Tetrahedron Letters,Vol.24,No.31,pp 3213-3216,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain 

# INFLUENCE OF CATION COMPLEXING SOLVENT ADDITIVES AND FUNCTIONAL GROUPS IN ASYMMETRIC ALKYLATIONS OF ESTERS VIA LITHIUM ENOLATES

Günter Helmchen*, Adel Selim, Dieter Dorsch and Irmtraud Taufer

Institut für Organische Chemie der Universität, Am Hubland, D-8700 Würzburg, FRG[1]

Summary. Highly diastereoselective alkylations of propionates of chiral alcohols derived from (+)-camphor are described. It is demonstrated that steric shielding as well as cation complexation are important for stereoselection. The latter effects are in part rationalized on the basis of preferential formation of (Z)- or (E)-lithium enolates.

Guided by general considerations concerning morphological aspects of molecular achitecture (functional groups at concave sites[2]) we have recently introduced a class of chiral alcohols R*OH derived from camphor (Scheme 1, 1, 2, related compounds); esters of these produced very high stereoselectivity in diastereoselective asymmetric syntheses of widely differing mechanistic type:

- alkylations of esters R*-OOC-$CH_2$-R (R = alkyl, Ph, OR', $SiMe_3$) via lithium enolates[3],
- Diels-Alder additions of acrylates and methyl fumarates to cyclopentadiene and anthracene[2],
- addition of benzylsulfenyl chloride to acrylates[4], and related β-additions.

In the field of enolate chemistry, our initial planning and interpretations of results were based on evaluating conformational and steric (diastereoface-differentiating shielding) effects. However, new results indicate that complexing interactions must also be considered. Here, we want to introduce several potentially useful new reagents of the type characterized above (3-7, Scheme 1). Furthermore, we report on two aspects of the alkylation reaction which demonstrate the importance of complexation:

- influence of an external lithium complexing agent (HMPT[5]), and
- influence of groups (R and X, Scheme 1) capable of shielding as well as complexation.

Results pertaining to the first aspect are displayed in Figure 1. These are discussed with reference to Scheme 2. Curves Aa and Ab describe series of alkylations of the propionate 8 at different concentrations (Aa: highest attainable concentration) using LICA[5]-HMPT mixtures as base, THF[5] as solvent and n-tetradecyl iodide as alkylating agent[6]. A smooth sigmoid changeover from selectivities favouring diastereomer (2'R)-10 to selectivities favouring diastereomer (2'S)-10 is observed. The turning point is at LICA/HMPT 1:1 molar ratio. According to a rationale previously proposed[3] on the basis of limited evidence this configurational inversion is caused by kinetically controlled formation of isomeric enolates, (Z)-9 and (E)-9, by deprotonation with LICA and LICA-HMPT complex, respectively. Using techniques developed by Ireland and co-workers[7] we were able to proof this assumption by quenching enolates with TBS-Cl[5] to give (oily) silylketene acetals of composition (E)-11 : (Z)-11 = 98:2 and 4:96 with LICA and LICA-HMPT (2.2 eq./Li, cond. Aa, Fig. 1), respectively[8]. Furthermore, this mechanistic rationale requires the postulation of


1 R = $PhSO_2\dot{N}$– 2

R = $CHPh_2$ 3

4 X = $CH_2$, R = 5

X = S, R = $(CH_2)_2$ 6

X = O, R = $(CH_2)_2$ 7

Scheme 1

front-face attack[9] by the electrophile and enolate conformations as shown in Scheme 2[10].

A further interesting observation was made when dependence of alkylation stereoselectivity on concentration of HMPT added after deprotonation was investigated (Fig. 1B): increase of selectivity with increasing concentration of HMPT. Suspecting that this effect might be caused by disruption of conformationally unfavourable Li···R interactions we examined closer the role of the shielding group R. To this end alkylations of a series of propionates derived from alcohols 2-7 were carried out (Table 1). As described in Scheme 3 all these alcohols are available via highly selective routes from natural (+)-camphor. Alkylations of propionates 12 (Table 1) of alcohols 1-5 via (Z)-enolates (LICA/THF, conditions A) result in excellent to good diastereoselectivities. Excepting esters of 1, metallations by the LICA-HMPT complex (conditions B) yield lower levels of diastereoselection (cf. ref. 3). In all these cases configurations of products 13 (entries 1-10 of Table 1) conform to the rationale involving only shielding by R (R = alkyl, aryl[9]). In view of this regularity, results obtained with the propionate of dithioacetal 6 (entries 11,12) are surprising: configurations are opposite to what was expected (cf. entries 11,12 vs. 9,10). Diastereoselectivity (absolute) values though are very similar to those for the topographically analogous propionate of 5. At a low level of stereoselection the propionate of acetal 7 shows properties similar to that of the thioacetal. Current knowledge about monomolecular or associated enolates does not allow to "explain" the effects uncovered here[11]. As a working hypothesis we assume that groups R/X not only provide shielding but also control conformations around O-(C-1') bonds of the enolate moieties via cation chelation.

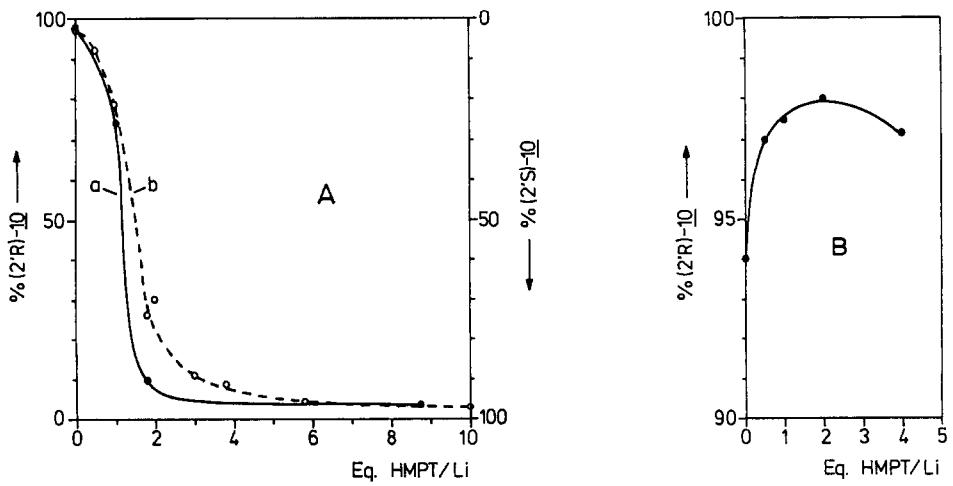



Fig. 1. Influence of HMPT on alkylations of propionate 8 with n-tetradecyl iodide (cf. Scheme 2).

Aa Base system: 1.2 mmol LICA in 2.0 ml THF + HMPT as g. on abscissa; deprot.: 1 mmol 8 in 4.0 ml THF, -80 °C; alk.: 2.2 mmol n-$C_{14}H_{29}I$ in 3.0 ml THF + 1.9 mmol HMPT, -40 °C.

Ab Base system: 1.6 mmol LICA in 10.0 ml THF + HMPT as g. on abscissa; deprot.: 1 mmol 8 in 10 ml THF, -80 °C; alkylation: as Aa, but 5 ml THF.

B Base system, deprot.: as Aa, but without HMPT; alk.: as Aa, but HMPT as given on abscissa.

Scheme 2

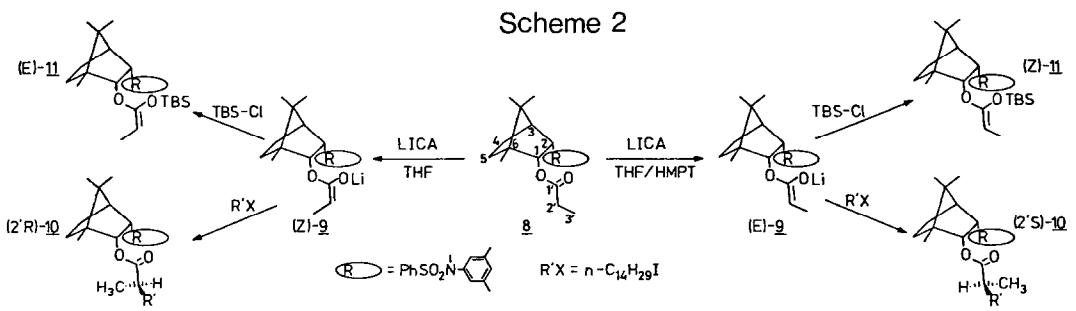
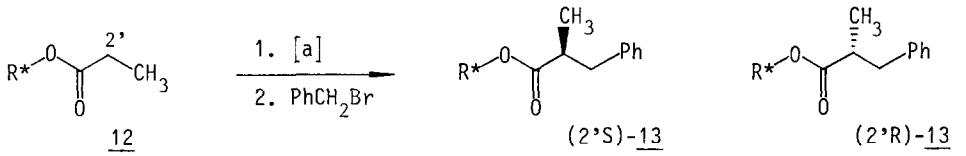
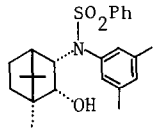
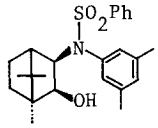
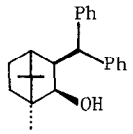
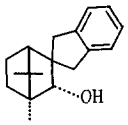
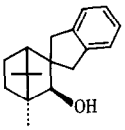
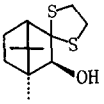
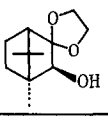
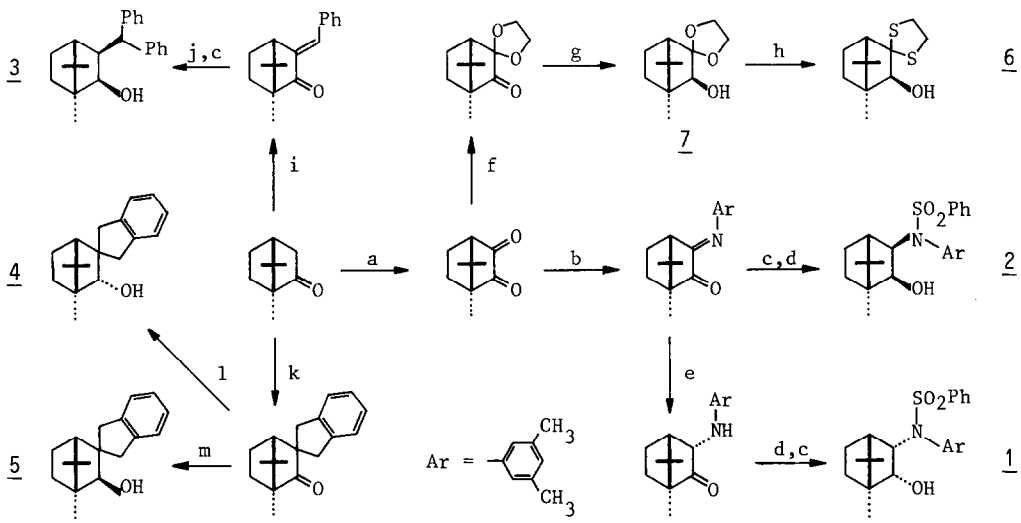


Table 1. Asymmetric alkylations of propionates 12 of chiral alcohols R*-OH (1-7).




| | R*-OH | Entry | Depr. cond. [a] | Equiv. LICA [b] | Diastereoselectivity [c] (2'R):(2'S)-13 | | % Yield [d] (2'R)+(2'S)-13 |
|---|---|---|---|---|---|---|---|
| 1 |  | 1 | A | 1.6 | 97 : 3 | [e] | 89 (97) |
| | | 2 | B | 1.6 | 5 : 95 | | 94 (98) |
| 2 |  | 3 | A | 1.6 | 2 : 98 | [e] | 87 (90) |
| | | 4 | B | 1.6 | 76 : 24 | | 70 (98) |
| 3 |  | 5 | A | 1.2 | 10 : 90 | [f] | 87 |
| | | 6 | B | 1.2 | 81 : 19 | | 82 |
| 4 |  | 7 | A | 1.3 | 84 : 16 | [g] | 69/ 5 |
| | | 8 | B | 1.3 | 30 : 70 | | 60/ - |
| 5 |  | 9 | A | 1.2 | 19 : 81 | [g] | 87/ 5 |
| | | 10 | B | 1.2 | 57 : 43 | | 82/ 4 |
| 6 |  | 11 | A | 2.0 | 86 : 14 | [e] | 53/36 |
| | | 12 | B | 2.0 | 31 : 69 | | 56/ 9 |
| 7 |  | 13 | A | 2.0 | 65 : 35 | | 54/35 |
| | | 14 | A | 1.2 | 67 : 33 | [e] | 43/ - |
| | | 15 | B | 2.0 | 42 : 58 | | 60/32 |

[a] Deprotonation conditions: -80 °C, A: LICA in THF, B: LICA in THF/HMPT (23 %); alkylations were carried out at -63 °C, with 2 eq. of HMPT added for activation (A only). [b] Optimized with respect to avoidance of ester condensation. [c] Product configurations were determined by comparison with authentic samples prepared by reaction of R*-OH with enantiomerically pure 2-benzylpropionyl chloride. [d] Reaction products were isolated by MPLC[5] and characterized by elemental analysis and spectra; values in brackets: yields corrected with respect to recovered starting material 12; values after diagonal strokes: yields of dialkylated products (2,2-dibenzylpropionates). [e] Analysis by HPLC[5] (silica gel, hexane-ethyl acetate, 254 nm). [f] Analysis by HPLC ($C_{18}$ reversed phase, methanol-water, 254 nm). [g] Analysis by $^{13}C$-NMR.



Scheme 3. a: $SeO_2$, 96 % (ref.12a); b: $ArNH_2/H^+$ (ref.12b); c: $Ca(BH_4)_2$/EtOH-$H_2O$; d: $PhSO_2Cl$/pyridine (3 eq.)-$CHCl_3$, 25 °C; overall yield of 2 via b,c,d: 80-85 %; e: Zn/KOH/EtOH, 25 °C; overall yield of 1 via b,e,d,c: 70-75 %; f: $(CH_2OH)_2$/pTsOH, 70 %; g: c at -40 °C, 99 % containing 6 % of endo-isomer, removed via propionate; f,g: ref.12c modified; h. 1. $H_2SO_4/Et_2O$, 2. $(CH_2SH)_2/BF_3 \cdot Et_2O$, 70 %; i: 1. Na/toluene, 2. PhCHO, 64 % (ref.12d); j: PhMgBr/$Et_2O$; 3 via i,j,c: 53 %; k: 1. $NaNH_2$/toluene, 2. 1,2-$(CH_2Cl)_2C_6H_4$, 39 %; l: Na (trace Hg)/EtOH, 90 %; m: $LiAlH_4$, 94 %.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Hoechst AG. Chemicals were donated by Thomae GmbH (Dr. Kutter) and Bayer AC (Dr. Singer).

[1] The work of A.S. (contained in Fig. 1) was carried out at the Institute für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart.

[2] G.Helmchen, R.Schmierer, Angew.Chem. 93, 208 (1981), Int.Ed.Engl. 20, 205 (1981); T.Poll, Dipl.-Arbeit, Würzburg 1982; our results have been confirmed: W.Oppolzer, C.Chapuis, G.M.Dao, D. Reichlin, T.Godel, Tetrahedron Lett. 1982, 4781.

[3] E.Ade, G.Helmchen, G.Heiligenmann, Tetrahedron Lett. 1980, 1137; R.Schmierer, G.Grotemeier, G. Helmchen, A.Selim, Angew.Chem. 93, 209 (1981), Int.Ed.Engl. 20, 207 (1981); G.Helmchen, R.Schmierer, Tetrahedron Lett. 1983, 1235.

[4] T.Beisswenger, Doktorarbeit, Universität Stuttgart 1982 (supervisor: F.Effenberger).

[5] Abbreviations: HMPT hexamethylphosphoric triamide, LICA lithium cyclohexylisopropylamide, THF tetrahydrofuran, TBS t-butyldimethylsilyl, H/MPLC high/medium pressure liquid chromatography.

[6] n-Tetradecyl iodide was chosen as test alkylation agent because of our interest in synthesizing lipids (cf. ref. 3).

[7] R.E.Ireland, R.H.Mueller, A.K.Willard, J.Am.Chem.Soc. 98, 2868 (1976).

[8] Assignment of configurations to (Z)- and (E)-11 is based on chemical shift values of carbinyl hydrogens (2-H) which acc. to ref.7 resonate at higher field in (Z)-silylketene acetals. It must be noted that there is no unambiguous evidence for this assignment. Furthermore, please observe that Z/E descriptors are opposite for corresponding lithium enolates and silylketene acetals.

[9] It is assumed that in esters of 1 and 2 backface shielding is provided by 3,5-dimethylphenyl rather than phenylsulfonyl groups. This is inferred from the fact that substantial rotational barriers around N-C($sp^2$) bonds occur which in a series of derivatives increase with increasing steric bulk of C-2 endo substituents: R.Wierzchowski, Diplomarbeit, Universität Stuttgart 1981.

[10] For a similar configurational dichotomy, based on kinetic vs. thermodynamic control of lithioenamine generation, see A.I.Meyers et al., J.Am.Chem.Soc. 103, 3088 (1981).

[11] Effects that might be related to those shown by esters of 6 have been reported for amide enolates: P.E.Sonnet et al., J.Org.Chem. 45, 3139 (1980), D.A.Evans et al., Tetrahedr.Lett. 1980, 4233.

[12] (a) W.C.Evans, J.M.Ridgion, J.L.Simonsen, J.Chem.Soc. 1934, 137; (b) M.O.Forster, T.Thornley, ibid. 1909, 924; (c) I.Fleming, R.B.Woodward, J.Chem.Soc.(C), 1968, 1289; (d) H.Rupe, A.Blechschmidt, Ber.Dtsch.Chem.Ges. 31, 170 (1918).

(Received in Germany 2 May 1983)