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Chemoselective Claisen–Schmidt bis-substitutional condensation catalyzed by an alkoxy-bridged dinuclear Ti(IV) cluster

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ABSTRACT

The highly efficient and chemoselective α,α′-bis-substitution of alkanones is important in organic synthesis. Herein, a dimeric titanium cluster, $Ti_2Cl_2(OPr^i)_6{\cdot}2HOPr^i$ (**Ti_2**), is used in the Claisen–Schmidt condensation reaction, for the selectively activation of symmetrical ketones containing α,α′-methylene groups and production of α,α′-bis-substituted alkanones in high efficiency and chemoselectivity. The high efficiency and chemoselectivity can be extended to a variety of typical alkanones and aromatic aldehydes. Both of the oxo-bridged dimeric motif of **Ti_2** and the ionic Ti–Cl bond are responsible for the high efficiency and chemoselectivity.

1. Introduction

The α,α′-bis-substituted alkanones are an important and versatile class of pharmacophores that possess a broad spectrum of biological activities such as HIV-1 integrase inhibitory,[1] antimalarial activity,[2] cytotoxic,[3] cancer chemopreventive[4] and *anti*-oxidant[5] activity, and are the precursors of potentially bioactive pyrimidine derivatives as well as new organic materials for nonlinear optical applications.[6] They are also an important class of natural products which are useful for pharmaceutical applications. The Claisen–Schmidt reaction (also known as cross Aldol condensation), an important C–C bond formation strategy, provides an efficient way to form the α,α′-bis-substituted alkanone moiety by bis-substitution of ketones containing α,α′-methylene groups.

Generally, Claisen–Schmidt reactions could be catalyzed by strong acids or bases like HCl or NaOH. Recently, many Lewis acidic metal(II) complexes (M=Mn, Fe, Co, Ni and Zn, etc.) are employed as well. However, those reaction yields are usually not satisfying.[7] Other Lewis acidic/basic metal complexes[8] such as SmI_3,[9] $RuCl_3$,[10] Rh(III)/porphyrin,[11] $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$,[12] $TiCl_3OTf$,[13] $InCl_3{\cdot}4H_2O$,[14] Cp_2TiPh_2,[15] and $Cp_2ZrH_2/NiCl_2$[16] have also been intensively used. Despite some of the above cases gave good or modest yields and selectivities under the certain conditions, these catalysts indeed suffer from containing expensive scarce elements, toxicity, difficulty to handle (e.g., high/low temperature or moisture-sensitive), low accessibility, or undesired side reactions. Moreover, cross aldol-type reactions of alkanones with aldehydes catalyzed by traditional acids or bases are reversible,[17] which gives α-mono-substituted and α,α′-bis-substituted alkanone products via two sequential steps, leading to modest yields and long reaction time and poor selectivity. A low-efficient aldol condensation may also cause disproportionation of the aldehydes, leading to formation of a variety of undesired byproducts.[18] Hence, the development of safe, eco-friendly, efficient, and highly-chemoselective catalysts for Claisen–Schmidt α,α′-bis-substitution reaction is intriguing for organic synthesis. We anticipate the highly efficient bis-substitution could be accomplished by a multinuclear cluster compound like a dititanium alkoxide.

Titanium compounds (e.g., $TiCl_4$) have been extensively adopted in aldol condensation reactions[8b–d,f] due to its earth-abundance, non-toxicity character and easily quenching by water with formation of harmless TiO_2. Recently, dozens of reports for the synthesis and catalytic applications of dititanium clusters have been reported.[19] These Lewis acidic compounds may be very active in aldol reactions and show unique selectivities, for example, the regioselectivity at the more steric α-encumbered side of unsymmetrical ketones.[20] The characteristic oxo-bridged dititanium centers,

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analogous to many metal complexes characteristic of the oxo-bridged dimeric metal motifs,[21] may cause more predominant activity and chemoselectivity than the traditional Lewis acid catalysts. Such catalysis also offers the opportunity to provide information on both structure and activity in Ti-complex catalyzed reactions.

In this paper, we report a simple, efficient, and chemoselective method to prepare bis(arylmethylidene)alkanones with excellent yields using a dititanium alkoxide cluster, $Ti_2Cl_2(OPr^i)_6\cdot 2HOPr^i$ (**Ti_2**; Fig. 1).[19k] **Ti_2** can be easily obtained in high yields via the reaction of $TiCl_4$ and titanium tetraisopropoxide (TTIP) heated to 100 °C. It works selectively only for symmetric carbonyl moieties containing α,α′-methylene groups giving α,α′-bis-substituted alkanone as the sole product. Mechanism regarding this chemoselectivity versus the specific interaction between the substrates and the catalytic centers is discussed.

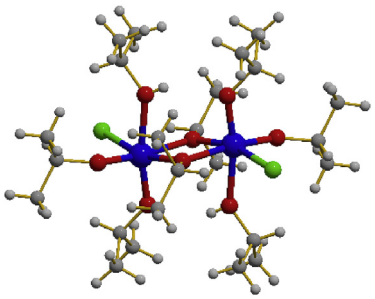
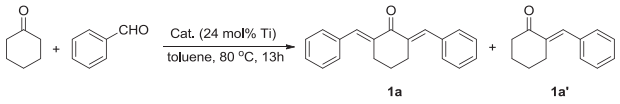


Fig. 1. Ball-and-stick representation of the $[Ti_2Cl_2(OPr^i)_6\cdot 2HOPr^i]$ (**Ti_2**) structure.[19k] Color scheme: blue, Ti; red, O; green, Cl; gray, C; pale, H. In order to highlight the core structure, the diameter of C and H atoms are not drawn to the scale of their atomic sizes.

2. Results and discussion

2.1. Model reaction

Firstly, the reaction of cyclohexanone and benzaldehyde was used as the model reaction (Scheme 1) whose products are α,α′-bis-benzylidenecycloalkanone (**1a**) and α-benzylidenecycloalkanone (**1a′**).



Scheme 1. The model Claisen–Schmidt condensation reaction.

This reaction cannot occur under the tested conditions without a catalyst. However, as shown in Scheme 1, with the addition of 12.0 mol % **Ti_2**, this reaction (1 mmol scale) afforded the main product **1a** in 97.8% isolated yield and trace amount (detected by GC–MS but could not be isolated) of the by-product **1a′**, indicating that **Ti_2** is a potentially highly active catalyst with good chemoselectivity for Claisen–Schmidt reactions (Table 1).

Table 1
Outcome of the model Claisen–Schmidt condensation reaction

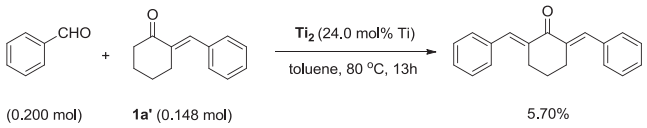
Cat.[a]	Yield (%)[b] of **1a**	Yield (%)[b] of **1a′**	Sel. (%)[c] of **1a**
Ti_2	97.8	Trace	100
$TiBr_4$	73.6	0.200	99.7
NaOH[d]	67.4	6.60	91.1
TTIP	39.0	12.0	76.5
Ti_2Br	75.9	3.00	96.2

[a] Catalyst loading: Ti, 24 mol %, 80 °C, 13 h.
[b] Isolated yield.
[c] Sel. (%) of **1a** $= n_{\mathbf{1a}}/(n_{\mathbf{1a}}+n_{\mathbf{1a'}})\times 100\%$.
[d] 10.0 mol %, EtOH as solvent.

For comparison, $TiBr_4$, NaOH and TTIP were also applied as catalysts for this reaction, the first two of which are well-known active and most-conceivable catalysts for aldol condensation reactions,[8] while $TiBr_4$ and TTIP are precursors for the synthesis of $[Ti_2Br_2(OPr^i)_6\cdot 2HOPr^i]$ (**Ti_2Br**), which is isostructural to **Ti_2** by replacing Cl atoms with Br atoms. Under otherwise identical conditions and the same catalyst dosages (in 24.0 mol % Ti) and reaction time (13 h), with all the reactants consumed, $TiBr_4$ yielded 73.6% of **1a** and 0.200% of **1a′**, NaOH gave 67.4% of **1a** and 6.60% of **1a′**, while TTIP afforded only 39.0% of **1a** and 12.0% of **1a′**. Therefore, for the model reaction, **Ti_2** showed excellent efficiency and chemoselectivity for the production of α,α′-bis-substituted alkanone, superior to TTIP, $TiBr_4$ and NaOH.

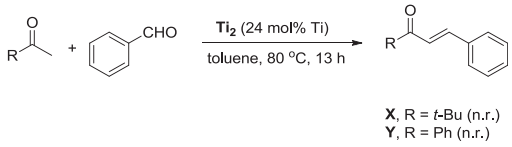
2.2. Chemoselectivity

To examine the chemoselectivity, the α-mono-substituted alkanone (i.e., **1a′**) was deliberately reacted with benzaldehyde (Scheme 2) in the presence of **Ti_2**. The data show the conversion ratio of the reactants and the yield (5.70%) of the bis-substituted product (**1a**) are both very low, indicating that the **1a′** is not active in further Claisen–Schmidt reaction to yield **1a**. Namely, the **1a′** *must not* be the intermediate in the formation of the major product **1a** but is merely a byproduct of the bis-substitution reaction. Therefore, the α,α′-bis-substitution of the alkanone must occur simultaneously in the **Ti_2**-catalyzed Claisen–Schmidt condensation reaction.



Scheme 2. Claisen–Schmidt condensation of **1a′** with benzaldehyde.

When pinacolone or acetophenone (both are typical asymmetrical ketones) is reacted with benzaldehyde (Scheme 3) catalyzed by **Ti_2**, no reaction occurred. By contrast, both $TiBr_4$ and NaOH exhibit moderate catalytic activities for both reactions. Yield of **X** reached 43.8% and 77.9% in the presence of $TiBr_4$ and NaOH (10.0 mol %), respectively.



Scheme 3. Claisen–Schmidt reaction of asymmetric ketones.

Therefore, the above results have clearly shown that only the ketones which contain two symmetrical α-methylene groups can be activated by **Ti_2** and form α,α′-bis-substituted alkanones in a single step. To the best of our knowledge, this has been the first catalyst that can accomplish such a chemoselective Claisen–Schmidt bis-substitution of a symmetrical alkanone reaction. We believe this unique chemoselectivity is useful and will find applications in many organic synthesis.

2.3. Scaled-up test

Nonetheless, the high catalytic activity and selectivity of **Ti_2** in the model reaction (Scheme 1) can be maintained in scaled-up reactions. For this, water produced during the reaction was removed using a segregator under reflux conditions to inhibit the hydrolysis of **Ti_2** into amorphous TiO_2. As a test, the catalyzed

reaction was conducted in molar scale with merely 0.00680 mol % **Ti_2** (140 °C, 24 h), and afforded high yields (i.e., isolated yield=89.4% for **1a** and 4.80% for **1a**′) with acceptable selectivities (95.9% for **1a**). The turnover number (**TON**) reached 13,044. This means that nearly 120 g of **1a** can be isolated with a minimum amount of the **Ti_2** catalyst, i.e., 38.0 mg. It is also noteworthy that after the reaction, no precipitates formed, suggesting that **Ti_2** maintained its activity (very high durability) and chemoselectivity and was capable of catalyzing the conversion of larger amounts of substrates. This suggests **Ti_2** may satisfy one of the requirement of industrial applications.

Typical catalysts for aldol reactions like $TiCl_4$ suffer from their high hygroscopicity and must be handled essentially under strict anaerobic conditions. However, we found the **Ti_2** catalyst is much less sensitive to humidity than $TiCl_4$. For example, a solid sample of **Ti_2** was deliberately exposed in air at 40% R.H. at 18 °C. After 2 h exposure, **Ti_2** still preserved its catalytic activity and yielded 63.8% of **1a** (selectivity 94.0%).

2.4. Substrates

Encouraged by the high activity and chemoselectivity, as well as the large TON of **Ti_2** in the model Claisen–Schmidt condensation reaction (Scheme 1), we next examined a variety of ketones and aldehydes, in order to investigate the scope and the limitation of **Ti_2** (Table 2).

Table 2
Mixed-aldol condensation of various aldehydes with ketones in the presence of **Ti_2**

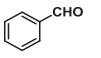
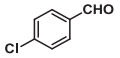
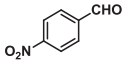
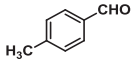
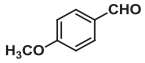
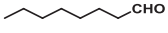
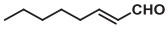
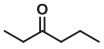
#	Ketone	Aldehyde	Yield of bis-product (%)[a,b]	Yield of mono-product (%)
1			97.8	Trace
2			92.0	Trace
3			94.2	Trace
4			71.9	2.80
5			57.6	0
6			40.5	11.3
7			90.3	0
8			37.1	15.9[c]
9			29.6	9.40
10			90.0	Trace

Table 2 (*continued*)

#	Ketone	Aldehyde	Yield of bis-product (%)[a,b]	Yield of mono-product (%)
11			90.2[d]	0
12			0	59.4[e]
13			0	20.6
14			0	17.7[f]

[a] Catalyst loading: Ti, 24 mol %, 80 °C, 13 h.
[b] Isolated yield.
[c] Along with 27.8% self-condensation product. Octanal alone under the same condition gave 72.6% self-condensation product.
[d] 50 °C and excess acetone was employed.
[e] The mono-product is 3-methyl-4-phenylbut-3-en-2-one.
[f] The mono-product is 2-methyl-1-phenylhex-1-en-3-one.

For reactions in which cyclohexanone participates (entries 1–9), the yields and chemoselectivities of **Ti_2** are high in catalysis for aromatic aldehydes (entries 1–7) while less efficient for aliphatic aldehydes (entries 8–9) in the production of α,α′-bis-substituted alkanone. Among the aromatic aldehydes, the presence of any substituent appears to decrease the activities and chemoselectivities of **Ti_2** (entries 1 and 6). Further, aromatic aldehydes with electron-withdrawing groups afford higher yields and selectivities of α,α′-bis-substituted alkanone than with electron-donating groups (entries 2–5). It is worth noting that excellent yields and chemoselectivities are also realized for cyclopentanone—another representative cyclic ketones, and acetone—a typical saturated aliphatic alkanone. Other simple nonsymmetrical linear ketones are less reactive than the cycloketones and yield only the mono-products (entries 12–14). These mono-products could not be converted to bis-products with extended time, additional aldehydes and additional catalysts. In all, **Ti_2** is capable of catalyzing the Claisen–Schmidt condensation reaction of a variety of aromatic aldehydes with alkanones (especially cycloketones) which contain two α-methylene groups to selectively form α,α′-bis-substituted alkanones in a single step.

2.5. Kinetics

In order to understand the mechanism for the high activity and chemoselectivity of **Ti_2** in catalyzing Claisen–Schmidt condensation reactions, a kinetic study was conducted as the first piece of evidence. For this, **Ti_2**, **Ti_2Br** and TTIP were also applied as a catalyst for comparison to understand the effect of catalyst structure on initial reaction rates.

The condensation reactions occurred immediately at t=0 without any induction period. This indicates that these systems did not need accumulation of any catalytic-active species. Namely, the native structures in solution of the added compounds, **Ti_2**, **Ti_2Br** and TTIP, are possibly the true catalysts for the reactions. Next, because the conversion kinetics of the substrates all follows a near-linear decay in the very early stages of the condensation reactions (e.g., 0.8 h for TTIP and **Ti_2**, as well as 0.2 h for **Ti_2Br**), the catalytic active species, i.e., **Ti_2**, **Ti_2Br** and TTIP, were likely to keep intact. Hence, the kinetics of conversion in Fig. 2 is used to evaluate the true catalytic activities of **Ti_2**, **Ti_2Br** and TTIP.

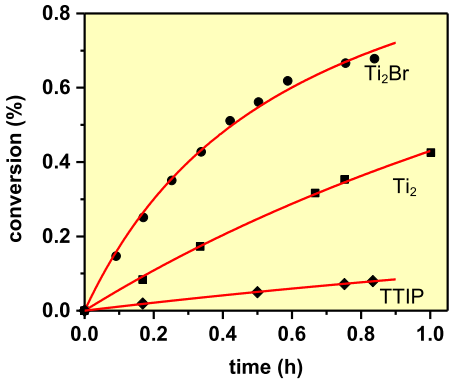


Fig. 2. Conversion (of benzaldehyde) kinetics of the Claisen–Schmidt model reaction (Scheme 1) using various catalysts. The red curves are guides to eye. Temperature, 60 °C.

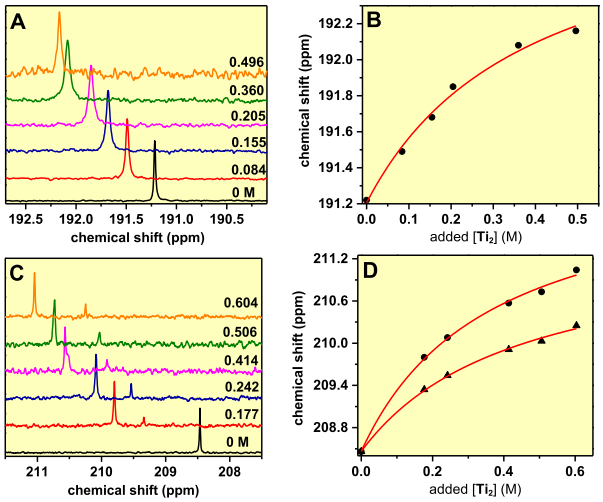


Fig. 3. ^{13}C NMR and chemical shift of carbonyl-*C* of (**A** and **B**) benzaldehyde (0.622 M) and (**C** and **D**) cyclohexanone (0.622 M) with incremental additions of $\mathbf{Ti_2}$ in C_6D_6. The red curves in panels **B** and **D** are fits to a rectangular hyperbolic function[23] as guides to eye.

The average rates of the first 0.18 h in Fig. 2 are used to calculate the initial rate constants of the catalytic reactions (Scheme 1). The values are 1.2, 0.49, and 0.094 h^{-1} for $\mathbf{Ti_2Br}$, $\mathbf{Ti_2}$ and TTIP, respectively. Because $\mathbf{Ti_2Br}$ is isostructural to $\mathbf{Ti_2}$ but exhibiting two Ti–Br bonds (Fig. 1), the higher activity of $\mathbf{Ti_2Br}$ than $\mathbf{Ti_2}$ is consistent with the weaker Ti–Br bond and indicates that cleavage of Ti–X (X=Cl, Br) bonds should be involved in rate-limiting steps of the present catalytic Claisen–Schmidt condensation reactions (e.g., Scheme 1). This is best explained by an associative cleavage of the Ti–X bond as the carbonyl moieties of the substrates approaching the catalytic centers (possibly an S_N2 mechanism).

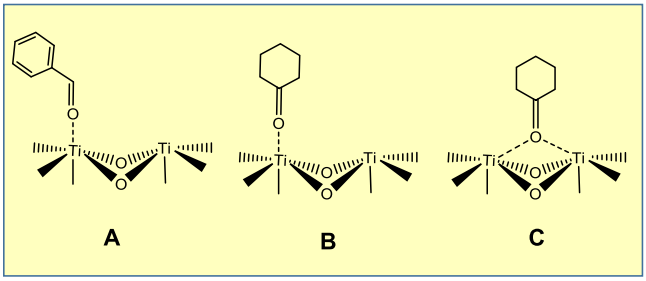
2.6. Kinetic isotope effects

A pronounced kinetic isotope effect (KIE; defined as k_H/k_D) would exist if the abstraction of α-H of alkanone (or α-D of cyclohexanone-2,2,6,6-d_4) was involved in the rate-limiting steps. To examine this, initial rates were used to calculate KIE. For $\mathbf{Ti_2}$-catalyzed Claisen–Schmidt condensation of cyclohexanone and benzaldehyde (Scheme 1), no KIE was observed (KIE=1.06, see Supplementary data section S2), while for the same reaction catalyzed by TTIP a pronounced KIE of 2.03 existed. A negligible KIE (≈1) means little barrier exists in the cleavage of α-C–H bond. Hence the KIE data indicates that $\mathbf{Ti_2}$ greatly activates the α-H thereby enhancing the nucleophilicity of α-C of alkanone. This is different from a typical Claisen–Schmidt reaction, in which abstraction of α-H from ketone is an important primary step[22] as observed in the above TTIP catalysis. Vanishing of the KIE in $\mathbf{Ti_2}$ catalysis is likely resulted from the rapid nucleophilic addition and the relatively slow associative binding of carbonyl-*O* to Ti(VI) accompanied with leaving of Cl-atoms (like the S_N2 mechanism as aforementioned). We speculate the nucleophilic addition could be facilitated if both cyclohexanone and aldehyde were brought together by the catalytic dititanium center.

2.7. Interaction of substrates and the catalytic centers

To obtain more insights into the reaction mechanism, ^{13}C NMR was applied to analyze the interaction between the substrates and the catalytic centers of $\mathbf{Ti_2}$ (Fig. 3).

The chemical shift of carbonyl-*C* of benzaldehyde (panel A) is located at 191.2 ppm and gradually moves down to the lower magnetic field with incremental additions of $\mathbf{Ti_2}$. Further analysis (panel B) reveals a decay (the red curve) of chemical shift versus added $\mathbf{Ti_2}$ concentration. This is understandable only if we assume the free and the associated (with $\mathbf{Ti_2}$) benzaldehyde undergo rapid exchange on the ^{13}C NMR time scale. As a result, the observed chemical shift is the weighted mean of the chemical shifts of the signals due to free and associated C=O moieties.[24] Notably, ketones without enolizable hydrogen atoms readily anchor their O-atoms at the carbonyl moieties to Ti(IV) centers and hence deshielding is presumably due to the transfer of electron density from the ligand to the Lewis acid.[24d,25] Anchoring of carbonyl-*O* to Ti(IV) was also recognized in an X-ray crystallography analysis of the $TiCl_4$–diethyl ketone adduct[26] isolated in the $TiCl_4$-catalyzed aldol addition of aldehydes and ketones in the absence of a base. In that structure, the dititanium catalytic centers are bridged with two μ_2-Cl and two ketone molecules bind with their carbonyl-*O* to the two Ti(IV) centers from the opposite sides. Therefore, it is reasonable to propose an analogous binding mode (panel A in Scheme 4) of benzaldehyde to $\mathbf{Ti_2}$ for the present catalytic reactions.



Scheme 4. Proposed and viable binding modes of the substrates with $\mathbf{Ti_2}$: (**A**) benzaldehyde, (**B**) and (**C**) cyclohexanone.

On the other hand for the case of cyclohexanone, additions of $\mathbf{Ti_2}$ result in a set of two peaks of carbonyl-*C* (Fig. 3, panel C) whose chemical shifts also decay with added $\mathbf{Ti_2}$ concentration (panel D). Hence this must be correlated with two types of binding modes of the carbonyl-*O* of cyclohexanone to the dititanium centers of $\mathbf{Ti_2}$, e.g., two viable binding modes for interaction of cyclohexanone with $\mathbf{Ti_2}$ illustrated in Scheme 4.

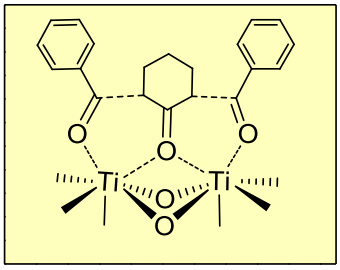
The interaction between the substrates and the mono-nuclear $TiBr_4$ was also studied as shown in Fig. S4. Addition of $TiBr_4$ to cyclohexanone caused the chemical shift of carbonyl-*C* to move downfield by 5.8 ppm (no splitting of the carbonyl-*C* was observed), comparing to the 1.3 ppm downfield shift caused by $\mathbf{Ti_2}$. This indicates that cyclohexanone adopts only one binding mode and interacts very strongly with $TiBr_4$. On the other hand, additions of

0.174 M $TiBr_4$ to 0.622 M benzaldehyde results in a dark red precipitate, which implies a very strong interaction exists between the two. These results are consistent with the stronger Lewis acidity of $TiBr_4$ than **Ti_2** which may be responsible for the higher activity of $TiBr_4$ (and lower selectivity) in the model reaction (Scheme 1).

2.8. Mechanistic considerations

The oxo-bridged dimeric motif (also known as $M_2(\mu\text{-}O)_2$ diamond core motif)[21] can be formed with a variety of transition-metals like Ti,[27] V,[28] Fe,[21,29] Co,[30] Zn,[31] Mn,[29a,31] Cd,[31] and Cu,[21] and represents a large family of important molecular materials especially characteristic of their superior catalytic activities and selectivities.[21,30,32] Notably, in the catalytic reactions where the dinuclear complexes are used, the substrate molecules can bind to the catalytic centers as terminal and/or bridging ligands, and hence the reactants are brought close enough and activated at the catalytic sites, leading to superior catalysis due to the cooperation of the multi catalytic centers.[27a,30] Specifically, this motif for complexes of Ti(IV) is known to be quite stable and catalytically active.[21,27a] We speculate that the oxo-bridged dimeric motif in **Ti_2** is also responsible for the high efficiency of the present Claisen–Schmidt bis-substitution reaction.

In order to explain the present unique chemoselectivity of **Ti_2**-catalyzed bis-substitution reaction, herein based on the kinetic data and binding mode study (of the alkanone and the aldehyde to **Ti_2**), an intermediary structure for simultaneous bis-substitution is proposed and shown as Scheme 5. In this model, the benzaldehyde and alkanone are brought together by the oxo-bridged dititanium motif of **Ti_2** through binding modes of panel A and C, respectively in Scheme 4. In contrast, the mononuclear catalysts like NaOH and $TiBr_4$ cannot accomplish the bis-substitution in a single step through an analogous binding mode. Yet it is not clear what paths do the **Ti_2**-catalyzed reaction undergo. Further studies are being carried out to explore the detailed mechanism.



Scheme 5. Proposed intermediary structure for simultaneous bis-substitution of cyclohexanone by benzoaldehyde at the dititanium center of **Ti_2**.

3. Conclusions

In summary, a dinuclear titanium alkoxide cluster, $[Ti_2Cl_2(O\text{-}Pr^i)_6{\cdot}2HOPr^i]$ (**Ti_2**), has been applied to catalyze the Claisen–Schmidt condensation reaction. The advantage of **Ti_2** holds not only for its high efficiency (rapid; TON>13,000) but also for the unique chemoselectivity toward the one-step bis-substitution of the symmetrical $-CH_2(C{=}O)CH_2-$ moiety. Meanwhile, the high efficiency and chemoselectivity can be extended to other alkanones and aromatic aldehydes. The ionic Ti–Cl bond, breaking of which determines the whole reaction rate, contributes to the outstanding catalytic activity of **Ti_2**. More importantly, the oxo-bridged dimeric motif of **Ti_2** is proposed to be responsible for the high efficiency and chemoselectivity of the present Claisen–Schmidt bis-substitution reaction. This study could be helpful not only for selective functionalization of alkanones but also for further exploration of the catalytic applications of titanium clusters.

4. Experimental section

4.1. Materials

Cyclohexanone-2,2,6,6-d_4, and $TiBr_4$ (98%) were purchased from Sigma–Aldrich. Cyclohexanone (GC), benzaldehyde (GC), 4-nitrobenzaldehyde (AR), 4-methylbenzaldehyde (97%), 4-methoxybenzaldehyde (99%) and cyclopentanone (99.5%) were purchased from Macklin. Acetophenone (AR), 4-chlorobenzaldehyde (98%), 2-butanone (AR), 3-pentanone (98) and 3-hexanone (98%), 1-naphthaldehyde (97%), 3-thiophenaldehyde (98%) and *n*-tetradecane (96%) were obtained from Aladdin. Pinacolone (98%) was purchased from 9-Ding-Chemistry. $TiCl_4$ (99%), and TTIP (99%) were obtained from Energy-Chemical. All other organic substrates (AR or AG) were obtained from commercial sources and used without further purification.

4.2. Instruments

^1H NMR and ^{13}C NMR spectra were obtained using the Bruker 300 MHz Fourier transform NMR spectrometer in 5 mm NMR tubes. Chemical shifts are reported relative to tetramethylsilane and benzene-d_6 as the internal standards for ^1H NMR and ^{13}C NMR, respectively. FTIR data were obtained on a Perkin Elmer Spectrum Two IR Spectrometer. Gas chromatography (GC) analyses were performed on a Techcomp 7980 gas chromatograph equipped with an FID detector and a capillary column (TM-5, 30 m×0.32 mm×0.5 μm). GC–MS measurements were conducted using Shimadzu QP2010 SE system. The air-sensitive materials were handled in a glovebox (Mikrouna China).

4.3. Syntheses of $Ti_2Cl_2(OPr^i)_6{\cdot}2HOPr^i$ (**Ti_2**) and $Ti_2Br_2(OPr^i)_6{\cdot}2HOPr^i$ (**Ti_2Br**)

Previously, **Ti_2** was synthesized by reaction of TTIP, $NaOPr^i$ with VCl_3 in toluene under reflux for a few days.[19k] The resultant precipitate was fractionally crystallized in isopropanol to give relatively low yield (ca. 55%) of **Ti_2**. Herein an optimized protocol by us which gave very high yield was used. In a glovebox, $TiCl_4$ or $TiBr_4$ (13.3 mmol) and TTIP (40.0 mmol) were dissolved in 20 mL isopropanol. Fine crystals were obtained after the mixture was heated in an autoclave at 100 °C for 1 day followed by cooling to room temperature at a ramp rate of 1 °C/h. Crystalline yield: 21.4 mmol **Ti_2** (80.3% based on Ti) and 18.7 mmol **Ti_2Br** (70.1% based on Ti). No byproduct was detected. Single crystal crystallography, ICP-AES and infrared spectroscopy were used for characterization (see Supplementary data). Anal. Calcd Ti: 14.9% in **Ti_2** and 13.1% in **Ti_2Br**. Found Ti (by ICP-AES after dissolution in 1 M HNO_3): 14.7% in **Ti_2** and 14.0% in **Ti_2Br**.

4.4. General procedure for catalytic reactions

Reactions were carried out using 10 mL vials sealed with butyl rubber stoppers. The vials were charged with ketone (1.00 mmol), aldehyde (1.00 mmol), catalyst (24.0 mol% of Ti) and toluene (10.0 mL). The reaction mixtures were stirred and maintained certain temperatures. The reaction was quenched with water as necessary and the precipitate was removed by filtration through 0.22 μm membrane. The filtrate was concentrated to give a residue which was purified by column chromatography for further analysis (e.g., FTIR, GC, GC–MS and NMR).

4.5. TON calculation

Cyclohexanone (85.7 g, 0.874 mol), benzaldehyde (92.7 g, 0.874 mol) and catalyst (0.0600 mmol **Ti_2**) were dissolved in toluene (500 mL). The mixture was stirred and refluxed at 140 °C with a water segregator for 13 h. After the reaction, a small amount of the sample was withdrawn from the solution, purified by column chromatography, and analyzed with an analytical balance. TON was then calculated as amount of reacted cyclohexanone/amount of catalyst.

4.6. Reaction kinetics

The vials were charged with cyclohexanone (98.0 mg, 1.00 mmol), benzaldehyde (106 mg, 1.00 mmol), *n*-tetradecane (198 mg, 1.00 mmol)—as internal standard for GC analysis, catalyst (24.0 mol % of Ti) and toluene (10.0 mL). The reaction solution was stirred at 60 °C to slow down the reaction. Samples were regularly taken, quenched with water, filtered and diluted with toluene before GC analysis.

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Supplementary data

Supplementary data (Characterization of the catalysts, kinetic isotope effects, proposed intermediary structure and selected NMR data.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.01.055.

References and notes

1. (a) Artico, M.; Di Santo, R.; Costi, R.; Novellino, E.; Greco, G.; Massa, S.; Tramontano, E.; Marongiu, M. E.; De Montis, A.; La Colla, P. *J. Med. Chem.* **1998**, *41*, 3948–3960; (b) Costi, R.; Santo, R. D.; Artico, M.; Massa, S.; Ragno, R.; Loddo, R.; La Colla, M.; Tramontano, E.; La Colla, P.; Pani, A. *Bioorg. Med. Chem.* **2004**, *12*, 199–215.
2. Franco, L. L.; De Almeida, M. V.; E Silva, L. F. R.; Vieira, P. P. R.; Pohlit, A. M.; Valle, M. S. *Chem. Biol. Drug Des.* **2012**, *79*, 790–797.
3. (a) Dimmock, J. R.; Kumar, P.; Nazarali, A. J.; Motaganahalli, N. L.; Kowalchuk, T. P.; Beazely, M. A.; Wilson, Q. J.; Oloo, E. O.; Allen, T. M.; Szydlowski, J.; DeClercq, E.; Balzarini, J. *Eur. J. Med. Chem.* **2000**, *35*, 967–977; (b) Dimmock, J. R.; Padmanilayam, M. P.; Zello, G. A.; Nienaber, K. H.; Allen, T. M.; Santos, C. L.; De Clercq, E.; Balzarini, J.; Manavathu, E. K.; Stables, J. P. *Eur. J. Med. Chem.* **2003**, *38*, 169–177.
4. Gafner, S.; Lee, S.; Cuendet, M.; Barthélémy, S.; Vergnes, L.; Labidalle, S.; Mehta, R. G.; Boone, C. W.; Pezzuto, J. M. *Phytochemistry* **2004**, *65*, 2849–2859.
5. Weber, W. M.; Hunsaker, L. A.; Abcouwer, S. F.; Deck, L. M.; Vander Jagt, D. L. *Bioorg. Med. Chem.* **2005**, *13*, 3811–3820.
6. Nakano, T.; Migita, T. *Chem. Lett.* **1993**, 2157–2158.
7. Mohammadi Ziarani, G.; Badiei, A.; Abbasi, A.; Farahani, Z. *Chin. J. Chem.* **2009**, *27*, 1537–1542.
8. (a) Kitanosonoa, T.; Kobayashia, S. *Adv. Synth. Catal.* **2013**, *355*, 3095–3118; (b) Matsuo, J.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9109–9118; (c) Beutner, G. L.; Denmark, S. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 9086–9096; (d) Kan, S. B. J.; Ng, K. K. H.; Paterson, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 9097–9108; (e) Bukhari, S. N. A.; Jasamai, M.; Jantan, I.; Ahmad, W. *Mini-Rev. Org. Chem.* **2013**, *10*, 73–83; (f) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.—Eur. J.* **2002**, *8*, 37–46; (g) Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307–4366.
9. Bao, W.; Zhang, Y.; Ying, T. *Synth. Commun.* **1996**, *26*, 503–507.
10. Iranpoor, N.; Kazemi, F. *Tetrahedron* **1998**, *54*, 9475–9480.
11. Aoyama, Y.; Tanaka, Y.; Yoshida, T.; Toi, H.; Ogoshi, H. *J. Org. Chem.* **1987**, *329*, 251–266.
12. Zhang, L.; Wang, S.; Sheng, E.; Zhou, S. *Green Chem.* **2005**, *7*, 683–686.
13. Iranpoor, N.; Zeynizadeh, B.; Aghapour, A. *J. Chem. Res., Synop.* **1999**, 554–555.
14. Deng, G.; Ren, T. *Synth. Commun.* **2003**, *33*, 2995–3001.
15. Kawamata, J.; Inoue, K.; Inabe, T.; Kiguchi, M.; Kato, M.; Taniguchi, Y. *Chem. Phys.* **1996**, *249*, 29–34.
16. Nakano, T.; Irifune, S.; Umano, S.; Inada, A.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 2239–2244.
17. Mestres, R. *Green Chem.* **2004**, *6*, 583–603.
18. Rahman, A. F. M. M.; Ali, R.; Jahng, Y.; Kadi, A. A. *Molecules* **2012**, *17*, 571–583.
19. (a) Sobota, P.; Drag-Jarzabek, A.; Utko, J.; Jerzykiewicz, L. B. *Organometallics* **2011**, *30*, 1741–1743; (b) Cazaux, J.; Braunstein, P.; Magna, L.; Saussine, L.; Olivier-Bourbigou, H. *Eur. J. Inorg. Chem.* **2009**, 2942–2950; (c) Boyle, T. J.; Ottley, L. A. M.; Rodriguez, M. A.; Sewell, R. M.; Alam, T. M.; McIntyre, S. K. *Inorg. Chem.* **2008**, *47*, 10708–10717; (d) Hu, H.; Gao, H.; Song, K.; Liu, F.; Long, J.; Zhang, L.; Zhu, F.; Wu, Q. *Polymer* **2008**, *49*, 4552–4558; (e) Zhang, D. *Eur. J. Inorg. Chem.* **2007**, 3077–3082; (f) Gueta-Neyroud, T.; Tumanskii, B.; Kapon, M.; Eisen, M. S. *Macromolecules* **2007**, *40*, 5261–5270; (g) Schröder, K.; Haase, D.; Saak, W.; Lützen, A.; Beckhaus, R.; Wichmann, S.; Schellenberg, J. *Organometallics* **2006**, *25*, 3824–3836; (h) Nielson, A. J.; Shen, C.; Waters, J. M. *Polyhedron* **2006**, *25*, 2039–2054; (i) Nielson, A. J.; Shen, C.; Schwerdtfeger, P.; Waters, J. M. *Eur. J. Inorg. Chem.* **2005**, 1343–1352; (j) Janas, Z.; Jerzykiewicz, L. B.; Przybylak, K.; Sobota, P.; Szczegot, K.; Wiśniewska, D. *Eur. J. Inorg. Chem.* **2005**, 1063–1070; (k) Nunes, G. G.; Reis, D. M.; Camargo, P. H. C.; Hitchcock, P. B.; Hörner, M.; Matos, R. M.; Mangrich, A. S.; de Sá, E. L.; Leigh, G. J.; Soares, J. F. *J. Braz. Chem. Soc.* **2003**, *14*, 922–929; (l) Wu, Y.; Ho, Y.; Lin, C.; Gau, H. *Inorg. Chem.* **1996**, *35*, 5948–5952.
20. Mahrwald, R.; Schetter, B. *Org. Lett.* **2006**, *8*, 281–284.
21. Que, Lawrence, Jr.; Tolman, W. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1114–1137.
22. Di Cosimo, J. I.; Díez, V. K.; Apesteguía, C. R. *Appl. Catal., A* **1996**, *137*, 149–166.
23. Connors, K. A. *Binding Constants: the Measurement of Molecular Complex Stability*; John Wiley & Sons: New York, 1987.
24. (a) Krishnarao, D. *Nulear Magnetic Resonance (NMR): Theory, Applications and Technology*; Nova Science: New York, 2014; (b) *Nuclear Magnetic Resonance*; Kamienska-Trela, K., Wójcik, J., Eds.; RSC: Cambridge, 2012; Vol. 41; (c) Grigoriev, V. A.; Cheng, D.; Hill, C. L.; Weinstock, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 5292–5307; (d) Allred, A. L.; Thompson, D. W. *Inorg. Chem.* **1968**, *7*, 1196–1201.
25. (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (b) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
26. Mahrwald, R.; Ziemer, B.; Troyanov, S. *Tetrahedron Lett.* **2001**, *42*, 6843–6845.
27. (a) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348; (b) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973.
28. Duan, Z.; Schmidt, M.; Young, Victor G., Jr.; Xie, X.; McCarley, R. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 5302–5303.
29. (a) Zuo, W.; Rosa, V.; Tourbillon, C.; Specklin, D.; Khaled, C.; Kurmoo, M.; Welter, R. *RSC Adv.* **2012**, *2*, 2517–2526; (b) Vincent, J. B.; Olivier-Lilley, Gay L.; Averill, B. A. *Chem. Rev.* **1990**, *90*, 1447–1467.
30. Hayashi, Y.; Santoro, S.; Azuma, Y.; Himo, F.; Ohshima, T.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 6192–6199.
31. Jiang, J.; Chu, Z.; Huang, W.; Wang, G.; You, X. *Inorg. Chem.* **2010**, *49*, 5897–5911.
32. (a) Maegawa, Y.; Ohshima, T.; Hayashi, Y.; Agura, K.; Iwasaki, T.; Mashima, K. *ACS Catal.* **2011**, *1*, 1178–1182; (b) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944–2945.