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Clean and Selective Catalytic C-H alkylation of Alkenes with Environmental friendly Alcohols

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Supporting information for this article includes alternative reaction pathways, providing energies, Cartesian coordinates, and 3D view for all DFT optimized species discussed in this work are also given.

Graphical Abstract

Highlights

- The reaction mechanism for $[(C_6H_6)(PCy_3)(CO)RuH]^+$ (**1**; Cy, cyclohexyl) mediated alkylation of indene substrate using ethanol as solvent
- The plausible reaction mechanism involves a cationic Ru-alkenyl species
- The functionalization of alkenes here by means of alcohols fits perfectly in the field of green chemistry

Abstract: Bearing the alkylation of alkene substrates using alcohol as solvent, catalysed by the cationic Ru-based catalyst $[(C_6H_6)(PCy_3)(CO)RuH]^+$, DFT calculations have been carried out to get mechanistic insights of such an environmental friendly reaction. Hard experimental conditions of Yi and coworkers [*Science* **2011**, 333, 1613] allow the formation of a C-C bond between indene and ethanol. The predicted mechanism suggests a cationic Ru-alkenyl species once two equivalents of indene interact releasing a molecule of indane subproduct. Then, oxidative addition of the C–O bond of alcohol to Ru-alkenyl species leads to Ru-alkenyl-alkyl species, followed by the reductive elimination process produces the desired alkylation product and a Ru-hydroxo complex. Finally, vinylic C–H activation and water elimination regenerates the Ru-alkenyl species. In this paper we present a full description of the complete reaction pathway along with possible alternative pathways, which are predicted to display higher upper barriers. Furthermore, the present study explains the possible reasons for the absence of undesired products such as indene dimer or hydroxylated indene in the experiments.

Introduction

Carbon–carbon (C–C) bond forming reactions represents an important tool in the field of organic chemistry for the synthesis of complex natural products, bioactive molecules developed as drugs and agro-chemicals [1]. In general, traditional Friedel-Crafts alkylation [2] is the most extensively used method in industry for the construction of C-C bond. However, this method has the serious drawback of requiring stoichiometric amounts of a Lewis acid acting as promoter, and of a base to neutralize acid by-products [3]. A powerful and more selective method is the so-called Mizoroki-Heck coupling,[4] which is successful for the alkenylation of arenes but again requires stoichiometric amount of a wasted reagent, in this case a base [5], and is quite limited in substrate scope [6]. These limitations explain the reason for the intensive search of alternative and more sustainable methods for C-C bond formation [7]. In this context, the discovery that Ru- catalysts can promote the coupling of olefins and arenes without formation of stoichiometric byproduct [8], opened the route to different strategies for the alkylation and alkenylation methods of arenes assisted by coordination of a heteroatom to the Ru-center [9,10]. Despite their catalytic efficiency [11,12], these methods are quite limited in substrate scope and often still require stoichiometric oxidants and additives [13,14]. This calls for the development of more sustainable methods for C–C bond formation, with the requirement of starting from inexpensive and naturally abundant precursors while avoiding the use of stoichiometric additives.

Scheme 1. CH alkylation of alkenes with alcohols

In response to this open challenge, Yi *et al.* reported a selective catalytic alkylation reaction of alkenes with alcohols using a well-defined Ru-complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**; Cy, cyclohexyl) as catalyst (see Scheme 1) [15]. The reaction was carried out using a broad range of substrate functionality, including amines and carbonyls, for 2 to 8 hours at temperatures ranging from 75° to 110°C [16]. The reaction proceeds via the formation of new carbon-carbon bond between vinyl carbon-hydrogen (C–H) and carbon-hydroxo centers with the concomitant loss of water. Interestingly, an excess of alcohol seems to avoid the undesired dimerization of the substrate. Preliminary mechanistic studies are inconsistent with Friedel-Crafts–type electrophilic activation of the alcohols, suggesting instead a vinylic C–H activation pathway with opposite electronic polarization.

Scheme 2. Potential mechanism of CH alkylation of alkenes with alcohols by a Ru-complex **1**.

The plausible reaction mechanism proposed by Yi *et al.* is given in Scheme 2. Activation of the cationic Ru-complex **1** was proposed to occur through the reaction between two olefin molecules via vinylic C–H activation and alkane elimination, resulting in the formation of the Ru-alkenyl species **A** inside the catalytic cycle. The existence of **A** was supported experimentally. Then, it was hypothesized that oxidative addition of the C–O bond of the alcohol to the Ru-alkenyl species followed by the reductive elimination of the C–C coupled alkenyl-alkyl product with formation of the Ru-hydroxo complex **B** could occur. In line with the known reactivity of Ru-hydroxo species towards C–H activation [17], closure of the catalytic cycle was proposed to occur by vinylic C–H activation and water elimination from **B**, regenerating species **A**.

Given the relevance of this seminal protocol for the sustainable formation of C–C bonds, we decided to shed light on the energetics within the catalytic cycle, including catalyst activation. This understanding could provide the basis for further developments of this important reaction. In this manuscript, we use density functional theory (DFT) calculations to investigate in detail the reaction mechanism proposed in Scheme 2 using indene as the substrate and ethanol as the alcohol (and solvent), pointing out that the yield for such specific reactants was 84%, bearing a temperature of 90°C and 5 hours of reaction. Additionally, we also investigated the possible role of ethanol in preventing the un/desired indene dimerization reaction.

Results and Discussion

Figure 1 shows the free energy reaction pathway. Bearing the no coordinating character of the counteranion BF_4 [18], the reaction starts with activation of the cationic pre-catalyst species **1**. A concerted transition state replaces the benzene ligand by the entering indene substrate molecule, overcoming a barrier of 10.3 kcal/mol. On the contrary, the decooordination of benzene molecule from **1** is calculated to be endothermic in nature, requiring an energy input of 23.5 kcal/mol. On the other hand, dissociation of PCy_3 ligand from species **1** costs 23.8 kcal/mol more than dissociation of benzene molecule. Therefore, we here considered the dissociation of benzene molecule. Then, thermodynamically intermediate **3** lies 25.0 kcal/mol below **2** (or 1.8 kcal/mol below **1**). The next step corresponds to the insertion of the $\text{C}_\alpha\text{--C}_\beta$ double bond of indene into the Ru–H bond to give intermediate **3**. From an energetic point of view, intermediate **3** lies 14.6 kcal/mol above **2** and requires the overcoming of a barrier of 20.5 kcal/mol above **2**. Coordination of a second indene molecule to metal in **3** leads to intermediate **4**, lying 13.7 kcal/mol below **3**. Activation of the $\text{C}_\alpha\text{--H}$ bond of the coordinated indene by the Ru-alkyl bond results in the formation of the Ru-alkenyl intermediate **5** and release of indane. From an energetic point of view, intermediate **5** lies 12.9 kcal/mol above **4** and requires the overcoming of an overall barrier of 23.7 kcal/mol from **3**. In the next step, an ethanol solvent molecule coordinates to intermediate **5** in trans to the phosphine, leading to intermediate **6**. This step completes the activation pathway, with intermediate **6** the first species within the catalytic cycle. Before discussing the catalytic cycle, we remark that for intermediates **2**, **4** and **5**, we have also

considered substitution of PCy₃ by ethanol or indene. However, our results show that the resulting substituted intermediates are thermodynamically less stable than the PCy₃ complex (see Figure S1). Thus, we kept the PCy₃ ligand bound to Ru in the description of the catalytic cycle.

Focusing discussion on the catalytic cycle starting from **6**, the first step is the oxidative addition of EtOH to the Ru center by cleavage of the C–O bond and formation of intermediate **7**. This step is predicted to be quite expensive, with a free energy barrier of 30.8 kcal/mol with respect to **8**. Formation of a new C–C bond between the ethyl and indenyl group leads to intermediate **8**, which lies 25.1 kcal/mol below **7** and requires the overcoming of a barrier of 19.6 kcal/mol above **7**. From a structural point of view, intermediate **8** holds the alkylated indene, *i.e.* the organic product of the reaction, via a Ru–C bond. The next step corresponds to the product release from **8**, giving intermediate **9**, followed by the coordination of third molecule of indene leads to intermediate **10**. This intermediate **10** lies 4.5 kcal/mol above **8** or 4.3 kcal/mol below **9**. In the penultimate step, we considered coordination of ethanol to Ru in **10**, leading to the formation of intermediate **11**. From a thermodynamic point of view, intermediate **11** lies 7.6 kcal/mol below **10**, suggesting the feasibility of indene coordination to **10**. Next, evolution of **11** towards intermediate **12** requires passing through transition state **11-12**, with a barrier of 21.5 kcal/mol. This latter step consists of a transfer of H from indene to the hydroxyl group in **11**, resulting in the formation of intermediate **12** with a coordinated water ligand. Finally, the subsequent dissociation of water ligand from **12** results in the formation of **6**, and thus closing the catalytic cycle.

Figure 1. Computed stationary points for [(C₆H₆)(PCy₃)(CO)RuH]⁺ (**1**) mediated alkylation of indene substrate with ethanol. Free energies in solution are given in kcal/mol (ethanol as the solvent) relative to species **1** (all Ru-based species are charged +1).

Figure 2. Computed high energy transition states for the studied reaction mechanism in Figure 1: (a) **4-5** corresponds to the release of indane, (b) **6-7** corresponds to the C-O bond activation of ethanol molecule, (c) **7-8** corresponds to the formation of new C-C bond, and (d) **10-11** to the proton transfer from the former indane to the hydroxyl group. Selected distances are given in Å.

Having completed the description of the whole reaction mechanism, we note that there are four rather high energy transition state barriers, namely **4-5**, **6-7**, **7-8** and **11-12** (see Figure 2): first barrier (**4-5**) corresponds to the release of one substrate indene as indane molecule and has an overall barrier of 22.8 kcal/mol from the starting species **1**; second barrier (**6-7**) corresponds to the C-O bond breaking of ethanol molecule and has an overall energy barrier of 28.4 kcal/mol from **1**; whereas the barrier described by the transition state **7-8** corresponds to the formation of a new C-C bond that results in the desired alkylated indene product and has an overall energy barrier of 28.1 kcal/mol from **1**; and the final barrier (**11-12**) corresponds to the proton transfer to form the water ligand overcoming a barrier of 21.5 kcal/mol. To summarize, the studied reaction pathway clearly presented high energy barriers, which are however consistent with the remarkably high temperature of 100 °C needed experimentally to achieve a yield of at least 80% in 5 h [14,18]. Nevertheless, to investigate the possible existence of alternative pathways from the key intermediates **4**, **5**, and **6** that could present lower energy barriers, we performed additional calculations and the corresponding results are discussed in the following sections (see Figures 3-7).

Figure 3. Computed structures for H transfer from indene to Ru metal in **4** (Cy groups on P atom are omitted for clarity). Selected distances are given in Å.

From intermediate **4**, focusing on the competition between the H transfer from one indene molecule to the other or Ru metal in **4** (see Figure 3), we located a transition state **4-13**, corresponding to the transfer of H to the Ru metal. This alternative transition state depicted in Figure 2 costs 13.5 kcal/mol more than transition state barrier **4-5**. Furthermore, intermediate **13** is 15.5 kcal/mol higher in energy with respect to **5**, which excludes the possibility of H transfer to Ru metal in **4**.

Figure 4. Computed stationary points for dimerization of indene from intermediate **5**. Energies are given in kcal/mol (all Ru-based species are charged +1).

Next, we investigated the possible reasons for the improved experimental performance of the studied reaction given in Scheme 1 (see Figure 4) in the presence of ethanol in excess with respect to indene. To this end, we studied the coordination of a new molecule of indene to Ru metal in **5** that leads to intermediate **14**, lying 20.5 kcal/mol below **5**. Therefore, coordination of an indene molecule to **5** is thermodynamically favorable by 6.1 kcal/mol when compared with the coordination of a molecule of ethanol (intermediate **6** in Figure 1), however we must point out that the second coordination of an ethanol molecule to **6** is 10.6 kcal/mol more stable, and overall 4.5 kcal/mol more stable than the coordination of an indene molecule. Thus, in excess of ethanol as here the indene coordination is not favored. Next, transfer of H from the newly coordinated indene to Ru metal in **14** leads to intermediate **15**, which The barrier for this step is calculated to be 34.6 kcal/mol from **14**. Then, from intermediate **15**

indene dimerization occurs, leading to the intermediate **16**. This dimerization step is rather a low energy step requiring only 3.0 kcal/mol from **15**. By a new insertion of an indene molecule, the final step corresponds to the release of indene dimer to generate intermediate **2** of Figure 1. To summarize this part, the results suggest that due to the competitive coordination of either ethanol or indene to intermediate **5**, better experimental performance is obtained only by adding an excess of ethanol over indene in order to avoid the undesired dimerization reaction.

Then, from intermediate **6**, we considered the H transfer from the hydroxyl group of ethanol to either of the carbon atoms (C_α or C_β) of indene molecule or Ru metal (see Figure 5). Our results show that the H transfer to C_β atom of indene molecule (**17**) is much more favorable when compared with transfer to C_α atom (**18**) as the predicted barrier for the former transfer, **6-17** is 30.7 kcal/mol lower in energy than the barrier for the latter case, **6-18**. Surprisingly, the transition state **7-18** is 17.7 kcal/mol lower in energy than the rate determining step barrier **6-7** of Figure 1. However, the resulting intermediate **17** is believed to be a non-productive intermediate as the further steps from **17** do not lead to the desired alkylated indene product **8**. Thus, we considered the step **6**→**7** instead of **6**→**17** for the reaction mechanism given in Figure 1. On the other hand, the H transfer from hydroxyl group of ethanol to Ru metal in **6**, giving a metal hydride intermediate **19**, requires the overcoming of a huge barrier of 35.9 kcal/mol from **6**. Taken together, these observations suggest that the presented alternative pathway from intermediate **7** should not be operative.

Figure 5. Computed stationary points for H transfer reaction from ethanol to C_α and C_β carbon atoms of indene in intermediate **6**. Energies are given in kcal/mol (all Ru-based species are charged +1).

Figure 6. Computed stationary points for the transfer of ethyl group to C_α and C_β carbon atoms of indene in intermediate **7**. Energies are given in kcal/mol (all Ru-based species are charged +1).

Next, we focused on the steps starting from intermediate **7** (see Figure 6). From **7**, repositioning the ethyl group from *trans* to *cis* with respect to PCy_3 ligand leads to a *cis* isomer **20**, which lies 23.2 kcal/mol above **7**. A point worth mentioning here is that we located the transition state **7TS** (see the SI for the details) for the rotation of ethyl group with a barrier only 2.0 kcal/mol above **7**, indicating that the ethyl group in **7** is free to rotate. From intermediate **20**, the barrier for the formation of alkylated indene **8** (**20-8**) is predicted to be 12.5 kcal/mol higher in energy than the corresponding barrier **7-8** of Figure 1. Furthermore, we also evaluated the ethyl group attack onto the C_β of the indenyl ligand, giving alkylated indene isomer **21**, which is 7.4 kcal/mol higher in energy than **8**. This step proceeds through the transition state **20-21** that costs only 0.1 kcal/mol, but still 3.6 kcal/mol higher in energy than the **7-8** of Figure 1. To summarize, this profile is so high in energy that it can be excluded from occurring even under the drastic conditions used experimentally.

In the following, we considered the hydroxylation of indenyl ligand in **7** (see Figure 7). The predicted barrier for this hydroxylation step (**7-22**) is 2.8 kcal/mol higher in energy than the product formation barrier **7-8** of Figure 1, suggesting that both reactions are competitive experimentally [13,16]. However, the resulting intermediate **22** is 19.8 kcal/mol less stable than **8**, which indicates that the indene hydroxylation pathway is thermodynamically inhibited. The final step corresponds to the release of hydroxylated indene from **22**, giving intermediate **23**, and the next coordination of EtOH, with an overall relative energy destabilization of 1.3 kcal/mol.

Figure 7. Computed stationary points for the hydroxylation of indene from intermediate **7**. Energies are given in kcal/mol (all Ru-based species are charged +1).

Finally, we studied possible alternative reactivity from intermediate **10** as shown in Figure 8. A transfer of H from indene to the hydroxyl group in **10** results in the formation of intermediate **25** with a coordinated water ligand. From an energetic point of view, intermediate **25** is nearly isoenergetic with respect to **10** and obtained through overcoming a considerable barrier of 24.0 kcal/mol from **10**. Finally, intermediate **25** would coordinate a new ethanol molecule to form intermediate **12** and the subsequent dissociation of water ligand from **12** results in the formation of **6**, and thus closing the catalytic cycle. However, evolution of **10** towards intermediate **12**, through species **25**, requires passing through transition state **10-25**, with a barrier of 24.0 kcal/mol, which is 2.5 kcal/mol higher in energy than the barrier for evolution of **10** towards **12**, ruling out the possible formation of **25**.

On taking a different route from **10**, activation of one of the vinylic C-H bonds of indene can result in the H atom transferred to Ru rather than to the OH group, leading to the formation of the metal hydride **26**. The calculated barrier for this step **10-26** is 6.1 kcal/mol higher in energy than the barrier **11-12** of Figure 1, suggesting that the formation of **26** is neither kinetically favored over formation of **12**, through **11**, nor thermodynamic stable (**26** is 27.0 kcal/mol above **11**) indicates this as a no viable pathway. Additionally, we have located other isomers of metal hydrides (see SI for structural details), which are different with respect to **26** only for the positioning of the hydride around the Ru metal, i.e., *trans* to either the CO or the PCy₃ ligand. Our results suggest that although the formation of different metal hydride intermediates is competitive, the predicted poor thermodynamic stability of these hydrides and the significantly high barriers for the release of water ligand from these hydrides should be enough to conclude that the alternative pathway presented in Figure 8 should not be operative.

Figure 8. Computed stationary points for the possible alternative reactions from intermediate **10**. Energies are given in kcal/mol (all Ru-based species are charged +1).

Conclusions

In conclusion, we have reported the first theoretical study describing the complete reaction pathway for $[(C_6H_6)(PCy_3)(CO)RuH]^+$ (**1**) mediated alkylation of indene substrate with ethanol using DFT calculations. Our results suggest that the presented reaction pathway is the most favorable pathway for the studied reaction both from a thermodynamic and kinetic perspective. After an energy demanding activation of **1**, the system enters the catalytic cycle, with two high energy barriers corresponding to the breaking of the C–O bond of ethanol (30.8 kcal/mol), and to the next formation of the C–C bond of the alkylate indene product (30.5 kcal/mol). Although experimentally the latter process is thought to be the rate determining step we can conclude that the former cleavage of the C–O of ethanol is part of the same process. Overall, these calculated high barriers are consistent with the necessity to run the experiments at over 100 °C to achieve a yield of at least 80% in 5 h.

We also investigated possible competitive pathways from the key intermediates of the studied reaction pathway. Our results showed that these pathways contain intermediates that are either endothermic in nature or connected by high energy barriers, making them not viable even under the drastic experimental conditions. Even though further studies, computational and basically experimental, are desirable, our calculations explain the C–H alkylation and C–O bond cleavage of ethanol[20] in avoiding the formation of undesired reaction products, such as indene dimer and hydroxylated indene.

Computational Details

All the DFT static calculations were performed at the GGA level with the Gaussian09 set of programs [20], using the BP86 functional of Becke and Perdew [21]. The electronic configuration of the molecular systems was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, O, and P (TZVP keyword in Gaussian) [22]. For Ru we used the small-core, quasi-relativistic Stuttgart/Dresden effective core potential, with an associated valence basis set contracted (standard SDD keywords in gaussian09 [23]). The geometry optimizations were performed without symmetry constraints, and the characterization of the located stationary points was performed by analytical frequency calculations. The complete reaction pathways for all the mechanisms discussed in this study were verified using IRC analysis for all transition states. Structures at the last IRC points were optimized to positively identify the reactants and products to which each transition state is connected. Zero point energies and thermal corrections were calculated at the BP86 level. Moreover we also included the D3 Grimme pairwise scheme in the geometry optimizations [24]. Solvent effects were included with the polarizable continuous solvation model PCM using CH_2Cl_2 as solvent [25]. Since entropic contribution calculated within the ideal gas approximation at $P = 1$ atm is likely exaggerating the expected values for the dissociative steps in the condensed phase [26,27] all the thermochemical analysis was performed at $P = 1354$ atm, as suggested by Martin et al [28].

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Keywords: homogeneous catalysis • ruthenium catalysis • DFT calculations • green chemistry • alkene • C–H alkylation

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