Evidence for oxacarbenium ion intermediates in the Lewis acid promoted cleavage of spirocyclic dioxanes

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Studies on the Lewis acid mediated cleavage of spiro-1,3-dioxanes indicate that this process proceeds *via* an oxacarbenium ion intermediate. With the correct choice of nucleophile and Lewis acid, high selectivities can be obtained.

Introduction

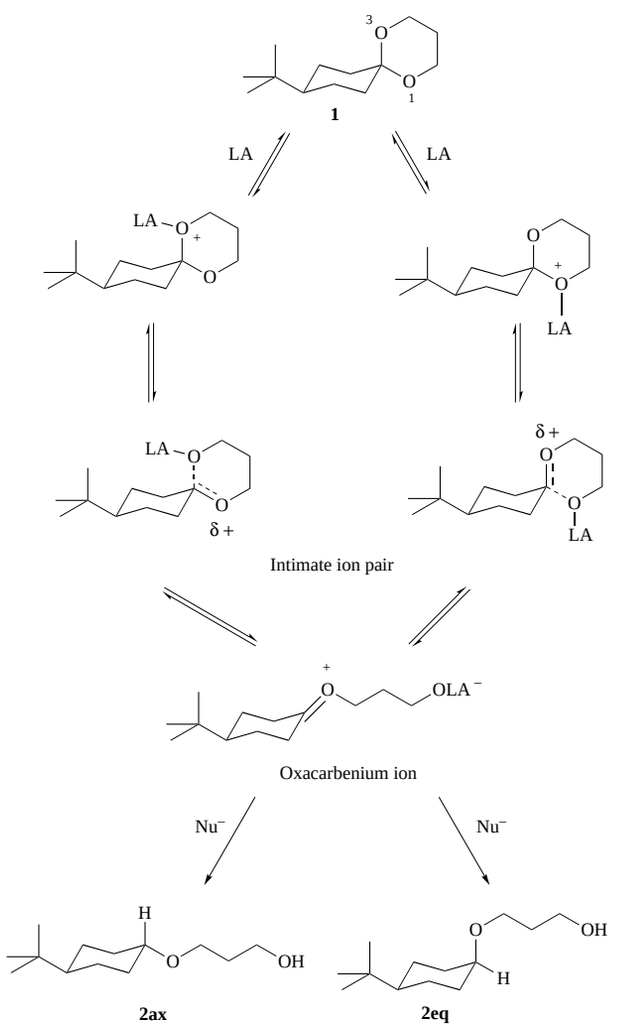
Since the first report by Johnson *et al*. on the use of acetals as chiral controllers in polyolefin cyclisations[1] there have been a plethora of reports on the use of asymmetric acetals in organic synthesis.[2] One particular area has been the use of acetals as carbonyl equivalents in nucleophilic addition. Concomitant with these developments there have been considerable efforts to elucidate the mechanism and hence rationalise the asymmetric induction so obtained.[3–6] A general view has emerged which invokes a reaction mechanism continuum with the extremes being a synchronous S_N2 type invertive displacement on a tight ion pair and a dissociative S_N1 type process proceeding *via* a free oxacarbenium ion followed by rapid non-selective nucleophilic attack. As a component of a general study in asymmetric synthesis involving chiral Lewis acids we had cause to examine the diastereoselective cleavage of conformationally locked (unsubstituted) 2-cyclohexyldioxanes and in this paper we report our results which provide further evidence to support the dominant role of an oxacarbenium ion in this system.

Results and discussion

Whilst the use of chiral acetals in these processes does afford high diastereocontrol in the ring cleavage step the removal of the chiral auxiliary requires destruction of its stereochemical information. In an attempt to circumvent this problem we have been considering the use of unsubstituted dioxane acetals in conjunction with chiral Lewis acids. In these processes, a requirement for asymmetric induction is that the chiral auxiliary must be close to the reaction centre, *i.e.* an intimate ion pair type intermediate is required. Since we failed to detect any significant asymmetric induction with these acetals we opted to examine this aspect through a study of the reductive cleavage of spirodioxane **1**, derived from 4-*tert*-butylcyclohexanone, in which the products can be either *trans* **2ax** or *cis* **2eq** to the *tert*-butyl group, Scheme 1.

Within this area spirocyclic acetals have been employed in synthesis, notably by the groups of Yamamoto[5] and Oku.[7] The former has shown that through the use of either DIBAL or a titanium tetrachloride–triethylsilane combination it is possible to generate either epimer at the new chiral centre starting from the same acetal. This is rationalised as resulting from intra- and inter-molecular hydride delivery *via* an intimate ion pair–oxacarbenium ion intermediate. Oku, employing menthone as a chiral auxiliary, obtained highly selective cleavage of the equatorial oxygen of the corresponding spiroketal. This was explained as the result of selective complexation of the equatorial oxygen of the spiroacetals[8] followed by antiattack on an intimate ion pair intermediate. However, in all cases involving an external nucleophile source the same result would have been obtained from nucleophilic attack on a menthone based oxacarbenium ion.

Following the precedents established by Oku, Lewis acid complexation is envisaged to occur at (O)1 to produce an intimate ion pair which will subsequently open to form the oxacarbenium ion. Reaction *via* the oxacarbenium ion intermediate should exhibit comparable selectivities to that of the reaction with 4-*tert*-butylcyclohexanone. Significant deviation from the latter can be attributed to the reaction proceeding along a pathway involving an invertive type process with attack *anti* to the Lewis acid complex, Scheme 1.



Scheme 1 Lewis acid mediated cleavage of spirodioxane **1**

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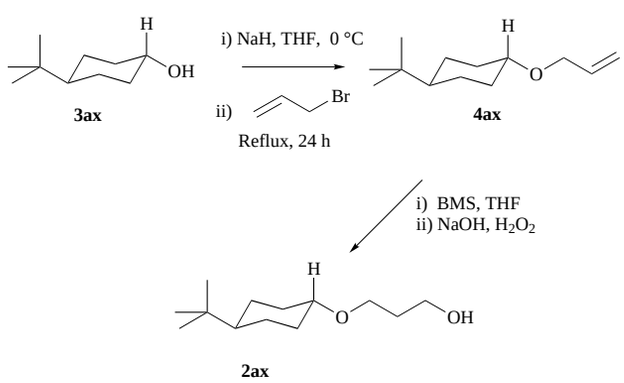
Table 1 Reaction of spirodioxane **1** and 4-*tert*-butylcyclohexanone with R_3SiH–Lewis acid combinations

Run	Silane	Lewis acid	Solvent	Yield of **2** (eq + ax) (%)	Ratio **2eq**:**2ax**	Yield of **3** (eq + ax) (%)	Ratio **3eq**:**3ax**
1	Et_3SiH	$Sc(OTf)_3$	CH_2Cl_2	44	51:49	—	—
2	Et_3SiH	$AlCl_3$	CH_2Cl_2	81	44:56	—	—
3	Et_3SiH	BCl_3	CH_2Cl_2	45	42:58	—	—
4	Et_3SiH	Et_2AlCl	CH_2Cl_2	14	42:58	—	—
5	Et_3SiH	$EtAlCl_2$	CH_2Cl_2	87	39:61	—	—
6	Et_3SiH	$TiCl_4$	CH_2Cl_2	83	36:64	87	20:80
7	Me_3SiH	$Sc(OTf)_3$	CH_2Cl_2	35	2:98	—	—
8	Me_3SiH	$AlCl_3$	CH_2Cl_2	72	13:87	—	—
9	Me_3SiH	BCl_3	CH_2Cl_2	74	2:98	61	5:95
10	Me_3SiH	$EtAlCl_2$	CH_2Cl_2	97	9:91	—	—
11	Me_3SiH	$TiCl_4$	CH_2Cl_2	95	19:81	92	35:65
12	Et_3SiH	$TiCl_4$	Toluene	56	41:59	—	—
13	Et_3SiH	$TiCl_4$	Pentane	36	22:78	—	—
14	Me_3SiH	$TiCl_4$	Toluene	57	15:85	—	—
15	Me_3SiH	$TiCl_4$	Pentane	94	16:84	—	—
16	Ph_2SiH_2	$TiCl_4$	CH_2Cl_2	71	17:83	—	—
17	Ph_3SiH	$TiCl_4$	CH_2Cl_2	91	31:69	87	45:55
18	$EtMe_2SiH$	$TiCl_4$	CH_2Cl_2	93	23:77	90	39:61
19	DIBAL	—	CH_2Cl_2	58	86:14	86	36:64

In each case in Table 1, the spirodioxane was treated with the reducing agent then the Lewis acid at −78 °C and the reaction monitored by TLC until there was no further change. After aqueous quenching the reaction was subjected to a standard extraction. The isolated products were purified by column chromatography to afford material that had the correct spectroscopic and analytical data. The diastereoselectivity was determined by both GC and ^{1}H NMR analysis of the crude material with the results being consistent over at least two independent runs. Confirmation of the isomer assignment was achieved by converting a known sample of *trans* 4-*tert*-butylcyclohexanol to the corresponding hydroxypropyl ether **2ax** by allylation with NaH–allyl bromide and subsequent hydroboration–oxidation, Scheme 2.



Scheme 2

Given our ultimate goal of achieving stereochemical control through the use of chiral Lewis acids we commenced these studies with an investigation of the effect of varying Lewis acidity. In general these experiments showed, runs 1–6, 7–11, that for a given nucleophile the Lewis acid exerted relatively little influence on the reaction.

To investigate nucleophile dependency in the system, silanes with differing size R groups were employed. Although the increase in selectivity observed on decrease in effective nucleophile size (runs 6, 11, 17–19) can be attributed to an increasing role for an intimate ion pair, the results are equally consistent with the general idea that an oxacarbenium ion represents the most likely reactive state. This latter suggestion would be in agreement with the general theory of attack on unencumbered cyclohexanones in which axial approach is favoured by smaller nucleophiles. This appears to be borne out by a comparison with the results obtained from the reduction of 4-*tert*-butylcyclohexanone under similar conditions. However, the very high selectivities obtained with trimethylsilane as compared with the more commonly employed triethylsilane are noteworthy in the quest for greater synthetic efficiency.

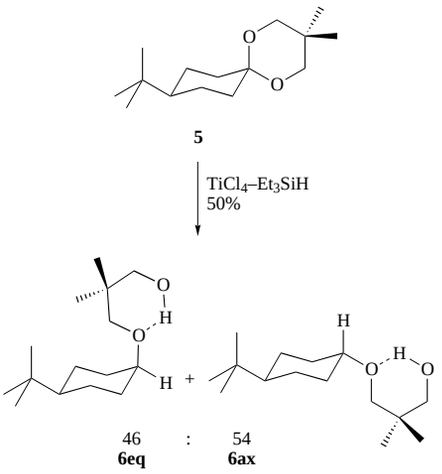
A brief study of variation of the nature of the solvent was also undertaken with the hope that the use of less polar solvents would favour an increased proportion of ion pair intermediates. In a marginal sense this was realised in that the use of pentane resulted in a slight increase in the diastereoselectivity (runs 6, 12–15).

Confirmation of preferential equatorial binding of the Lewis acid was achieved through reduction with DIBAL in dichloromethane (run 19). This produced the *cis* isomer **2eq** whilst use of a silane–Lewis acid system favoured the *trans* isomer **2ax** formation. These results are consistent with the Yamamoto–Oku hypothesis for selective equatorial binding of the Lewis acid and intramolecular hydride delivery with DIBAL and attack on an external ion pair–oxacarbenium ion intermediate for silane nucleophiles. In contrast, reduction of 4-*tert*-butylcyclohexanone under similar conditions favours production of the equatorial alcohol **3ax** with both classes of reducing systems.

Conclusions

In conclusion these studies suggest that acetal cleavage processes are highly substrate structure dependent and that with unsubstituted dioxane acetals preferential reaction occurs *via* an oxacarbenium ion intermediate.[9] The high selectivity observed with the substituted dioxane acetals developed by Johnson *et al.* may be attributable to a reactive conformation effect in which backbone substitution increases the population of intimate ion pair intermediates. However, use of spirodioxane **5** in which the *gem*-dimethyl substitution would be expected to provide enhanced intimate ion pair concentration (Thorpe–Ingold effect)[10] afforded only modest selectivity, Scheme 3.

Finally, all attempts to influence the diastereoselectivity of acetal cleavage with this and related acyclic dioxane acetals through the use of Lewis acids bearing a variety of chiral ligands (diols, amino alcohols and diamines) have failed to show any promise. This is further evidence in support of the predominant generation of an oxacarbenium ion intermediate in which the Lewis acid is removed from the site of reaction thus minimising any steric influence it may exert over nucleophile approach.



Scheme 3

Experimental

All reactions were undertaken in an inert gas atmosphere of dry nitrogen or argon in pre-dried glassware. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Gemini 200 (^{1}H at 199.975 MHz, ^{13}C at 50.289 MHz), Varian XL-200 (^{1}H at 200.057 MHz) and Varian VXR-400(s) (^{1}H at 399.952 MHz, ^{13}C at 100.577 MHz) spectrometers with $CDCl_3$ as solvent ($\delta = 7.26$) and are recorded in ppm (δ units) downfield of tetramethylsilane ($\delta = 0$). *J* Values are given in Hz. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1720X spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E organic mass spectrometer, and gas chromatography–mass spectra (GC–MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG mass Lab trio 1000. To follow reactions, thin layer chromatography (TLC) or gas chromatography (GC) on Hewlett Packard 5890A or 5890 series II instruments were used. Flash Column Chromatography was performed on silica (60–240 mesh). Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. All solvents were distilled prior to use following standard protocols.[11] Petrol refers to the fraction boiling in the 40–60 °C range unless otherwise stated. Titanium(IV) tetrachloride was redistilled under nitrogen. All other reagents were reagent grade and used as supplied unless otherwise stated. Alcohol **3** is commercially available, acetals **1** and **5** were prepared by standard ketalisation procedures.

Reductions with silanes

The Lewis acid (1 equiv.) was added dropwise to a pre-cooled solution (−78 °C) of the substrate and silane (1 equiv.) in solvent (5 ml). The reaction was followed by TLC and on complete consumption of starting material was quenched with methanolic sodium hydroxide solution. The mixture was extracted with dichloromethane (3 × 50 ml) and the organic extracts washed with aqueous sodium hydrogen carbonate, brine, dried and concentrated. Diastereoisomer ratios were determined *via* GC analysis, GC–MS and ^{1}H NMR (400 MHz) on the crude mixtures. Purification was achieved through column chromatography with petrol and diethyl ether systems.

Reductions with DIBAL

To a solution of **1** (300 mg, 1.4 mmol) in dichloromethane (6 ml) was added DIBAL (1 M in hexane; 1.4 ml, 1.4 mmol) with stirring at 0 °C over 5 min. The mixture was stirred at 0 °C until TLC indicated completion of the reaction. The reaction was quenched by pouring into cold dilute hydrochloric acid and the mixture was extracted with diethyl ether to yield a yellow oil.

3-(4′-*tert*-Butylcyclohexyloxy)propan-1-ol 2

Method a: *via* reduction of 1. Purification by flash column chromatography using a gradient of 15:1 to 2:1 petrol–diethyl ether solvent system afforded the title compound as a colourless oil (175 mg, 58%) as a mixture 86:14 of equatorial **2eq** and axial **2ax** isomers. For $C_{13}H_{27}O_2^+$ calc: 215.2011. Found: 215.2011. **2eq**: δ_H(200 MHz) 3.8 (2H, t, *J* 5.0, HOCH_2), 3.6 (2H, t, *J* 5.6, O–CH_2), 3.5 (1H, m, C1′-Heq), 3.0 (1H, s, HO), 1.9 (2H, m, OCH$_2$CH_2CH$_2$O), 0.8–1.7 (18H, m, CH_2, cyclohexyl, Bu^t); δ_C(50 MHz) 74.2, 68.4, 63.5, 48.3, 33.0, 32.5, 30.8, 27.9, 21.8; *m/z* (CI^+) 215 (100%, MH^+); ν_{max}/cm^{-1} 3374 (OH), 2940, 2865, 1477, 1445, 1392, 1365, 1180, 1159, 1083, 1032, 979, 964, 929, 909; GC retention time (t_r) 15.39 min. **2ax**: δ_H(400 MHz) 3.7 (2H, t, *J* 5.6, HOCH_2), 3.6 (2H, t, *J* 6.4, OCH_2), 3.1 (1H, m, C1′-Hax), 2.7 (1H, s, HO), 2.0 (2H, m, OCH$_2$CH_2CH$_2$O), 0.8–1.7 (18H, m, CH_2, cyclohexyl, Bu^t); δ_C(200 MHz) 78.9, 67.6, 62.5, 47.3, 32.6, 32.2, 32.1, 27.6, 25.6; *m/z* (CI^+) 215 (100%, MH^+); ν_{max}/cm^{-1} 3395, 2941, 2864, 1480, 1451, 1370, 1112, 1036, 928, 738; GC retention time (t_r) 17.15 min.

Method b: from *trans*-4-*tert*-butylcyclohexanol 3ax. A solution of **3ax** (300 mg, 2.0 mmol) in THF (5 ml) was added to a stirred slurry of sodium hydride (60% dispersion in mineral oil; 85 mg, 1.9 mmol) in THF (5 ml) at 0 °C and the mixture stirred for 1 h. A solution of allyl bromide (0.23 g, 2.0 mmol) in THF (5 ml) was then added at 0 °C. On completion of the addition the mixture was refluxed overnight and then quenched with water and extracted with diethyl ether (3 × 50 ml). The organic extracts were washed with brine, dried and concentrated to yield a yellow oil (335 mg). Purification by flash column chromatography (2:1 petrol–diethyl ether) afforded the allylic ether **4ax** as a colourless oil (199 mg, 53%).

Borane–methyl sulfide complex (BMS) (0.03 ml, 0.3 mmol) was added to a solution of allylic ether **4ax** (200 mg, 1.0 mmol) in THF (10 ml) at 0° C. On completion of the addition the solution was refluxed for 1 h. To the cooled reaction mixture was then added sodium hydroxide (3 M; 0.37 ml, 0.3 mmol) and then hydrogen peroxide (30% solution; 0.13 ml, 0.3 mmol). After a further 1 h reflux the colourless solution was diluted with aqueous potassium carbonate and extracted with diethyl ether (3 × 50 ml). The organic extracts were washed with brine, dried and concentrated to yield the title compound as a colourless oil identical in all respects to that obtained above.

3-(4′-*tert*-Butylcyclohexyloxy)-2,2-dimethylpropan-1-ol 6

Alcohol **6** was prepared from acetal **5** following the same protocol as described for **2** above. Purification by flash column chromatography using 12:1 petrol–diethyl ether as eluent afforded the title compound as a mixture of isomers, **6ax** and **6eq**, as a colourless oil (**6ax**:**6eq** 54:46) (Found: C, 74.1; H, 12.5. $C_{15}H_{30}O_2$ requires C, 74.3; H, 12.5%). **6eq**: δ_H(400 MHz; $CDCl_3$) 3.47 (2H, d, *J* 5.6, HOCH_2), 3.48 [1H, br t, HO (H-bonded)], 3.33 (1H, t, *J* 5.6, C1′-H), 3.26 (2H, s, OCH_2), 1.93–1.97 [2H, m, CHH (C2′,C6′)], 1.49–1.52 [2H, m, CHH (C2′,C6′)], 1.24–1.32 (5H, m, C3′H_2,C4′H,C5′H_2), 0.94 (6H, s, 2CH_3), 0.83 [9H, s, C(CH_3)$_3$]; δ_C(50 MHz; $CDCl_3$) 80.2, 75.8, 75.0, 49.7, 37.8, 34.5, 32.1, 29.4, 24.0, 23.3; ν_{max}/cm^{-1} 3452 (OH–H bonded), 2943, 2867, 1475, 1365, 1335, 1180, 1159, 1085, 1048, 908, 734; GC retention time (t_r) 14.27 min. **6ax**: δ_H(200 MHz; $CDCl_3$) 3.43 (2H, d, *J* 5.4, HOCH_2), 3.33 (2H, s, OCH_2), 3.17 [1H, t, *J* 5.4, HO (H-bonded)], 3.09 (1H, tt, *J* 4.1 and 10.6, C1′-H), 2.02–2.13 [2H, m, CHH (C2′,C6′)], 1.69–1.84 [2H, m, CHH (C2′,C6′)], 0.92–1.28 (5H, m, C3′H_2,C4′H,C5′H_2), 0.90 (6H, s, 2CH_3), 0.83 [9H, s, C(CH_3)$_3$]; δ_C(50 MHz; $CDCl_3$) 81.4, 80.3, 74.8, 49.4, 37.8, 34.5, 34.3, 29.6, 27.2, 24.0; ν_{max}/cm^{-1} 3450 (OH–H bonded), 2943, 2860, 1473, 1365, 1264, 1087, 1044, 742; GC retention time (t_r) 16.18 min.

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