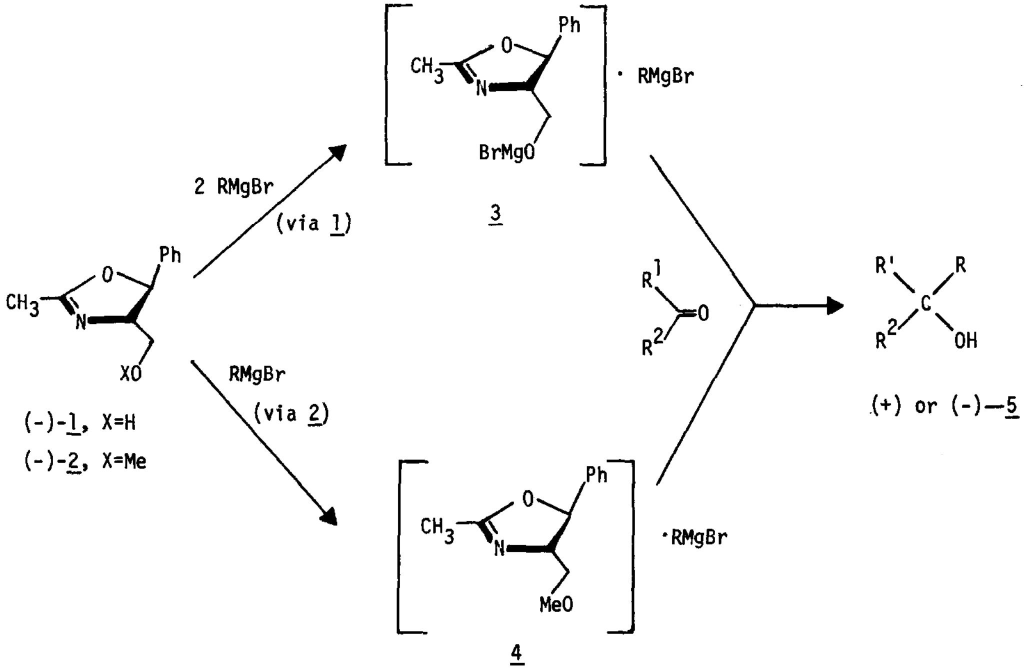

Table I Addition of Grignard Reagents to Carbonyls Using 1 and 2 in THF[a]

Exp	Carbonyl[b]	RMgBr[b]	Oxazoline[b]	Temp°[c]	Carbinols 5			
					$[\alpha]^{25}_{589}$[d]	Config.(lit.)	Optical[e] Purity %	% Yield[f]
1	PhCOEt	Me	1	25°	-3.40	S[k]	20	81
2	PhCOEt	Me	1	-20-r.t.	-4.35	S	25	80
3	PhCOEt	Me	1[g]	-20-r.t.	-3.98	S	23	85
4	PhCOEt	Me	2[h]	-5-r.t.	+2.95	R	17	89
5	MeCOEt	Ph	1	-20-r.t.	-2.45	S[k]	9	98
6	$C_6H_{11}COPh$	Me	1	-20-r.t.	-2.13	S[ℓ]	11	90
7	$C_6H_{11}COMe$	Ph	1	-20-r.t.	-2.57	S[ℓ]	13	98
8	PhCHO	Me	1	-20-r.t.	+5.03	R[m]	12	92
9	*n*-HexCHO	Me	1	-20-r.t.	-1.63	R[n]	17	86
10	*t*-BuCHO	Me	1	-20-r.t.	-0.44[i]	R[o]	12	80
11	*t*-BuCHO	Ph	1	-20-r.t.	-0.58	S[p]	21	95
12	*t*-BuCHO	Ph	2[h]	-5-r.t.	-0.02[j]	S	0.5	84

a) All reactions carried out on 10 mmoles of carbonyl compound; b) Molar ratio of carbonyl:RMgX:oxazoline was 1:3.5:2 unless otherwise noted; c) Reactions maintained at the lower temperature for 1 h and then allowed to warm to room temperature; d) Rotations taken on neat samples unless otherwise noted; e) Based upon highest rotation available in literature, c.f. ref k-p; f) Distilled yields of carbinols, vpc purity 98%; g) Molar ratio of carbonyl:RMgX:oxazoline was 1:5:3.3; h) Molar ratio of carbonyl:RMgX:oxazoline was 1:1.5:4.9; i) c 51, hexane; j) c 20, benzene; k) C. Blomberg and J. Coops. *Rec. Trav. Chim.*, 83, 1083 (1964); ℓ) see ref. 4; m) G. Vavon, C. Riviere, and B. Angelo, *Compt. Rend.*, 222, 959 (1946); n) S. R. Landor and A. R. Tatchell, *J. Chem. Soc.* (C) 2280 (1966); o) S. R. Landor, B. J. Miller and A. R. Tatchell, *Proc. Chem. Soc.*, 227 (1964); p) R. MacLeod, F. J. Welch and H. S. Mosher, *J. Amer. Chem. Soc.*, 82, 876 (1960).

presence of the ether 2 as a chiral co-solvent (4). In both instances, the oxazolines 1 and 2 were recovered after the reaction in 78-96% yield.[3] A study of the effect of temperature on the reaction was carried out using propiophenone (Table 1, exp. 1, 2); and slightly greater stereoselectivity was exhibited at lower temperatures. Also, the stoichiometric quantities of ketone, RMgBr, oxazoline (1) were found to be optimum at 1:3.5:2, respectively (exp. 2 vs. exp. 3). Under all conditions complex 3 gave 2-phenyl-2-butanol 5 possessing the S-configuration. When 2 was employed as a chiral co-solvent (exp. 4) 2-phenyl-2-butanol was formed with 17% optical purity and possessed the R configuration. The alkoxymagnesium complex 3 was evaluated with a variety of other prochiral aldehydes and ketones and gave excellent yields of Grignard additions. The optical purities of the resulting alcohols 5, however, were rather modest (Table I, exp. 5-11). It is important to note, however, that these optical yields are in most cases comparable to the alkoxymagnesium halide-RMgX complex of a glucofuranose derivative reported recently.[4] Furthermore, other methods which employ chiral media (e.g. 4) to induce asymmetric Grignard addition generally lead to rather poor optical yields (0-5% in most cases).[5] In the present study, 4 was effective to the extent of 17% o.p. (exp. 4), whereas it was poorly effective as a chiral medium in the reaction of pivaldehyde and phenylmagnesium bromide (exp. 12). For reasons still not understood, chiral magnesium alcoholates (e.g. 3) appear to be much more effective in Grignard additions than the corresponding chiral ethers. Comprehension of this result must await detailed information on the structures of the so-called "double-salts" 3.

As stated in the previous report,[2] although the percent asymmetric synthesis of carbinols is still far from perfect, the ready availability of 1 and the simplicity of its use,[6] renders it competitive with a host of different chiral reagents. We are continuing to investigate modifications in 1 and 2 in order to determine its optimum structural features.

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REFERENCES

1. A. I. Meyers and G. Knaus, Tetrahedron Letters, 0000 (1974).
2. A. I. Meyers and P. M. Kendall, ibid., 0000 (1974).
3. Oxazolines have been shown to be inert to Grignard reagents which makes the technique feasible [A. I. Meyers and D. L. Temple, J. Amer. Chem. Soc., 92, 6646 (1970)].
4. T. D. Inch, G. J. Lewis, G. L. Sainsburg, and D. J. Sellers, Tetrahedron Letters, 3657 (1969).
5. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, 1971, pp 415-417.
6. A general procedure for exp. 1, 5-11 follows: A solution of 1 (20 mmoles) in 50 ml THF is prepared under nitrogen at -20°, The Grignard reagent (20 mmoles) is added slowly and the resulting homogeneous solution stirred at -20° for 30 min. An additional 15 mmoles of Grignard reagent is introduced and stirred at -20° for 30 min. The carbonyl compound (10 mmoles) is added in THF (-20°), the resulting suspension stirred for 1 h, and then allowed to warm to r.t. The reaction mixture is quenched in 50 ml ether and 100 ml saturated NH_4Cl. The organic phase is washed with cold 0.25 N HCl to remove 1, and then dried and concentrated to provide the carbinol. The acidic aqueous phase is neutralized and extracted with ether to recover 1.