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Condensation of β-Diester Titanium Enolates with Carbonyl Substrates: A Combined DFT and Experimental Investigation

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Abstract: The condensation of dialkyl β -diesters with various aldehydes promoted by TiCl₄ has been studied by DFT approaches and experimental methods, including NMR, IR and UV/ Vis spectroscopy. Various possible reaction pathways have been investigated and their energy profiles evaluated to find out a plausible mechanism of the reaction. Theoretical results and experimental evidence point to a three-step mechanism: 1) Ti-induced formation of

Keywords: aldol reaction • density functional calculations • elimination • Knoevenagel condensation • titanium the enolate ion; 2) aldol reaction between the enolate ion and the aldehyde, both coordinated to titanium; and 3) intramolecular elimination that leads to a titanyl complex. The presented mechanistic hypothesis allows one to better understand the pivotal role of titanium(IV) in the reaction.

Introduction

The formation of carbon–carbon bonds is one of the most common organic reactions. Among the synthetic routes developed to achieve this goal, an aldol reaction is a cornerstone and has been subjected to considerable investigation, especially in terms of diastereo- and enantiocontrol.^[1–4] Metal ions are particularly useful in catalyzing this reaction because they can activate both the nucleophile and the electrophile by metal complexation (Scheme 1). Indeed, the coordination of carbonyl compounds to metal centres increases their electrophilicity, thus accelerating the reaction with nucleophiles such as enolates. At the same time, the com-

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Scheme 1. Metal ions catalyze an aldol reaction through activation of both the nucleophile and the electrophile by metal complexation.

plexation of carbonyl compounds bearing α -hydrogen atoms allows the generation of the corresponding enolates under mild reaction conditions.

Titanium(IV) derivatives are effective catalysts for several reactions.^[5] In particular, the TiCl₄–Et₃N reagent system is widely used to generate titanium enolates for applications in aldol condensations^[6] and related reactions.^[7] This method is simpler than others based on transmetalation from alkalimetal enolates,^[8] silyl enol ethers^[9] or acylation of a titanocene methylene complex,^[10] because in this way titanium enolates are directly generated in the reaction mixture.^[11] Recently, Renzetti et al.^[12] have developed a one-pot trimolecular condensation of isobutyraldehyde, indole and di-





Scheme 2. TiCl₄-promoted trimolecular condensation.

methyl malonate in the presence of $TiCl_4$ and Et_3N (Scheme 2).

This process belongs to the class of multicomponent reactions, which are particularly useful in combinatorial chemistry to prepare libraries of compounds having a common scaffold.^[13] Scheme 3 reports the initially proposed mechanism^[12] for this trimolecular reaction. Titanium tetrachloride forms a complex with dimethyl malonate (Scheme 3, step I). The complexation increases the acidity of the α -hydrogen atoms because of the electron-withdrawing effect of the electron-poor titanium(IV). Thus the diester can be easily deprotonated by a weak base (triethylamine) and converted into the enolate ion, which is the reactive species (Scheme 3, step II). The enolate reacts with the aldehyde (Scheme 3, step III) and generates the Knoevenagel adduct K after the protonation of the resulting alkoxide and the elimination of a water molecule (Scheme 3, step IV). The Michael addition of indole to K followed by deprotonation leads to the condensation product CP (Scheme 3, steps V and VI). According to this mechanism, titanium promotes both the Knoevenagel condensation (steps I-IV) and the Michael addition (steps V-VI). The Knoevenagel condensation promoted by TiCl₄ and Et₃N has been known for almost forty years. This reaction was first performed by Lehnert between aldehydes or ketones and a wide range of methylene active compounds.^[14] It has been used to synthesise some natural products^[15] and its stereochemistry has also been studied.^[16,17]



Scheme 3. Mechanism for the TiCl₄-promoted trimolecular condensation proposed in ref. [12]. R = Me, Et, *i*Pr; R' = H, Ph, *i*Pr.

However, neither experimental nor theoretical studies have ever been performed to explain the role of titanium in this reaction. In the present work, we investigated the mechanism of the condensation of three dialkyl β -diesters oted by TiCl (steps L W) by a

with various aldehydes promoted by $TiCl_4$ (steps I–IV) by a combination of experimental techniques and DFT calculations. The elucidation of the trimolecular condensation reaction mechanism would allow the experimental procedure to be tuned and might shed light on the mechanism of analogous reactions.

Results and Discussion

Formation of the enolate

OCH-

81% yield

Experimental evidence: To gain an insight into the reaction mechanism, NMR spectroscopic studies were undertaken on three different diesters: dimethyl malonate, diethyl malonate and diisopropyl malonate. A first set of experiments confirmed the formation of the enolate for all of the three compounds (Scheme 3, steps I and II). The addition of one molar equivalent of TiCl₄ to a solution of diethyl malonate in CD₂Cl₂ at 25 °C resulted in a dramatic change of the ¹³C NMR spectrum. The α -carbon atom showed the most significant change in chemical shift, passing from δ =41.4 to 39.1 ppm (Figure 1, compare spectra a and b). Addition of one molar equivalent of triethylamine caused a new shift in the signal to δ =75.6 ppm and resulted in the formation of a titanium enolate (Figure 1c), according to previous evidence

on similar enolates.[18] Quenching with a solution of DCl in D₂O resulted in the tautomerisation to the deuterated ester (results not shown). The coupled ¹³C NMR spectrum confirmed the formation of the enolate. As a matter of fact, the α -carbon atom provided a doublet rather than a triplet on addition of one molar equivalent of triethylamine (Table 1, entries 5 and 6). Moreover, the large increase of ${}^{1}J({}^{13}C,H)$ on passing from the ester to the enolate (from about 130 to 170 Hz) points to a change in the C_a hybridisation. Both observations are consistent with deprotonation.^[16] A similar behaviour was observed for the other two diesters (Table 1, en-

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Figure 1. ¹³C NMR spectra of diethyl malonate a) pure; b) after the addition of TiCl₄ (1.0 equiv); c) after the addition of TiCl₄ (1.0 equiv) and Et_3N (1.0 equiv) (solvent: CD_2Cl_2).

Table 1. Enolate formation tests for dimethyl malonate, diethyl malonate and diisopropyl malonate upon addition of TiCl₄ and Et₃N (T=25.0 °C).

Entry	Species	$\delta(C_{\alpha})$ [ppm]	Multiplicity (J [Hz])	
1	dimethyl malonate ^[a]	41.4	t (132.3)	
2	+TiCl ₄ (1 equiv)	39.1	t (133.4)	
3	$+Et_3N$ (1 equiv	76.2	d (170.9)	
4	diethyl malonate ^[b]	41.4	t (132.3)	
5	+TiCl₄ (1 equiv)	39.1	t (133.4)	
6	$+Et_3N$ (1 equiv)	75.6	d (170.9)	
7	diisopropyl malonate ^[a]	42.4	t (132.0)	
8	+TiCl ₄ (1 equiv)	38.3	t (132.0)	
9	$+Et_3N$ (1 equiv)	70.8	d (172.0)	

[a] The solvent is CDCl₃. [b] The solvent is CD₂Cl₂.

tries 1–3 and 7–9). The ¹H NMR spectrum also showed a shift of signals upon addition of $TiCl_4$ and Et_3N . However, the peaks of the enolate were broad and partly overlapped, thus making their attribution difficult. The formation of the enolate ion could be followed visually as well. Actually, the starting ester is uncoloured; its complex with $TiCl_4$ is yellow and the titanium enolate is dark red.

We further investigated the TiCl₄-diethyl malonate complex to elucidate its structure and stability in solution. The corresponding Job plot^[19] for a constant [diethyl malonate+ TiCl₄] concentration of 0.82 M, shows a maximum at χ_{TiCl_4} = 0.5 (Figure S1 in the Supporting Information). This evidence indicates that the complex has a 1:1 stoichiometry at the investigated concentration of substrate.^[20] The apparent formation constant K_{app} of the complex, obtained by ¹H NMR spectroscopic titration^[21] (Figure 2), indicates a highly stable complex. Three different NMR spectroscopic titrations point to a strong dependence of K_{app} on the initial concentration of diester (Table 2). This is not surprising because in concentrated solutions, such as those used in the present ex-



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Figure 2. Titration plot of diethyl malonate (at the initial concentration of 0.41 m in CD₂Cl₂) with TiCl₄ (*T*=25.0 °C, *n*=mol number).

Table 2. Apparent formation constant of the TiCl₄-diethyl malonate complex at various initial concentrations of ester (DEM) (in CD₂Cl₂ at T=25.0 °C).

[DEM] [M]	$K_{\mathrm{app}} [\mathrm{m}^{-1}]$	R^2 (Points)
8.24×10^{-2}	6.77×10^{2}	0.71213 (10)
2.23×10^{-1}	1.10×10^{3}	0.99311 (11)
4.10×10^{-1}	3.02×10^{3}	0.99083 (13)

periments, concentrations should be replaced with activities to obtain true equilibrium constants.

Theoretical calculations: The formation of titanium enolate was investigated in detail by a DFT approach that considered the simplest dimethyl malonate (Scheme 4). An octahe-



Scheme 4. Formation of titanium enolates.

dral geometry was assumed for the initial complex formed by this β -diester with TiCl₄ on the basis of previous experimental investigations.^[22] This [TiCl₄{(O=COCH₃)₂CH₂}] complex was optimised and the comparison of the calculated geometry with the X-ray data was used to assess the accuracy of the employed level of theory. Because no X-ray structure is available for the complex, we considered the diethyl malonate analogue, the geometry of which has been

characterised by X-ray diffraction^[22] and is expected to be very close to that of $[TiCl_4{(O=COCH_3)_2CH_2}]$.

The calculated geometrical parameters are in good agreement with the experimental X-ray data (Table S1 in the Supporting Information), with most bond lengths and bond angles within 0.05 Å and 5°. Only the calculated Ti–O bond lengths are slightly overestimated by approximately 0.10 Å, whereas most of the remaining bond lengths differ by less than 0.05 Å from the experimental values. Recent DFT calculations^[23] also showed a similar overestimate of the Ti–O bond lengths in TiCl₄ complexes with carbonyl compounds (0.05–0.10 Å) at the same level of theory. However, the error on the Ti–O bond length at this level of theory is quite low and is not expected to affect the energy profiles of the considered reactions that occur in the second-coordination sphere of titanium.

The formation of the enolate ion by deprotonation with Et₃N has been investigated for both the [TiCl₄{(O= $COCH_3_2CH_2$ complex and the free dimethyl malonate to point out the role played by the metal centre. We calculated the proton-exchange enthalpies and free energies between triethylamine and both the metal complex and the free diester. Results (Table S2 in the Supporting Information) show the pivotal role played by solvation due to dichloromethane. Indeed, in the gas phase the proton-exchange free energies are positive in both cases, but that of the complex is about 50 kcalmol⁻¹ lower than that for the free diester, thus indicating that the metal coordination strongly increases the H_{α} acidity of dimethyl malonate. The inclusion of solvation reduces the proton-exchange free energies by approximately $80-100 \text{ kcal mol}^{-1}$, as the reaction implies the formation of ionic products from neutral reactants and thus it is favoured only in a polar solvent. The calculated free energies in CH_2Cl_2 were -15.4 and 19.7 kcalmol⁻¹ for the complexed and the free diester, respectively. These results indicate that the dicarbonyl compound can be deprotonated in dichloromethane solution only if it is complexed with TiCl₄.

Actually, the deprotonation of the metal complex 1 may lead to the formation of either the anionic tetrachlorotitanium enolate 2 (titanium ate enolate; Scheme 4, step I.a), as assumed in the calculations above, or the neutral trichlorotitanium enolate 2', if a chloride ion dissociates from the complex (Scheme 4, step I.b).

The calculated geometries of the ate and the neutral titanium enolates are reported in Table S3 in the Supporting Information. Deprotonation causes a lengthening of the Ti–Cl bonds and a shortening of the Ti–O bonds of about 0.2 Å with respect to the [TiCl₄{(O=COCH₃)₂CH₂}] complex. Deprotonation also leads to minor effects: 1) a shortening of the C_{α} – C_{ester} bond and a lengthening of the C=O bond, and 2) a flattening of the boat-like conformation of the chelating diesters in the [TiCl₄{(O=COCH₃)₂CH₂}] complex, which reflects the change in the C_{α} hybridisation from sp³ to sp² and the conjugation within the enolate form.

The calculated free energies for the formation of the titanium enolates 2 and 2' in dichloromethane are -15.4 and -4.3 kcalmol⁻¹, respectively (see Table 3 below). The ate enolate 2 is thermodynamically favoured over the neutral complex 2', probably due to the energy required for the chloride dissociation in the latter case. These results indicate that the deprotonation of complex 1 is almost complete and occurs through step I.a, which leads to the titanium ate enolate. However, a small amount of the neutral enolate is expected to be present at the equilibrium, as its free energy is not exceedingly higher (11.1 kcalmol⁻¹). The results of theoretical calculations are in agreement with experimental evidence. Indeed, if the reaction mixture coming from the addition of triethylamine to the titanium complex of diethyl malonate is treated with an excess of AgSbF₆, AgCl precipitates and the solution changes colour; it passes from dark red to light orange. This result suggests the presence of a equilibrium [Eq. (1)], although shifted towards the titanium ate enolate.

(titanium ate enolate)
$$\leftarrow =$$
 (titanium neutral enolate) + Cl⁻
(1)

The addition of $AgSbF_6$ favours the dissociation of chloride ions from the ate enolate and shifts the equilibrium towards the neutral trichlorotitanium enolate (Scheme 5). The pre-



Scheme 5. Equilibrium between the tetrachloro- and the trichlorotitanium enolate of diethyl malonate.

cipitation of AgCl from tetrachlorotitanium enolates has been previously observed in several aldol-type reactions.^[11h,i] Moreover, calculated ¹³C NMR spectroscopic shifts for the CO and the C_{α} on passing from the ate to the neutral enolate (Table S4 in the Supporting Information) are roughly consistent with the experimentally observed shifts (Table S5 in the Supporting Information).

Practical implications: An in-depth knowledge of the mechanism of the investigated trimolecular condensation is crucial for tuning the experimental procedure. Because the onset of the entire process is the formation of the enolate ion, any strategy that favours the formation of the enolate may improve the reaction yields. Firstly, the order of addition of the reactants is important. If reactants are mixed simultaneously, the enolate ion does not form properly and the yield of the condensation product **A** is low (Scheme 6). In this case, a secondary reaction takes place leading mainly to the bis-indolic derivative **B**. The best procedure is to mix the reactants in the following order: 1) dimethyl malonate plus TiCl₄, 2) Et₃N, 3) isobutyraldehyde and 4) indole. The



Scheme 6. Dependence of the trimolecular reaction yield on the experimental procedure.

base has to be added to the reaction mixture containing the diester and TiCl₄ to allow the formation of the enolate. In the absence of the diester, the base reduces titanium(IV) to titanium(III) and undergoes irreversible reactions in the presence of aldehydes.^[24] Secondly, one must wait enough time (30 min at 0°C) before adding the base to allow the complexation of all of the diester and to favour its deprotonation. This procedure is general because it also works with linear carbon acids different from β -diesters and heterocycles other than indole (Scheme 7).^[12]

$$(Het) + R^{1} H + R^{3} OR^{2} OR^{$$

Scheme 7. Variation of the reactants in the trimolecular condensation. Het=substituted indoles and furans; R^1 =alkyl, aryl; R^2 =Me, Et, *i*Pr; R^3 =COOR₂, COMe, PO(OEt)₂, NO₂.

Formation of the Knoevenagel adduct by means of elimination of a water molecule

In the mechanism originally proposed for the considered trimolecular reaction (Scheme 2), the Knoevenagel condensation was assumed to involve the nucleophilic addition of the titanium enolate to the free aldehyde, thereby leading to an alkoxide species which, after protonation, eliminates a water molecule (Scheme 3, steps III and IV). However, some experimental evidence cast some doubts on the proposed steps of this condensation. Indeed, it is not clear how alkoxide is protonated in a basic environment. The elimination of a water molecule (Scheme 3, step IV) in the reaction mixture is also unlikely because water reacts vigorously with titanium tetrachloride according to the Equation (2):

$$TiCl_4 + 2H_2O \rightarrow TiO_2 + 4HCl$$
(2)

The elimination of water in the presence of titanium(IV) would still be possible if water were trapped by molecular sieves added into the reaction vessel. However, the trimolecular condensation of indole, dimethyl malonate and isobutyraldehyde promoted by $TiCl_4$ takes place also in the absence of molecular sieves, even if the yield of the reaction decreases (the yield is 81% in the presence of molecular sieves and 42% in their absence). Lehnert himself used

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TiCl₄ without molecular sieves in his Knoevenagel condensations.^[15] The limited role of molecular sieves in the investigated reactions indicates that another species that traps water is present in the reaction mixture, probably a titanium species.

Theoretical results also suggest a different pathway for

this condensation reaction. The nucleophilic attack of [TiCl₄- $\{(O=COCH_3)_2CH\}]^-$ to the free formaldehyde (Scheme 3, step III) was simulated by linear transit calculations in which the distance between the two carbon atoms involved in the formation of the new bond (i.e., the C_a of the enolate and the carbonyl carbon of the aldehyde) was gradually reduced from 2.15 to 1.60 Å. These calculations indicate that the electronic energy of the enolate-aldehyde system increases monotonically by about 25 kcalmol⁻¹ on decreasing the C-C distance (Figure S2 in the Supporting Information). Accordingly, any attempt to obtain an energy minimum of the enolate-aldehyde covalent adduct led to the separation of the two molecules. The C-C bond formation is thus thermodynamically unfavoured, that is, the aldol adduct is not stable under these conditions. A possible explanation for this result is that the metal fragment reduces the nucleophilicity of the coordinated enolate by electron withdrawal and that the carbonyl carbon of the aldehyde is not electrophilic enough to be attacked by the enolate ion. As a matter of fact, Brønsted acid catalysis is generally advised for aldol reactions.[1-3]

Formation of the Knoevenagel adduct by means of formation of a titanyl chloride

Theoretical thermodynamics: The presence of TiCl_4 in the reaction medium suggests a possible method to enhance the electrophilicity of the aldehyde by its coordination to the metal centre of the titanium enolate complex, followed by its intramolecular reaction with the adjacent enolate ligand. Although the hexacoordinated anionic titanium enolate **2** is coordinatively saturated, the aldehyde can easily replace either one of the carbonyl groups of the malonate or a chloride ion (Scheme 8, steps II.a and II.b, respectively). However, the pentacoordinated neutral titanium enolate **2'** is already coordinatively unsaturated and can straightforwardly coordinate the aldehyde to give the corresponding octahedral complex **3'** (Scheme 8, step II.c).

Table 3 reports the calculated enthalpies and free energies—in the gas phase and in solution—for the coordination of dimethyl malonate with three aldehydes, that is, formaldehyde (R=H), benzaldehyde (R=Ph) and isobutyraldehyde (R=*i*Pr). Steps II.a and II.b, which involve the ate enolate complex, are endothermic, with ΔH^{298} values in solution in the range of 14–18 and 1–9 kcal mol⁻¹, respectively. On the other hand, step II.c, which involves the neutral eno-

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Scheme 8. Possible pathways for aldehyde coordination to titanium.

Table 3. Calculated reaction enthalpies and free energies in the gas phase and dichloromethane for the steps I-IV of the Knoevenagel condensation. Values are in kcalmol⁻¹.



late, is exothermic, with ΔH^{298} in solution in the range from -12 to -4 kcalmol⁻¹. These results are not surprising, because the coordination of the aldehyde to the pentacoordinated neutral enolate occurs without the cleavage of any bond. As expected, the entropic effect in steps II.a and II.c is unfavourable by approximately 11 kcalmol⁻¹, as the alde-

hyde coordination implies the loss of a translational degree of freedom.

The subsequent aldol reaction within complexes **3** and **3'** was investigated by addressing the intramolecular nucleophilic attack of the C_{α} of the enolate to the carbonyl carbon of the aldehyde (Scheme 9 and Table 3, steps III.a and III.b).



Scheme 9. Proposed pathways for the intramolecular aldol reaction and Newman projections of **4** and **4**'.

For the simplest formaldehyde substrate, the reaction is exothermic with reaction enthalpies in solution of -17.3 and -5.9 kcalmol⁻¹ for steps III.a and III.b, respectively. For the more sterically hindered isobutyraldehyde and benzaldehyde substrates, the corresponding processes III.a and III.b are less exothermic or slightly endothermic. Indeed, the enthalpies in solution of processes III.a and III.b are -3.3 and 7.7 kcalmol⁻¹ for R=Ph, or -5.7 and -4.4 kcalmol⁻¹ for R=*i*Pr, respectively. Notice that for all aldehydes the intramolecular aldol reaction is more favourable for **3** (step III.a) than for **3'** (step III.b), probably due to the higher ring strain in **4'**.

Indeed, products **4** and **4'** have quite different structures: the former is a metallacycle and the latter is a metallabicycle. The metallacycle unit in **4** assumes a chair-like conformation. For R = H, the uncoordinated ester group of the product occupies an equatorial position. For R = Ph and R = iPr, the alkyl group and the carboxymethyl group may assume two different conformations: equatorial–equatorial, which corresponds to the *anti*-aldol product, and axial–equatorial, which corresponds to the *syn*-aldol (non-Evans) product.^[6a, 11g-i] However, the formation of the *anti* adduct is prevented by the steric clashes between the axial group and the TiCl₄ metal moiety. For these reasons, in the case of benzaldehyde and isobutyraldehyde the geometry could be optimised only for the *syn* adduct (see Scheme 9).

The final elimination that leads to the Knoevenagel adduct requires the breaking of the aldehyde C–O bond. On the basis of the high oxophilicity of titanium,^[25] we assumed that the aldehyde oxygen leaves as a titanyl group (Ti=O, Scheme 10). The titanyl group has a double-bond character,^[26] so it can be formed only if a chloride ion leaves

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Scheme 10. Possible pathways for the formation of the Knoevenagel adduct.

the metal and the coordination number of titanium decreases from six to five.

Large and positive gas-phase enthalpies are calculated for steps IV.a and IV.b (Table 3), thereby underlining the high energy cost associated with the cleavage of three bonds, that is, C–H, C–O and Ti–Cl. This energy is only partially counterbalanced by the strengthening of the Ti–O and $C_{aldehyde}$ – C_{α} bonds and by the base protonation. However, the formation of the ions Et₃NH⁺ and Cl⁻ gives rise to large and negative solvation contributions that overcome the energy costs, thus making both processes exothermic and exoergonic in solution. The calculated reaction enthalpies and free energies for steps IV.a and IV.b are not significantly affected by the nature of R, probably implying that substituent steric effects are negligible, as confirmed by the calculated geometries. The titanium complexes **5** and **5'** maintain the pyramidal-square coordination geometry, with apical oxygen.

Figure 3 reports the enthalpy diagram for the Knoevenagel condensation of isobutyraldehyde and dimethyl malonate in solution. Two pathways are possible for this reaction:



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A (I.a–II.a–III.a–IV.a, solid line) and B (I.a–II.b.–III.b–IV.b or I.b–II.c–III.b–IV.b, dashed line), leading respectively to **5** and **5'**. Indeed, the two alternative routes of pathway B are equivalent because **2** and **2'** are in equilibrium. In both pathways the overall reaction is highly exothermic in solution, with ΔH values of –23.7 and –25.9 kcalmol⁻¹, respectively (Figure 3). Similar values are observed for formaldehyde and benzaldehyde. To see which is the most favoured pathway, we studied the kinetics of the Knoevenagel condensation.

Theoretical kinetics: We investigated the kinetics of the aldehyde coordination to the titanium enolate (steps II.a-II.c). The reaction II.c is a simple ligand association in which the aldehyde binds to the trichlorotitanium enolate 2'. This process is expected to have a small barrier mainly resulting from the metal-fragment reorganisation. The coordination of the aldehyde with the titanium ate enolate 2 occurs through a ligand-exchange process in which either an ester carbonyl group (II.a) or a chloride ion (II.b) is replaced with the carbonyl oxygen of the aldehyde. We assumed a dissociative mechanism for this ligand exchange, in which titanium loses the leaving ligand before binding to the incoming one. The energy barriers of steps II.a and II.b were first estimated by linear transit calculations in which the distances between titanium and the leaving ligand (O= Cester for II.a and Cl for II.b) are increased from the value they assume in 2 (2.0 and 2.4 Å respectively) to a value (4.5 Å) large enough to consider the ligand uncoordinated (Figure S3 in the Supporting Information). The results indicate that the energy barriers of steps II.a and II.b are 23.8 and 20.7 kcal mol⁻¹, respectively, in solution.

We then investigated the kinetics of reactions III.a and III.b. The aldol reactions are characterised by relatively low activation enthalpies of $6-16 \text{ kcal mol}^{-1}$, and activation free

energies of $8-19 \text{ kcal mol}^{-1}$, in solution (Table 4). The three aldehydes show a different trend of reactivity. In path III.a, the activation enthalpies follow both the hindrance and the electronic effect order (i.e., $i Pr \approx Ph > H$), with formaldehyde being the most reactive one. In path III.b, the activation enthalpies follow the order Ph > H > iPr with isobutyraldehyde being unexpectedly the most reactive. The lower reactivity of 3' with R= Ph could be due to the conjugation between the carbonyl group and the phenyl ring, which reduces the electrophilicity of the aldehyde substrate. To gain further insight into the influence of steric effects on

Figure 3. Calculated enthalpy diagrams for the Knoevenagel condensation of isobutyraldehyde and dimethyl malonate in CH_2Cl_2 . Solid line (-----): path A. Dashed line (-----): path B.

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Table 4. Calculated activation enthalpies and free energies in the gas phase and dichloromethane for the aldol reaction (step III). Values are in kcal mol^{-1} .

Step	R	$\Delta H^{*}(g)$	$\Delta G^*(g)$	$\Delta H^{+}(sol)$	$\Delta G^{*}(\mathrm{sol})$	$\Delta\Delta G^{*}_{ m solv}$
III.a	Н	10.7	12.0	7.1	8.4	-3.6
	Ph	13.7	16.0	13.0	15.3	-0.7
	iPr	17.2	14.3	13.3	10.4	-3.9
III.b	Н	11.2	14.1	10.3	13.2	-0.9
	Ph	16.8	20.1	16.0	19.2	-0.8
	iPr	9.0	12.1	6.3	9.4	-2.7

the kinetics of these aldol reactions, we analyzed in detail the geometries of the calculated transition states for $\mathbf{R} = i\mathbf{P}\mathbf{r}$ in the two paths, $\mathbf{TS}_{\mathbf{IIIa}}$ and $\mathbf{TS}_{\mathbf{IIIb}}$ (Figure 4). They are both late transition states and reflect essentially the typical Zimmerman–Traxler cyclic structure.^[27] In both transition states the isopropyl group is close to one of the ester groups. However, in $\mathbf{TS}_{\mathbf{IIIa}}$ this ester group is not coordinated to the metal and can exert a steric hindrance towards the isopropyl group. In $\mathbf{TS}_{\mathbf{IIIb}}$ the ester group is held far away by the metal coordination, which leads to a less hindered transition state.



Figure 4. Calculated transition state geometries a) of the transition states TS_{IIIa} and TS_{IIIb} for the paths III.a and III.b and b) of the intermediate and the transition states TS_{IVa1} . TS_{IVa2} and TS_{IVb} for the paths IV.a and IV.b. Interatomic distances and bond angles are reported in Angstrom [Å] and degrees [°], respectively.

This difference could explain why the isobutyrraldehyde is more reactive in III.b rather than in III.a.

Two different mechanisms have been considered for the elimination reactions: an E1cB-like mechanism (route IV.a) and an E_2 -like mechanism (route IV.b). Route IV.a occurs in two steps (Scheme 11a): 1) deprotonation of C_a in 4 by Et₃N



Scheme 11. Proposed mechanisms for the Knoevenagel condensation in CH_2Cl_2 : a) step IV.a and b) step IV.b.

(the strongest base in the reaction medium) with formation of the corresponding carbanion I; 2) formation of the C= C_{α} double bond with the breaking of the Caldehyde-O bond, formation of a titanyl group and dissociation of a chloride ion. The intermediate I is relatively stable due to the delocalisation of the negative charge on the proximal ester group (Scheme 11a), thus making the deprotonation of 4 a relatively favourable process. Route IV.b is characterised by a concerted proton transfer from C_{α} to Et_3N , the formation of a titanyl complex and the release of a chloride ion from the metal complex. The deprotonation of 4' (Scheme 11b) is an unfavourable process because the corresponding carbanion lacks of any resonance stabilisation. Figure 4 reports the optimised geometries of the intermediate I and the transition states TS_{IVa1}, TS_{IVa2} and TS_{IVb}. The discussion will be limited to the most representative structures with R = iPr because the nature of R did not significantly affect the geometry of the calculated structures.

The geometry of $\mathbf{TS}_{\mathbf{IVa1}}$ is that expected for a typical proton exchange from the acidic C_{α} to the basic nitrogen of Et₃N. The proton transfer occurs along the direction of the C_{α} -H bond, thus minimising the steric repulsion between the base and the equatorial R group. The geometry of $\mathbf{TS}_{\mathbf{IVa2}}$ is characterised by the incipient breaking of C–O and Ti–Cl bonds and the formation of Ti–O and C– C_{α} π bonds. The

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energy imbalance between the breaking of two strong bonds and the formation of two weak bonds suggests a highenergy TS_{IVa2} . Nevertheless, TS_{IVa2} is a late transition state and benefits from the stabilisation associated with the incipient formation of two monocharged and highly stabilised anions. The relatively high value of 2.177 Å for the length of the breaking C–O bond confirms the late transition state.

The molecular structure of $\mathbf{TS}_{\mathbf{IVb}}$ is formed by three molecular fragments: the basic Et₃N that accepts the proton from the acidic C_a, the incipient titanyl complex and the dissociating chloride ion. The calculated distances were 1.561 for N–H, 1.480 for C_a–H, 1.783 for C–O, 1.724 for Ti–O and 2.773 Å for Ti–Cl . Figure 5 reports the energy profiles calculated for routes IV.a and IV.b. The activation enthalpies corresponding to transition states $\mathbf{TS}_{\mathbf{IVa1}}$ and $\mathbf{TS}_{\mathbf{Iva2}}$ are quite



Figure 5. Calculated enthalpy paths for the processes IV.a and IV.b of isobutyraldehyde in CH_2Cl_2 . R.C. = reaction coordinate.

low, 11.0 and 11.8 kcal mol⁻¹, respectively, thereby suggesting that IV.a is a kinetically facile process. On the other hand, the activation enthalpy corresponding to \mathbf{TS}_{IVb} is 39.9 kcal mol⁻¹ and is therefore a kinetically unfavoured process.

In summary, reaction IV.a is kinetically much more favoured than reaction IV.b, so the Knoevenagel condensation takes place through pathway A (steps I.a–II.a–III.a–IV.a, Figure 3).

Experimental evidence: Experimental evidence agrees with the picture emerging from theoretical calculations, thereby indicating two possible pathways for the Knoevenagel condensation: one passing through the fully chlorinated complex **3** (pathway A) and one passing through complex **3'**, in which titanium has lost a chloride ion (pathway B), the latter being significantly kinetically unfavoured. Indeed, if

the Knoevenagel condensation is carried out in the presence of a chloride scavenger, such as $AgSbF_6$, the reaction is forced to follow pathway B (I.a–II.b–III.b–IV.b or I.b–II.c– III.b–IV.b, Figure 3) and, due to the high activation enthalpy foreseen for step IV.b, the Knoevenagel adduct hardly forms. As a consequence, the final trimolecular condensation product is obtained only in traces (Table S7 in the Supporting Information, entry 1).

Calculations indicate that the solvent plays an important role in the overall Knoevenagel condensation, with $\Delta\Delta G_{solv}$ values being essential to make the condensation exothermic (Table 3). Experimental evidence also supports these theoretical results, thus showing that the yield of the trimolecular condensation product increases by increasing the solvent polarity (14% in toluene and 81% in dichloromethane).^[12]

The formation of titanyl chloride has been hypothesised in various reactions promoted by titanium(IV) that formally imply the elimination of a water molecule;^[7d,26] these include the Knoevenagel condensation performed by Lehnert.^[21d]

The formation of titanyl chloride has practical implications on the reaction conditions that are also consistent with the experimental evidence. The fact that TiCl₄ is consumed during the Knoevenagel condensation explains why the trimolecular reaction is not catalytic and requires a stoichiometric amount of TiCl₄. Unfortunately, to the best of our knowledge, there is no reagent able to recover TiCl₄ from TiOCl₂, so there is no way to make this reaction

catalytic. One possible drawback of the proposed mechanism is that it requires two molar equivalents of base whereas only one is experimentally used. However, because the final β elimination (step IV.a) is a highly favoured process, any base may easily deprotonate compound **4**, thus explaining why the whole Knoevenagel condensation requires only one molar equivalent of Et₃N.

To get further experimental evidence for the formation of titanyl complexes in the last step of the Knoevenagel condensation (β elimination), we performed some analytical and synthetic investigations.

NMR spectra: Three separate experiments were performed on the Knoevenagel adduct of benzaldehyde. In the first one, we recorded the ¹H NMR and the ¹³C NMR spectra of the purified Knoevenagel adduct **Ky** (Tables 5 and 6, entry 1). In the second experiment, we prepared the adduct

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Table 5. ¹ H NMR spectra of benzylidene malonate Ky . MeO_{3} $\stackrel{0}{\downarrow}$ $\stackrel{0}{\downarrow}$ OMe_{2} $\stackrel{0}{\downarrow}$ $\stackrel{0}{\downarrow}$ Ky					
Entry		δ(H2) [ppm]	$\delta(H_{Ar})$ [ppm]	δ(OCH ₃) [ppm]	
1	Ку	7.78	7.36– 7.45	3.85 and 3.84 (6 H)	
2	Ky in the reaction mix- ture	7.77 (br)	7.41 (br)	3.82 (6H)	
3	Ky+ TiCl ₄ (1.0 equiv)	8.62	7.45– 7.58	4.27 (3H) and 4.01 (3H)	

Table 6. ¹³C NMR spectra of benzylidene malonate Ky.

Entry		δ(C1), δ(C2) [ppm]	δ(C3), δ(C4) [ppm]	δ(OCH ₃) [ppm]	$\delta(C_{Ar})$ [ppm]
1	Ку	143.3, 125.9	167.5, 164.8	53.0	129.2– 133.2
2	Ky in the reac- tion mixture	135.0, 128.6	168.2, 168.7	55.3	129.2– 131.2
3	Ky+ TiCl ₄ (1.0 equiv)	134.5, 132.4	171.4, 176.0	57.9, 56.8	129.5– 134.5

directly in the NMR spectroscopy tube by adding TiCl₄ and Et₃N to benzaldehyde and dimethyl malonate (see the Experimental Section; Tables 5 and 6, entry 2). In the third experiment, we recorded the NMR spectra of the pure adduct Ky in the presence of one equivalent of TiCl₄ (Tables 5 and 6, entry 3). We found different ¹H NMR and ¹³C NMR spectra for each of the three experiments. In particular, the Knoevenagel adduct prepared in the NMR spectroscopy tube showed NMR spectroscopic signals shifted with respect to those of the pure adduct (Tables 5 and 6; compare entries 1 and 2). These results highlight that the Knoevenagel adduct is bound to titanium in the reaction mixture. However, the spectra of this complexed adduct are different from those of the complex TiCl₄-Ky (Tables 5 and 6; compare entries 2 and 3). The only explanation for these results is that titanium is not present as a tetrachloride complex in the reaction mixture. This result is consistent with the formation of the titanyl complex 5. The same behaviour was observed for the Knoevenagel adduct of isobutyraldehyde (Tables S8 and S9 in the Supporting Information).

UV/Vis spectra: UV/Vis absorbance studies were performed to further support the hypothesis of the formation of **5**. Indeed, titanium coordination is expected to affect the UV/ Vis profile of the Knoevenagel adduct through the electronic transitions involving metal d orbitals. This is particularly true for benzaldehyde complexes because the presence of an aromatic group conjugated with the first coordination shell of the metal is expected to give some UV/Vis signals that are diagnostic of the metal coordination. Analogously to NMR spectroscopic measurements, we recorded the UV/ Vis spectra of the free Knoevenagel adduct of benzaldehyde (**Ky**), its complex with TiCl₄ (TiCl₄–**Ky**) and the corresponding adduct formed in the reaction mixture. The most intense absorbance bands are reported in Table S10 in the Supporting Information. The UV/Vis profile of the adduct formed in the reaction mixture and that of TiCl₄–**Ky** are dominated by a broad band at $\lambda = 350$ nm (Table S10 in the Supporting Information, entries 11 and 7, respectively). This band is probably due to the presence of the metal because it is not detected in the free Knoevenagel adduct **Ky**.

The spectra of TiCl₄–**Ky** and the adduct in the reaction mixture show some differences as well. The UV region of the former spectrum is characterised by one band at 281 nm and one at 350 nm, whereas the latter is characterised by four bands at 245, 290, 332 and 350 nm. These results indicate that the two complexes are different from each other, which is in agreement with the formation of the titanyl complex **5** in the latter mixture.

Time-dependent density functional theory (TDDFT) calculations were carried out on free Ky, TiCl₄-Ky and 5 in solution. These calculations allowed us to assign the absorbance bands observed in the experimental UV/Vis spectra to specific electronic transitions (Table S10 in the Supporting Information). The observed bands for the free Knoevenagel adduct at 281 nm (calcd: 253, 277 and 284 nm) and 220 nm (calcd: 215 nm) are due to $\pi \rightarrow \pi^*$ transitions involving the aromatic moiety with only slight contributions due to $n(O) \rightarrow \pi^*$ transitions from the ester oxygen lone pairs. A band at 281 nm (calcd: 289 nm) is also detected in the TiCl₄-**Ky** spectrum, but is assigned to an $n(Cl) \rightarrow \pi^*$ transition from the chlorine lone pairs of the TiCl₄ moiety. The two bands observed for the reaction mixture at 290 and 245 nm (calcd: 278 and 246 nm, respectively) are assigned to $n(Cl,O) \rightarrow \pi^*$ electronic transitions in 5. The signal at 290 nm corresponds to the $n(Cl) \rightarrow \pi^*$ transition involving the chlorine lone pairs, the same observed for the peak at 281 nm of the $TiCl_4$ -Ky adduct. The signal at 245 nm is due to $n(Cl,O) \rightarrow \pi^*$ transitions from the titanyl oxygen and its presence supports the formation of complex 5. TDDFT calculations also allowed us to assign the broad band at 330-350 nm observed for TiCl₄-Ky and for the adduct in the reaction mixture. For both complexes the most intense transition is calculated at 330 nm with less intense peaks around this value, which is in agreement with the broad experimental spectral shape. However, the peak at 330 nm involves different transitions in the two cases: $d \rightarrow \pi^*$ and $d \rightarrow d^*$ for the TiCl₄-Ky adduct and $n(Cl,O) \rightarrow \pi^*$ transition for 5. The transition at 424 nm calculated for 5, although weak, is responsible for the yellow colour of the reaction mixture; no band is experimentally observed in this region of the spectrum, probably due to the low concentration used in the experiment.

IR spectra: IR spectroscopy provided further evidence of the formation of a titanyl complex. The adducts **Ky** and **Kz** in the reaction mixture show two peaks at around 1000 cm^{-1} that are absent in the pure adduct and in its complex with TiCl₄ (Tables S11 and S12 in the Supporting Information,

entries 1–3). These signals can be assigned to the titanyl group Ti=O, based on the analogy with the spectra of similar titanyl complexes.^[26,28a] If the complex **Ky** in the reaction mixture is treated with water, thus causing the hydrolysis of titanium(IV), the same signals around 1000 cm⁻¹ are observed (Table S11 in the Supporting Information, entry 4), thus supporting their attribution to the titanyl group.

Synthesis and reaction of the proposed intermediate **5**: One way to investigate a reaction mechanism is to isolate a possible intermediate from the reaction mixture and to use it for the preparation of the final product under the same experimental conditions. In our case, the intermediate **5** is unstable in air because of the presence of reactive Ti–Cl bonds and therefore could not be isolated. Nevertheless, we could prepare **5** directly using a different procedure. The further addition of indole, under the same experimental conditions, allowed to obtain the final trimolecular condensation product.

If isobutylidene malonate \mathbf{Kz} is treated with one equivalent of indole in CH_2Cl_2 in the absence of $TiCl_4$, no reaction takes place (Scheme 12a). If \mathbf{Kz} is treated with one equiva-



Scheme 12. Reaction of isobutylidene malonate **Kz** and indole under various reaction conditions.

lent of TiCl₄ in CH₂Cl₂, the solution becomes yellow and the NMR spectrum of the adduct changes (Tables S8 and S9 in the Supporting Information), thereby suggesting again the formation of a TiCl₄-Kz complex. Nevertheless, upon further addition of one equivalent of indole, the condensation product is not obtained and a complex mixture of compounds is recovered (Scheme 12b). Because neither the pure Knoevenagel adduct nor its complex with TiCl₄ afford the final product under the adopted reaction conditions, it can be inferred that neither of them is the intermediate of the trimolecular condensation. On the contrary, if TiCl₄-Kz is treated with one equivalent of water, only two of the Ti-Cl bonds are expected to hydrolyse, thus leading to 5. Upon further addition of one equivalent of Et₃N and one equivalent of indole, the condensation product forms in 33% yield (Scheme 12c). These results indicate that titanyl complex 5

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has to be formed for the Knoevenagel adduct to undergo the Michael addition.

Conclusion

The titanium-promoted Knoevenagel condensation of dimethyl malonate and three different aldehydes has been investigated by theoretical and experimental approaches. A plausible three-step mechanism has been proposed and each step is assisted by the presence of titanium: 1) the initial deprotonation of diethyl malonate is favoured by the acidifying effect due to the coordination of titanium(IV) to the diester; 2) the following aldol condensation is promoted by the coordination of titanium(IV) to both the reagents, the enolate and the aldehyde; 3) the intramolecular elimination of water is feasible because of the formation of a titanyl complex. The results of this study are very interesting because they would allow for the tuning of the experimental procedure of the trimolecular condensation, thereby reducing the formation of secondary products and improving the reaction yield. Moreover, the information provided by DFT calculations, such as the structures of transition states and intermediates, can be used to design stereocontrolled TiCl4-Et₃N-promoted trimolecular condensation. In the light of these results, we are currently investigating synthetic approaches based on the stereochemical implications of this model.

Experimental Section

Computational details: All calculations were carried out at density functional theory level by using the Jaguar 6.0 program.^[29] Geometry optimisation has been performed by using the B3LYP functional^[30,31] with the 6-31G** basis set for main groups elements (C, O, N, H) and by the Los Alamos LACV3P^[32-34] basis for Ti; this includes relativistic effective core potentials. This basis set will be thereafter referred to as LACV3P**. The geometry of reactants, intermediates, products (local minima) and transition states (saddle points) of reaction obtained at this level of theory have been used to calculate the reaction path in both the gas and solution phase. Intrinsic reaction coordinate (IRC) calculations^[35,36] have been further carried out to assess the configuration of reactants and products that are connected through the involved TS. Subsequent vibrational frequency calculations based on analytical second derivatives at the B3LYP/ LACV3P** level of theory have been carried out to confirm the nature of the local minima and transition state and to compute the zero-pointenergy (ZPE) and vibrational entropy corrections at 298.15 K. Solvation free energies were evaluated by a self-consistent reaction field (SCRF) approach^[37,38] based on accurate numerical solutions of the Poisson– Boltzmann equation.^[39,40] Solvation calculations were carried out on the gas-phase geometry at the B3LYP/LACV3P** level of theory by employing a dielectric constant of 8.93 and a solvent radius of 2.67 for dichloromethane. The activation and reaction enthalpies in solution have been estimated by adding the solvation free energy to the corresponding gasphase enthalpies. Their variations are expected to be reliable since the solvation entropy variations are likely to be negligible. UV/Vis spectra have been calculated for benzylidene malonate, its complex with TiCl₄ and the hypothesised titanyl complex 5' by using Gaussian 03 program package.[41] Geometry optimisations have been first performed at B3LYP/ LACV3P** level of theory in a vacuum, then time-dependent DFT calculations at the same level of theory have been carried out to calculate the

Jaguar code.^[42] **General remarks**: All solvents were dried and purified by standard procedures prior to use. Melting points were determined using a Reichert Thermovar hot-stage apparatus. Reactions were monitored with Fluka TLC aluminium sheets (Kieselgel $60F_{254}$) and flash chromatography was carried out with silica gel 60 (230–400 mesh ASTM) supplied by Fluka. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were acquired using a Varian AC 300 spectrometer at (25.0 ± 0.1) °C. UV/Vis spectra were acquired using a Cary 100 Bio spectrophotometer at (25.0 ± 0.1) °C with 1 mm cuvettes. IR spectra were measured using a Varian spectrophotometer (4000–400 cm⁻¹). The solutions in CH₂Cl₂ were prepared in a glove box under a nitrogen atmosphere and placed between two KBr discs. The adherence of the liquid film to the discs prevented the hydrolysis of the complex.

ed at the same level of theory by using the approach implemented in the

Enolate formation test, general procedure: A solution of carbon acid (1.0 equiv) in deuterated solvent (700 µL) was prepared. TiCl₄ (1.0 equiv), Et₃N (1.0 equiv) and DCl/D₂O 35% w/w (3.0 equiv) were added in sequence. ¹H NMR, ¹³C NMR and coupled ¹³C NMR spectra of the solution were acquired after each addition. The concentrations of the carbon acids were 8.75×10^{-2} M in CDCl₃ for dimethyl malonate and diisopropyl malonate and 4.10×10^{-1} M in CD₂Cl₂ for diethyl malonate.

NMR spectroscopic titrations: An NMR spectroscopy tube was filled with a solution of the host diester, *H*, in a deuterated solvent (CDCl₃ or CD₂Cl₂) at three different concentrations ([H]=8.24×10⁻², 2.23×10⁻¹ and 4.10×10⁻¹M). TiCl₄ [i.e., the guest *G* of the following Eq. (3)] was added to the diester [i.e., the host *H* of the following Eq. (3)] solution in the NMR spectroscopy tube with increasing volumes from 0 to 2 equiv (relative to the diester). Volume and concentration changes were taken into account in the calculation. The binding constants were determined by nonlinear regression of Equation (3):

$$\delta_{\text{obsd}} - \delta_0 = \frac{\frac{1}{K} + [G]_0 + [H]_0 - \sqrt{\left(\frac{1}{K} + [G]_0 + [H]_0\right)^2 - 4[G]_0[H]_0}}{2[G]_0} (\delta_{\text{INF}} - \delta_0)$$
(3)

in which the binding constant $K = [\text{complex}]/([H]_{eq}[G]_{eq})$, δ_{obsd} is the experimentally measured chemical shift after each addition of titrant, δ_0 is the chemical shift of a nucleus in the host molecule, δ_{INF} is the chemical shift of a nucleus in the host-guest complex, $[H]_0$ is the initial concentration of the host and $[G]_0$ the added concentration of the guest.

Job plots: Several solutions of host and guest compounds were prepared, at a total concentration of 8.21×10^{-1} M in CDCl₃ and with host molar ratio varying from 0.02 to 1. ¹H NMR spectra of the mixtures were recorded and the chemical shifts were analysed by the Job method,^[19] modified for NMR spectroscopic data.

Test with AgSbF₆: AgSbF₆ (182.7 mg, 5.32×10^{-4} mol, 1.7 equiv) was added to a solution of the titanium enolate of diethyl malonate in CD₂Cl₂ previously obtained. ¹H and ¹³C NMR spectra were acquired before and after the addition of AgSbF₆.

Dimethyl benzylidenemalonate (Ky):^[43] Dimethyl malonate (8.76 mmol; 1.0 equiv) was added to a solution of TiCl₄ (1.0 equiv) in dry dichloromethane (20 mL) at 0 °C while stirring under nitrogen atmosphere, in the presence of 3 Å molecular sieves. After 30 min, triethylamine was added (1.0 equiv) to the resulting yellow suspension and the mixture turned immediately dark red. Benzaldehyde (1.0 equiv) was added and the mixture was stirred for 3 h at 0 °C. On addition of a 1 M HCl aqueous solution (20 mL), two phases formed. The aqueous layer was separated, the organic phase was dried over MgSO₄ and evaporated to dryness under reduced pressure. The crude residue was purified by flash chromatography

on silica gel (eluent petroleum ether/ethyl acetate 9:1), then put in the refrigerator. Product **6** crystallised spontaneously (36%). ¹H NMR (300 MHz, CD₂Cl₂): δ =3.84 (s, 3H; OCH₃), 3.85 (s, 3H; OCH₃), 7.36–7.45 (m, 5H), 7.78 ppm (s, 1H; H2); ¹³C NMR (75 MHz, CDCl₃): δ =53.0 (OCH₃); 125.9 and 143.3 (C1 and C2); 129.2–133.2 (C_{Ar}); 164.8 and 167.5 ppm (C3 and C4).

Synthesis of Ky in the NMR spectroscopy tube: A solution of dimethyl malonate in deuterated solvent (500 μ L, 4.38 × 10⁻¹ M) was prepared in an NMR spectroscopy tube. The tube was cooled in an ice-water bath. TiCl₄ (2.19×10⁻⁴ mol, 1.0 equiv), Et₃N (2.19×10⁻⁴ mol, 1.0 equiv) and benzal-dehyde (2.19×10⁻⁴ mol, 1.0 equiv) were added in sequence. The mixture was left in the bath for 3 h before the ¹H NMR and ¹³C NMR spectra of the solution were recorded at 25.0 °C.

Complexation of Ky with TiCl₄: Titanium tetrachloride $(3.63 \times 10^{-5} \text{ mol}, 1.0 \text{ equiv})$ was added to a solution of **Ky** (8.00 mg, $3.63 \times 10^{-5} \text{ mol}, 1.0 \text{ equiv})$ in deuterated solvent (500 µL). ¹H NMR and ¹³C NMR spectra of the mixture were recorded before and after the addition of TiCl₄.

Dimethyl isobutylidenemalonate (Kz):^[44] Dimethyl malonate (8.76 mmol, 1.0 equiv) was added to a solution of TiCl₄ (1.0 equiv) in of dry dichloromethane (20 mL) at 0°C while stirring under a nitrogen atmosphere, in the presence of 3 Å molecular sieves. After 30 min, triethylamine was added (1.0 equiv) to the resulting vellow suspension and the mixture turned immediately dark red. Isobutyraldehyde (1.0 equiv) was added and the mixture was stirred for 3 h at 0°C. On addition of a 1 M HCl aqueous solution (20 mL), two phases formed. The aqueous layer was separated, the organic phase was dried over MgSO4 and evaporated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent petroleum ether/ethyl acetate 9:1), then distilled at reduced pressure to afford 7 as an uncoloured liquid (76%). ¹H NMR (300 MHz, CD₂Cl₂): $\delta = 1.05$ (d, $J_{3,4} = J_{3,5} = 6.6$ Hz, 1H; H4 and H5), 2.65 (dst, $J_{23}=10.8$ Hz, $J_{34}=J_{35}=6.6$ Hz, 1H; H3), 3.73 (s, 3H; OCH₃), 3.78 (s, 3H; OCH₃), 6.78 ppm (d, J_{2,3}=10.8 Hz, 1H; H2); ¹³C NMR (75 MHz, CD₂Cl₂): δ = 22.1 (C4 and C5), 29.8 (C3), 52.5 (OCH₃), 52.6 (OCH₃), 126.1 (C1), 156.1 (C2), 164.8 and 166.3 ppm (C6 and C7).

Synthesis of Kz in the NMR spectroscopy tube: A solution of dimethyl malonate in deuterated solvent ($500 \ \mu$ L, $4.38 \times 10^{-1} \ m$) was prepared in an NMR spectroscopy tube. The tube was cooled in an ice-water bath. TiCl₄ ($2.19 \times 10^{-4} \ m$ ol, $1.0 \ equiv$), Et₃N ($2.19 \times 10^{-4} \ m$ ol, $1.0 \ equiv$) and isobutyr-aldehyde ($2.19 \times 10^{-4} \ m$ ol; $1.0 \ equiv$) were added in sequence. The mixture was left in the bath for 3 h before the ¹H NMR and ¹³C NMR spectra of the solution were recorded at 25.0°C.

Complexation of Kz with TiCl₄: Titanium tetrachloride $(3.63 \times 10^{-5} \text{ mol}, 1.0 \text{ equiv})$ was added to a solution of **Kz** (8.00 mg, $3.63 \times 10^{-5} \text{ mol}, 1.0 \text{ equiv})$ in deuterated solvent (500 µL). ¹H NMR and ¹³C NMR spectra of the mixture were recorded before and after the addition of TiCl₄.

UV/Vis spectra of the free Knoevenagel adduct (Ky), its complex with TiCl₄ (TiCl₄-Ky) and the complex in the reaction mixture: (See Table S10 in the Supporting Information). Three solutions in CH₂Cl₂ were prepared having a concentration of 2.00×10^{-3} M for each compound and their UV/Vis spectrum was recorded: 1) Ky, 2) Ky+TiCl₄, 3) dimethyl malonate+TiCl₄+Et₃N+benzaldehyde.

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