Asymmetric Synthesis. Part 5.[1] Asymmetric Reduction of Phenyl Trifluoromethyl Ketone with Chiral Alkoxy-aluminium and -magnesium Halides

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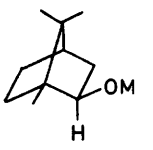
Phenyl trifluoromethyl ketone has been asymmetrically reduced with a number of chiral alkoxy-aluminium and -magnesium halides derived from bornan-2-*exo*- and -*endo*-ols, *p*-menthan-3-ol, and 1-phenylethanol. Bornan-2-*endo*-yloxyaluminium dichloride and *p*-menthan-3-yloxyaluminium dichloride are highly stereoselective and reduce the ketone to give 2,2,2-trifluoro-1-phenylethanol with 68 and 77% enantiomeric excess, respectively. The results are discussed in terms of appropriate transition states.

OPTICALLY active alkoxyaluminium dichlorides and alkoxymagnesium bromides derived from bornan-2-*endo*-ol (borneol) and -2-*exo*-ol (isoborneol) have been successfully employed for asymmetric reduction of aromatic ketones [2,3] and aldehydes.[4] Some ketones, however, are reduced only slowly, particularly with borneol-derived reagents, and adoption of more drastic conditions is often undesirable because of the possibility of partial racemisation of the products. Recently, Morrison and Ridgway [5] have shown that phenyl trifluoromethyl ketone undergoes a ready and virtually irreversible Meerwein–Ponndorf–Verley-type reduction, and thus is an ideal substrate for quantitative comparison of asymmetric induction by a group of reducing agents. Moreover, in most of the reported asymmetric reductions of this ketone, the stereoselectivity is opposite [6] to that for alkyl phenyl ketones under similar circumstances and does not conform to the conventional transition state model [as (9)].[7] A systematic reduction of the ketone was, therefore, undertaken to gain further insight into the mechanism.

Four optically active alcohols, namely (—)-bornan-2-*exo*-ol, (—)-bornan-2-*endo*-ol, (—)-*p*-menthan-3-ol, and (+)-1-phenylethanol, all having the *R*-configuration at the carbinol carbon atom, were converted by the normal procedure [8] into their dichloroaluminio- and bromomagnesio-derivatives [(*R*)-B^{i}OAlCl$_2$ (1), (*R*)-B^{i}OMgBr (2), (*R*)-BOAlCl$_2$ (3), (*R*)-BOMgBr (4), (*R*)-MenOAlCl$_2$ (5), (*R*)-MenOMgBr (6), (*R*)-PeOAlCl$_2$ (7), and (*R*)-PeOMgBr (8)]. The reductions of phenyl trifluoromethyl ketone were carried out in diethyl ether at 0—25 °C by using a four-fold excess of reagents for 1—4 h. 2,2,2-Trifluoro-1-phenylethanol [(10) and enantiomer] was isolated in high purity by way of its hydrogen phthalate, which on warming in alkaline solution liberated † the fluoro-alcohol almost quantitatively, the hydrolysis taking place presumably by the participation of the neighbouring carboxylate anion and aided by the strongly electron-withdrawing trifluoromethyl group.[9] The hydrogen phthalates of the reagent alcohols remained unchanged under these conditions. Further purification was carried out by taking advantage of the solubility of the fluoro-alcohol in aqueous alkali. The purity of the final product in each case was over 99% (by g.l.c.). The results are summarized in the Table (entries 1—10), along with some data from the literature.



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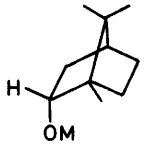
(2) M = MgBr



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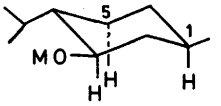

(5) M = AlCl$_2$
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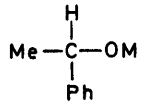

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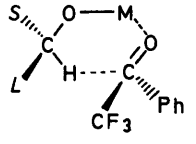

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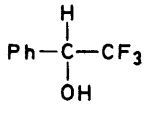

(+)-(S)-enantiomer
(10)

The following general observations may be made. (i) Only two of the reagents studied, BOAlCl$_2$ (3) and MenOAlCl$_2$ (5), are of high stereoselectivity, affording 2,2,2-trifluoro-1-phenylethanol (10) with 68 and 77% enantiomeric excess respectively (entries 4 and 7). This alcohol is a common chiral solvent used in n.m.r.

† One of the experiments is described in ref. 1.

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experiments for determining the absolute configuration and optical purity of compounds such as alcohols, amines, sulphoxides, *etc.*[10] in which it induces enantiomeric non-equivalence.[11] The present method offers a convenient route to this alcohol of sufficient optical purity to be used directly for this purpose. (ii) For the same (*R*)-alcohol, a change from dichloroaluminio-complex to bromomagnesio-derivative leads to an enrichment of the product in (*R*)-fluoro-alcohol (*cf.* entries 1 and 3, 4 and 6, 7 and 8, and 9 and 10), in some cases even reversing the sign of rotation. (iii) The addition of Lewis acid ($MgBr_2$) does not affect the stereochemistry to any significant extent. (iv) Barring one or two cases (entries 3 and 8), the stereochemical results fall under two broad categories: (*a*) reduction with reagents derived from cyclic (*R*)-alcohols gives a preponderance of (*S*)-2,2,2-trifluoro-1-phenylethanol; (*b*) reduction with reagents derived from acyclic alcohols (halides or alkyl derivatives) gives opposite stereochemistry, *i.e.* (*R*)-alcohol from (*R*)-reagents and (*S*)-alcohol from (*S*)-reagents (entries 8—14). The result (*a*) agrees

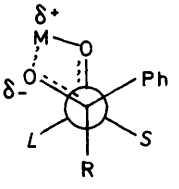
Asymmetric reduction of phenyl trifluoromethyl ketone with chiral alkoxy- and alkyl-metal halides

Entry no.	Reagents	Yield [a] of carbinol (%)	α_D^{25} (°) [b] (neat)	Asymmetric induction (%)	Config.
1	(*R*)-B^{i}OAlCl$_2$	85	+3.44	8.4	(+)-(*S*)
2	(*R*)-B^{i}OAlCl$_2$,MgBr$_2$	65	+6.62	16.1	(+)-(*S*)
3	(*R*)-B^{i}OMgBr	60	−0.82	2.0	(−)-(*R*)
4	(*R*)-BOAlCl$_2$	85	+28.0	68.0	(+)-(*S*)
5	(*R*)-BOAlCl$_2$,MgBr$_2$	40	+25.6	62.0	(+)-(*S*)
6	(*R*)-BOMgBr	50	+9.6	23.3	(+)-(*S*)
7	(*R*)-MenOAlCl$_2$	50	+31.7	77.0	(+)-(*S*)
8	(*R*)-MenOMgBr	50	−4.2	10.0	(−)-(*R*)
9	(*R*)-PeOAlCl$_2$ [c]	80	−1.6	4.0	(−)-(*R*)
10	(*R*)-PeOMgBr [c]	80	−6.5	15.8	(−)-(*R*)
11	(*S*)-2MbMgCl [d]			22.0	(+)-(*S*)
12	(*S*)-2PpMgCl [e]			47.0	(+)-(*S*)
13	(*S*)-Al2Mb,OEt$_2$ [f]		+3.42	11.6	(+)-(*S*)
14	(*S*)-Zn2Mb [g]		+1.62	5.2	(+)-(*S*)

[a] Based on material isolated. [b] Maximum value for $[\alpha]_D^{25}$, 41.18° (D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, 1968, **33**, 4242). [c] Corrected for maximum optical purity of the reagent. [d] (*S*)-2-Methylbutylmagnesium chloride.[6] [e] (*S*)-2-Phenylpropylmagnesium chloride.[6] [f] Tris-[(*S*)-2-methylbutyl]aluminium–diethyl ether complex.[19] [g] Bis-[(*S*)-2-methylbutyl]zinc (G. P. Giacomelli, L. Lardicci, and R. Santi, *J. Org. Chem.*, 1974, **39**, 2736).

with those encountered in asymmetric reduction of alkyl phenyl ketones * with similar reagents, and is predictable from Whitmore's cyclic transition state (9). However the result (*b*) cannot be accounted for from steric considerations alone.

We have suggested previously[12] that the stereochemical results of these hydride transfer reactions may best be explained in terms of four competing transition states (11)—(14); these are viewed along the linear[13] C · · · H–C* bond which holds the two reactants together and permits formation of a loose bond between the two opposite dipoles, O–M$^{\delta+}$ and C$^{\delta-}$–O$^{\delta-}$ with the rest of the substituents staggered as shown. Two factors are thought to be important: an electronic effect which favours the placement of C–Ph$^{\delta-}$ next to O–M$^{\delta+}$, stabilising the conformations (11) and (13) over their counterparts (12) and (14), and a steric factor to be assessed from the near-*gauche* interactions in the Newman-type formulae supporting the same general conclusion. As a consequence, (11) is the preferred transition state for



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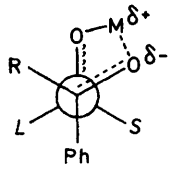
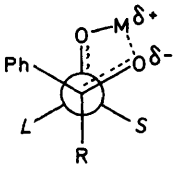


(12)



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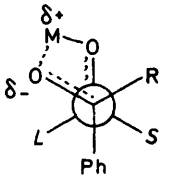

(14)

the (*R*)-alcohol and (13) that for the (*S*)-alcohol; since the former is the more stable, from steric considerations,[8] the (*R*)-alcohol predominates. This follows equally well from Whitmore's cyclic mechanism [as (9)] but the present model also offers a satisfactory explanation of the fact[14-16] that asymmetric induction increases in the phenyl alkyl series as the alkyl group changes from methyl to isopropyl and also in some cases t-butyl.[17] The model has since then been used extensively[16,18] to rationalise the results of asymmetric reduction of ketones with chiral organometallic reagents.

Regarding the reduction of phenyl trifluoromethyl ketone (R = CF_3), it has been pointed out[8,16] that since C–CF_3 is a stronger negative dipole than C–Ph it is better placed next to O–M$^{\delta+}$ in the transition state. Conformations (12) and (14), which fulfil this condition, are, therefore, more favoured and will control the stereoselectivity. Since the latter (14) is of lesser energy on

* (+)-(*S*)-2,2,2-Trifluoro-1-phenylethanol is configurationally related to (+)-(*R*)-1-phenylethanol.

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[18] L. Lardicci and G. Giacommelli, *J.C.S. Perkin I*, 1974, 337; and earlier papers.

steric grounds,[8] (*R*)-2,2,2-trifluoro-1-phenylethanol will be formed predominently, leading to stereoselectivity opposite to that in the alkyl phenyl series. This happens to be the case in asymmetric reductions of phenyl trifluoromethyl ketone with a large number of acyclic chiral reagents (Table, entries 9—14) (for other examples see ref. 6) providing strong support for the proposed model (see ref. 19 for the contribution of the entropy factor). The reducing agents derived from the cyclic alcohols, on the other hand, give results incompatible with this picture. Dreiding models, however, show that in these reagents (*L* and *S* joined to form a ring), conformations (12) and (14) are seriously destabilised by strong steric interactions: between Ph and 9-Me in the case of borneol, between Ph and the axial 1-H and 5-H in the case of menthol, and between Ph and the two *endo*-protons in the case of isoborneol. The stereochemical control is, therefore, relayed back to the reacting conformations (11) and (13), and the results fall in line with those of the phenyl alkyl series.

Alkoxymagnesium bromides, as already pointed out, show a preference for the opposite stereoselectivity in some cases (Table, entries 3 and 8). The degrees of asymmetric induction are, however, small and the result may be due to a number of factors such as differences in M–O bond lengths, in degree of solvation, and, more importantly perhaps, in the degree of dissociation of this bond, which can alter the entire electronic situation.[20]

Attempted reduction of 1-naphthyl trifluoromethyl ketone with bornan-2-*exo*-yloxyaluminium dichloride (1) was incomplete, and the reaction did not occur at all with the other reagents. The fluoro-alcohol, isolated in 20% yield, was enriched in the (−)-(*R*)-enantiomer, showing a rotation corresponding to 30% optical purity. Alkyl naphthyl ketones have been reported [2] to resist reduction; presumably, the naphthalene rings complex with these reagents, which are also effective Lewis acids,[21] rendering the carbonyl group resistant to reduction. The electronic effects are also considerably modified and the stereoselectivity is no longer predictable.

The picture of the transition states presented here is by no means complete; nevertheless it provides a good working model for asymmetric reductions of ketones with most of the hydride transfer reagents.

EXPERIMENTAL

G.l.c. analyses were carried out on a column (6 ft × ¼ in) of 10% polyester of diethylene glycol adipate (DEGA) on GasChrom Z (60—80 mesh) or a column (6½ ft × ⅛ in) of Carbowax 20M on Chromosorb with nitrogen (40 ml min^{-1} at 20 lb in^{-2}) as carrier gas, at 100 °C for 2,2,2-trifluoro-1-phenylethanol and at 170 °C for 2,2,2-trifluoro-1-(1-naphthyl)ethanol (flame ionisation detector). Specific rotations were taken with a Hilger–Watts M-511 micro-optic photoelectric polarimeter and also with a Perkin-Elmer 241 polarimeter.

Materials.—(+)-Bornan-2-one, (−)-bornan-2-*endo*-ol, and (−)-*p*-menthan-3-ol were obtained from Aldrich Chemical Company Inc. A mixture of (−)-bornan-2-*exo*-ol (90%) and (+)-bornan-2-*endo*-ol (10%), obtained by reduction of (+)-bornan-2-one with lithium aluminium hydride, was used directly [8] instead of (−)-bornan-2-*exo*-ol. A *ca.* 1M-solution of lithium aluminium hydride in ether was standardised before use against iodine solution.[22]

Reduction Procedures.—All reductions were carried out in duplicate or triplicate by the procedure described earlier.[8]

(a) *Reduction with* (R)-p-*menthan-3-yloxyaluminium dichloride* (5). The reduction was carried out as described in ref. 1, but with (−)-bornan-2-*endo*-ol replaced by (−)-*p*-menthan-3-ol. 2,2,2-Trifluoro-1-phenylethanol, after regeneration from the hydrogen phthalate, had b.p. 80° at 10 mmHg; α_D^{25} +30.7° (neat). It was further purified by dissolving in dilute aqueous alkali and regenerating with acid. The final product showed a single peak in g.l.c. and had α_D^{25} +31.7°.

(b) *Reduction with* (R)-1-*phenylethoxymagnesium bromide* (8). To a Grignard solution prepared from propyl bromide (4.92 g, 0.04 mol), magnesium (1.0 g, 0.041 mol), and ether (100 ml), was added (+)-1-phenylethanol (5.5 g, 0.045 mol) of 30% optical purity obtained directly from the reduction of acetophenone with (*R*)-bornan-2-*exo*-yloxyaluminium dichloride [8]. Dry benzene (50 ml) was then introduced and ether was partially removed by distillation. The clear solution was cooled and to it was added a solution of phenyl trifluoromethyl ketone (1.9 g, 0.011 mol) in benzene (15 ml) with stirring at room temperature. After 4 h, the mixture was decomposed with cold 2N-sulphuric acid and the product was worked up as in (a). 2,2,2-Trifluoro-1-phenylethanol was obtained after final purification as a clear liquid (1.60 g), b.p. 80° at 10 mmHg, α_D^{25} −1.95° (neat) (−6.50°, corrected for maximum optical purity).

(c) 2,2,2-*Trifluoro*-1-(1-*naphthyl*)*ethanol.* To a solution of bornan-2-*exo*-yloxyaluminium dichloride prepared from bornan-2-*exo*-ol (10.8 g, 0.069 mol), anhydrous aluminium chloride (9.1 g, 0.068 mol), ethereal 1M-lithium aluminium hydride (17 ml, 0.017 mol), and ether (60 ml), was added 1-naphthyl trifluoromethyl ketone (3.1 g, 0.017 mol) in ether (10 ml). After 4 h at 20 °C the solution was cooled and worked up as before, and 2,2,2-trifluoro-1-(1-naphthyl)-ethanol was purified through its hydrogen phthalate as in (a). The gummy product was dissolved in cold aqueous alkali and the neutral impurity, if any, removed by extraction with petroleum (b.p. 60—80 °C). The fluoro-alcohol after regeneration was obtained as a low-melting solid (0.6 g), α_D^{25} −8.4° (*c* 2.0 in EtOH) (lit.,[23] α_D^{25} 25.8°), corresponding to an optical purity of 33.6%. The alcohol was over 90% pure by g.l.c.

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