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Alkylation of carbonyl compounds in the $TiCl_4$-promoted reaction of trimethylsilyl enol ethers with epoxides

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Abstract—Titanium tetrachloride promoted reaction of trimethylsilyl enol ethers with ethylene oxide affords homoaldol type products in moderate/good yields. Monosubstituted epoxides react regioselectively: the nucleophilic attack of the enolate occurs at the more substituted position of propene oxide whereas epichlorohydrin reacts at the less substituted end.

1. Introduction

Epoxide ring opening with organometallic nucleophiles is a well-known reaction and a synthetically useful method of C–C bond formation.[1] However, the analogous reaction of epoxides with enolates, which would represent a highly useful method for the synthesis of homoaldol type products, is less well investigated (Fig. 1).[2] Consequently, homoaldols are usually prepared by other methods, such as the addition of homoenolates or metallated allylic carbamates to carbonyl compounds.[3] The successful examples of direct enolate/epoxide reaction include structurally simple carboxylic acid dianions, malonate and amide anions as reaction intermediates, often under forcing conditions, or reactions of aluminium ester-enolates, where the desired products were obtained in moderate to good yields.[4] To the best of our knowledge, the reaction of cyclononanone lithium enolate with propene oxide, catalyzed by excess Me_3Al, has been for a long time the sole example of a successful direct alkylation of a ketone with an epoxide, which seemingly lacks generality.[5] More recently, $LiClO_4$ and lanthanum triflates were shown to be potentially useful promoters of the reaction.[6] Given the low reactivity of ketone enolates towards epoxides, indirect routes to the products of ketone/epoxide coupling were devised, relying on the enhanced nucleophilicity of the corresponding imine or hydrazone carbanions.[7] While these methods work well with a range of ketones, we experienced difficulties during the attempted alkylation of sterically hindered ketones and enones; thus, the formation of the *N*,*N*-dimethylhydrazone from 4,4-dimethylcyclopentenone required 14 days, and it proved unreactive towards ethylene oxide under the reported conditions.[7c] Therefore, we endeavoured to develop a new method for the alkylation of carbonyl compounds with epoxides, based on the anticipated reactivity of silyl enol ethers towards epoxides, under the conditions of the Mukaiyama reaction.[8] In this paper, we wish to present the results of our study giving full experimental details, together with some additional obsevations on the scope of the reaction and its mechanism.[9]

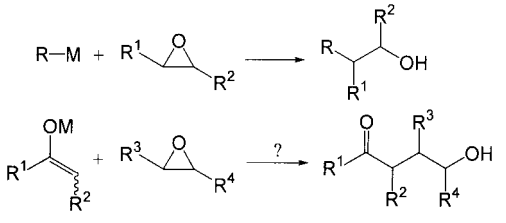

Figure 1.

2. Results and discussion

The feasibility of enoxysilane/epoxide coupling, under the conditions of the Mukaiyama reaction, was first tested using the smallest, symmetric member of the epoxide family, i.e. ethylene oxide. In the first experiment, $TiCl_4$ (1 equiv.) was added to a CH_2Cl_2 solution of cyclopentanone TMS–ether **1** (1 equiv.) and ethylene oxide (1 equiv.) at −78°C. To our pleasure, the desired alkylation product **2** was obtained, albeit in low yield, along with a large amount of cyclopentanone. In addition to **2**, TLC monitoring of the reaction mixture indicated the presence of two less polar products, (tentatively assigned as silylated derivatives **3** and **4**), which, upon brief treatment with diluted aqueous HF, converged to a single product **2**. An interesting observation was made in this reaction: immediately after the addition of $TiCl_4$ the reaction mixture turned dark-red—a

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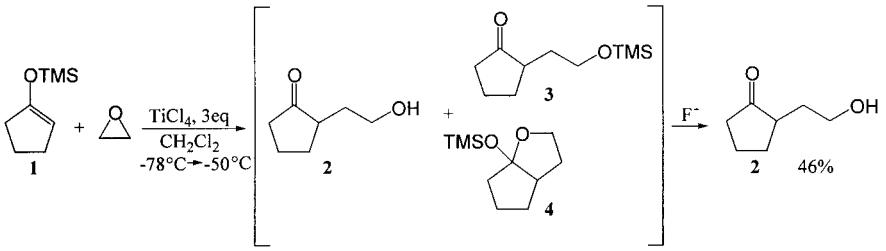


Scheme 1.

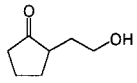
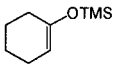
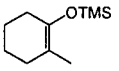
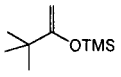
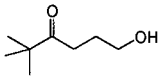
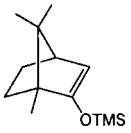
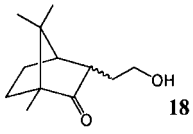
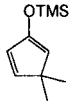
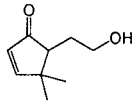
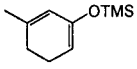
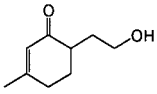
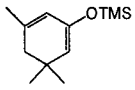
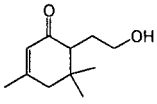
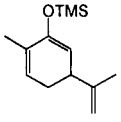
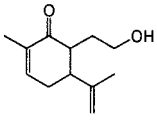
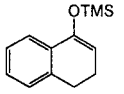
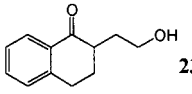
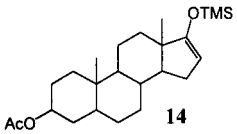
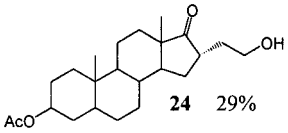
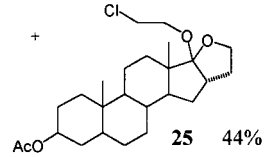
characteristic color of titanium enolates.[10] This phenomenon, along with some additional observations (see below), led us to consider a possibility that the reaction might proceed through the intermediacy of titanium enolates, although their formation from silyl enol ethers and $TiCl_4$ was reported to take place only at room temperature, where so-formed intermediates undergo rapid decomposition.[11] Attempts to pre-form the titanium enolate, by allowing the TMS–enol ether to react with $TiCl_4$ prior to the addition of ethylene oxide, resulted in exclusive formation of a cyclopentanone self-condensation product. However, in situ formation of 'cyclopentanone titanium enolate' by the addition of excess $TiCl_4$ (3 equiv.) to a solution of the silyl enol ether **1** (1 equiv.) and ethylene oxide (2 equiv.), allowing the reaction mixture to reach −50°C, and quenching the reaction *after* the red coloration fades, afforded 2-(2-hydroxyethyl)-cyclopentanone **2** in 46% isolated yield (Scheme 1).

In order to test the generality of this new reaction, a range of structurally different TMS–enol ethers was prepared and submitted to the above reaction conditions. As summarized in Table 1, in all cases except one the desired products were obtained in moderate to good yields. Silyl enol ethers derived from acyclic, cyclic, aromatic ketones and enones all reacted cleanly giving the alkylated products and, in some cases, varying amounts of the starting ketone, as the only constituents of the reaction mixtures after work-up. The silyl enol ether **6**, derived from the unsymmetrical ketone, 2-methylcyclohexanone, reacted regioselectively at the more substituted position (Entry 3). In the reaction of carvone TMS–enol ether **12** (Entry 9) a complex mixture of products was obtained, probably reflecting the instability of the polyunsaturated compound under the acidic conditions employed. The products containing the cyclohexanone structural subunit (Entries 2, 3 and 10) showed strong proclivity towards cyclization into hemiacetal forms on standing, which may complicate the purification and thus lower the isolated yield. In the case of 2-methylcyclohexanone TMS–ether **6**, we found it advantageous to submit the crude reaction mixture to the acetalization conditions, prior to purification, which allowed for the isolation of the pure methoxyacetal **16** in reasonable yield (Entries 2 and 3). In the case of the steroid **14** two products were isolated, namely **24** and its acetal derivative **25** (Entry 11). The latter was subsequently hydrolyzed, (H_2O, HCl, THF, 93%), to afford the desired compound **24** in 70% total yield. Remarkably, this reaction proceeded with complete stereoselectivity, as a single isomer was obtained, tentatively assigned as **24**α.

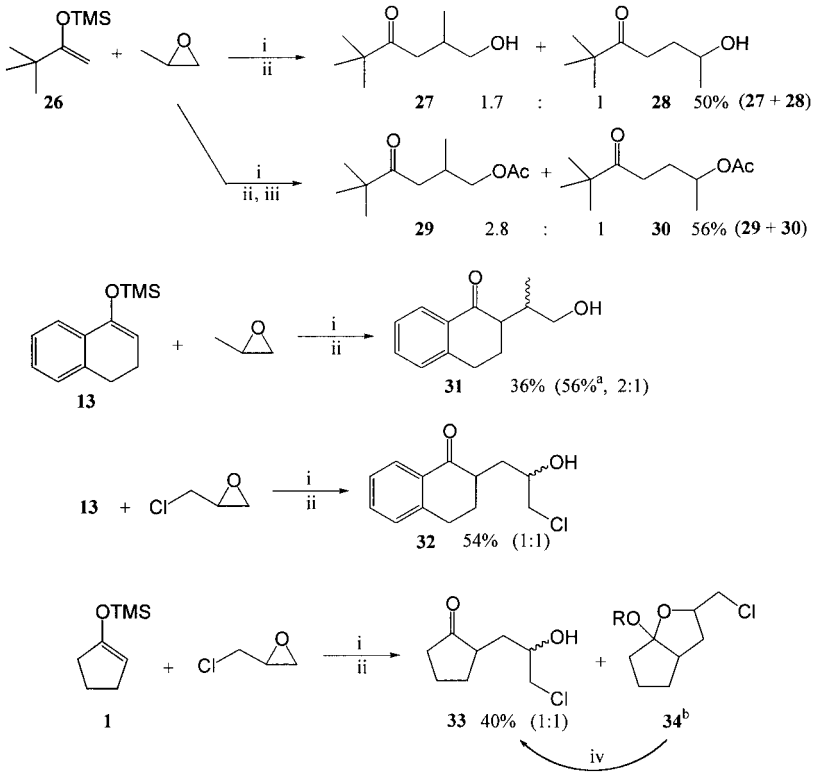
Reactions of enoxysilanes with unsymmetrical epoxides were also investigated (Scheme 2). The reaction of pinacolone silyl enol ether **26** with propene oxide afforded a mixture of regioisomers **27** and **28** (1.7:1) in 50% combined yield (when the crude reaction mixture was subjected to acetylation prior to purification, the corresponding acetates were isolated in 56% yield; **29**:**30**=2.8:1). However, under the same reaction conditions, the cyclic silyl enol ether **13** gave a single regioisomer **31**, resulting from the *attack at the more substituted* epoxide end (isolated as a mixture of diastereoisomers in a 2:1 ratio).[12] On the contrary, with epichlorohydrin, the product of *attack at the less substituted* epoxide carbon atom **32** was exclusively formed (54%, diastereoisomer ratio 1:1). Cyclopentanone enoxysilane **1** behaved similarly, affording a single regioisomer **33** in 40% isolated yield.[13] The reversal of regioselectivity, observed with epichlorohydrin, (with respect to the regiochemical outcome of the reaction with propene oxide), can be explained by electronic destabilization of the transition state leading to a primary alcohol, due to *-I* effect of the vicinal chloro substituent.

Although the exact mechanism of the Mukaiyama reaction is not known, it has been generally accepted that it does not involve titanium enolates.[14] However, several observations support the hypothesis that the reaction with oxiranes might proceed through the intermediacy of these reactive species: (a) the reaction mixture is intensely red colored, and the coloration vanishes immediately upon aqueous quenching; (b) yields are substantially reduced, and the amount of unreacted parent ketone increased, when quenching is performed before the color fades out; (c) the reactions of TMS–enol ethers with oxiranes were tried with other Mukaiyama-type activators, such as TMSI, TMSOTf, $BF_3{\cdot}Et_2O$ or $SnCl_4$, under the same, or even more forcing conditions; however, in any of these reactions no detectable amounts of products could be obtained, indicating that the presence of $TiCl_4$ is essential for the success of the reaction. In order to obtain more decisive mechanistic evidence, titanium enolate **35** was prepared from α-tetralone and *N*,*N*-diisopropylethylamine (DIPEA) as previously described,[15] and submitted to the reaction with ethylene oxide (Scheme 3). No homoaldol type products could be detected in the reaction mixture, even after prolonged reaction time. That the titanium enolate **35** was indeed formed under the employed reaction conditions was confirmed by a control experiment, where **35** was treated with isobutyraldehyde, which afforded aldol **36** in 59% yield. Addition of TMS–Cl to the reaction mixture, (which would be formed from silyl enol ethers under the

Table 1. $TiCl_4$-promoted reactions of TMS–enol ethers with ethylene oxide

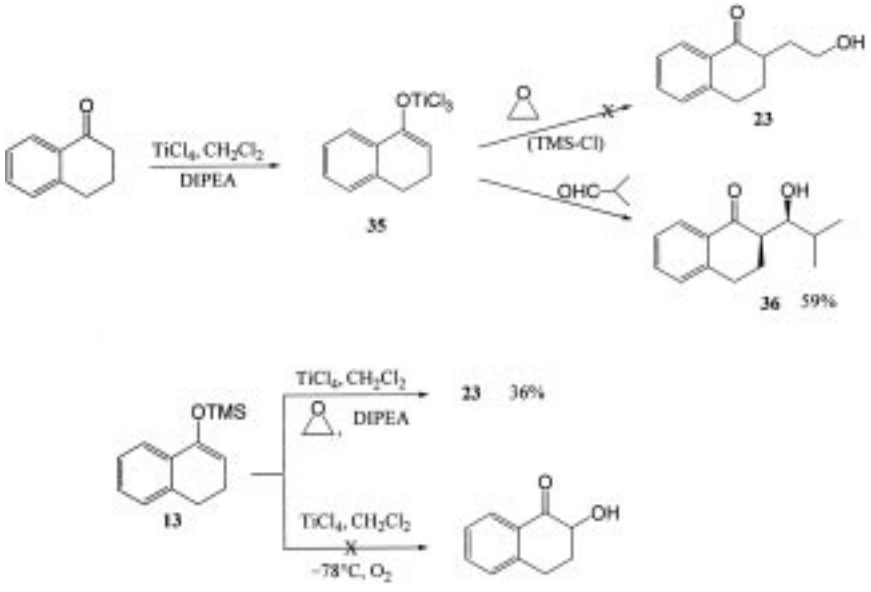
Entry	Silyl enol ether	Product	Yield [a,b]
1	 **1**	 **2**	46%
2	 **5**	 **15**	55%[c,d]
3	 **6**	 **16**	41%[d] (78%)
4	 **7**	 **17**	61%
5	 **8**	 **18**	22% 1:1 (65%)
6	 **9**	 **19**	60%
7	 **10**	 **20**	60%
8	 **11**	 **21**	77%
9	 **12**	 **22**	0%[e]
10	 **13**	 **23**	38% (79%)
11	 **14**	 **24** 29% 93%  **25** 44%	70%[f] (73%)[g]

[a] Yields of isolated, pure compounds.
[b] Values in brackets correspond to yields calculated on the basis of recovered starting compound.
[c] Determined by GC.
[d] After treatment of the crude reaction mixture with CH_2Cl_2/MeOH/*p*-TsOH.
[e] Complex mixture of products.
[f] Total yield of the isolated hydroxy compound **24** after the hydrolysis of chloro derivative **25**.
[g] Combined yield of both products **24** and **25**.



Scheme 2. Key (i) $TiCl_4$, 3 equiv., CH_2Cl_2, −78 to −50°C; (ii) NH_4Cl aq, −50 to 0°C; (iii) Ac_2O, Pyr; (iv) HCl, THF, H_2O, rt. (a) yield based on the recovered 2-tetralone; (b) the structure of **34** was not fully elucidated, the exact structure of R remaining ambiguous.

Mukaiyama conditions, and which might activate epoxide towards enolate addition), did not change the course of the reaction. On the other hand, performing the reaction of enoxysilane **13** with ethylene oxide in the presence of excess DIPEA afforded the homoaldol product **23**, (although in somewhat diminished yield), thus eliminating the possibility that DIPEA, which is present in the reaction medium when pre-formed titanium enolates are used, might inhibit their reactions with epoxides. In addition, in the presence of $TiCl_4$, enoxysilane **13** did not undergo the reaction with molecular oxygen, which is characteristic for titanium enolates.[16] On the basis of these experiments, the intermediacy of titanium enolates can be ruled out, and the aforementioned observations (color, etc) can be considered as misleading. The fact that $TiCl_4$ is the only Lewis acid (of the five tested) capable to promote the



Scheme 3.

reaction is most likely related to the open coordination sphere of the early transition metal, capable of coordinating both enoxysilane and epoxide ligands simultaneously.[17]

To summarize, $TiCl_4$-promoted reactions of enoxysilanes with epoxides offer a new method for the synthesis of homoaldol products from carbonyl compounds. The reactions with monosubstituted epoxides proceed regioselectively, where the sense of regioselectivity is determined by substituents on the epoxide moiety. Further studies will be necessary to establish the full scope and limitations of this promising reaction.

3. Experimental

3.1. General remarks

All chromatographic separations were performed on Silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Varian Genmini 200, ^1H NMR at 200 MHz, ^{13}C NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard, coupling constants (J) are in Hz. IR spectra were recorded on a Perkin–Elmer 457 grating FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on a Finnigan ITDS 700 instrument. Microanalyses were performed at the Center for Instrumental Analysis, Faculty of Chemistry, University of Belgrade. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. GC analyses were performed on a Varian 3400 instrument, equipped with Varian 4270 integrator, VOCOL™ column (105 m, ID: 0.53 mm, film thickness 3.0 μm, carrier gas H_2, 10 ml/min), FI detector. GC/MS analyses were performed on Finnigan Ion Trap Detector ITD-705 with varian 3400 GC eqipped with Split/Splitless injector (1:20) operated at 250°C, Column Supelco PTE-5, 30 m, 0.25 mm id, 0.25 μm film, inserted directly in Ion Trap via transfer line at 240°C. Carrier gas hydrogen, 1 ml/min measured at 210°C. Ion manifold and exit nozzle temperatures of 240°C were used. Column temperature was linearly programmed from 60 to 285°C at 4.3°C/min. Petroleum-ether refers to the fraction with distillation range 70–90°C. Silyl enol ethers were prepared from the corresponding ketones according to described procedures.[18] Titanium tetrachloride was used as a 1 M solution in dichloromethane.

3.2. General procedure for the $TiCl_4$-promoted alkylation of silyl enol ethers with epoxides. Synthesis of 3,3-dimethyl-4-(2-hydroxyethyl)-cyclopent-3-en-1-one (19)

To a cold (−78°C) solution of **9** (860 mg; 3.97 mmol) and ethylene oxide (396 μL; 7.94 mmol) in CH_2Cl_2 (58 mL), $TiCl_4$ (11.91 mL of 1 M solution; 11.91 mmol) was added dropwise, with stirring under an argon atmosphere. After the addition was complete, the reaction mixture was allowed to reach −60°C. After 2 h the initially dark-red colored reaction mixture turned faint-pink, when the reaction was quenched with H_2O (20 mL). The CH_2Cl_2 layer was separated, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extract was evaporated under reduced pressure. The crude reaction product was dissolved in CH_3CN (30 mL), and stirred for 2 h at room temperature with few drops of dilute aqueous HF. The reaction mixture was partitioned between water and CH_2Cl_2, the organic extract was washed with dilute aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=9/1) afforded 370 mg (60%) of the *title compound* **19** as a colorless oil; ν_{max} (liquid film): 3403 (br.), 2960, 2871, 1697, 1590, 1046; δ_H: 7.52 (1H, d, J=5.6 Hz, *H*C:CHC:O), 6.05 (1H, d, J=5.6 Hz,:C*H*C:O), 3.92–3.76 (3H, m, CH_2OH), 2.26–2.19 (1H, m, *H*CC:O), 1.81–1.74 (2H, m, C$H_2$$CH_2$OH), 1.26 (3H, s, C$H_3$), 1.07 (3H, s, C$H_3$); δ_C: 212.8 (C), 173.5 (CH), 129.9 (CH), 62.4 (CH_2), 56.8 (CH), 44.8 (C), 28.6 (CH_2), 26.9 (CH_3), 24.7 (CH_3); MS (CI, isobutane): 155 $(M+1)^+$, 137 $(M+1-H_2O)^+$; HRMS (EI): M^+, found 154.0997. $C_9H_{14}O_2$ requires 154.0994.

3.2.1. 2-(2-Hydroxyethyl)-cyclopentanone (2). This compound was prepared from cyclopentanone TMS–enol ether **1** according to the general procedure. Purification by dry-flash chromatography (eluent: benzene/ethyl acetate=4/1) afforded the *title compound* **2** in 46% yield, as a colorless oil. ^1H NMR and IR spectra consistent with the literature.[19] ^{13}C NMR spectrum of this compound has not been reported: δ_C: 222.8 (C), 61.4 (CH_2), 47.7 (CH), 38.0 (CH_2), 32.4 (CH_2), 30.1 (CH_2), 20.9 (CH_2).

3.2.2. 1-Methoxy-9-oxabicyclo[4.3.0]nonane (15). The reaction of cyclohexanone TMS–enol ether **5** with ethylene oxide was performed according to the general procedure. The crude reaction product was dissolved in CH_2Cl_2/methanol (3/1), a catalytic quantity of *p*-toluenesulfonic acid was added, and the reaction mixture was stirred 2 h at rt, then diluted with CH_2Cl_2, washed with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The product was unsuitable for purification on SiO_2 column, due to hydrolytic instability on silica. However, a small amount of **15** was purified by dry-flash chromatography (eluent: petroleum-ether/acetone=19/1), to afford a colorless oil; yield determined by GC was 55%. ^1H NMR and IR spectra consistent with the literature.[20] ^{13}C NMR spectrum of this compound has not been reported: δ_C: 107.0 (C), 65.6 (CH_2), 47.5 (CH_3), 43.0 (CH), 30.5 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 24.5 (CH_2), 22.8 (CH_2).

3.2.3. 1-Methoxy-6-methyl-9-oxabicyclo[4.3.0]nonane (16). This compound was obtained from 2-methylcyclohexanone TMS–enol ether **6** and ethylene oxide, according to the general procedure and the modification described for the preparation of **15** (the preceeding procedure). Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=19/5 to 9/1) gave the *title compound* **16** as a colorless oil in 41% yield (78% yield calculated on the basis of recovered 2-methylcyclohexanone). ν_{max} (liquid film): 2922, 2853, 1463, 1378, 1096, 1026; δ_H: 4.00–3.75 (2H, m, OCH_2), 3.20 (3H, s, OCH_3), 2.20–1.95 (2H, m, OCH_2CH_2), 1.70–1.30 (8H, m, $CH_2CH_2CH_2CH_2$), 1.10 (3H, s, CCH_3); δ_C: 107.1 (C), 64.1 (CH_2), 47.3 (CH_3), 44.1 (C), 38.5 (CH_2), 36.7 (CH_2), 27.0 (CH_2), 23.0 (CH_2), 21.8 (CH_2), 18.7 (CH_3); MS (CI, isobutane): 171 $(M+1)^+$,

139 $(M+1-CH_3OH)^+$; HRMS (EI): $M-CH_3OH^+$, found 138.1046. $C_9H_{14}O$ requires 138.1045.

3.2.4. 2,2-Dimethyl-6-hydroxy-3-hexanone (17). This compound was obtained from pinacolone TMS–enol ether **7** according to the general procedure. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=9/1) gave the *title compound* **17** as a colorless oil in 61% yield. ^{1}H NMR and IR spectra consistent with the literature.[21] ^{13}C NMR spectrum of this compound has not been reported: δ_C: 216.7 (C), 61.7 (CH_2), 43.9 (C), 33.0 (CH_2), 26.5 (CH_2), 26.2 (CH_3).

3.2.5. 3-(2-Hydroxyethyl)-camphor (18). This compound was obtained from camphor TMS–ether **8** according to the general procedure. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=9/1 to 4/1) gave the *title compound* **18** as a colorless oil, in 22% yield (65% yield calculated on the basis of recovered camphor; isolated as an inseparable 1:1 mixture of diastereoisomers). ν_{max} (liquid film): 3441 (br.), 2959, 2873, 1738, 1053; δ_H: 3.83–3.64 (2H, m), 3.25 (br. s), 3.06 (br. s), δ3.25+δ3.06=1H, 2.50 (br. dt, J_1=8.2 Hz, J_2=4.1 Hz), 2.09–1.26 (m), from δ2.50 to δ1.26: 8H, 1.01 (s), 0.94 (s), 0.92 (s), 0.92 (s), 0.90 (s), 0.86 (s), 9H for 6 singlets; δ_C: 223.6 (C), 223.4 (C), 62.4 (CH_2), 61.9 (CH_2), 58.9 (C), 57.7 (C), 53.6 (CH), 48.8 (CH), 48.4 (CH), 47.5 (CH), 46.8 (C), 46.0 (C), 35.0 (CH_2), 31.0 (CH_2), 30.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 21.6 (CH_3), 20.4 (CH_2), 20.2 (CH_3), 19.4 (CH_3), 19.0 (CH_3), 9.4 (CH_3), 9.3 (CH_3); HRMS (EI): M^+, found 196.1471. $C_{12}H_{20}O_2$ requires 196.1463.

3.2.6. 6-(2-Hydroxyethyl)-3-methylcyclohex-2-en-1-one (20). This compound was prepared from 3-methylcyclohex-2-enone TMS–enol ether **10** according to the general procedure. Purification by dry-flash chromatography (eluent: petroleum-ether/ethyl acetate=3/1) gave the *title compound* **20** in 60% yield, as a colorless oil; ν_{max}(liquid film): 3421 (br.), 2917, 2867, 1662, 1435, 1382, 1059, 1029; δ_H: 5.90 (1H, br. s, C:C*H*C:O), 3.84–3.62 (2H, m, CH_2OH), 3.10 (1H, br. s, O*H*), 2.48–2.30 (3H, m, C:CCH_2+O:CC*H*), 2.16–2.00 (2H, m, CH_2CH$_2$OH), 1.95 (3H, br. s, CH_3), 1.90–1.70 (1H, m, C:CCH_AH$_B$), 1.72–1.53 (1H, m, C:CCH$_A$$H_B$); δ_C: 202.9 (C) 163.0 (C), 126.2 (CH), 61.4 (CH_2), 44.2 (CH), 33.1 (CH_2), 30.7 (CH_2), 29.1 (CH_2), 24.2 (CH_3); HRMS (CI, NH_3): MH^+, found 155.1069. $C_9H_{15}O_2$ requires 155.1072.

3.2.7. 6-(2-Hydroxyethyl)-3,5,5-trimethylcyclohex-2-enone (21). This compound was prepared from isophorone TMS–enol ether **11** according to the general procedure. Purification by dry-flash chromatography (eluent: benzene/ethyl acetate=9/1 to 4/1) gave the *title compound* **21** in 77% yield, as a colorless oil; ν_{max}(liquid film): 3425 (br.), 2960, 2932, 1722, 1662, 1436, 1381, 1051; δ_H: 5.88 (1H, d, J=1.4 Hz,:C*H*C:O), 3.65 (2H, app. q, J=6 Hz, CH_2OH), 2.20 (3H, m, O:CC*H*+C:CMeCH_2), 1.94 (3H, s, C:CCH_3), 1.76 (2H, m, HOCH$_2$CH_2), 1.07 (3H, s, CH_3), 0.92 (3H, s, CH_3); δ_C: 203.5 (C), 159.9 (C), 124.8 (CH), 61.8 (CH_2), 54.4 (CH), 44.9 (CH_2), 36.2 (C), 28.5 (CH_3), 27.8 (CH_2), 24.1 (CH_3), 23.2 (CH_3); HRMS (EI): M^+, found 182.13096. $C_{11}H_{18}O_2$ requires 182.13068.

3.2.8. 2-(2-Hydroxyethyl)-1-tetralone (23). This compound was prepared from 1-tetralone TMS–enol ether **13** according to the general procedure. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=9/1 to 4/1) gave the *title compound* **23** in 38% yield, (79% yield calculated on the basis of recovered 1-tetralone), as a colorless oil; ν_{max}(liquid film): 3500 (br.), 2936, 1680, 1600, 1455, 1231, 741; δ_H: 8.04 (1H, dd, J_1=7.9 Hz, J_2=1.1 Hz, *o*-Ar*H*), 7.48 (1H, dt, J_1=7.4 Hz, J_2=1.6 Hz, *p*-Ar*H*), 7.34–7.23 (2H, m, *m*-Ar*H*), 3.87–3.61 (2H, m, CH_2OH), 3.07–3.00 (2H, m, ArCH_2), 2.81–2.63 (2H, m, O:CC*H*+O*H*), 2.32–2.12 (2H, m, ArCH$_2$CH_2), 2.06–1.67 (2H, m, HOCH$_2$CH_2); δ_C: 201.2 (C), 144.1 (C), 133.2 (CH), 132.1 (C), 128.5 (CH), 127.2 (CH), 126.4 (CH), 60.5 (CH_2), 45.1 (CH), 32.8 (CH_2), 29.0 (CH_2), 28.5 (CH_2); MS (CI, isobutane): 191 $(M+1)^+$, 173 $(M+1-H_2O)^+$; HRMS (EI): $M-H_2O^+$, found 172.0890. $C_{12}H_{12}O$ requires 172.0888.

3.2.9. 16-(2-Hydroxyethyl)-androsterone acetate (24). This compound was prepared from androsterone acetate TMS–enol ether **14** according to the general procedure. Purification of the crude reaction mixture by column chromatography (eluent: petroleum-ether/ethyl acetate=9/1 to 4/1) afforded chloroacetal **25** (first eluted, 44% yield), followed by **24** (29% yield). The compound **25** (40.6 mg) was dissolved in THF/water (15/1), few drops of HCl aq. were added, and the reaction mixture was stirred for 3 h at rt. Standard work-up afforded 32.3 mg (93%) of **24**. Crystallization of combined fractions of **24** from dichloromethane/*n*-hexane afforded the *title compound* as white crystals (combined yield 70%). Physical data for **24**: mp 169–171°C. ν_{max} (KBr): 3528 (br.), 2938, 1725, 1254, 1029; δ_H: 4.69 (1H, m, AcOC*H*), 3.82–3.60 (2H, m, CH_2OH), 2.62 (1H, br. q, J=8 Hz, O:CC*H*), 2.03 (3H, s, CH_3COO), 1.97–0.98 (21H, m), 0.92 (3H, s, CCH_3), 0.85 (3H, s, CCH_3), 0.79–0.63 (1H, m); δ_C: 223.6 (C), 170.7 (C), 73.5 (CH), 61.5 (CH_2), 54.2 (CH), 49.1 (CH), 48.6 (C), 44.6 (CH), 42.5 (CH), 36.6 (CH_2), 35.6 (CH), 34.9 (C), 34.4 (CH_2), 33.8 (CH_2), 31.6 (CH_2), 30.6 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 27.3 (CH_2), 21.4 (CH_3), 20.3 (CH_2), 14.5 (CH_3), 12.1 (CH_3); HRMS (CI, NH_3): MH^+, found 377.2705. $C_{23}H_{37}O_4^+$ requires 377.2692. Physical data for **25**: mp 124–127°C. ν_{max}(KBr): 2975, 2944, 2928, 2913, 2893, 2861, 2851, 1737, 1451, 1388, 1368, 1251, 1104, 1052, 1028; δ_H: 4.68 (1H, m, AcOC*H*), 3.98–3.78 (3H, m, OCH_2CH$_2$CH+OCH_AH$_B$CH$_2$Cl), 3.75–3.61 (1H, m, OCH$_A$$H_BCH_2$Cl), 3.55 (2H, t, J=5.9 Hz, ClCH_2), 2.58–2.43 (1H, m), 2.38–2.20 (1H, m), 2.02 (3H, s, CH_3COO), 1.90–0.93 (20H, m), 0.89 (3H, s, CH_3), 0.82 (3H, s, CH_3); δ_C: 170.6 (C), 119.7 (C), 73.6 (CH), 68.6 (CH_2), 62.9 (CH_2), 53.8 (CH), 49.8 (CH), 46.3 (C), 46.1 (CH), 44.5 (CH), 43.8 (CH_2), 36.6 (CH_2), 35.4 (C), 35.0 (CH), 34.3 (CH_2), 33.8 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 31.4 (CH_2), 28.3 (CH_2), 27.3 (CH_2), 21.4 (CH_3), 20.6 (CH_2), 14.5 (CH_3), 12.1 (CH_3); MS (CI, isobutane): 441, 439 $(M+1)^+$, 379 $(M+1-AcOH)^+$, 358.

3.2.10. 2,2,5-Trimethyl-6-hydroxy-3-hexanone (27) and 2,2-dimethyl-6-hydroxy-3-heptanone (28). These compounds were obtained according to the general procedure, from pinacolone TMS–enol ether **26** and propene oxide. The compounds could not been separated by TLC; purification by dry-flash chromatography (eluent: petroleum-ether/

ethyl acetate=39/1 to 4/1) gave the mixture of the *title compounds* **27**+**28** as a colorless oil. Compound **28** has been described in the literature.[19] Spectral data for the mixture of isomers: ν_{max}(liquid film): 3416 (br.), 2967, 2874, 1704, 1479, 1062, 1043; δ_H: 3.84–3.74 (1H, m, **28**, *H*COH), 3.53 (1H, dd, J_1=11.5 Hz, J_2=6.4 Hz, **27**, C*H*$_A$H$_B$OH), 3.40 (1H, dd, J_1=11.5 Hz, J_2=7.5 Hz, **27**, CH$_A$*H*$_B$OH), 2.65 (2H, t, J=7.2 Hz, **28**, O:CC*H*$_2$), 2.52 (2H, dd, J_1=20.1 Hz, J_2=6.4 Hz, **27**, O:CC*H*$_2$), 2.23 (1H, oct., J=6.4 Hz, **27**, CH$_2$C*H*(Me)CH$_2$OH), 1.75–1.65 (2H, m, **28**, O:CCH$_2$C*H*$_2$), 1.20 (3H, d, J=6.1 Hz, **28**, *H*$_3$CCHOH), 1.15 (9H, s, **28**, *t*-Bu), 1.14 (9H, s, **27**, *t*-Bu), 0.91 (3H, d, J=6.8 Hz, **27**, O:CCH$_2$CHC*H*$_3$); δ_C: 217.1 (C, **28**), 216.5 (C, **27**), 67.7 (CH$_2$, **27**), 67.4 (CH, **28**), 44.2 (C), 40.7 (CH$_2$, **27**), 32.9 (CH$_2$, **28**), 32.8 (CH$_2$, **28**), 31.5 (CH, **27**), 26.4 (3×CH$_3$, **28**), 26.2 (3×CH$_3$, **27**), 23.6 (CH$_3$, **28**), 16.9 (CH$_3$, **27**); one quaternary signal is missing, or is superimposed with the peak at 44.19; MS (CI, isobutane): 159 (M+1)$^+$, 141 (M+1−H$_2$O)$^+$; HRMS (CI, NH$_3$): MNH$_4^+$, found 176.1652. C$_9$H$_{22}$NO$_2$ requires 176.1651.

3.2.11. 2,2,5-Trimethyl-6-acetoxy-3-hexanone (29) and 2,2-dimethyl-6-acetoxy-3-heptanone (30). Same as above, with the following modification: the crude reaction mixture was treated with excess acetic anhydride/pyridine/DMAP in CH$_2$Cl$_2$ at rt. After the standard work-up, purification by dry-flash chromatography (eluent: *n*-hexane/ethyl acetate=19/1 to 9/1) afforded the mixture of the *title compounds* **29** and **30** as a colorless oil (**29**:**30**=2.8:1, determined by GC). Spectral data for the mixture of isomers: ν_{max}(liquid film): 2970, 1739, 1707, 1369, 1243, 1039; δ_H: 4.38 (1H, sext., J=6.3 Hz, **30**, AcOC*H*), 3.90 (1H, dd, J_1=12.0 Hz, J_2=6.3 Hz, **29**, AcOC*H*$_A$H$_B$), 3.77 (1H, dd, J_1=12.0 Hz, J_2=6.3 Hz, **29**, AcOCH$_A$*H*$_B$), 2.63–2.32 (5H, m, **29** O:CC*H*$_2$C*H*CH$_3$+**30** O:CC*H*$_2$), 2.06 (3H, s, **29**, C*H*$_3$COO), 2.04 (3H, s, **30**, C*H*$_3$COO), 1.92–1.68 (2H, m, **30**, O:CCH$_2$C*H*$_2$), 1.24 (3H, d, J=6.3 Hz, **30**, AcOCHC*H*$_3$), 1.14 (18H, s, **29**+**30**, *t*-Bu), 0.92 (3H, d, J=6.7 Hz, **29**, AcOCHC*H*$_3$); δ_C: 171.1 (C, **29**), 170.6 (C, **30**), 70.4 (CH, **30**), 68.7 (CH$_2$, **29**), 44.1 (C), 40.1 (CH$_2$, **29**), 32.2 (CH$_2$, **30**), 29.9 (CH$_2$, **30**), 28.2 (CH, **29**), 26.3 (3×CH$_3$, **30**), 26.1 (3×CH$_3$, **29**), 21.2 (CH$_3$, **30**), 20.9 (CH$_3$, **29**), 20.1 (CH$_3$, **30**), 16.9 (CH$_3$, **29**); two signals corresponding to the ketone carbonyls and one quaternary signal (*t*-Bu) were not detected under the recording conditions; MS (CI, isobutane): 201 (M+1)$^+$, 141 (M+1−AcOH)$^+$.

3.2.12. 2-(1-Hydroxy-2-propyl)-1-tetralone (31). This compound was prepared according to the general procedure, starting from 2-tetralone TMS–enol ether **13** and propene oxide. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=39/1 to 4/1) gave the *title compound* **31** as a colorless oil in 36% yield (56% yield based on the recovered 2-tetralone; isolated as inseparable 2:1 mixture of diastereoisomers). ν_{max}(liquid film): 3406 (br.), 2935, 2875, 1682, 1600, 1455, 1225, 1046, 746; δ_H: 8.00 (1H, d, J=7.0 Hz, *o*-Ar*H*), 7.45 (1H, t, J=7.0 Hz, *p*-Ar*H*), 7.24 (2H, m, *m*-Ar*H*), 3.68–3.48 (2H, m, C*H*$_2$OH), 3.00 (2H, m, ArC*H*$_2$), 2.83–2.42 (2H, m, ArC(O)C*H*+O*H*), 2.23–1.84 (3H, m, ArCH$_2$C*H*$_2$+HOCH$_2$C*H*), 1.01 (d, J=6.6 Hz, C*H*$_3$), 0.95 (d, J=6.6 Hz, C*H*$_3$), δ1.01+δ0.95=3H; δ_C: 204.1 (C), 200.6 (C), 144.0 (C), 133.3 (CH), 133.2 (CH), 132.8 (C), 132.7 (C), 128.6 (CH), 128.5 (CH), 127.5 (C), 127.4 (CH), 127.3 (CH), 126.5 (CH), 126.5 (CH), 65.9 (CH$_2$), 65.6 (CH$_2$), 51.3 (CH), 48.6 (CH), 35.5 (CH), 34.0 (CH), 29.3 (CH$_2$), 29.4 (CH$_2$), 25.2 (CH$_2$), 23.5 (CH$_2$), 13.8 (CH$_3$), 13.0 (CH$_3$); MS (CI, isobutane): 205 (M+1)$^+$, 187 (M+1−H$_2$O)$^+$. Due to the instability of the compound **31**, for the purpose of HRM spectra this compound was converted to the corresponding acetate. MS (CI, NH$_3$): 264 (M+NH$_4$)$^+$, 247 (M+1)$^+$; HRMS (EI): M−AcOH$^+$, found 186.1040. C$_{13}$H$_{14}$O$^+$ requires 186.1045.

3.2.13. 2-(1-Chloro-2-hydroxy-3-propyl)-1-tetralone (32). This compound was prepared according to the general procedure starting from 2-tetralone TMS–enol ether **13** and epichlorohydrin. Purification by dry-flash chromatography (eluent: petroleum-ether/ethyl acetate=975/25 to 85/15) gave the *title compound* **32** in 54% yield (1:1 inseparable mixture of diastereoisomers) as white powder, mp 58–59°C; [Found: C, 65.20; H, 6.11. C$_{13}$H$_{15}$ClO$_2$ requires C, 65.41, H 6,.33]; ν_{max}(KBr): 3436 (br.), 2361, 1682, 1670, 1599, 740; δ_H: 8.06–8.00 (1H, m, *o*-Ar*H*), 7.49 (1H, app. tt, J_1=7.5 Hz, J_2=1.8 Hz, *p*-Ar*H*), 7.35–7.24 (2H, m, *m*-Ar*H*), 4.13 (br. s, O*H*), 4.01 (br. s+m, O*H*+C*H*OH), δ4.13+δ4.01=2H, 3.68–3.50 (2H, m, C*H*$_2$Cl), 3.20–2.95 (2H, m, ArC*H*$_2$); 2.87–2.71 (1H, m, O:CC*H*), 2.32–1.66 (4H, m, ArCH$_2$-C*H*$_2$+O:CCHC*H*$_2$CHOH); δ_C: 201.6 (C), 201.2 (C), 144.2 (C), 144.0 (C), 133.6 (CH), 133.4 (CH), 132.0 (C), 128.6 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 126.5 (CH), 70.1 (CH), 69.6 (CH), 49.9 (CH$_2$), 49.6 (CH$_2$), 45.6 (CH), 44.0 (CH), 35.0 (CH$_2$), 34.7 (CH$_2$), 30.0 (CH$_2$), 29.8 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$); GC/MS: two peaks in 1:1 ratio; R_t 31.87 min, 239, 241 (M+1)$^+$; R_t 32.25 min, 239, 241 (M+1)$^+$.

3.2.14. 2-(1-Chloro-2-hydroxy-3-propyl)-cyclopentanone (33). This compound was prepared according to the general procedure starting from cyclopentanone TMS–enol ether **1** and epichlorohydrin. Purification by dry-flash chromatography (eluent: petroleum-ether/acetone=39/1 to 4/1) afforded **34** (first eluted), followed by **33**. The compound **34** was hydrolysed into **33** under the conditions described for **24**, affording the *title compound* **33** in 40% combined yield (1:1 inseparable mixture of diastereoisomers) as a colorless oil; ν_{max}(liquid film): 3419 (br.), 2955, 2873, 1732, 1405, 1159, 1073, 1050; δ_H: 4.12–4.01 (m, C*H*OH), 3.95–3.76 (m, C*H*OH), δ4.12–3.76=1H, 3.65–3.46 (2H, m, C*H*$_2$Cl), 3.08 (1H, br. s, O*H*), 2.64–1.26 (9H, m); δ_C: 223.0 (C), 222.1 (C), 70.4 (CH), 69.6 (CH), 49.7 (CH$_2$), 49.4 (CH$_2$), 47.4 (CH), 45.9 (CH), 37.8 (CH$_2$), 37.7 (CH$_2$), 34.1 (CH$_2$), 33.5 (CH$_2$), 30.3 (CH$_2$), 30.2 (CH$_2$), 20.8 (CH$_2$), 20.8 (CH$_2$); HRMS (EI): M$^+$, found 176.0601. C$_8$H$_{13}$ClO$_2^+$ requires 176.0604.

3.3. Attempted alkylation of silyl enol ethers with ethylene oxide using other Lewis acid catalysts

These reactions were performed with cyclopentanone TMS–enol ether **1**, according to the general procedure, with the following modifications: TMSI, TMSOTf, BF$_3$·Et$_2$O, SnCl$_4$, Ti(O^{i}Pr)$_4$, Cp$_2$TiCl$_2$ and (^{i}PrO)$_2$TiCl$_2$ were used as catalysts instead of TiCl$_4$, and the reaction mixtures were allowed to reach the room temperature before quenching. In the (^{i}PrO)$_2$TiCl$_2$-promoted reaction the

compound **2** was isolated in 15% yield. In all the other reactions no traces of **2** could be detected.

3.4. Attempted reaction of α-tetralone Ti-enolate (35) with ethylene oxide

To a cold (−78°C) solution of α-tetralone (267 mg; 1.83 mmol) in CH_2Cl_2 (8.2 mL) a solution of $TiCl_4$ in CH_2Cl_2 (2.01 mL; 2.01 mmol) was added dropwise, with stirring under an argon atmosphere. After 2 min DIPEA (375 μL; 2.19 mmol) was added dropwise, and the resulting dark-red solution was stirred 1.5 h at −78°C. Ethylene oxide (109 μL; 2.19 mmol) was added dropwise, the reaction mixture was allowed to reach room temperature, when quenched by the addition of saturated aqueous NH_4Cl (9 mL). The crude reaction product consisted mostly of recovered α-tetralone, where no product **23** could be detected.

In the control experiment isobutyraldehyde (200 μL; 2.19 mmol) was added instead of ethylene oxide, and the reaction mixture was quenched at −55°C. Standard work-up afforded aldol **36** (233.8 mg; 59% yield, single diastereoisomer), thus confirming the formation of the Ti-enolate under the conditions employed. Spectral data for **36**: Yellow solid; ν_{max} (liquid film): 3494 (br.), 2959, 2933, 2873, 1666, 1600, 1457, 1242, 1227, 991; δ_H: 8.00 (1H, dd, J_1=7.7 Hz, J_2=0.9 Hz, *o*-Ar*H*), 7.48 (1H, dt, J_1=6.7 Hz, J_2=1.5 Hz, *p*-Ar*H*), 7.44–7.21 (2H, m, 2 *m*-Ar*H*), 4.60 (1H, br. s, O*H*), 3.76 (1H, dd, J_1=7.8 Hz, J_2=3.5 Hz, C*H*OH), 3.04–2.97 (2H, m, O:CC*H*+ArCH_AH$_B$), 2.63–2.50 (1H, m, ArCH$_A$*H*$_B$), 2.21–2.12 (1H, m, C*H*Me$_2$), 1.97–1.80 (2H, m, ArCH$_2$C*H*$_2$), 1.06 (3H, d, *J*=6.7 Hz, C*H*$_3$), 0.96 (3H, d, *J*=6.9 Hz, C*H*$_3$); δ_C: 202.9 (C), 144.0 (C), 133.7 (CH), 132.4 (C), 128.5 (CH), 127.2 (CH), 126.6 (CH), 75.7 (CH), 50.6 (CH), 29.4 (CH), 28.7 (CH$_2$), 25.6 (CH$_2$), 19.9 (CH$_3$), 14.7 (CH$_3$); GC/MS: R_t 27.11 min, 219 $(M+1)^+$; HRMS (FAB): $M+1^+$, found 219.1369. $C_{14}H_{19}O_2$ requires 219.1385.

References

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