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Mild acetalisation of mono and dicarbonyl compounds catalysed by titanium tetrachloride. Facile synthesis of β-keto enol ethers

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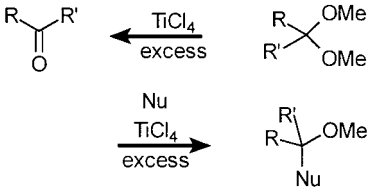
Abstract—The use of $TiCl_4$, as a catalyst for the acetalisation, at room temperature, of carbonyl compounds is reported. Cyclic ketones and cyclic 1,4-diketones easily afford dimethyl acetals, but cyclic 1,3-diketones give β-keto enol ethers. Additionally, aryl ketones and acyclic ketones failed to react. β-keto aldehydes can be monoprotected either as β-keto enol ethers or β-keto dimethyl acetals depending on the reaction time and catalyst amount. Some mechanistic features are accounted for.

1. Introduction

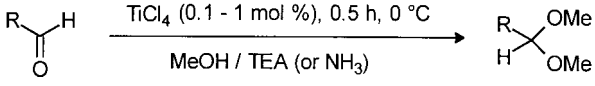
Acetals are not only the most widely used protective groups for carbonyl compounds,[1] but they have also been increasingly employed as efficient chiral auxiliaries for the synthesis of enantiomerically pure compounds.[2] In recent years several transition metal complexes have been shown[3] to offer major advantages over general Bronsted acid catalysis, but the search for new Lewis acid catalysts, to generate acetals under aprotic and milder conditions, is still actively pursued.

$TiCl_4$, when used in slight excess, either converts dimethyl and cyclic acetals to the corresponding carbonyl compounds[4] or has proven to be the Lewis acid of choice[2,5] to activate the addition of carbon nucleophiles to acetals, via a direct displacement of a $TiCl_4$–ether complex and/or a prior formation of an oxocarbenium ion[5,6] (Eq. (1)).



(1)

On the contrary, as we recently reported,[7] a catalytic amount of $TiCl_4$ in methanol solution containing triethylamine (TEA) or ammonia gas easily converts aliphatic, α,β-unsaturated and aromatic aldehydes to the corresponding acetals under very mild reaction conditions (Eq. (2)).



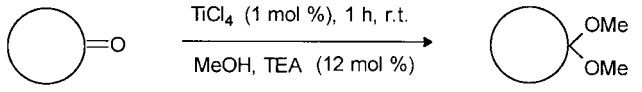
(2)

As the yields are very good and the reactions very simple to perform, it was of interest to further investigate the extent of applicability of this protocol with ketones and dicarbonyl compounds.

The results herein reported widen the use of $TiCl_4$ as a highly efficient and chemoselective catalyst for acetalisation reactions, and emphasise the sharp contrast between aldehydes and ketones.

2. Results and discussion

The cycloalkanones of Table 1, when allowed to react for 1 h at room temperature in a methanolic solution containing 1 mol% of $TiCl_4$ and 12 mol% of TEA, gave the corresponding dimethyl acetals **1–12** in good to excellent yields (Eq. (3)).



1-12

(3)

In line with the mechanism already proposed,[7] the efficiency of the catalytic cycle will depend on the ability of $TiCl_4$ to act both as a dehydrating agent and as a template for the

Keywords: acetalisation; titanium tetrachloride; cyclic ketones; 1,3-dicarbonyl compounds; β-keto enol ethers.

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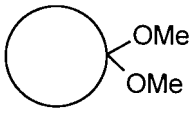
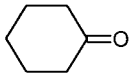
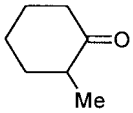
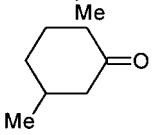
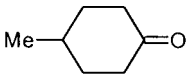
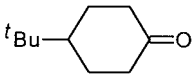
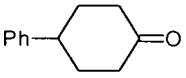
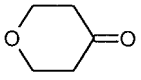
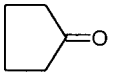
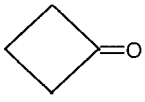
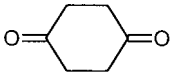
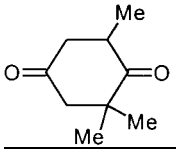
Table 1. $TiCl_4$/TEA Catalysed acetalisation of aliphatic cyclic ketones

Ketone		Conversion (%)[a]	Isolated yield (%)
	**1**	95	83[b]
	**2**	49	
	**3**	88	80[c]
	**4**	90	85[c]
	**5**	quant.	95[b]
	**6**	90	84[c]
	**7**	quant.	97[b]
	**8**	75	
	**9**	quant.	95[b]
	**10**+**11**	quant.[d]	96[b]
	**12**[e]	84[f]	78[c]

[a] Conversion was determined by ^1H NMR analysis of the crude reaction mixture (the remainder to 100% was the starting ketone).
[b] When the conversion was ≥95%, isolated yields (%) refer to the recovered crude acetal without further purification.
[c] Purified by Kugelrohr distillation.
[d] GC analysis of the crude acetal revealed the presence of dimethyl acetal **10** (10%) and of tetramethyl acetal **11** (90%).
[e] Acetalisation occurred only at the less hindered 4-position.
[f] NH_3 gas, instead of TEA, was used.[7] TEA gave a lower conversion.

simultaneous activation of the carbonyl compound and of MeOH before coupling. Small differences in steric and electronic properties of the carbonyl impact upon the metal ion's ability to allow formation of the reactive intermediate. As a consequence, the equatorial[8] 2-Me group of 2-Me-cyclohexanone sterically interferes with the Ti(IV)–carbonyl oxygen complexation, lowering the yield of acetal **2** with respect to the other cyclic ketones having a substituent remote from the reaction centre.

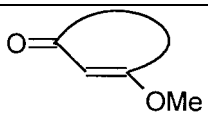
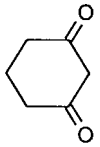
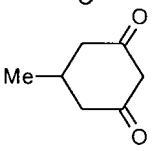
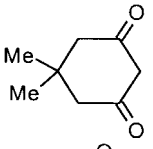
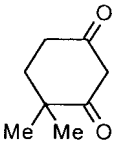
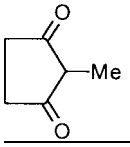
A result which is noteworthy, based on the sensitivity to steric hindrance, is the clean regioselective monoacetalisation of 2,2,6-trimethylcyclohexan-1,4-dione at the less hindered 4-position, whereas cyclohexan-1,4-dione gives 90% conversion to the tetramethylacetal **11** and only 10% conversion to the monoprotected ketone **10**.

The more sterically hindered aromatic ketones (e.g. acetophenone, propiophenone) and the conformationally more flexible acyclic ketones (e.g. 2-butanone, 2-hexanone) failed to react.

Importantly, the synthetic restriction regarding these ketones allows the use of $TiCl_4$ as a specific acetalisation catalyst to selectively protect a carbonyl group in the presence of another more sterically hindered carbonyl unit.

In fact, as expected, intermolecular competitive acetalisation

Table 2. $TiCl_4$-Catalysed synthesis of β-methoxycycloalkenones from 1,3-cycloalkanediones

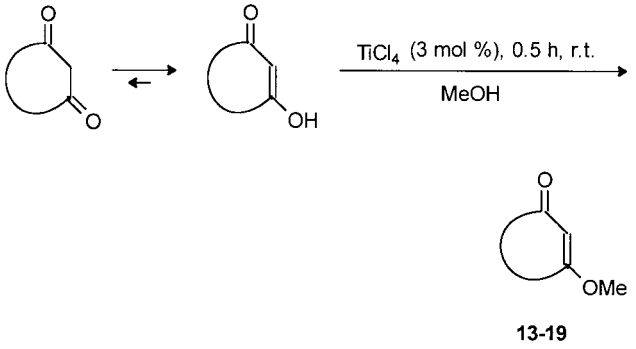
β-Diketone		Isolated yield (%)[a]
	**13**	95
	**14**	90
	**15**	97
	**16**+**17** (77:23)	96[b]
	**18**	92
	**19**	80

[a] Yields (%), based on the starting substrate, refer to the crude recovered product, which always showed an ^1H NMR purity ≥95%.

[b] ^1H NMR analysis revealed a 77:23 mixture of 3-methoxy-6,6-dimethylcyclohex-2-enone **16** and of 3-methyl-4,4-dimethylcyclohex-2-enone **17**.

of a 1:1 mixture of either benzaldehyde/acetophenone or 4-^{t}Bu-cyclohexanone/acetophenone delivered only the benzaldehyde or the 4-^{t}Bu-cyclohexanone dimethyl acetals (conversion >95%) and a 1:1 mixture of cyclohexanone/2-hexanone afforded a 92:8 mixture of cyclohexanone/2-hexanone dimethyl acetals.

We next investigated the acetalisation reaction of β-dicarbonyl compounds. Treatment of cycloalkane-1,3-diones of Table 2 with a 3 mol% of $TiCl_4$ in a methanolic solution, for half an hour at room temperature, invariably afforded the corresponding β-methoxycycloalkenones **13**–**19** in very high yields, rather than β-keto dimethyl acetals (Eq. (4)).

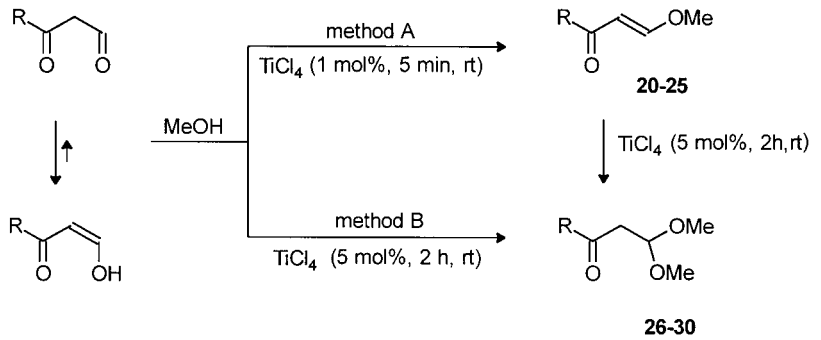


13-19 (4)

4,4-Dimethyl-1,3-cyclohexanedione afforded a 77:23 mixture of 3-methoxy-6,6-dimethylcyclohex-2-enone **16**/3-methoxy-4,4-dimethylcyclohexen-2-one **17**. Addition of NH_3[7] gas to the reaction mixture did not substantially change the yields of enol ethers, but increased the isomers ratio **16**:**17** to 96/4.

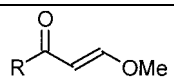
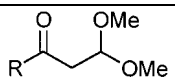
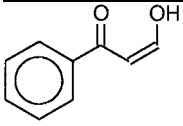
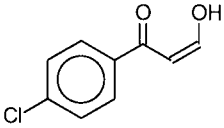
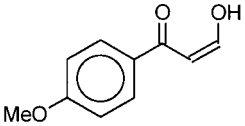
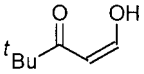
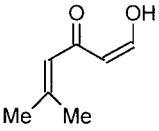
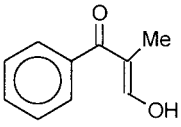
The $TiCl_4$-catalysed synthesis of these compounds is simpler, milder and higher yielding than the previously reported techniques for the preparation of the same compounds. Compounds **13**–**19** are key intermediates in organic synthesis[9–12] and they have been usually prepared starting from cyclic-β-diketones with diazomethane[9] or prolonged reflux under acid catalysis[10] and from 3-Cl-cycloalkenones with methoxide.[11,12]

However, open chain aliphatic and aromatic 1,3-diketones (e.g. dibenzoylmethane, acetylacetone, benzoylacetone) remained unaffected under the reaction conditions used. These compounds exist in solution in the *cis*-enol form[13] and are capable of serving as bidentate ligands in the formation of very stable strongly mesomeric bis(β-diketonato)-$Ti(IV)X_2$ compounds[14] (X=Cl, OR) where the six-coordinative valence of the metal is fully saturated. Thus neither coordination of methanol to the metal, nor regeneration of the catalyst will be possible, *conditio sine qua non* for an efficient catalytic cycle.



Scheme 1.

Table 3. $TiCl_4$-Catalysed synthesis of β-methoxyenones (Method A) or β-keto dimethyl acetals (Method B) from β-keto aldehydes

β-Ketoaldehyde (95% enol form)[15]	Method (reaction time)	Yield (%)[a]		Yield (%)[a]	
	A (5 min) A (2 h) B (5 min) B (2 h)	54 40 50 traces	**20**	6 40 20 95[b]	**26**
	A (10 min) A (2 h) B (5 min) B (2 h)	76 56 61 –	**21**	traces 22 20 95[b]	**27**
	A (5 min) B (2 h)	63 traces	**22**	7 92[b]	**28**
	A (5 min) B (2 h)	78 –	**23**	6 90[b]	**29**
	A (5 min) B (2 h)	70 –	**24**	20 93[b]	**30**
	A (5 min) B (2 h)	95[b] 95[b]	**25**		

[a] Yields (%) are based on ^{1}H NMR analysis of the crude reaction mixture; the difference to 100 was the unreacted aldehyde.
[b] Yields (%) refer to the recovered crude product, which always showed an ^{1}H NMR purity >95%, making further purification unnecessary.

The cyclic 1,3-diones of Table 2 largely exist in the enol form also, but enolization gives 'fixed' *trans*-enols[13] where intramolecular Ti(IV) bonding is sterically impossible. As a consequence fast regeneration of the catalyst, after water[7] and product formation, allows the reaction to proceed.

With β-keto aldehydes acetalisation was very straightforward[15a] (Scheme 1).

All substrates of Table 3 rapidly reacted (5 min) with methanol, at room temperature, in the presence of a 1 mol% of $TiCl_4$ to give the corresponding *trans*-β-methoxyenones **20**–**25** as the almost exclusive products (Method A), but prolonged reaction time (2 h) afforded a mixture of both enol ethers and dimethyl acetals (Table 3). More specifically, an higher amount of catalyst (5 mol%, method B) gave instead, after 2 h, only the β-keto dimethyl acetals **26**–**30** in high yields (≥90%) and high purity (^{1}H NMR, ≥95%), making further purification of the crude products unnecessary. However, 2-methyl-3-oxo-3-phenyl- propionaldehyde constituted an exception since even under the conditions of method B gave the β-methoxyenone **25** with only traces amount of the acetal adduct (vide infra).

As expected, enol ethers **20**–**24**, but not **25**, upon standing 2 h at room temperature in a methanolic solution containing 5 mol% of $TiCl_4$, were quantitatively converted into their dimethyl acetals **26**–**30**.

The very interesting feature of this reaction is that it can be stopped at the stage of enol ethers. These intermediates have seldom been isolated on the way to β-keto acetals either starting from β-keto vinyl chlorides[16] or from the sodium salt of β-keto aldehydes[17] or from β-keto vinyl sulfides.[18] Instead, they have usually been prepared by pyrolysis of the corresponding β-keto dimethyl acetals both under strongly basic[19] or acidic[16,20] catalysis. In a more recent paper,[21] illustrating the synthetic potential of β-methoxy enones, a $Rh_2(OAc)_4$ catalysed procedure starting from diazoketones has been reported.

The failure of cyclic enol ethers **13**–**19** (Table 2) and of the acyclic enol ether **25** (Table 3) to further react with methanol, under the conditions of method B, is in strong contrast with the successful quantitative conversion of enol ethers **20**–**24** into the corresponding dimethyl acetals.

The type of reactivity of *trans*-β-methoxy enones may be strongly affected by varying the rigidity and coplanarity of the conjugated system.[9a] The conjugation is most effective in a near planar system causing significant resonance stabilisation, which is crucial for elimination rather than for further methanol addition.

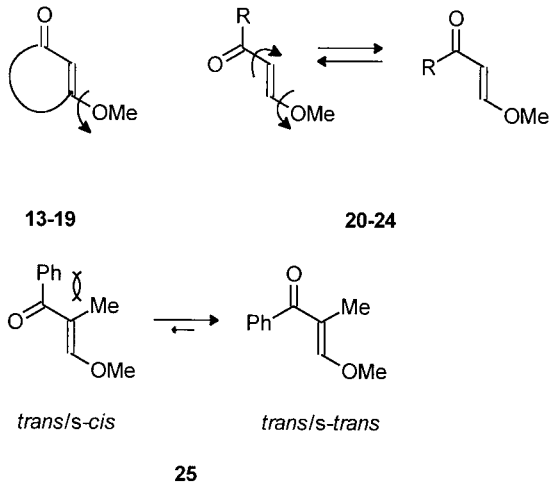


Chart 1.

By comparing enol ethers **20**–**24** with **13**–**19** and **25** (Chart 1), it is clear that **20**–**24** are the least rigid molecules since both the methoxy and the R–CO groups are free to rotate. However, if the substituent in the α-position is a methyl group, instead of an hydrogen atom, the non-bonded interactions with the phenyl group in the *trans*/s-*cis* rotamer **25** dramatically[19b] increase, resulting in an equilibrium shifted towards the energetically favoured *trans*/s-*trans* rotamer, as clearly shown by the ^{1}H NMR spectrum[15b] and NOE experiments[15c] carried out on compound **25**. Because of the restricted rotation around the Csp^2–Csp^2 single bond, the two double bonds in **25** s-*trans* are held nearly coplanar in a favourable position for conjugation, as it is for cyclic enol ethers **13**–**19**, where no part of the conjugated system can rotate.

As a consequence for these near planar and resonance stabilised β-methoxy enones $TiCl_4$-assisted addition-elimination[22,23] at the β-carbon can be observed. In fact, we proved that both **13** and **25** reacted with ethanol or deuterated methanol, under conditions of method B, yielding the corresponding ethyl (**25A** and **13A**) or deuterated methyl enol ethers (**25B** and **13B**) in almost quantitative yields (>95%) according to Scheme 2 (shown for **25**).

However, when **25** was allowed to react in a CH_2Cl_2 solution containing 1.4 equiv. of D,L-2,3-butanediol and 5 mol% of $TiCl_4$, the more stable 1,3-dioxolane **31** was obtained in 85% yield, via internal displacement of methanol. Under comparable experimental conditions, enol ether **13** gave instead a mixture of 1,3-cyclohexanedione mono- and bis-cyclic acetal,[24] even starting from an equimolar amount of D,L-2,3-butanediol. Thus 1,3-diketones of Table 2 can be selectively monoprotected as enol ethers but double protection occurs in the formation of cyclic acetals.

3. Conclusions

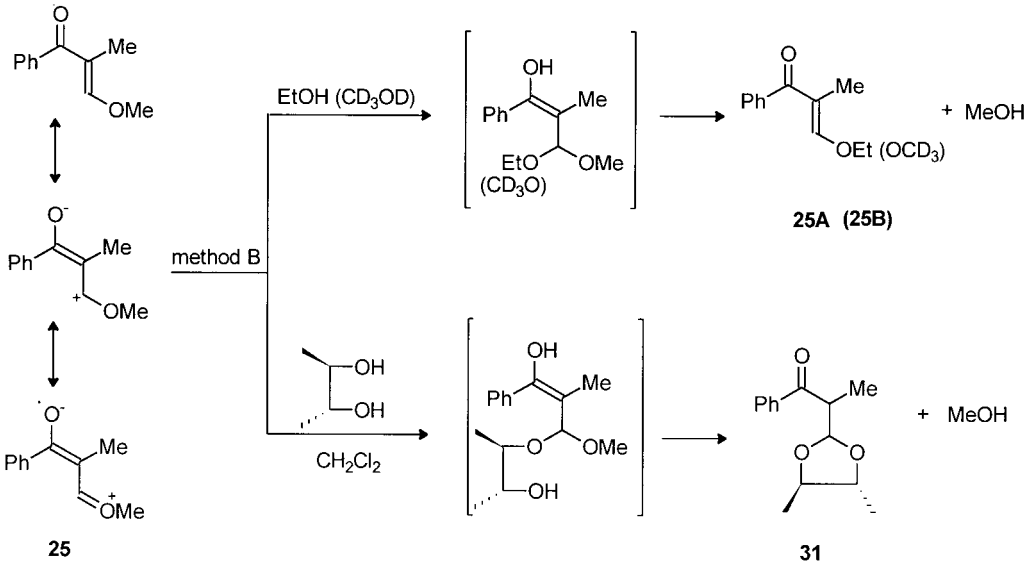
On considering the very simple and mild reaction conditions, the high conversions and yields, this methodology for the synthesis of acetals and/or β-keto enol ethers represents a valid alternative to the existing procedures, especially for carbonyl compounds bearing acid-sensitive groups.

The success of this method lies in the use of $TiCl_4$, which acting both as a catalyst and as dehydrating agent, makes unnecessary the azeotropic removal of the water generated during the reaction and allows the acetalisation to occur at room temperature.

4. Experimental

4.1. General remarks

All reactions were carried out at room temperature without protection from moisture or oxygen. NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC-250 MHz instrument with Me_4Si as an internal standard. Mass spectra were taken on a Finnigan MAT-TS Q70 spectrometer.



Scheme 2.

Melting points (uncorrected) were taken on a Kofler apparatus. Flash column chromatography was performed by using Silica gel 60 (particle size 0.004–0.063).

Triethylamine (TEA) was distilled prior to use. $TiCl_4$ (1.0 M solution in CH_2Cl_2) and methanol ACS (HPLC grade) were purchased from Aldrich and used as received. Ketones of Tables 1 and 2 are commercially available and were used without further purification. The β-Keto aldehydes of Table 3 were readily prepared by acylation of the appropriate ketones using slight modifications of the standard methods.[25a,b] Procedure **A** was adopted for solid β-Keto aldehydes and procedure **B** for liquid β-Keto aldehydes.

Procedure A. Sodium methoxide (5.40 g, 0.10 mol) was suspended in THF (100 mL) and treated at room temperature with ethyl formate (8.1 mL, 0.10 mol), followed by dropwise addition of the appropriate ketone (8×10^{-2} mol of 4-methoxyacetophenone or 4-chloroacetophenone or propriophenone). The reaction mixture was stirred for 2.5 h at room temperature, quenched by the addition of water (300 mL), and extracted with two 100 mL portions of diethyl ether. These extracts were discarded. The aqueous phase was acidified with 18 mL of 6 M H_2SO_4 and extracted with diethyl ether (2×100 mL). This extract was washed with water and brine, dried, and concentrated to give a thick yellow oil, which was purified by crystallization from the appropriate solvent to afford the β-Keto aldehydes reported in succession.

4.1.1. 3-(4-Methoxyphenyl)-3-oxo-propionaldehyde. Yield 60%, yellow crystals; mp 53–56°C (hexane). Lit.[25c] 54–56°C.

4.1.2. 3-(4-Chlorophenyl)-3-oxo-propionaldehyde. Yield 72%, yellow crystals; mp 45–47°C (hexane). Lit.[25d] 46–48°C.

4.1.3. 2-Methyl-3-oxo-3-phenyl-propionaldehyde. Yield 67%, yellow crystals; mp 118–120°C (chloroform). Lit.[25e] 118°C.

Procedure B. The reactions were conducted according to the procedure given in A, but the products were obtained pure by first preparing the copper derivatives. The crude residue, obtained after work-up as in procedure A, was dissolved in MeOH (10 mL) and treated with a hot filtered solution of 10 g of copper acetate in 100 mL of water. The copper salt of the β-Keto aldehyde separated out on cooling (one night at 0°C).

4.1.4. Copper salt of 3-oxo-3-phenyl-propionaldehyde. Yield 68%, dark green needles; mp 210–215°C, dec. Lit.[25f] 212–213°C, dec.

4.1.5. Copper salt of 4,4-dimethyl-3-oxo-pentanal. Yield 52%, blue crystals; mp 124–126°C. Lit.[25g] 125–126°C.

4.1.6. Copper salt of 5-methyl-3-oxo-hex-4-enal. Yield 50%, black crystals; mp 134°C. Lit.[25h] 134°C.

The free β-Keto aldehyde was prepared from the copper derivative by shaking with diethyl ether, dilute sulphuric acid, and ice until the salt was completely decomposed. The aqueous layer was again extracted with diethyl ether. The combined ether extracts were washed with sodium bicarbonate solution, dried and evaporated to dryness. The crude β-Keto aldehydes (purity >95% by ^1H NMR) was employed at once.

4.2. General procedure for the $TiCl_4/Et_3N$ catalysed synthesis of cyclic dimethyl acetals 1–12 (Table 1)

50 μL (5×10^{-2} mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 was added in one portion with a syringe, to a stirred solution of the cyclic ketone (5 mmol) in MeOH (10 mL) at room temperature. After ca 10 min, Et_3N (83 μL, 0.6 mmol) was added to the resulting solution, which was stirred for an additional 45 min before the addition of H_2O (3 mL). The reaction mixture was then extracted with diethyl ether (3×10 mL) and the combined organic layers were successively washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. Conversion was determined by ^1H NMR analysis of the crude reaction mixture (the remainder to 100% was the starting ketone, by-product have never been detected). When the crude residue showed an ^1H NMR purity ≥95%, no further purification was undertaken, and the isolated yields (%) of Table 1 refer to the recovered crude acetals. When the ^1H NMR purity was <95%, the crude residue was purified by Kugelrohr distillation.

4.3. General procedure for competition acetalisation experiments

50 μL (5×10^{-2} mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 was added in one portion with a syringe, to a stirred solution containing a 1:1 mixture of benzaldehyde and acetophenone (2.5 mmol each) in 10 mL of MeOH. After 10 min, Et_3N (83 μL, 0.6 mmol) was introduced, and stirring was continued for an additional 45 min. GLC analysis of the reaction mixture was performed on sample taken up in diethyl ether and washed with small quantity of water. By comparison of the retention times with those of authentic samples,[7a] the GLC analysis confirmed that the benzaldehyde dimethyl acetal was the only reaction product.

Comparable experimental conditions were adopted for the competitive acetalisations of 4-^{t}Bu-cyclohexanone/acetophenone and cyclohexanone/2-hexanone.[7b]

4.4. General procedure for the $TiCl_4$-catalysed synthesis of β-methoxy-cycloalkenones 13–19 (Table 2)

0.15 mL (0.15 mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 was added in one portion with a syringe, at room temperature, to a well stirred solution of the cyclic 1,3-diketone (5 mmol) in MeOH (10 mL). The reaction mixture was then stirred for an additional 30 min before the addition of H_2O (3 mL). Further work up was similar to the preceding procedure. The isolated yields (%) of Table 2 refer to the crude recovered products, which always showed an ^1H NMR purity ≥95%, making further purification unnecessary.

4.5. General procedure for the $TiCl_4$-catalysed synthesis of β-methoxyenones 20–25 (Method A) and of β-keto dimethyl acetals 26–30 (Method B) (Table 3)

Method A. The β-keto aldehyde (10 mmol) was dissolved in

20 mL of MeOH. To the stirred solution was added in one portion with a syringe, at room temperature, 0.1 mL (1.0×10^{-1} mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2. After 5–10 min, the reaction was quenched with H_2O (5 mL). Work up was as in the preceding procedures. Compounds **20–24** were purified by flash column chromatography (hexane/EtOAc, 8:2) and the solid β-methoxyenone **21** was recrystallized from hexane. The crude **25** showed an ^1H NMR purity >95%, making its further purification unnecessary. *Method B.* A larger amount (0.5 mL, 0.5 mmol) of the $TiCl_4$ solution in CH_2Cl_2 was added to the methanolic solution (20 mL) of the β-keto aldehyde (10 mmol) and stirring was continued for 2 h (or 5 min; see Table 3) at room temperature. Work up was as in the preceding procedures. The purity of the β-keto dimethyl acetals **26–30** was judged to be >95% by ^1H NMR analysis.

4.6. General procedure for the $TiCl_4$-catalysed conversion of enol ethers 20–24 to the corresponding dimethyl acetals 26–30

The enol ether (5 mmol) was dissolved in 10 mL of MeOH. To the stirred solution was added in one portion with a syringe, 0.25 mL (0.25 mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 and stirring was continued for 2 h at room temperature. After work up as in the preceding procedures, the ^1H NMR analysis of the crude residue revealed the quantitative conversion of the enol ether into the corresponding dimethyl acetal.

4.7. Transacetalisation of β-keto enol ethers 13 and 25 to the corresponding ethyl ethers 13A and 25A or deuterated methyl ethers 13B and 25B (Scheme 2)

The reactions were performed under the conditions of method B: dissolution of **13** or **25** (5 mmol) in EtOH (10 mL) or CD_3OH (10 mL), followed by addition of 0.25 mL (0.25 mmol) of the $TiCl_4$ solution in CH_2Cl_2, quenching of the reaction after 2 h and usual work up.

4.8. Transacetalisation of 25 to the cyclic acetal 31 (Scheme 2)

The reaction was performed under the conditions of method B: dissolution of **25** (5 mmol) in a CH_2Cl_2 (10 mL) solution containing D,L-2,3-butanediol (7 mmol), followed by addition of the $TiCl_4$ (0.25 mL, 0.25 mmol) solution and quenching of the the reaction after 2 h. Usual work up afforded **31** in 85% isolated yield, as an inseparable 50:50 mixture of two diastereoisomers.

4.9. Spectroscopic data

With the exception of 2,6,6-trimethyl-4,4-dimethoxycyclohexan-1-one **12**, all the products listed in Tables 1 and 2 are known compounds, and their spectroscopic and physical data are in accord with those reported in the literature.[26] We include the spectroscopic data for all the compounds of Table 3, and for **13B**, **25A**, **25B** and **31** (Scheme 2) because most of them are new compounds and/or their spectral data in the literature is incomplete.

With the exception of compounds **13B** and **21** which are white solids all the synthesized new compounds are pale yellow liquids.

4.9.1. 2,6,6-Trimethyl-4,4-dimethoxycyclohexan-1-one (12). ^1H NMR ($CDCl_3$) δ 1.03 (3H, CH_3, d, J=6.5 Hz), 1.06 (3H, CH_3, s), 1.26 (3H, CH_3, s), 1.49 (1H, d, J=13.9 Hz), 1.65 (1H, d, J=13.9 Hz), 2.17 (1H, dd, J=3.9, 14.2 Hz), 2.25–2.35 (1H, m), 2.80–2.90 (1H, m), 3.22 (3H, OCH_3, s), 3.28 (3H, OCH_3, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 14.5, 26.3, 27.0, 36.6, 40.9, 43.5, 45.2, 47.9, 102.9, 216.3; IR (neat) ν_{max} 2966, 1713, 1100, 1050 cm^{-1}; MS (EI) *m/e* (relative intensity) 185 (M^+-1, 40), 170 (30), 169 (25), 153 (25), 125 (60), 109 (85), 99 (100), 88 (70), 83 (50), 69 (70), 59 (58); Anal. Calcd for $C_{10}H_{18}O_3$: C 64.49; H 9.77%. Found: C 64.47; H 9.80%.

4.9.2. 3-Deuteromethoxycyclohex-2-en-1-one (13B). Mp 44–46°C; ^1H NMR ($CDCl_3$) δ 1.93 (2H, dt, J=6.3, 9.5 Hz), 2.30 (2H, t, J=6.1 Hz), 2.36 (2H, t, J=6.1 Hz), 5.30 (1H, s); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 20.8, 28.4, 36.3, 55.3, 101.8, 178.5, 199.3; HRMS Calcd for $C_7H_7D_3O_2$ (M^+) 129.0680, found 129.0682.

4.9.3. 3-Methoxy-1-phenyl-2(*E*)-propen-1-one (20).[21] ^1H NMR ($CDCl_3$) δ 3.81 (3H, OCH_3, s), 6.35 (1H, CH, d, J=12.4 Hz), 7.4–7.6 (3H, PhH, m), 7.80 (1H, CH, d, J=12.4 Hz), 7.9–8.0 (2H., PhH, m);[15b] IR (neat) ν_{max} 1644, 1600, 1583, 1206 cm^{-1}; MS (EI) *m/e* (relative intensity) 162 ($M^{+\cdot}$, 5), 105 (100), 85, 77, 51.

4.9.4. 3-Methoxy-1-(4-chlorophenyl)-2(*E*)-propen-1-one (21). Mp 63–5°C (lit.[27] 63–4°C); ^1H NMR ($CDCl_3$) δ 3.80 (3H, OCH_3, s), 6.3 (1H, CH, d, J=11.9 Hz), 7.4 (2H, ArH, A_2B_2), 7.78 (1H, CH, d, J=11.9 Hz), 7.85 (2H., ArH, A_2B_2); IR (KBr) ν_{max} 1655, 1580, 1260, 1205 cm^{-1}; Anal. Calcd for $C_{10}H_9ClO_2$: C 61.07; H 4.58%. Found: C 60.95; H 4.61%.

4.9.5. 3-Methoxy-1-(4-methoxyphenyl)-2(*E*)-propen-1-one (22). ^1H NMR ($CDCl_3$) δ 3.82 (3H, OCH_3, s), 3.85 (3H, OCH_3, s), 6.33 (1H, CH, d, J=11.9 Hz), 6.92 (2H, ArH, m), 7.75 (1H, CH, d, J=11.9 Hz), 7.9 (2H., ArH, m); IR (neat) ν_{max} 2937, 1660, 1603, 1257, 1209, 1171 cm^{-1}; proton-decoupled ^{13}C NMR ($CDCl_3$) δ 55.3 (OCH_3), 57.9 (OCH_3), 101.0 (=CH), 113.6 ($2CH_{arom}$), 130.5 ($2CH_{arom}$), 132.5 (C_{arom}), 163.6 (C_{arom}), 164.0 (=CH),188.0 (C=O); MS (EI) *m/e* (relative intensity) 192 (M^+, 20), 135 (100); Anal. Calcd for $C_{11}H_{12}O_3$: C 68.74; H 6.29%. Found: C 68.78; H 6.31%.

4.9.6. 1-Methoxy-4,4-dimethyl-1(*E*)-penten-3-one (23).[19] ^1H NMR ($CDCl_3$) δ 1.08 (9H, $3CH_3$, s), 3.70 (3H, OCH_3, s), 5.77 (1H, CH, d, J=11.9 Hz), 7.47 (1H, CH, d, J=11.9 Hz); IR[19b] (CH_2Cl_2) ν_{max} 1689, 1611, 1596 cm^{-1}.

4.9.7. 1-Methoxy-5-methylhexan-1(*E*),4-dien-3-one (24). ^1H NMR ($CDCl_3$) δ 1.19 (6H, $2CH_3$, s), 3.68 (3H, OCH_3, s), 5.30 (1H, CH, s), 5.55 (1H, CH, d, J=12.4 Hz); 7.45 (1H, CH=, d, J=12.4 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 24.9 (CH_3), 27.8 (CH_3), 53.5 (OCH_3), 119.3 (=CH), 123.8 (=CH), 156.5 (=C), 159.1 (=CH), 196.8 (C=O); IR (neat) ν_{max} 2976, 1622, 1075 cm^{-1}; MS (EI) *m/e* (relative intensity) 140 ($M^{+\cdot}$, 5), 100 (5), 85 (100);

Anal. Calcd for $C_8H_{12}O_2$: C 68.55; H 8.63%. Found: C 68.61; H 8.72%.

4.9.8. 3-Methoxy-2-methyl-1-phenyl-2(*E*)-propen-1-one (25). ^{1}H NMR ($CDCl_3$) δ 1.88 (3H, CH_3, d, J_{all}=1.1 Hz), 3.80 (3H, OCH_3, s), 6.92 (1H, CH=, q, J_{all}=1.1 Hz), 7.36–7.48 (3H, PhH, m), 7.50–7.59 (2H, PhH, m);[15b] ^{13}C NMR ($CDCl_3$) δ (and ^1J C-1, H-1) 8.9 (CH_3, q, J=129 Hz), 61.5 (OCH_3, q, J=145 Hz), 117.3 (=C, s), 128.1 ($2CH_{arom}$, d, J=160 Hz), 128.6 ($2CH_{arom}$, d, J=161 Hz), 130.6 (CH_{arom}, d, J=130 Hz), 139.3 (C_{arom}, s), 164.4 (=CH, d, J=177 Hz), 197.1 (C=O, s); IR (neat) ν_{max} 2940, 1677, 1626, 1247, 1143 cm^{-1}; MS (EI) *m/e* (relative intensity) 176 ($M^{+\cdot}$, 60), 175 (M^+-1, 70), 105 (100), 77 (73); HRMS Calcd for $C_{11}H_{12}O_2$ (M^+) 176.0837, found 176.0839.

4.9.9. 3-Ethoxy-2-methyl-1-phenyl-2(*E*)-propen-1-one (25A). ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, CH_3, t, J=7.1 Hz), 1.89 (3H, CH_3, d, J_{all}=1.1 Hz), 4.00 (2H, CH_2, q, J=7.1 Hz), 6.99 (1H, CH=, q, J_{all}=1.1 Hz), 7.35–7.48 (3H, PhH, m), 7.50–7.56 (2H, PhH, m);[15b] proton-decoupled ^{13}C NMR ($CDCl_3$) δ, 8.8 (CH_3), 15.3 (CH_3), 67.9 (OCH_2), 117.3 (=C), 128.2 ($2CH_{arom}$), 128.6 ($2CH_{arom}$), 130.5 (CH_{arom}), 139.3 (C_{arom}), 150.3 (=CH), 197.3 (C=O); IR (neat) ν_{max} 2982, 1676, 1625, 1212, 1143, 1014 cm^{-1}; MS (EI) *m/e* (relative intensity) 190 ($M^{+\cdot}$, 52), 161 (40), 113 (18), 105 (100), 77 (80). Anal. Calcd for $C_{12}H_{14}O_2$: C 75.76; H 7.42%. Found C 75.80; H 7.50%.

4.9.10. 3-Deuteromethoxy-2-methyl-1-phenyl-2(*E*)-propen-1-one (25B). ^{1}H NMR ($CDCl_3$) δ 1.89 (3H, CH_3, d, J=1.1 Hz), 6.91 (1H, CH=, q, J=1.1 Hz), 7.35–7.45 (3H, PhH, m), 7.50–7.60 (2H, PhH, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 8.9(CH_3), 61.4 (OCD_3), 117.3 (=C), 128.1 ($2CH_{arom}$), 128.5 ($2CH_{arom}$), 130.6 (CH_{arom}), 139.0 (C_{arom}), 164.4 (=CH),197.2 (C=O); IR (neat) ν_{max} 2940, 1678, 1625, 1248, 1143 cm^{-1}; MS (EI) *m/e* (relative intensity) 179 ($M^{+\cdot}$, 58), 177 (60), 105 (100), 77 (70); HRMS Calcd for $C_{11}H_9D_3O_2$ (M^+) 179.0837, found 179.0831.

4.9.11. 3,3-Dimethoxy-1-phenylpropan-1-one (26). ^{181}H NMR δ 3.30 (2H, CH_2, d, J=5.2 Hz), 3.45 (6H, $2OCH_3$, s), 5.02 (1H, CH, t, J=5.2 Hz), 7.40–7.60 (3H, PhH, m), 7.9–8.0 (2H., PhH, m); IR (neat) ν_{max} 1685, 1600, 750, 690 cm^{-1}; MS (EI) *m/e* (relative intensity) 194 ($M^{+\cdot}$, 2), 163 (M^+-OCH_3), 136, 105 (100), 85, 77, 75 (MeO^+=CHOMe), 58, 51.

4.9.12. 3,3-Dimethoxy-1-(4-chlorophenyl)propan-1-one (27). ^{1}H NMR ($CDCl_3$) δ 3.22 (2H, CH_2, d, J=5.4 Hz), 3.41 (6H, $2OCH_3$, s), 4.97 (1H, CH, t, J=5.4 Hz), 7.44 (2H, ArH, A_2B_2), 7.90 (2H, ArH, A_2B_2); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 42.7 (CH_2), 54.3 ($2OCH_3$), 102.3 (CH), 128.8 ($2CH_{arom}$), 129.8 ($2CH_{arom}$), 135.5 (C_{arom}), 139.8 (C_{arom}), 195.8 (C=O); IR (neat) ν_{max} 2940, 1686, 1594, 1092, 1012 cm^{-1}; MS (EI) *m/e* (relative intensity) 230–228 ($M^{+\cdot}$, 4), 213 (13), 182 (13), 181 (13), 139 (53), 111 (23), 75 (100); HRMS Calcd for $C_{11}H_{13}ClO_3$ (M^+, Cl-35 isotope) 228.0553, found 228.0557.

4.9.13. 3,3-Dimethoxy-1-(4-methoxyphenyl)propan-1-one (28). ^{1}H NMR ($CDCl_3$) δ 3.22 (2H, CH_2, d, J=5.4 Hz), 3.41 (6H, $2OCH_3$, s), 3.89 (3H, OCH_3, s), 5.00 (1H, CH, t, J= 5.4 Hz), 6.95 (2H, ArH, m), 7.95 (2H., ArH, m); proton-decoupled ^{13}C NMR ($CDCl_3$) δ 42.2 (CH_2), 54.1 ($2OCH_3$), 55.4 (OCH_3), 102.3 (CH), 113.7 ($2CH_{arom}$), 129.5 (C_{arom}), 130.5 ($2CH_{arom}$), 163.6 (C_{arom}), 195.3 (C=O); IR (neat) ν_{max} 2937, 1678, 1602, 1092, 1316, 1172, 1122, 1053 cm^{-1}; M (EI) *m/e* (relative intensity) 224 (M^+, 4), 209 (25), 135 (100), 92 (50), 77 (50); HRMS Calcd for $C_{12}H_{16}O_4$ (M^+) 224.1048, found 224.1045.

4.9.14. 1,1-Dimethoxy-4,4-dimethylpentan-3-one (29).[19a] ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, $3CH_3$, s), 2.63 (2H, CH_2, d, J= 5.4 Hz), 3.29 (6H, $2OCH_3$, s), 4.71 (1H, CH, t, J=5.4 Hz).

4.9.15. 1,1-Dimethoxy-5-methylhex-4-en-3-one (30). ^{1}H NMR δ 1.18 (6H, $2CH_3$, s), 2.63 (2H, CH_2, d, J=5.6 Hz), 3.28 (6H, $2OCH_3$, s), 4.67 (1H, CH, t, J=5.6 Hz), 5.30 (1H, CH=, s); IR (neat) ν_{max} 2976, 1710, 1619, 1366, 1190, 1123, 1075 cm^{-1}; proton-decoupled ^{13}C NMR ($CDCl_3$) δ 24.7 (CH_3), 27.6 (CH_3), 47.6 (CH_2), 53.6 ($2OCH_3$), 101.8 (CH), 124.0 (=CH), 155.9 (=C), 206.4 (C=O); MS (EI) *m/e* (relative intensity) 172 ($M^{+\cdot}$, 3), 157 (10), 131 (10), 99 (18), 75 (80), 73 (100); HRMS Calcd for $C_9H_{16}O_3$ (M^+) 172.1099, found 172.1096.

4.9.16. 1-Phenyl-2-[4,5-(*trans*)dimethyl-⟨1,3⟩-dioxolan-2-yl]propan-1-one (31). Isolated in 85% yield as an inseparable 50:50 mixture of two diastereomers; ^{1}H NMR δ 1.17–1.24 (6H, $2CH_3$, 4d, J=5.8, 5.8, 5.4, 5.4 Hz), 1.29 (3H, CH_3, d, J=6.9 Hz), 3.60 (2H, CH_2, m), 3.65–3.77 (1H, CH, 2qd, J=6.9, 3.8; 6.9, 4.2 Hz), 5.31–5.36 (1H, CH, 2d, J=4.2, 3.8 Hz), 7.42–7.60 (3H, PhH, m), 7.95–8.01 (2H, PhH, m); IR (neat) ν_{max} 2977, 1683, 1597, 1216, 1104, 968 cm^{-1}; MS (EI) *m/e* (relative intensity) 234 ($M^{+\cdot}$, 1), 219 (11), 179 (13), 161 (6), 146 (8), 134 (10), 133 (18), 105 (100), 101 (99), 77 (92), 73 (44), 55 (31); HRMS calcd for the mixture of isomers $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1260.

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15. (a) It should be underlined that β-keto aldehydes of Table 3 were shown to be in the *cis*-enol form to an extent of about 90–95%, by ^{1}H NMR, with the aldehydic carbonyl enolized. Thus, on the basis of their reactivity, we must deduce that they will form much less stable Ti(IV)-complexes in methanolic solution than the unreactive acyclic 1,3-diketones do. (b) In the ^{1}H NMR spectra of **20**–**22** (see Spectroscopic data), the signal of the two aromatic protons *ortho* to the carbonyl group occurs at ca 7.9 ppm as expected, whereas in that of **25** there are two different signals for the two *ortho*-aromatic protons, the more intense H (≅95%) occurring at ca 7.5 ppm and the other H (≅5%) at ca 8 ppm. This fact can be interpreted in terms of an equilibrium shifted in favour of the resonance stabilised *trans*/s-*trans* rotamer (Chart 1). In fact, in the s-*trans* rotamer, the two aromatic protons *ortho* to the carbonyl group lie in the shielding zone of both the carbonyl group and the C–C double bond, thus, adsorbing at much higher field (7.5 ppm) than those of the *trans*/s-*cis* rotamer (8 ppm). For a similar reason, the two *ortho*-aromatic protons of β-ethoxy-2-methyl-1-phenylprop-2-en-1-one **25A** are found at ca 7.5 ppm (see Spectroscopic data). (c) Irradiation of the vinylic proton of compound **25** raises the two aromatic protons *ortho* to the carbonyl group (7%) and the methylenic protons of the methoxy group (4%), whereas the methyl group does not show a NOE effect, indicating that it is remote from the irradiated vinylic proton and that compound **25** has the conformation *trans*/s-*trans* reported in Chart 1. Additional NOE experiments show that the methyl group sterically interacts with the methoxy group also, causing restricted rotation around the Csp^2–O single bond: in fact, irradiation of the methyl group does not show a NOE effect either with the vinylic proton or with the methoxy group, thus the energetically favoured rotamer **25** has the conformation *trans*/s-*trans*/O-s-*trans* (for nomenclature see Ref. 19b).
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22. Stabilized carbanions react with **13** via exclusive addition–elimination at the β-carbon to give products resulting from the substitution of the methoxy group by the nucleophiles (see Ref. 11).
23. Most probably, the mechanism depicted in Scheme 2 is also operative in the formation of β-methoxyenones, either from 1,3-cyclohexanediones (Eq. 4) or β-keto aldehydes (Scheme 1), that is: Ti(IV)-assisted MeOH addition to the olefinic bond of the enol form, followed by Ti(IV)-assisted water departure.
24. Instead, the susceptibility of carbonyl groups of **13**–**19** to nucleophilic attack by MeOH is strongly attenuated by electron donation of the OCH_3 group through the conjugated double bond.
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26. For each known compound of Tables 1 and 2, the relevant reference is given in succession: **1**: commercial product (Aldrich); **2**, **3**, **4**, **5** and **11**: Tateiwa, J.; Hiroki, H.; Sakae, U. *J. Org. Chem.* **1995**, *60*, 4039; **6**: Takeshi, O.; Yuichi, I.; Gen, K. *Bull. Chem. Soc. Jpn* **1991**, *64*, 2581; **7**: commercial product (Fluka); **8**: Kropp, P. J.; McNeely, S.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907; **9**: Zajac, W. W.; Byrne, K. J. *J. Org. Chem.* **1970**, *35*, 3375; **10**: Nilsson, A.; Ronlàn, A. *Tetrahedron Lett.* **1975**, *16*, 1107; **13A**: commercial product (Aldrich); **13**, **18** and **19**: see Ref. 11; **14**: see Ref. 9d; **15**: see Ref. 12; **16** and **17**: see Ref. 10.
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