This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Mechanistic Insight of TiCl4 Catalyzed formal [3+3] Cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles

Riffat Un Nisa, Maria, Fatima Waseem, Tariq Mahmood, Ralf Ludwig, Khurshid Ayub*

The mechanism of TiCl4 mediated formal [3+3] Cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles is studied at B3LYP method of density functional theory (DFT) to rationalize the experimental regioselectivity. Methyl and trifluoromethyl substituted 1,3 dielectrophiles are studied theoretically since they show different regioselectivities. Two different mechanism involving 1,2 and 1,4 addition of 1,3 –bis(silyl enol ethers) on 1,3-dielectrophiles are studied for each dienophile. The intramolecular transition metal catalyzed and non-catalyzed dynamic shift of silyl moiety is also studied. The structure of 1,3 dienophile and the associated Mullikan charges are the driving forces for different regioselectivities in methyl and trifluoromethyl dienophiles.

Introduction:

Functionalized arenes are interesting class of organic molecules in natural products, polymers and medicinal chemistry. The traditional approaches for substituted arenes synthesis involve direct substitution of already existing benzene scaffold. The widely used strategies based on this classical approach involves electrophilic, nucleophilic substitution (in case of aryl halide) and transition metal catalyzed coupling reactions. However, these strategies suffers from some serious drawbacks such as activating/deactivating effects of electron-donating /withdrawing groups, sequences of multistep reaction, low yields and decreased availability of functionalized arenes as starting materials.

A significant alternative method is the “acyclic approach” for the synthesis of highly functionalized arenes, which are based on acyclic precursors. These cyclocondensation reactions include [3 + 2 + 1] Dötz reaction, transition metal catalyzed [2 + 2 + 2] cyclisation, [4 + 2] cycloadditions, [4 + 2] Danheiser alkene-cyclobutene cyclization, 1,6-electrocyclization reactions, and cyclocondensations of dielectrophiles with dinucleophiles and [5 + 1] benzannulations between alkenoyl keteneacetalts and nitroalkanes. However, these annulations proceed in harsh reaction conditions, require highly expensive catalysts, suffers from regiochemical ambiguities and lack of substrate generality.

The [3 + 3] addition of 1,3-bis(silyloxy)-1,3-butanediene with 3-silyloxy-2-ene-1-ones is an important TiCl4 mediated one pot cyclization reaction based on the “acyclic approach”. The significance of the reaction includes its high regioselectivity, excellent yields, moderate reaction conditions, and commercial availability of the catalyst. TiCl4 is an efficient Lewis acid and shows significant affinity for oxygen containing organic compounds. The catalyst is effective in many organic transformations, particularly in Pinacol coupling reaction, pyrrolidine synthesis, Claisen rearrangements, and asymmetric aldol reaction. The alkene production from molecular reductive coupling of carbonyl compounds such as aldehydes, ketones, acylsilanes, ketoesters, and oxoamides are also prominent applications of titanium in organic chemistry.

Chan and coworkers (in 1979) reported the synthesis of arenes by formal [3+3] cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles, using titanium (IV) as a Lewis acid (Scheme 1). The reaction is widely used for synthesis of valuable functionalized arenes. For example, Lewis acid promoted reaction of 1,3-bis(silyl enol ether) 1 with 2 delivers functionalized biphenyl compound 3.

![Scheme 1. TiCl4 catalyzed cyclization of 1,3 bis(silyl enol ether) with 1,1,3,3-tetramethoxypropane.](image)

---

**ARTICLE**

**Mechanistic Insight of TiCl4 Catalyzed formal [3+3] Cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles**

Riffat Un Nisa, Maria, Fatima Waseem, Tariq Mahmood, Ralf Ludwig, Khurshid Ayub*

The mechanism of TiCl4 mediated formal [3+3] Cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles is studied at B3LYP method of density functional theory (DFT) to rationalize the experimental regioselectivity. Methyl and trifluoromethyl substituted 1,3 dielectrophiles are studied theoretically since they show different regioselectivities. Two different mechanism involving 1,2 and 1,4 addition of 1,3 –bis(silyl enol ethers) on 1,3-dielectrophiles are studied for each dienophile. The intramolecular transition metal catalyzed and non-catalyzed dynamic shift of silyl moiety is also studied. The structure of 1,3 dienophile and the associated Mullikan charges are the driving forces for different regioselectivities in methyl and trifluoromethyl dienophiles.

**Introduction:**

Functionalized arenes are interesting class of organic molecules in natural products, polymers and medicinal chemistry. The traditional approaches for substituted arenes synthesis involve direct substitution of already existing benzene scaffold. The widely used strategies based on this classical approach involves electrophilic, nucleophilic substitution (in case of aryl halide) and transition metal catalyzed coupling reactions. However, these strategies suffers from some serious drawbacks such as activating/deactivating effects of electron-donating /withdrawing groups, sequences of multistep reaction, low yields and decreased availability of functionalized arenes as starting materials.

A significant alternative method is the “acyclic approach” for the synthesis of highly functionalized arenes, which are based on acyclic precursors. These cyclocondensation reactions include [3 + 2 + 1] Dötz reaction, transition metal catalyzed [2 + 2 + 2] cyclisation, [4 + 2] cycloadditions, [4 + 2] Danheiser alkene-cyclobutene cyclization, 1,6-electrocyclization reactions, and cyclocondensations of dielectrophiles with dinucleophiles and [5 + 1] benzannulations between alkenoyl keteneacetals and nitroalkanes. However, these annulations proceed in harsh reaction conditions, require highly expensive catalysts, suffers from regiochemical ambiguities and lack of substrate generality.

The [3 + 3] addition of 1,3-bis(silyloxy)-1,3-butanediene with 3-silyloxy-2-ene-1-ones is an important TiCl4 mediated one pot cyclization reaction based on the “acyclic approach”. The significance of the reaction includes its high regioselectivity, excellent yields, moderate reaction conditions, and commercial availability of the catalyst. TiCl4 is an efficient Lewis acid and shows significant affinity for oxygen containing organic compounds. The catalyst is effective in many organic transformations, particularly in Pinacol coupling reaction, pyrrolidine synthesis, Claisen rearrangements, and asymmetric aldol reaction. The alkene production from molecular reductive coupling of carbonyl compounds such as aldehydes, ketones, acylsilanes, ketoesters, and oxoamides are also prominent applications of titanium in organic chemistry.

Chan and coworkers (in 1979) reported the synthesis of arenes by formal [3+3] cyclization of 1,3 –bis(silyl enol ethers) with 1,3-dielectrophiles, using titanium (IV) as a Lewis acid (Scheme 1). The reaction is widely used for synthesis of valuable functionalized arenes. For example, Lewis acid promoted reaction of 1,3-bis(silyl enol ether) 1 with 2 delivers functionalized biphenyl compound 3.

**Scheme 1. TiCl4 catalyzed cyclization of 1,3 bis(silyl enol ether) with 1,1,3,3-tetramethoxypropane.**

---

**This journal is © The Royal Society of Chemistry 20xx**

J. Name., 2013, 00, 1-3 | 1
With the computational tools in hand, we became interested to investigate the mechanism of the formal [3+3] addition and the results are presented here. There appears no theoretical reports on the mechanism of the titanium catalyzed [3 + 3] addition of 1,3-bis(silyloxy)-1,3-buta dienes with 3-silyloxy-2-en-1-ones.

Computational Methods

All calculations were performed with Gaussian 09. Geometries of the structures were optimized without any symmetry constraints at hybrid B3LYP method using 6-31G* basis set. The B3LYP method consists of three parameter hybrid functional of Becke in conjunction with the correlation functional of Lee, Yang, and Parr. The B3LYP method provides a nice balance between cost and accuracy, and it is known to perform reasonably well for the prediction of geometries and behaviour of neutral and charged species[23] including transition metals. The B3LYP method has been used in the theoretical simulations of properties and reactions catalysed by Titanium[24]. Each optimized structure was confirmed by frequency analysis at the same level (B3LYP/6-31G* as a true minimum (no imaginary frequency) or a transition state (with one imaginary frequency). Imaginary frequencies of transition states were also evaluated to confirm that their associated eigenvector correspond to the motion along the reaction coordinates. Moreover intrinsic reaction coordinates (IRC) calculations were performed to confirm that the transition state connect to the concerned starting materials and products. IRC was performed until the stationary point was reached with RMS gradient less than 1 x 10^-3. Stationary points located through IRC were then fully optimized at the above mentioned method. The reported energies for all structures are in kcal mol^{-1} and include unscaled zero point energy corrections.

Density functional theory (DFT) calculations were performed to gain mechanistic insight for the regioselectivity observed for the [3 + 3] addition of 1,3-bis(silyloxy)-1,3-buta dienes with 3-silyloxy-2-en-1-ones (Scheme 4). An ortho phenyl substituted benzoate ester 9 is the dominant product from 5 (a methyl ketone) whereas para phenyl substituted benzoate ester 10 is the major product from 9. The regioselectivity is altered when methyl ketone is replaced with a trifluoromethyl ketone, 9. A number of questions needs to be answered in order to logically investigate the mechanism; Is the silyl group in dielectrophiles 5 and 9 dynamic between the two oxygen atoms (5 → 5' and 9 → 9')? If yes, then which isomer is most stable? What is the stability order for these two isomers when they are bound to titanium? Is it a direct addition of 4 on 5, or a 1,4 addition?

Scheme 2. TiCl₄ catalysed regioselective [3 + 3] addition of 1,3-bis(silyloxy)-1,3-buta dienes with 3-silyloxy-2-en-1-ones

Similarly, A similar biphenyl derivative 6 can be generated (Scheme 2) by the reaction of 1,3-bis(silyl en ether) 4 and 3-silyloxy-2-en-1-one 5.

Despite much synthetic advancement, mechanistic details of formal [3+3] cyclization are very limited. A proposed mechanism by Langer and coworkers[7] is presented in scheme 3. TiCl₄ selectively activates one of the two electrophilic centers of the unsymmetrical 1,3-dielectrophile by forming six membered chelation ring, which leads to the formation of exclusively one isomer and results in regioselective cyclization. Nature of the Lewis acid also affects the reaction pathway because specific functional groups are activated by specific Lewis acid.

The proposed mechanism involves coordination of 7 with TiCl₄ to give intermediate Int1, which is then attacked by the terminal carbon atom of 4 to give intermediate Int2. The Int2 loses OSiMe₃ moiety to deliver Int3. Cyclization of Int3 followed by aromatization in Int4 deliver a functionalized arene 8 (Scheme 3). The above mechanism allows to rationalize the regioselectivity of a particular reaction pathway because specific functional groups are activated by specific Lewis acid.

Scheme 3. Proposed mechanism of TiCl₄ catalysed 3 + 3 addition of 1,3-bis(silyloxy)-1,3-buta dienes with 3-silyloxy-2-en-1-ones

Scheme 4. Illustration of observed regioselectivities in [3 + 3] addition of 1,3-bis(silyloxy)-1,3-buta dienes with 3-silyloxy-2-en-1-ones
Scheme 5. Reversible silyl shifts between oxygens of 3-silyloxy-2-en-1-ones

Therefore, in this study, we have attempted to address all these questions and the results are described below. However, to reduce the computational cost, SiMe₃ group is replaced with SiH₃.

Shift of the silyl group

α, β unsaturated ketones 5 and 9 can exist in isomeric species 5' and 9', respectively by the shift of the silyl group between two oxygen atoms (Scheme 5). The dynamic shift is studied both in the presence and absence of the transition metal (Ti) and it is observed that the shift of the silyl group both in fluorinated and non-fluorinated substrates, 9 and 5, respectively, is a kinetically favourable process even in the absence of the transition metal (titanium). A transition state for the silyl shift in 2 is located at a barrier of 2.91 kcal mol⁻¹ from 5 (titanium free conditions), and the reaction is exothermic by 0.36 kcal mol⁻¹. The low activation barrier for the silyl shift may be attributed to the close proximity of the silyl group to the keto oxygen in 5. The O1-Si bond (see Figure 1 for numbering) in the transition state slightly increases to 1.89 Å compared to 1.73 Å in 5. The O2-Si bond in the product 5' is 2.27 Å. On the other hand, the O2-Si bond decreases to 1.88 Å in TS1 from 2.22 Å in 5, and finally to 1.74 Å in 5'. The stronger bond of silicon with both oxygen atoms may be another reason for low activation barrier.

Figure 1. Numbering scheme for discussion, and description of 1,2 and 1,4 addition

A similar behaviour is also observed for the fluorinated substrate 9. A transition state (Figure 3) for silyl shift is observed at a barrier of 4.06 kcal mol⁻¹, and the reaction is exothermic by 0.9 kcal mol⁻¹. A relatively higher activation barrier from 9 (compare 5→5') may be attributed to the electron withdrawing effect of the CF₃ functional group which decreases the electron density on the keto oxygen. Therefore, the nucleophilic attack of the keto oxygen on the silyl group is relatively difficult. The shift of the silyl group in 4 and 9 is kinetically a favourable process even in the absence of transition metal.

Complexation with Titanium

Phenyl ketones 5' and 9' are more stable compared to their alkyl/trifluoroalkyl ketones 5 and 9, respectively, therefore, compounds 5' and 9' are anticipated as active species in the reaction. However, the situation is somewhat different after complexation with titanium. Although 5' is more stable than 5; however, its titanium tetrachloride complex 11' is relatively unstable by 2 kcal mol⁻¹ compared to 11, a complex from 5. The greater stability of 11 relative to 11' can be explained on the basis of attractive interaction between the hydrogens of CH₃ with the chlorides of TiCl₄. H—Cl bond distances are 2.89 Å and 2.85 Å (Figure 4).

Figure 2. Potential energy diagram for silyl shift between 5 and 5'. All values are relative to 5 at 0.0 kcal mol⁻¹. All bond distances are given in Angstroms. Unnecessary hydrogen atoms are removed for clarity.
ARTICLE

Figure 4. Potential energy diagram for complexation of 5 and 5' with titanium to deliver 11 and 11', respectively. All values are in kcal mol\(^{-1}\) with respect to 5 at 0 kcal mol\(^{-1}\). All bond lengths are in Angstroms, and unnecessary hydrogen atoms are removed for clarity.

For 9, this reversal of stability on complexation with titanium is not observed. The complex of 9' with titanium (12') is still more stable than 12 by 0.38 kcal mol\(^{-1}\). The higher stability of 12' over 12 is supportive to our hypothesis above that interaction of hydrogen of CH\(_3\) with the chlorides of TiCl\(_4\) is the main driving force for the higher stability of 11 over 11'. The attractive interactions (CH\(_3\)--Cl) in 11 are replaced by repulsive interactions in 12 (CF\(_3\) with chlorides). These interactions are shown in Figure 5.

Figure 5. Potential energy diagram for complexation of 9 and 9' with titanium to deliver 12 and 12', respectively. All values are in kcal mol\(^{-1}\) with respect to 9 at 0 kcal mol\(^{-1}\).

In the next step of our mechanistic investigation we analyzed the distribution of charges in 11, 11', 12 and 12' (shown in figure 6) in order to predict the reactivity based on charge densities. In both 11 and 11', the position of highest positive charge density is the carbon bearing the methyl group regardless of the fact whether this carbon is a keto carbon or silyloxy bearing carbon. In 11, C2 and C4 (see figure 1 for labelling) have 0.5 and 0.389 positive charges, respectively whereas in 11', C2 and C4 bear 0.46 and 0.45 positive charges respectively. Since 11 is more stable and has higher positive charge on methyl ketone carbon therefore we believe that this isomer will be the active participating species in the reaction. For the fluorinated arene 12, the situation is quite opposite; a high positive charge is observed on carbon bearing the phenyl ring (C4). In 12', carbons 2 and 4 have 0.327 and 0.439 positive charges, respectively whereas in 12, carbons 2 and 4 bear 0.394 and 0.414 positive charges, respectively. It is interesting to note that both isomers (of any system) have similar sequence of charge distribution.

Discussion in the subsequent section has been divided into fluorinated and methyl systems, an in each section 1,4 and 1,2 addition are discussed in detail.

Fluorinated 1,3 dielectrophile

1,2 Addition

The bis silyl ether 4 contains two oxygen atoms which are available for binding with titanium therefore, it is believed that the bis silyl ether binds to 12 before the reaction takes place. The titanium is penta coordinated in 12' and the binding of 4 with titanium of 12 would generate an octahedral complex, Int5. Coordination of oxygen with titanium is followed by loss of the silyl chloride (Scheme 4). The literature reveals that octahedral complexes of titanium are well known and are quite stable[25, 26].
A transition state for the concomitant elimination of the silyl and chloride groups is located at a barrier of 19.36 kcal mol\(^{-1}\). The transition state (TS3) has the geometry very similar to Int5 except for the bond lengths change at the reaction site. The Ti-Cl bond elongates to 2.45Å in TS3 from 2.24Å in Int5. Cl-Si and O3-Si2 bond distances are 2.35 and 1.96Å, respectively in the transition state. The reaction has a low activation barrier, and easily accessible at room temperature. Moreover this step is also driven thermodynamically. The product of the reaction, Int6 is 6.96 kcal mol\(^{-1}\) more stable than the starting material (Int5). The loss of the silane group generates an oxy ligand which is well suited for the nucleophilic attack on the a,b unsaturated keto moiety to generate C-C bond. In the product Int6, both organic ligands are not well suited for C-C bond formation. Conformation changes are required to bring both organic fragments in proper orientation for C-C bond formation. This conformational change costs 7.66 kcal mol\(^{-1}\). A transition state is located at a barrier of 5.2 kcal mol\(^{-1}\) from Int6. This low activation energy may be attributed to relatively higher positive and negative charge densities on C4 and C6 carbons, respectively. The C-C bond being formed has a bond length of 2.2Å in the transition state. Some other bond lengths also change considerably during the C-C coupling reaction. The O3-Ti bond length increases from 1.78Å in Int6 to 1.90Å in the TS4 whereas the O1-Ti bond length decreases from 2.06 to 1.94Å.

Since we have replaced the trimethylsilyl group with SiH3 in order to reduce the computational cost, it was of interest whether this simplification affects the activation barriers, and may change the regioselectivities. Towards this end, activation barriers for the key step (1,2 or 1,4 (vide infra)) are studied with Si(CH\(_3\))\(_3\) groups as well, and the activation barriers are given in the parenthesis (see Figure 7 and Figure 10). It is very obvious from Figure 7 that the activation barrier is not affected considerably by replacing trimethylsilyl (4.84 kcal mol\(^{-1}\)) group with SiH3 (5.20 kcal mol\(^{-1}\)).

Int6 is believed to undergo an interesting rearrangement of OTC\(_3\) to the silyl group which subsequently delivers Int9 by elimination of TiCl\(_4\)(OSiH\(_3\)). Although transition state for this oxy-titanium shift is located for methyl system (vide infra); however, no such transition state is located for fluorinated analogue. Rather, a true minimum Int8 is observed in which oxytitanium is bound to both, silyl moiety and carbon 5. The O3-C5 and O3-Si1 bond distances are 2.66Å and 3.04Å, respectively. Thermodynamic cost for this shift is 16.42 kcal mol\(^{-1}\). Int9 undergoes coordination of the 2nd silyloxy oxygen (O4), which is followed by elimination of another Si and Cl, very similar to the one observed in Int5. The transition state for the elimination of silyl chloride (TS5) is not modelled here. The activation barrier for the elimination of silyl chloride, is believed similar to the one observed in Int5. The product of the silyl chloride elimination, Int10 undergoes nucleophilic attack on the CF\(_3\)-CO group. Kinetic barrier for the step is 26.56 kcal mol\(^{-1}\). This reaction is also favourable thermodynamically; the product (Int11) lies 18.7 kcal mol\(^{-1}\) lower in energy than Int10 (Figure 9). The cyclized product is believed to undergo loss of a water molecule and finally tautomerization deliver the product. The possibility of elimination of silyl chloride with concomitant cyclization to deliver the final product cannot be excluded safely.

**Figure 7.** Potential energy diagram for elimination of H\(_2\)Si-Cl followed by C-C bond formation (Int5 \(\rightarrow\) Int8); All energies are relative to Int5 at 0 kcal mol\(^{-1}\). All bond lengths are in Angstroms. Unnecessary hydrogen atoms are removed for clarity. Values in parenthesis correspond to trimethylsilyl substituted derivatives.

Complexation of 4 with 12 generates an intermediate octahedral complex Int5 where both oxygen atoms are in cis orientation. O1-Ti and O3-Ti bond lengths are 2.12 and 2.38Å, respectively. The large bond distance of siloxy-Ti may be due to sterical reasons (Figure 7). The chlorides-Ti bonds trans to oxy ligands are relatively short (2.24Å) whereas other Ti-Cl bonds are somewhat elongated (2.28 and 2.32Å, shown in Figure 8). The cis orientation of the oxy ligands is necessary for subsequent addition reaction. Any trans orientation of these group will not be favourable for C-C bond formation. A chloride ligand on titanium in Int5 is parallel to the silyl group at a distance of 3.29Å.

**Figure 8.** Optimized geometries of Int5, TS3 and Int6. All bond lengths are in Angstroms, and unnecessary hydrogen atoms are removed for clarity.
The competitive reaction for \( \text{Int6}' \) is 1,4 addition on enone fragment instead of a 1,2 addition. The activation barrier for C-C bond formation through 1,4 addition was found higher compared to the 1,2 attack; 13.10 kcal mol\(^{-1}\) for 1,4 addition compared with 5.2 kcal mol\(^{-1}\) for the 1,2 attack. The higher activation barrier for \( \text{Int6} \rightarrow \text{Int12} \) (Figure 10) compared to \( \text{Int6} \rightarrow \text{Int7} \) may be due to steric crowding at the carbon bearing the siloxy and CF\(_3\) moieties, or may be due to electronic factors because of reduced charge density at keto carbon C2. The C6-C2 bond distance is 2.39Å in the transition state (TS7), compared to 2.29 Å in the transition state for the 1,2 attack, TS4. The titanium has trigonal bipyramidal geometry in TS7 where fluorine atoms of CF\(_3\) do not coordinate to the titanium. The reaction is thermodynamically favourable (\( E_R = 16.12 \) kcal mol\(^{-1}\)). The activation barrier for the similar reaction but involving Si(CH\(_3\))\(_3\) has a very similar activation barrier (12.37 kcal mol\(^{-1}\)). These findings are consistent with those in Figure 7 that replacing a trimethylsilyl group with SiH\(_3\) does not change the activation barrier to alter the regioselectivities.

\( \text{Int12} \) undergoes elimination of O-SiH\(_3\) (next to CF\(_3\)) and TiCl\(_3\) moiety to generate the species for the next step, \( \text{Int13} \). This process may be a direct one step process for the methyl ketone (vide infra) or may be a multistep process as in the case of trifluoro species. For the trifluoro species, first the silyl oxygen coordinates to titanium and a transition state TS8 has been located for this coordination. This is just an addition reaction because it does not involve elimination of any other group. The cyclic species undergoes cleavage of OSiH\(_3\) and TiCl\(_3\) to generate \( \text{Int14} \) (see supporting information). In \( \text{Int14} \), a silyl group is parallel to a chloride on titanium therefore, elimination of Silyl chloride generates the enolxy species \( \text{Int15} \). The geometry of \( \text{Int15} \) has some interesting features; C7 is coordinating with titanium at a distance of 2.34Å, the carboxylate oxygen (O4) along with the ortho carbon C7 behave as bidentate ligand for titanium, the titanium in \( \text{Int15} \) has distorted octahedral geometry. Nuclophilic attack of C7 on C4 in \( \text{Int15} \) generates the cyclic species \( \text{Int16} \). The reaction has kinetic demand of 33.20 kcal mol\(^{-1}\) (Figure 11). In the transition state, C7-C4 bond distance is 2.68Å whereas the C-Ti distance is increased to 2.75Å. Although kinetically unfavourable, the reaction is highly favourable thermodynamically. The reaction is exothermic by 19.32 kcal mol\(^{-1}\). Thermal energy available at room temperature is not sufficient to surpass this barrier which clearly illustrates that this is not the pathway which should be observed experimentally. The regioselectivity observed experimentally is in marked contradiction with the product obtained from 1,4 addition.

---

**Figure 9.** Potential energy diagram for cyclization in \( \text{Int10} \) to generate \( \text{Int11} \). All energies are in kcal mol\(^{-1}\) relative to \( \text{Int10} \) at 0.0 kcal mol\(^{-1}\).

**Figure 10.** Potential energy diagram for 1,4 addition in \( \text{Int6} \) to generated \( \text{Int12} \), followed by change in coordination to generate \( \text{Int13} \). Hydrogen atoms are removed for clarity. All bond lengths are in Angstroms. Values in parenthesis correspond to trimethylsilyl substituted derivatives.
Figure 11. Potential energy diagram for intramolecular cyclization in Int15 to generate Int16, all energy values are relative to Int15 at 0.0 kcal mol\(^{-1}\). Hydrogen atoms are removed for clarity. All bond lengths are in Angstroms.

The 1,2 addition is a favourable pathway energetically, and it explains the right regioselectivity. Although the calculations above reveal that 1,2 attack of enol on the keto oxygen delivers the product which is observed experimentally yet there is another set of similar calculations but with CF\(_3\) ketone bound to titanium in the first step rather than a phenyl ketone. We have also considered this as a possible reaction in our study.

1,2 attack on CF\(_3\) Ketone

Calculations have been performed on a titanium bound complex starting from CF\(_3\) ketone, Int17. Typically the nature and the number of step are almost comparable to those for phenyl ketone regarding both 1,2 and 1,4 attack. We have repeated the same set of calculations for CF\(_3\) ketone to explore the associated kinetics and thermodynamics. The first step is elimination of silyl chloride from Int17 for which a transition state has been located at a barrier of 19.67 kcal mol\(^{-1}\) from starting complex. The activation barrier is very comparable to the elimination of silyl chloride in Int5 (19.36 kcal mol\(^{-1}\)). The reaction is thermodynamically favourable by 8.52 kcal mol\(^{-1}\). A few important changes in bond distances on going to transition states are given in the table below.

Table 1. Comparison of some important geometric parameters in Int17 and TS10

<table>
<thead>
<tr>
<th>Bond</th>
<th>Int17</th>
<th>TS10</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl</td>
<td>2.24</td>
<td>2.45</td>
</tr>
<tr>
<td>Ti-O</td>
<td>2.36</td>
<td>2.00</td>
</tr>
<tr>
<td>O-Si</td>
<td>1.72</td>
<td>1.95</td>
</tr>
<tr>
<td>Si-Cl</td>
<td>3.31</td>
<td>2.35</td>
</tr>
</tbody>
</table>

Figure 12. Potential energy diagram of Ti catalyzed 1,2 addition of enol on CF\(_3\) ketone. All values are in kcal mol\(^{-1}\) relative to Int17 at 0.0 kcal mol\(^{-1}\).

Nucleophilic attack of enol on the C2 in Int18’ is a kinetically favourable (E\(_{\text{act}}\) = 6.22 kcal mol\(^{-1}\), see Figure 12) but this activation energy is slightly higher (1 kcal mol\(^{-1}\)) compared to the activation barrier for nucleophilic attack on phenyl ketone Int6 (E\(_{\text{act}}\) = 5.2 kcal mol\(^{-1}\)). This difference in activation barrier may be attributed to the density of the positive charge of 12’ and 12 (vide supra). The important C6-C2 bond (being formed) has bond length of 2.37 Å in the transition state TS11 compared to 3.61 Å and 1.54 Å in Int19 and Int18, respectively. The similar reaction using Si(CH\(_3\))\(_3\) group instead of SiH\(_3\) has the activation barrier of 6.63 kcal mol\(^{-1}\) (see supporting info, Figure S11).
The next key step in this pathway is the cyclization of Int20 to Int21, a reaction which generates the cyclic intermediate (Int21) from enol by nucleophilic attack (Figure 13). The calculated activation barrier for the cyclization is 20.60 kcal mol$^{-1}$. This activation barrier is although high but still accessible under the reaction conditions. Although energetics associated with this pathway are not very high (may proceed under reaction conditions); however, its comparison with 1,2 attack on phenyl ketone (1,2 attack starting from Int6) shows that this pathway is energetically less favourable. Moreover, the theoretical findings are consistent with the experimental regioselectivities (compare the structure of Int21 and Int10 with Int10).

The 1,4 attack on CF$_3$ ketone is expected to be kinetically demanding, although it delivers the desired product. The 1,4 addition on CF3 ketone is also modelled, and found to have high activation barriers (See Figures S12 and S13). The first 1,4 attack has an activation barrier of 15.99 kcal mol$^{-1}$ (much higher than any of the above three mechanisms). This high activation barrier is expected because this reaction not only involves 1,4 attack which is kinetically demanding but it involves intermediate 18 on which attack is even more demanding kinetically. Analysis of the pathways, shown above, clearly indicates that the charge density shown in Figure 6 is a good tool to predict the regioselectivity of the reaction. Moreover, pathways with 1,2 attack on ketone are energetically more favourable whereas conjugate addition is thermodynamically less favourable.

**Methyl system**

From Figure 6, it is apparent that the methyl ketone 11 has higher Mullikan charge density on C2; therefore, this structure is only considered for mechanistic studies. The phenyl ketone 11' is not considered for both 1,2 and 1,4 attack because higher activation barriers are expected than 11 (vide supra). Moreover, the regioselectivity expected through a 1,2 attack is in contradiction to what is observed experimentally.

![Figure 13. Potential energy diagram for cyclization in Int20. All values are in kcal mol$^{-1}$ relative to Int20 at 0.0 kcal mol$^{-1}$](image)

The first step is typically cleavage of a chloride and a silyl group in Int22. The titanium in Int22 has an octahedral geometry where both oxygen ligands are cis to each other. The O3-Ti-O2 bond angle is 81.77 degrees. The O3 –Ti and O2-Ti bond distances are 2.40 and 2.06Å, respectively. The Ti-Cl (trans to oxy ligands) bond lengths are in the range of 2.24-2.25Å whereas the other chloride – titanium bond lengths are 2.30-2.31Å. One of the chlorides is bent towards silyl group primarily because of the dipole dipole interactions (Figure 14). A transition state for the cleavage of silyl chloride in Int22 is located at a barrier of 18.74 kcal mol$^{-1}$ (from Int22, See Figure 15). In the transition state TS13, Cl-Ti bond distance increases to 2.46Å. The alkoxide-titanium bond distance decreases to 2.01Å in TS13. The geometry on titanium also changes. The Cl-Ti-O3 (silyl) angle drops to 159.0 degrees in TS13 from 176.18° in Int22. This activation barrier for the cleavage of silyl and a chloride is very comparable to the one observed for the trifluoro system (vide supra). These findings clearly illustrate that the cleavage is not significantly influenced by the structure of the complex. The reaction is exothermic by 6.5 kcal mol$^{-1}$. The complex Int23 has trigonal bipyramidal geometry around titanium. The two chlorides and alkoxide ligands do not make a perfect trigonal planar structure. O-Ti-Cl bond angles are 114-115 degrees, whereas Cl-Ti-O3 bond angle is 127.65 degrees. Two chlorides and the alkoxide ligands are in one plane (trigonal). The third chloride and keto oxygen are in the perpendicular plane. The alkoxide –Ti and keto titanium bond distances are 1.74 and 2.14Å, respectively. The subsequent C-C bond formation in Int23 has kinetic demand 11.23 kcal mol$^{-1}$, whereas the reaction is thermodynamically favourable by 12.03 kcal mol$^{-1}$. In the transition state, the C2-C6 bond distance is 2.23Å. Moreover, the O3-Ti and O3-C5 bond distances are 1.88 and 1.31 Å, respectively. The newly formed O2-Ti and C2-O2 bond distances are 1.94 and 1.30 Å, respectively. The Int23, generated as a result of C-C bond formation, undergoes an interesting cleavage/shift of titanium oxy group on the silyl group. This shift is predicted to have a kinetic demand of 19.12 kcal mol$^{-1}$. 

![Figure 14. Optimized geometries of Int22, TS13, Int23 and TS14. Unnecessary hydrogen atoms are removed for clarity. All bond lengths are in Angstroms](image)
In the transition state, O1-C2 bond distance is 2.15 Å whereas the O2-Si1 bond distance is 3.17 Å.

The titanium oxy group interacts very loosely with the silyl groups, as it is reflected with bond separation in the TS. This behaviour of the methyl system is remarkably different than what is observed for the trifluoromethyl analogue. In the case of trifluoromethyl system, this type of transition state is not observed rather an intermediate is observed in which titanium oxy species is located between carbon and silyl group (vide supra).

It is believed that the Int25 generated in the above step (Figure 16) soon loses Cl$_3$Ti-OsiH$_3$ species and binds to TiCl$_4$ to generate Int26, as a precursor for the next step. Cleavage of a silyl and chloride in Int26 generates an intermediate Int27 ready for cyclization. Cyclization in Int27 is a kinetically and thermodynamically favorable process (Figure 17). The titanium in TS16 has a trigonal bipyramidal geometry where two chlorides and an Oxo ligand lie in the plane.
trigon; however, the CH and chloride ligands are in the vertical axis. The CH- metal bond distance increases to 3.02 Å in the transition state from 2.22 Å in Int27. Moreover, the CH and keto carbon bond distance is 2.87 Å which indicates a very early transition state. The calculated activation barrier for the cyclization is 19.54 kcal mol⁻¹. Dehydration and tautomerization in Int28 may deliver the final aromatic product.

1,4 addition

Int23 generated by the loss of a silyl chloride molecule can also undergo a 1,4 addition on the α, β unsaturated ketone to deliver intermediate Int29 which is thermodynamically more stable than the intermediate Int23 by 3.03 kcal mol⁻¹. The reaction has kinetic demand of 19.57 kcal mol⁻¹ which is higher than the kinetic demand for the 1,2 addition in Int23' (11.23 kcal mol⁻¹). These observations are also consistent with the theoretical calculations for the trifluoromethyl system (vide supra) where direct attack is more favourable than the 1,4 addition. From these calculations, one can infer that 1,2-addition is a more feasible pathway compared to 1,4-addition for these formal [3+3] addition reactions (1,4 addition). The difference in activation barrier for 1,2 and 1,4 attack is about 7.9 kcal mol⁻¹ for the methyl system whereas this difference is about 7.9 kcal mol⁻¹ for the trifluoromethyl analogue.

The subsequent cyclization has a calculated activation barrier of 19.72 kcal mol⁻¹ which is not significantly different than the one calculated for the cyclization in Int27 which clearly illustrates that the selectivity is governed at the first addition step of the formal [3+3] addition reaction. The 1,2 addition (1,2 addition), shown in Figures 16 and 17, delivers the product with the experimentally observed regioselectivity. The 1,4 addition (shown in Figure 18), does not deliver the product with the correct regioselectivity. These findings are consistent with our the calculations that 1,2 addition is a favourable process with lower activation barriers compared to the 1,4 addition.

In summary, we have shown that the experimentally observed different regioselectivities for CH₃ and CF₃ enones can be explained by a common mechanism where 1,2 addition of 1,3 -bis(silyl enol ethers) on 1,3-dielectrophiles is a more favorable pathway than the competing 1,4 addition. The differences in regioselectivities originate from different isomeric structures of enones entering in the catalytic cycle.

Conclusions

Density functional theory calculations have been performed to gain mechanistic insight of the formal [3+3] addition of 1,3-bis(silyl enol ethers) and 1,3-dielectrophiles to explain the experimentally observed regioselectivities. For this purpose, reaction of 1,3-bis(silyl enol ethers) with two different 1,3-dielectrophiles (5 and 9) is studied. The silyl moieties in 1,3-dielectrophiles are dynamic even in the absence of a metal catalyst (E_{act} < 5 kcal mol⁻¹). The isomeric dielectrophiles (for example 5 and 5’) differ in their reactivity in formal [3+3] addition, and it depends on the strength of the positive charge (Mullikan charges) on the electrophilic carbon atom. Calculations reveal that a single mechanism can justify the experimentally observed different regioselectivities for 5 and depending on the isomeric species entering in the catalytic cycle (11 and 12’). 1,2 and 1,4 addition mechanisms have been studied for both isomeric forms of each dielectrophile. The calculations reveal that 2,1 addition of 1,3-bis(silyl enol ethers) on 1,3-dielectrophile is a favorable process over the conjugate (1,4) addition. A typical mechanism involves coordination of 1,3-bis(silyl enol ethers) and 1,3-dielectrophiles with TiCl₄ followed by elimination of Silyl chloride. The elimination of silyl chlorides has an activation barrier of about 19-20 kcal mol⁻¹. The elimination of the silyl chloride is followed by a nucleophilic attack on the dielectrophile. This nucleophilic addition governs the selectivity of the reaction. For trifluoromethyl, 1,2 addition (1,2 addition) is kinetically more favorable (E_{act} = 5.2 kcal mol⁻¹) than the 1,4 addition (E_{act} = 13.1 kcal mol⁻¹, Figure 18). For the methyl analogue, the difference in the activation barriers for the 1,2 and 1,4 addition is even more pronounced in the favor of 1,2 addition (about 8.34 kcal mol⁻¹). The trends in the activation barrier for 1,2 and 1,4 addition for both dielectrophiles can be correlated to Mullikan charges at the electrophilic centers.

Acknowledgements

Figure 18. Potential energy diagram for Ti catalyzed 1,4 addition of enol to enone in Int23 All values in kcal mol⁻¹ with respect to Int23 at 0.0 kcal mol⁻¹.
The authors acknowledge the financial support from Higher Education Commission of Pakistan (Grant No. 1899), COMSATS Institute of Information Technology, and University of Rostock. This work has also been supported by the project “Light2Hydrogen” of the BMWF and the project “Nano4Hydrogen” of the ESF and the state of Mecklenburg-Vorpommern.

Notes and references
RSC Advances Accepted Manuscript

133x93mm (300 x 300 DPI)