71837-46-2; **7c**, 89088-84-6; **7d**, 97997-11-0; *cis*-**8a**, 97997-12-1; *trans*-**8a**, 97997-13-2; *cis*-**8b**, 97997-14-3; *trans*-**8b**, 97997-15-4; **8c**, 97997-16-5; *cis*-**8d**, 97997-17-6; *trans*-**8d**, 97997-18-7; **9a**, 54781-30-5; **9b**, 71964-38-0; **10a**, 97997-19-8; **10b**, 97997-20-1; **10c**, 97997-21-2; *cis*-**11**, 97997-22-3; *trans*-**11**, 97997-23-4; *cis*-**12**, 97997-24-5; *trans*-**12**, 97997-25-6; *cis*-**13**, 97997-26-7; *trans*-**13**, 97997-27-8; *cis*-**14**, 97997-28-9; *trans*-**14**, 97997-29-0; *cis*-**14** (free acid), 97997-30-3; *trans*-**14** (free acid), 97997-31-4; **18**, 97997-32-5; **19**, 97997-33-6; vinyl bromide, 593-60-2; 2-hydroxy-6-cycloheptenone, 97997-34-7.

Asymmetric Synthesis Using Chiral Lithium Alkoxytrialkylaluminates: Obtention of (2*S*)-2-Hydroxy-2-phenyl-4-methylpentanoic Acid with 85% Optical Purity

D. Abenhaïm,* G. Boireau, and A. Deberly

Institut de Chimie Moléculaire d'Orsay, Laboratoire de Chimie Organométallique, Université de Paris-Sud, 91405 Orsay, France

Received March 28, 1984

The chiral reagent prepared by mixing equimolecular amounts of triisobutylaluminium and lithium alcoholate of (+)-Darvon alcohol reacts readily in hexane solvent with methyl phenylglyoxylate to give the expected α-isobutyl α-hydroxy ester in 95% chemical yield with no significant reduction byproduct, and best optical yields are achieved at 0 °C and high dilution (0.04 M) in hexane. Upon saponification of the ester, (2*S*)-2-hydroxy-2-phenyl-4-methylpropanoic acid is obtained in 85% enantiomeric excess. Reacting the lithium alkoxytriethylaluminate and lithium alkoxytri-*n*-butylaluminate with the same α-keto ester provided confirmatory evidence for the influence of dilution on the extent of asymmetric induction.

Stereoselective synthesis of chiral α-alkyl α-hydroxy acids is the subject of extended studies and many recent papers deal with it.[1-10]

In previous reports we have shown that alkoxytrialkylaluminates react with α-keto esters to give α-alkyl α-hydroxy esters (or acids).[11-14] We have also described a convenient synthesis of this type of reagent by mixing equimolecular amounts of trialkylaluminum and alkaline alcoholates obtained from an alcohol or an amino alcohol. If a chiral alkoxy radical is chosen, optically active α-alkyl α-hydroxy esters (or acids) may be obtained from nonchiral α-keto esters as, for example, in the reaction of methyl phenylglyoxylate with the alkoxytributylaluminates derived from (+)-(2*S*,3*R*)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol, (+)-Darvon alcohol,[14,15] and from (−)-*N*-methylephedrin.[11]

Results and Discussion

In the present work, we report in Table I the results obtained by the reaction of the lithium alkoxytriisobutylaluminate derived from (+)-Darvon alcohol with methyl phenylglyoxylate.

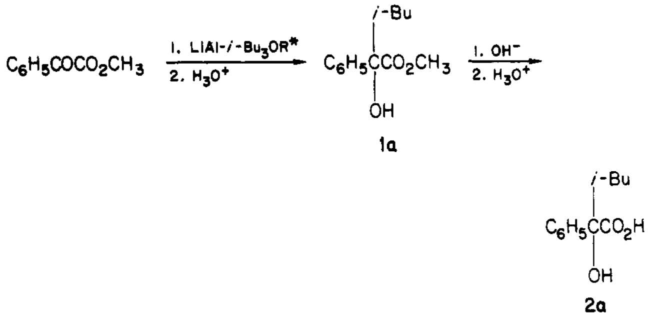
Scheme I[a]

$$R^*OH + n\text{-BuLi} \longrightarrow R^*OLi + C_4H_{10}$$

$$R^*OLi + Al\text{-}i\text{-}Bu_3 \longrightarrow LiAl\text{-}i\text{-}Bu_3OR^*$$

[a] R*OH = (+)-Darvon alcohol.

Scheme II



Examination of the results summarized in Table I highlight the following facts:

(1) The nature of the solvent is highly influential in determining the enantiomeric purity. For example, best enantiomeric excess is obtained in hexane, while adding diethyl ether results in an inversion of induction and a large decrease of enantiomeric excess (entry 2).

(2) In all experiments, appreciable amounts of reduction byproducts are not formed. According to GC analysis, the yields remain less than 10% and, in addition, the smallest values (<5%) are obtained in experiments for which the highest optical yields are obtained (temperature of 0 °C and low concentration). This is undoubtly the most striking fact with reference to the nature of the organometallic reagent. Indeed, it is well-known that Grignard reagents from isobutyl chloride and bromide, on reacting with carbonyl compounds, lead to mixtures with significant amounts of the corresponding reducted alcohols. As for

---

(1) Mukaiyama, T.; Sakito, Y.; Asami, M.; *Chem. Lett.* **1978**, 1253.

(2) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614.

(3) Eliel, E. L.; Frazee, W. J.; *J. Org. Chem.* **1979**, *44*, 3599.

(4) Kaneko, T.; Turner, D. L.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1979**, 103.

(5) Jew, S. S.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2337.

(6) Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.

(7) Frater, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221.

(8) Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1981**, *46*, 3933.

(9) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.

(10) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943.

(11) Abenhaïm, D.; Boireau, G.; Sabourault, B. *Tetrahedron Lett.* **1980**, *21*, 3043.

(12) Boireau, G.; Abenhaïm, D.; Deberly, A.; Sabourault, B. *Tetrahedron Lett.* **1982**, *23*, 1259.

(13) Deberly, A.; Boireau, G.; Abenhaïm, D. *Tetrahedron Lett.*, **1984**, *25*, 655.

(14) Vegh, D.; Boireau, G.; Henry-Basch, E. *J. Organomet. Chem.* **1984**, *267*, 127.

(15) Pohland, A.; Sullivan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 3400.

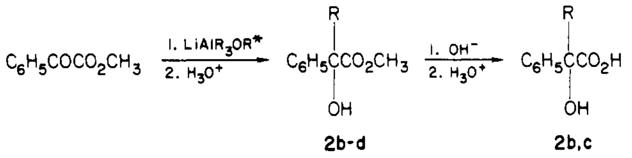
0022-3263/85/1950-4045$01.50/0 © 1985 American Chemical Society

Table I

expt[a]	solvent	temp, °C	[LiAl-*i*-Bu_3OR^*], mol/L	yield of **1a**,[b] %	$[\alpha]^{22}_D$ of **1a**,[c] deg (c, $CHCl_3$)	$[\alpha]^{22}_D$ of **2a**,[d] deg (*c*, ethanol)	ee of **2a**,[e] %
1	hexane	−40	0.4	90	+13.3 (1.6)	+9.8 (1.9)	49, *S*
2	hexane/ether, 50/50	−40	0.4	85	−1.8 (1.8)	−1.3 (1.7)	6, 5, *R*
3	hexane	0	0.4	90	+19 (1.9)	+14 (2)	70, *S*
4	hexane	0	0.075	95	+21.2 (2)	+15.8 (2.1)	79, *S*
5	hexane	0	0.04	95	+22.8 (1.9)	+17 (1.8)	85, *S*
6	hexane	19	0.04	93	+21.3 (1.8)	+15.8 (1.7)	79, *S*
7	hexane	14	0.4	91	+19.1 (1.3)	+14.2 (2)	71, *S*
8	hexane	30	0.4	90	+19.2 (1.3)	+14.3 (2.1)	72, *S*
9	hexane	60	0.4	88	+17.7 (1.4)	+13.1 (1.6)	66, *S*

[a] Reaction time 4 h. Ratio LiAl-*i*-Bu_3OR^*/α-keto ester, 5/4. [b] Determined by GC. **1a** is accompanied with slight quantities of reduction alcohol: $C_6H_5CHOHCO_2CH_3$ <10% in expt 1, 2, 3, 7, 8, 9 and <5% in expt 4, 5, 6. [c] Determined after purification of **1a** by GC (SE-30, 150 °C). [d] Determined on acids **2a** obtained after saponification of purified **1a**. [e] ee calculated from $[\alpha]_D$ of enantiomerically pure α-hydroxy acid **2a**.[19]

Scheme III[a]



[a] b, R = Me; c, R = Et; d, R = *n*-Bu.

triisobutylaluminum, it has been shown to behave as even a more efficient reductor.[17,18]

(3) The asymmetric induction is also temperature and concentration dependent. Greater optical purity is exhibited at lower concentration of the trialkylaluminate (entries 4–6 in Table I). One may reasonably assume that the organometallic reagent consists of a number of associated species (LiAl-*i*-Bu_3OR^*)$_n$ (Scheme I). A highly dilute medium would favor less associated (or even monomeric) species which would be particularly selective. On the other hand, an increase in concentration of the organometallic reagent would lead to a greater extent of aggregation of the species and account for the drop in optical yield, either because these species would be less selective or because they would lead to an inversion of the asymmetric induction. This is also consistent with the observation that the best optical yields are not obtained at the lowest temperatures, but at 0 °C.

Synthesis of α-hydroxy acid **2a** (Scheme II) in 98% enantiomeric excess is described in the Experimental Section. The role played by the concentration of the organometallic reagent in the extent of asymmetric induction, as it appears from the results of Table I, led us to reexamine the reaction of methyl phenylglyoxylate with lithium alkoxytri-*n*-butylaluminate, studied in a previous work.[11]

Reactions were performed in the best experimental conditions determined in the present work and we extended this study to other lithium alkoxytrialkylaluminates $LiAlR_3OR^*$ (Scheme III), where R = Me, Et, *n*-Bu, in dilute solutions (0.02–0.04 M) at 0 °C. The results obtained are reported in Tables II and III.

Table II

expt	LiAl-*n*-Bu_3OR^*, mol/L	temp, °C	yield of **1d**,[a] %	$[\alpha]^{20}_D$, deg (*c*, $CHCl_3$)	ee,[b] %
10	0.4	0	95	+15.9 (17.2)	42
11	0.04	0	92	+24 (11)	64
12	0.04	−20	92	+23.9 (11.7)	56

[a] Evaluated by GC. [b] Based on ee 43%: $[\alpha]^{20}_D$ +16.2° ($CHCl_3$, *c* 12.8).[11]

Table III[a]

expt	R	$LiAlR_3OR^*$	yield of **2**, %	$[\alpha]^{20}_D$, deg (*c*, ethanol)	ee of **2**,[b] %
13	Me	0.4	71	+0.2 (3.1)	<1, *S*
14	Me	0.04	68	+0.3 (3)	1, *S*
15	Et	0.56	74	−4 (1.1)	12, *R*
16	Et	0.02	72	+8.7 (1)	26, *S*

[a] Solvent, hexane; reaction time, 4 h; temperature, 0 °C. [b] ee calculated from $[\alpha]_D$ of enantiomerically pure α-hydroxy acids.[19]

As can be seen from Table II, the reaction of lithium alkoxytri-*n*-butylaluminate with methyl phenylglyoxylate brings confirmatory evidence for the marked influence of dilution and reacting the chiral reagent at lower concentrations causes the asymmetric induction to occur at a greater extent (entry 12). In Table III, with lithium alkoxytrimethylaluminate, no or very little asymmetric induction is observed, even with change in experimental conditions. This result may be correlated with the observed partial insolubility of the chiral reagent at the concentrations reported in Table III. One may reasonably assume that with this particular reagent a high number of associated species exist, even in dilute solutions (0.04 M).

Nevertheless another confirmation of the predominant role of dilution is shown with lithium alkoxytriethylaluminate, which is completely soluble (experiments 15 and 16). Best asymmetric induction is obtained at greater dilution while an inversion in asymmetric induction occurs at highest concentrations, probably due to the different reactivity of more associated species.

Conclusion

Many recent papers deal with chiral α-alkyl α-hydroxy esters or acids,[1-10] which may include one or several functional groups, in variety of reactions. The synthetic procedure of these compounds that was developed by reaction of chiral alkoxytrialkylaluminates and achiral α-keto ester[11] seems of great interest and chiral α-alkyl α-hydroxy esters are easily synthetised in this way by a one-pot reaction. These compounds can serve as bifunctional building blocks for the synthesis of a wide variety of optically active molecules. In the present work, the reaction of lithium alkoxytrialkylaluminates $LiAlR_3OR^*$ (R = Me, Et, *n*-Bu, *i*-Bu) with methyl phenylglyoxylate is shown to be closely dependant on the concentration of the chiral reagent and on the steric effect of the alkyl group relative to asymmetric induction. Optimal conditions to obtain

---

(16) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.

(17) Mole, T.; Jeffery E. A. "Organoaluminum Compounds"; Elsevier: New York; 1972.

(18) Ashby, E. C.; Yu, S. H. *J. Org. Chem.* **1970**, *35*, 1034.

(19) Meyers, A. I.; Slade, J.; *J. Org. Chem.* **1980**, *45*, 2912.

chiral α-alkyl α-hydroxy esters or acids with high optical purity were determined. This reaction has been now extended, with good results, to other substrates.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a Perkin-Elmer (90 MHz) spectrometer using tetramethylsilane as an internal standard. Optical rotations were taken on a Perkin-Elmer 241 polarimeter using a 1-dm cell.

Chiral Lithium Alkoxytrialkylaluminates. LiAl-*i*-Bu_3OR^*. This reagent can be prepared in stock quantities in the following manner: to 0.05 mol (14.17 g) of (+)-Darvon alcohol recovered with 20 mL of hexane is added 0.05 mol (31.25 mL) of *n*-BuLi (1.6 M solution in hexane) under argon at −78 °C. The mixture is allowed to warm to room temperature and 0.05 mol (55.5 mL) of a solution (0.9 M) of *i*-Bu_3Al in hexane is added. The concentration of the solution is brought to 0.5 M by adding hexane until the total volume reaches 100 mL. This solution can be stored during several months without modification of the reactivity or of the asymmetric induction.

LiAl-*n*-Bu_3OR^* and $LiAlEt_3OR^*$ are prepared by the same procedure. Owing to its lower solubility in hexane, $LiAlMe_3OR^*$ is prepared directly in the reaction flask, under argon, before use.

Typical Procedure. Reaction of LiAl-*i*-Bu_3OR^* (R^*OH = (+)-Darvon alcohol) with methyl phenylglyoxylate (Table I, expt 5). Hexane (100 mL) was added to 0.005 mol (10 mL) of LiAl-*i*-Bu_3OR^* (0.5 M in hexane). The solution was cooled to 0 °C and 0.0045 mol (0.738 g) of methyl phenylglyoxylate and 10 mL of hexane were added dropwise. The mixture was stirred 4 h at 0 °C and then hydrolized with 5 N HCl (5 equiv). Internal standard (tetradecane) was added, and the aqueous layer was extracted twice with 10 mL of 2 N HCl to remove the amino alcohol, washed with water saturated with NaCl, and dried over $MgSO_4$. Yield of **1a**, 2-hydroxy-2-phenyl-4-methylpentanoic acid methyl ester, determined by GC, is 95% with less than 5% of reduced alcohol.

After evaporation of the solvent, the α-hydroxy ester **1a** is purified by preparative GC (SE 30, 150 °C): $[\alpha]^{22}{}_D$ +22.8° (*c* 1.9, $CHCl_3$); NMR ($CDCl_3$) δ 0.9 (6 H, m), 1.6–2.3 (3 H, m), 3.72 (3 H, s), 3.82 (1 H, s, OH) 7.5 (5 H, m).

Saponification of the α-hydroxy ester **1a** was effected with 4 equiv of KOH in 20 mL of methanol and 2 mL of water, refluxing the mixture for 2 h. After the solvent was evaporated, the residue was acidified and extracted with diethyl ether to give **2a**, (2*S*)-2-hydroxy-2-phenyl-4-methylpentanoic acid: $[\alpha]^{22}{}_D$ +17° (*c* 1.8, ethanol); NMR ($CDCl_3$, Me_2SO-d_6) δ 0.87 (6 H, m), 2 (3 H, m), 7.1–7.9 (7 H, m, phenyl and 2 OH).

The above reaction was effected in a preparative way, using 5 g (30 mmol) of methyl phenylglyoxylate. After saponification of the α-hydroxy ester **1a**, 5.5 g (25 mmol) of crude acid (**2a** was obtained. Recrystallization in hexane–ethanol (94/6 by volume) gives 3.24 g (52% yield) of pure chiral α-hydroxy acid **2a** with 98% ee: $[\alpha]^{20}{}_D$ +19.6° (*c* 2.1, ethanol); mp 131 °C. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69; O, 23.07. Found: C, 69.21; H, 7.80; O, 22.85.

Registry No. (*S*)-**1a**, 97690-15-8; (+)-**1d**, 97690-16-9; (*S*)-**2a**, 73698-06-3; (*R*)-**2a**, 97690-17-0; (*S*)-**2b**, 13113-71-8; (*R*)-**2c**, 3966-31-2; (*S*)-**2c**, 24256-91-5; LiAl-*i*-Bu_3R^*, 97690-11-4; LiAl-*n*-Bu_3OR^*, 97690-12-5; $LiAlEt_3OR^*$, 97690-13-6; $LiAlMe_3OR^*$, 97690-14-7; methyl phenylglyoxylate, 15206-55-0.

Chemistry of Halogenoperfluoroalkanes. Synthesis of Fluorinated Ethers and Thioethers via Radical or Anionic Intermediates

Claude Wakselman* and Marc Tordeux

CNRS-CERCOA, 94320 Thiais, France

Received November 2, 1984

Condensation of bromotrifluoromethane with potassium thiophenoxides in DMF is performed under pressure (2–3 atm) in a glass apparatus. Inhibition by nitrobenzene shows that a $S_{RN}1$ mechanism is involved in the formation of aryl trifluoromethyl sulfides. Dichlorodifluoromethane itself reacts through a similar process to give aryl chlorodifluoromethyl sulfides. Condensation of 1,1,2-trichlorotrifluoroethane with potassium thiophenoxide or phenoxide occurs even in the presence of nitrobenzene. The formation of aryl 2,2-dichloro-1,1,2-trifluoroethyl sulfides or ethers can be explained by a chain carbanionic mechanism.

The reactivity of perhaloalkanes is known to decrease when the number of fluorine atoms increases. "Chlorofluorocarbons" are usually inert, which justifies their use as refrigerants, gas propellants, and solvents.[1] They are decomposed sometimes by powerful nucleophiles.[2] Bromofluorocarbons behave in such a way. A nucleophile attacks the heavy halogen (Br or Cl) with subsequent formation of an unstable carbanionic species which decomposes in the reaction medium. Iodoperfluoroalkanes are more reactive, and nucleophilic attack on iodine usually occurs.[3] However, $S_{RN}1$ substitutions have also been observed.[4-6] The two processes coexist in the reaction of $BrCF_2Cl$ with thiophenoxides.[7] We describe here the condensation of C_2F_5Br, $C_6F_{13}Br$, and $ClCF_2CFCl_2$ (F113) as well as that of the poorly reactive Freons CF_2Cl_2 (F12) and $BrCF_3$ (F13B1) with thiophenoxides and phenoxides.

$$\underset{1}{ArS^-} + \underset{2}{XCF_2X'} \rightarrow \underset{3}{ArSCF_2X'}$$

$$X = Br, Cl \qquad X' = F, Cl, CFCl_2, CF_3, C_5F_{11}$$

We show that the monosubstitution observed involves radical (preliminary note[8]) or carbanionic intermediates.

---

(1) Banks, R. E. "Organofluorine Chemicals and Their Industrial Applications"; Society of Chemical Industry: London, 1979.

(2) Franzen, V.; Fikentscher, L. *Chem. Ber.* **1962**, *95*, 1958. Schlosser, M.; Le Van, C.; Spahic, B. *Helv. Chim. Acta* **1975**, *58*, 2575.

(3) Banks, R. E. "Fluorocarbons and Their Derivatives", 2nd ed.; McDonald: London, 1970.

(4) Cantacuzene, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365.

(5) Boiko, V. N; Shchupak, G. M.; Yagupolskii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 972. Popov, V. I.; Boiko, V. N.; Yagupolskii, L. M. *J. Fluorine Chem.* **1982**, *21*, 365.

(6) Feiring, A. E. *J. Org. Chem.* **1983**, *48*, 347.

(7) Rico, I.; Cantacuzene, D.; Wakselman, C. *J. Org. Chem.* **1983**, *48*, 1979.

0022-3263/85/1950-4047$01.50/0