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COMMUNICATION

Phosphine-Free Pincer Ruthenium-Catalyzed α-Alkylation of Ketones with Secondary Alcohols to form β–Branched Ketones

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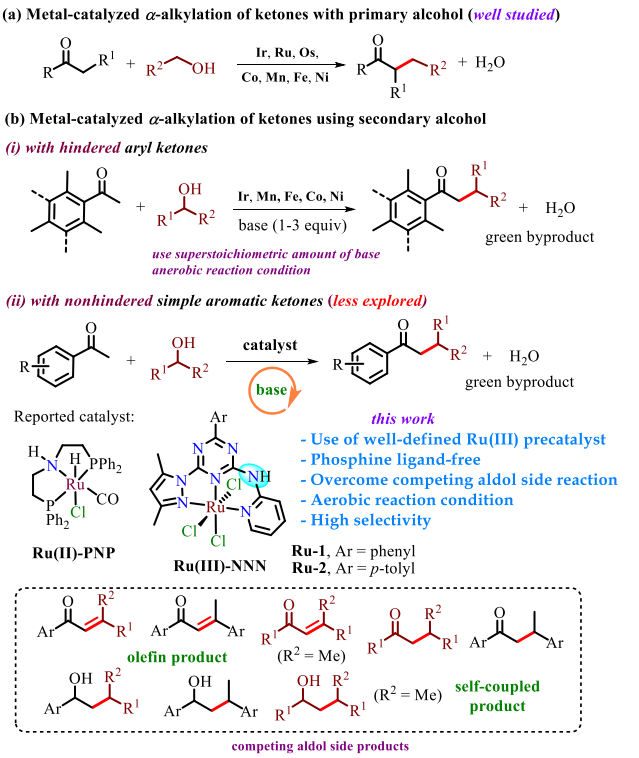
Abstract: Herein, an efficient and expedient method was developed for α-alkylation of aromatic ketones with secondary alcohols to produce *β*–disubstituted ketones using phosphine-free pincer ruthenium complexes as the catalyst. Single *α*-alkylated ketone is produced in high yields even in reactions where a mixture of products is possible. Interestingly, challenging substrates such as unsubstituted and nonhindered acetophenone compounds are effectively alkylated under the reaction conditions. The scope of the reaction can span with a verities of aliphatic, cyclic, and acyclic secondary alcohols. Functionalization of a cholesterol molecule is also possible under the reaction conditions. Substitution on cyclohexyl ring afforded products as a mixture of diasteroisomers, wherein the major isomer is found as 1,4-cis conformation of the cyclohexyl ring. Origin of the *cis* stereoselectivity in the alkylation process was explored by DFT calculation study. Mechanistic studies reveal that the dehydrogenation of alcohols follows a proton shuttle-type of TS, involvement of cross-aldol condensation and borrowing hydrogen catalysis. Notably, this selective, catalytic C-C bond forming reaction proceeds with low catalyst load, catalytic amount of base under air and produces H_2O as the only byproduct, making the process environmentally benign and atom efficient.

Introduction

Ketones are an important class of compounds that are extensively utilized in pharmaceutical and agrochemical industries, and also as expedient starting material for the construction of natural products.[1] In addition, they are widely used as industrial solvents in manufacturing industry.[1d] Traditionally, *α*-alkylated ketones and *β*-branched ketones are synthesized by the reaction of an alkyl halide with a ketone in the presence of a strong base such as ^{n}BuLi or LDA.[2] Such alkylation methods have multiple shortcomings, such as alkyl halides are toxic, the reaction often requires cryogenic condition, and the elimination can occur as a competitive side reaction while using secondary alkyl halides. Besides, the use of stoichiometric amount of base produces large amount of hazardous waste, presenting the process is less atom economy.[3] It is desirable to develop an alternative approach where these hazardous and toxic reagents can be replaced by cheap, readily available, and bio-renewable alcohols[4] and the process become more atom economical, practical, and environmentally friendly.



Scheme 1. Metal-catalyzed (a) *α*-alkylation of ketones using primary alcohols and (b) secondary alcohols.

In this context, transition-metal-catalysed α-alkylation of ketone using alcohol as alkylating agent is a promising approach.[5-8] Since the process does not rely on any external oxidant source, and by-product is only H_2O, which makes the method green, atom economical, and environmentally benign. The use of primary alcohol for *α*-alkylation of ketones has been well documented in

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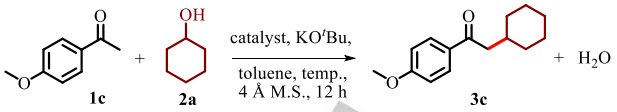
the literature[5-6] by using borrowing hydrogen catalysis[9] (Scheme 1a), however, limited attention has been given to use of secondary alcohols to generate *β*-branched ketones (Scheme 1b).[7,10] In a pioneering work, Donohoe and coworkers reported the *α*-alkylation of ketones with secondary alcohols to form *β*-branched products by using a Cp*Ir^{III} dimer.[7a] The major challenge in this transformation is to prevent the base-promoted self-condensation of the carbonyl substrate and the ketone derived from the alcohol.[7a, 11] It has been mostly addressed by employing a sterically bulkier aryl ketone as the carbonyl substrate. Inspired by this seminal work, Sundararaju,[7b] Renaud,[7c] Maji,[7d] and Adhikari[7e] have demonstrated the synthesis of *β*-branched carbonyl compounds with pentamethyl phenyl (Ph*) ketone or trisubstituted aryl ketones as the coupling partner. However, this methodology was found to be less-successful in the case of unsubstituted and nonhindered aryl ketones and thus, suffers from a limited substrate scope. Recently, Gunanathan and co-workers have demonstrated an effective protocol for the *α*-alkylation of non hindered aromatic ketones using Ru-MACHO complex as a catalyst.[10] Interestingly, this catalytic system does not necessitate equivalent or excess amount of base (viz., 1-3 equiv), making the method most attractive. The same research group was also established selective cross-coupling of two different secondary alcohols to β-disubstituted ketones with Ru−MACHO as catalyst.[12a] In spite of this pioneering work, some limitations are still present from sustainable chemistry point of view. The reaction requires anaerobic conditions and used ruthenium(II)-metal complexes with phosphine-supported PNP ligand (i.e., $HN(CH_2CH_2\ PPh_2)_2$). In practical aspects, they are associated with some limitations such as these are often air and moisture sensitive, involved in complex synthetic procedures, and relatively high cost. In this regard, development of a phosphine-free, air/moisture stable, efficient catalytic system for the *α*-alkylation of non-bulky ketones with secondary alcohols is highly appreciated.

Results and Discussion

We have recently demonstrated selective cross-coupling of secondary alcohols to β-disubstituted ketones using triazine-based NNN-pincer ruthenium (III) complex **Ru-1** & **Ru-2** as the catalyst.[12b] Nevertheless, there is no general method for *α*-alkylation of nonhindered acetophenones with secondary alcohols under air, and phosphine-free reaction conditions. The scope of the reaction was initiated using *p*-methoxyacetophenone **1c** (1 equiv) and cyclohexanol **2a** (1.5 equiv) as model substrates for the catalytic *α*-alkylation of ketone with secondary alcohol (see Table 1). The highest yield of product **3c** (94%, Table 1, entry 5) was obtained with 2 mol% of **Ru-2**, 20 mol% loading of the base KO^{t}Bu, when the reaction was carried out under air in toluene at 150 °C for 12 h (in the presence of 4 Å molecular sieves). Notably, no olefin product, self-coupled product or fully hydrogenated product **4c′** was observed under the reaction conditions. Surprisingly, self–coupled product 1,3–bis(4–methoxyphenyl) butan-1-one was obtained in 40% yield while the reaction was performed with 30 mol% of base KO^{t}Bu (entry 8). Hence, base load is critical to obtain the desired product in quantitative yield.



entry	catalyst	mol% catalyst	KO^{t}Bu (mol%)	temp (°C)	yield (%)
1	**Ru-1**	1	10	120	n.d.
2	**Ru-2**	1	10	120	n.d.
3	**Ru-1**	1	10	150	36
4	**Ru-2**	1	10	150	50
5	**Ru-2**	2	20	150	94
6[b]	**Ru-2**	2	20	150	84
7[c]	**Ru-2**	2	20	150	88
8[d]	**Ru-2**	2	30	150	0
9	**Ru-2**	2	-	150	0
10	**$RuCl_3$**	2	20	150	0
11	**-**	-	20	150	0

Table 1. Screening of reaction conditions for *α*-alkylation of ketone using secondary alcohols[a]

[a] Reaction conditions: 4–methoxyacetophenone (1 mmol), cyclohexanol (1.5 mmol), catalyst (x mol%), KO^{t}Bu (x mol%), and dry toluene (2 mL) were heated at 150 °C under air in a closed 50 mL reaction tube for 12 h in the presence of 4 Å M.S. Isolated yields. [b] 1 equiv. of cyclohexanol was used. [c] without 4 Å M.S. [d] Self-coupling product of 1,3-bis(4-methoxyphenyl)butan-1-one was obtained in 40% yield.

Encouraged by this result, we focused on exploring the catalytic reaction of various aromatic ketones. A wide variety of aromatic ketones **1a-l** was used for the synthesis of *β*-disubstituted ketones **3a-x (**Scheme 2). Acetophenone motifs bearing an array of diverse functionalities such as 4-methyl, 4-methoxy, 4-phenyl, 4-*tert*-butyl, 4-dimethylamino and 4-chloro groups (**1a-g**) reacted effectively with cyclohexanol 2a and were successfully transformed into the desired *β*-branched ketones **3a-g** in moderate to good yields (62-94%). Similarly, *meta- and ortho*-substituted aromatic ketones also provided the corresponding desired product **3h-j** effectively in high yields. Intriguingly, when substituted-cyclohexanol such as 4-methyl, 4-ethyl, 4-*tert*-butyl, and 4-phenyl cyclohexanol **2b-e** were used as alkylating agents, the corresponding products **3k-p** and **3o-p** were obtained in good yields with a mixture of diasteroisomers. The major isomer was found to be *cis*-isomer.[12] To our surprise a higher diasteroselectivity was obtained in **3n** (dr 93:7) with respect to **3m** (dr 85:15). Nevertheless, in general, the *trans* isomer is expected to be more stable than *cis* isomer as minimal 1,3-diaxial interactions is present in their chair conformation. hence, origin of high *cis* stereoselectivity is deliberated by DFT calculation study (*vide infra*). The scope of the reaction was then expanded to various other higher analogous cyclic alcohols, for example, cycloheptanol and cyclooctanol. Finally, the most challenging unactivated acyclic aliphatic secondary alcohols were also found to be amenable to this method, giving the desired *β*-substituted ketones **3t-w** in moderate to good yield. Surprisingly, the present protocol was found to be compatible with cholesterol also, when

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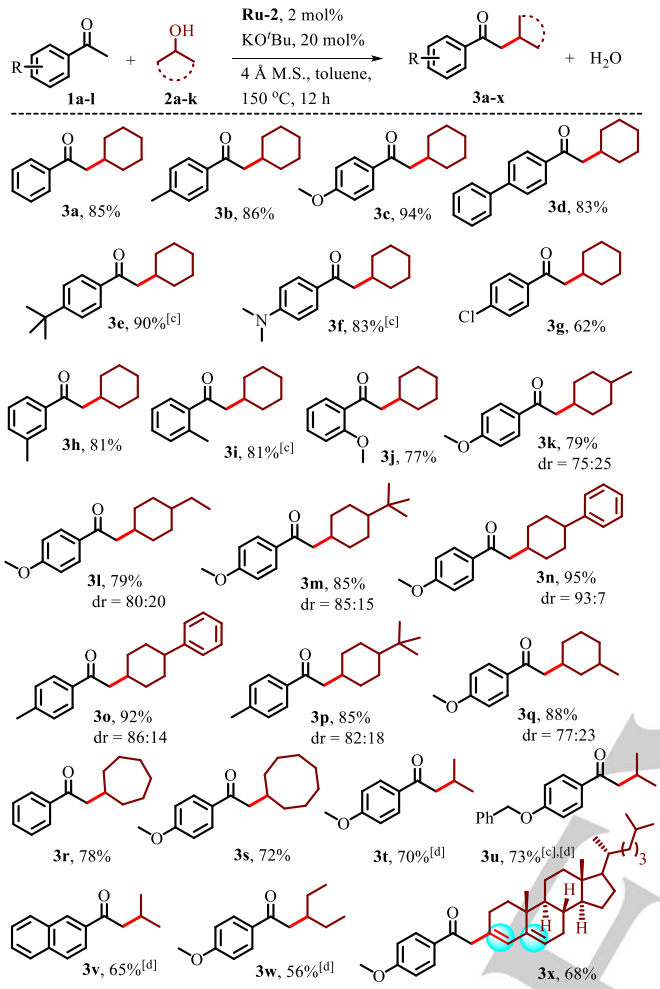
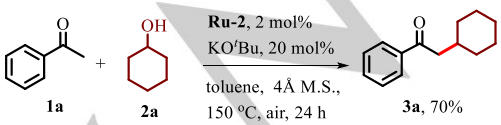
treated with **1c**, an unusual, dehydrogenative C-C coupling product **3x** was obtained in 68% yield.



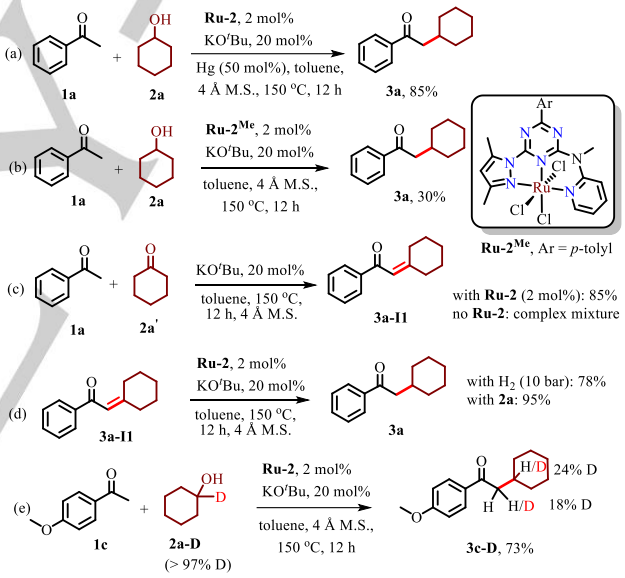
Scheme 2. Substrate scopes for the synthesis of *β*-branched ketones. Reaction conditions: [a] Aromatic ketones (1 mmol), aliphatic secondary alcohols (1.5 mmol), **Ru-2** (2 mol%), KO^{t}Bu (20 mol%), and dry toluene (2 mL) were heated at 150 °C under air in a closed 50 mL reaction tube for 12 h in the presence of 4 Å M.S. [b] Isolated yield. [c] GC yield. [d] 8 equiv. of aliphatic secondary alcohol was used.

The synthetic utility of the process was further corroborated by setting gram-scale reactions (Scheme 3). Simple acetophenone when reacted with cyclohexanol in large quantity, the corresponding alkylated ketone **3a** was obtained in 70% yield. The successful gram-scale reaction offers that the reaction is also efficient under scale-up process.



Scheme 3. Gram-scale *C*-alkylation reaction.

To understand homogeneous nature of the ruthenium complex **Ru-2** in the catalytic reaction, the mercury drop experiment was conducted, indicating no inhibition of the reaction or reduction of the product yield of **3a** (Scheme 4a). Then, role of the NH functionality was examined by using complex **Ru-2^{Me}** as the precatalyst, leading to lower yields of desired product (Scheme 4b). This infers the important role of NH functionality and metal-ligand cooperativity (MLC) in the catalysis.[13] Further to validate the formation of cyclohexanone **2a'** and unsaturated enone **3a-I1** as the reaction intermediates in the alkylation process, the reaction was carried out with acetophenone **1a** and cyclohexanone **2a'** (Scheme 4c) and the intermediate of **3a-I1** and cyclohexanol **2a** (or molecular H_2) under standard conditions (Scheme 4d). The *α,β*-unsaturated ketone **3a-I1** was observed in the first case, and alkylated product **3a** was obtained in the later case. This suggests that cyclohexanone and *α,β*-unsaturated ketone are formed as the reaction intermediates in the process, and the reaction is likely proceeded via ruthenium hydride species, either derived from dehydrogenation of alcohol or from produced molecular H2. Furthermore, deuterium-labeling experiment was performed to corroborate the involvement of hydrogen-borrowing methodology in C-alkylation reactions (Scheme 4e).



Scheme 4. Control experiments.

To gain more insight into the active ruthenium species [Ru(III) or Ru(II)] in the catalytic cycle, a titration experiment was performed by adding a base into precatalyst **Ru-2** and monitoring the EPR spectra. Upon loading the base, the paramagnetic signal of ruthenium(III) slowly disappeared and formed EPR-silent diamagnetic Ru(II) species by using 4 equiv of KO*t*Bu (Figure 1). It infers that 8 mol% of KO*t*Bu (compared to 2 mol% of **Ru-2**) is necessary for activation of pre-catalyst. Herein we are presuming that 8 mol% of base is required for the activation of 2 mol% of pre-catalyst and remaining 12 mol% base is necessary for the cross-coupling reactions. This is further substantiated by designing an experiment where active ruthenium species was generated *in-situ* by using 2 mol% of **Ru-2** and 8 mol% of base under the reaction condition, then after 12 h, coupling partner **1a** (0.5 mmol) and **2a** (0.75 mmol) along with 12 mol% of base was added to the

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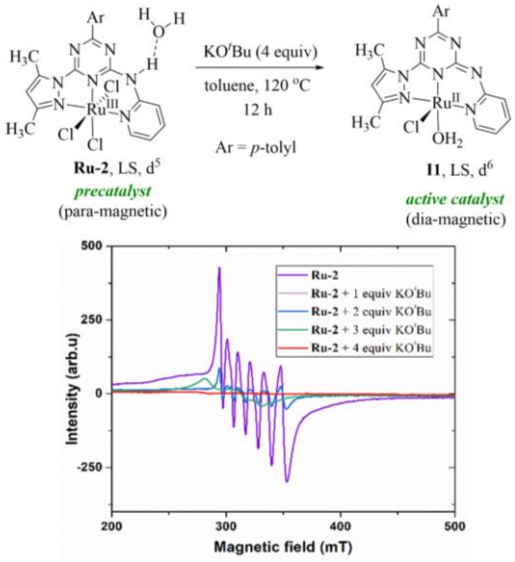
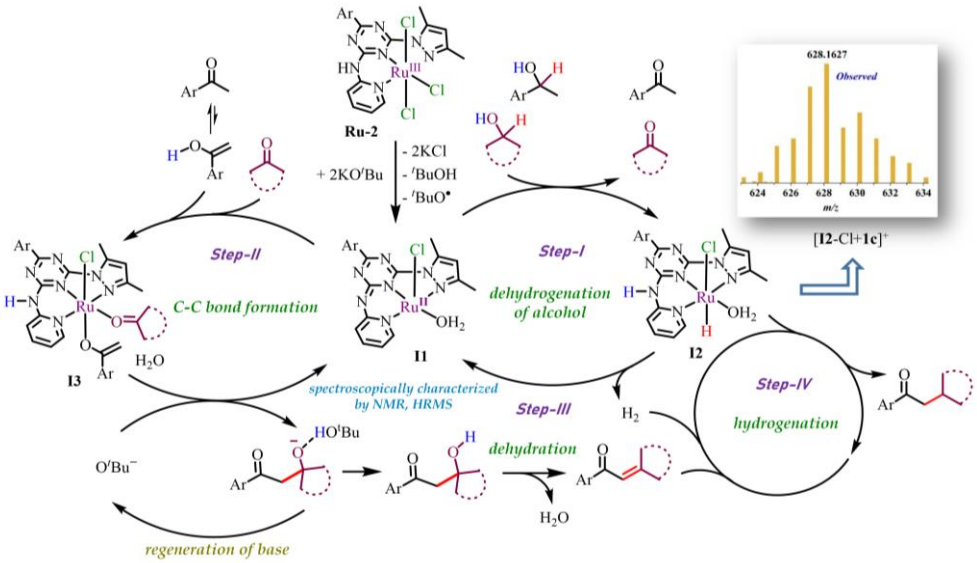


Figure 1: EPR spectrum of **Ru-2** with varying equivalent of base

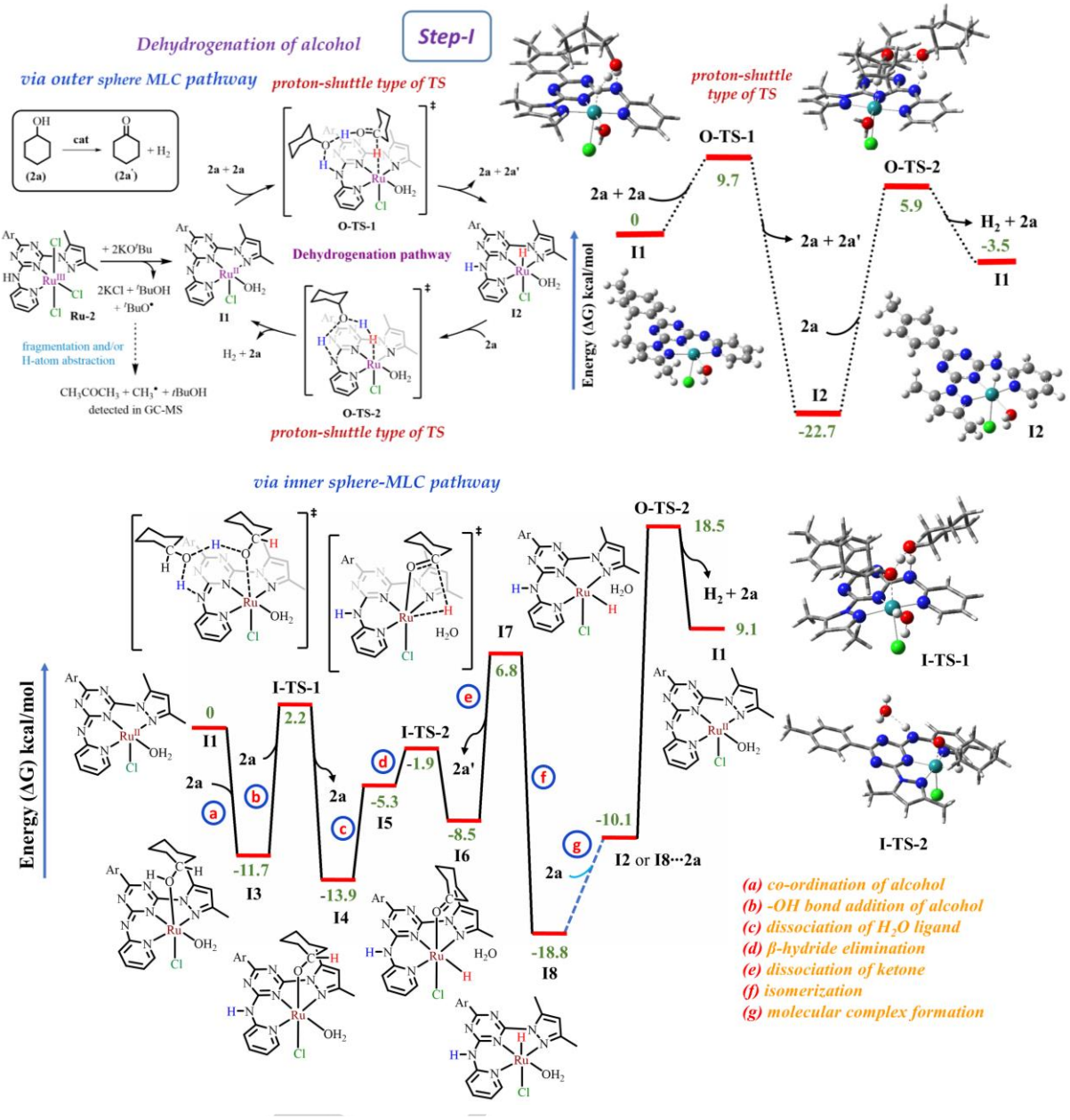
reaction mixture, a quantitave yield of **3a** (78%) was obtained, indicating Ru(II) is the active species in the catalytic process. Further, we have performed the following EPR experiments in the presence of coupling agents like alcohol **2a**, and/or ketone **1a** under the reaction conditions. In all case, EPR-silent diamagnetic species is formed after the completion of the reaction which suggests that Ru(III) species is possibly not exist under the reaction condition (see SI, Figure S3). Active ruthenium species **I1** was further validated by ^{1}H NMR and mass spectrometry analysis (see SI, Fig. S4, S6, S7).

Experimental observation is in line with our previous studies.[12b] Based on these experimental findings, we infer that the Ru(III) pre-catalyst is reduced *in-situ* to form Ru(II) species under the reaction conditions and the resulting active species **I1** is then reacted with alcohol to provide ruthenium hydride intermediate **I2**, which was supported by mass spectrometry analysis.[12b] We proposed an *in situ* formed Ru(II) hydride as the catalytically active species which promote the TH reaction *via* outer sphere pathway (*vide infra*). On the basis of previous reports, a plausible mechanistic pathway has been proposed and is presented in Scheme **5**.[12,14-16] The reaction involves four steps (a) dehydrogenation of alcohol on active catalyst to form corresponding ketone (b) aldol reaction of ketones to generate aldol product (c) condensation of aldol product to form *α, β*-unsaturated ketone (d) reduction of unsaturated ketones *via* hydrogenation and/or alcoholysis segment to form β–branched ketone. Nevertheless, the detailed mechanism and especially the origin of the diasteroselectivity are still not fully clear. Here these is discussed in systematic manner with the help of DFT calculations.

Step-I: We commenced our study with acetophenone **1a** and cyclohexanol **2a** as the model substrates (Scheme 6). At first, complex **Ru-2** is reduced *in situ* to form the Ru(II) species **I1**. Complex **I1** is then reacted with cyclohexanol **2a** converted into metal-hydride intermediate **I2** in a downhill fashion (ΔG = -22.7 kcal/mol) *via* outer sphere MLC pathway and proton shuttle type of TS (**O-TS-1**). The energy barrier acquired for this step is 9.7 kcal/mol. Alternatively, there is a possibility for the formation of complex **I2** *via* inner sphere MLC pathway. The complex **I1** converted into aromatized intermediate **I4** *via* coordination of alcohol (**I1**→ **I3**, ΔG = -11.7 kcal/mol), followed by the –OH bond addition of alcohol in a downhill process (**I-TS-1**→ **I4**, ΔG = -16.1 kcal/mol) and the proton shuttle type of mechanism. Then β-hydride elimination of **I4** to ketone coordinated intermediate **I6** in uphill way (**I4** → **I6**, ΔG = 5.4 kcal/mol). The energy barrier



Scheme 5. Plausible mechanistic pathway.



Scheme 6. Pathway for dehydrogenation of alcohol.

attained for this step is $\Delta G^{\ddagger}$ = 15.8 kcal/mol which is surprisingly comparable (**I6** → **I7**; ΔG = 15.3 kcal/mol) to release corresponding ketone **2a'** from **I6**. Subsequent isomerization can give to the complex **I8** in a downhill process of 25.6 kcal/mol (**I7** → **I8**).

Step-II: Next, cross-coupling reaction of acetophenone **1a** and *in-situ* formed cyclohexanone **2a'** to provide β-hydroxy ketone **4a** (Scheme 7). The alkenyloxo coordinated ruthenium species **I11** is formed in slightly uphill fashion (ΔG (**I1** → **I11**) = 4.5 kcal/mol) *via* an outer sphere MLC pathway of intermediate **I10** and proton shuttle type of **A-TS-1** ($\Delta G^{\ddagger}$ = 14.3 kcal/mol). The complex **I11** then transformed into a ruthenium alkoxo complex **I12** with an energy barrier of 13.2 kcal/mol ($\Delta G^{\ddagger}$ value). Thereafter, the complex **I12** follows at Ru-O bond cleavage and deprotonation of the N-H site in the ligand backbone to generate **I13** in which alkoxide species forms hydrogen bonding with ^{t}BuOH. The process (**I12** → **I13**) is thermodynamically downhill with 25.6 kcal/mol. The intermediate **I13** leads to ruthenium β-hydroxy ketone-coordinated complex **I15** *via* the intermediate **I14**. Subsequent complex **I15** releases aldol product **4a** and *ter*-butoxide in an endothermic fashion with concomitant regenerate the active catalyst **I1**.

Step-III: Then base-catalyzed dehydration of aldol product **4a** provides the *α, β*-unsaturated ketone **3a-I1** and **3a-I2** (Scheme 8). The α, β-enone **3a-I1** is formed *via* the E1cb mechanism, which involves the Cα–H deprotonation of **4a**, followed by hydroxyl elimination with **D-TS-1** ($\Delta G^{\ddagger}$ = 18.5 kcal/mol).

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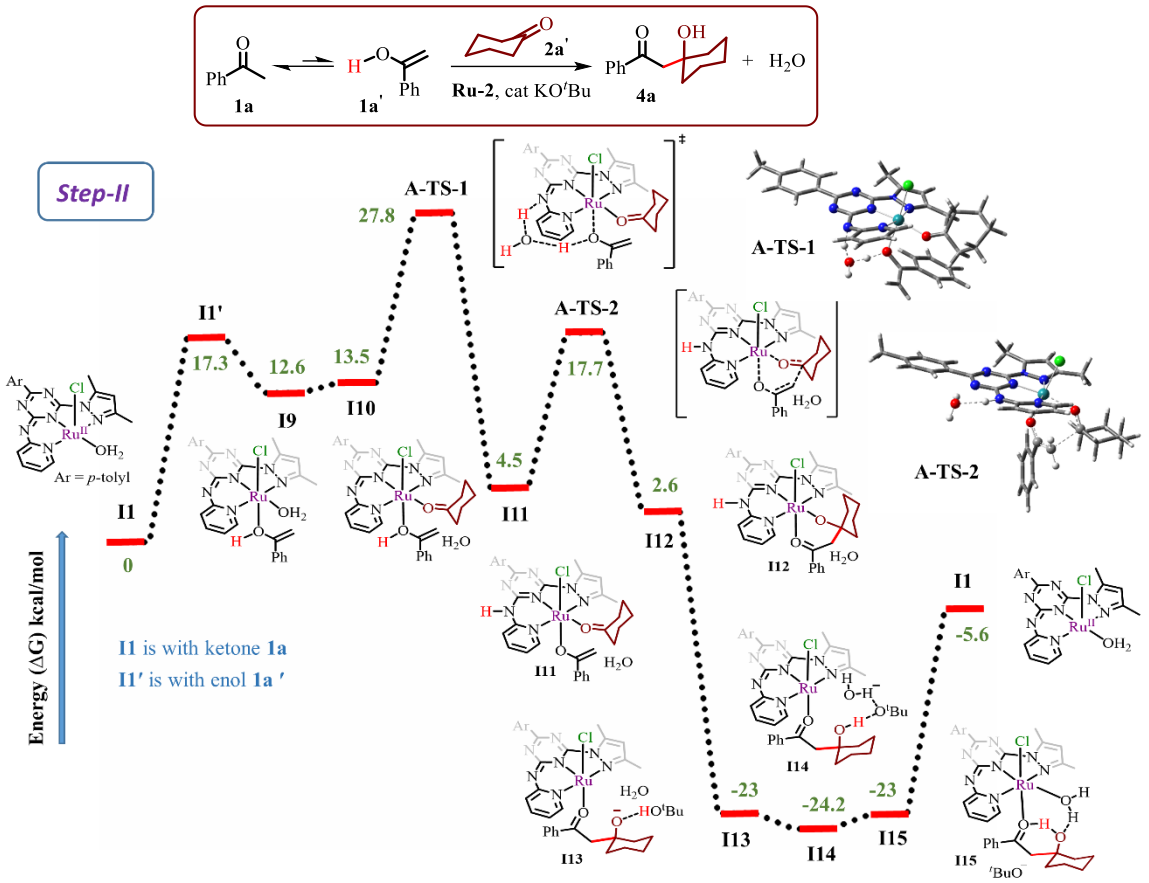
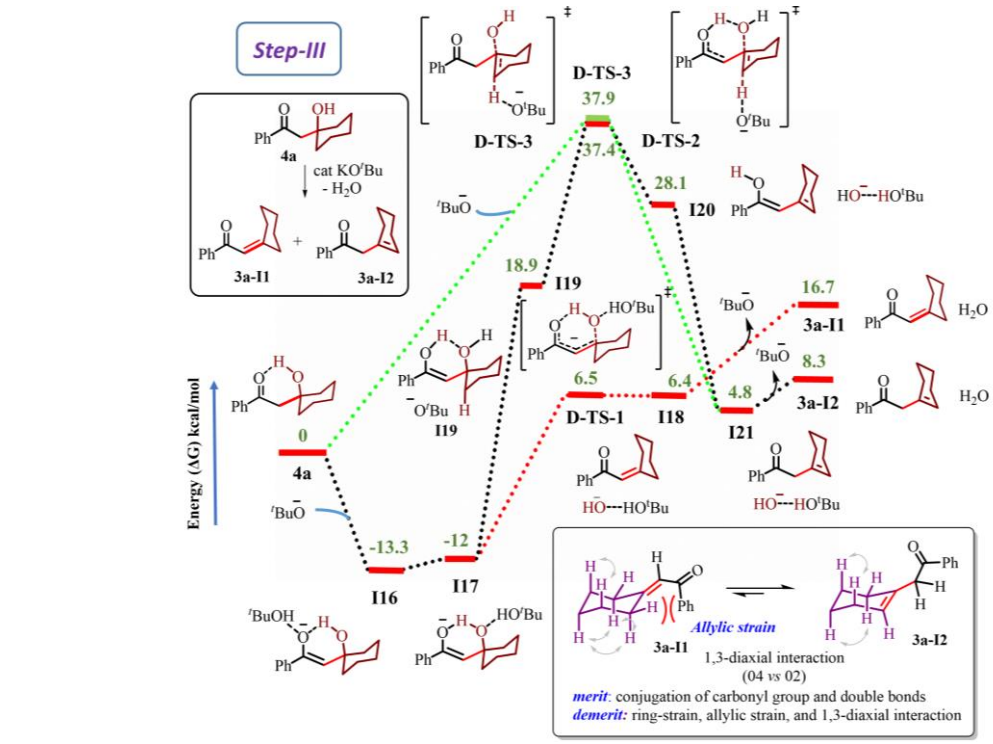


Scheme 7: Pathway for aldol product formation



Scheme 8. Pathway for the formation of *β*, *β*-disubstituted *α, β*-unsaturated ketone

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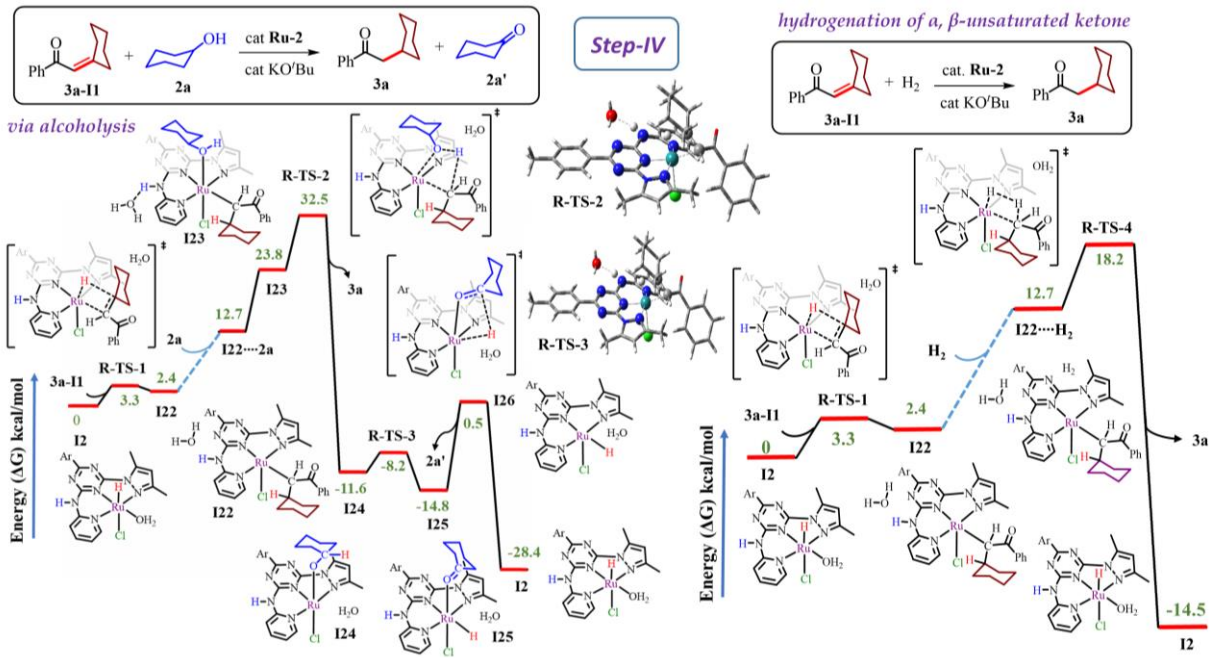
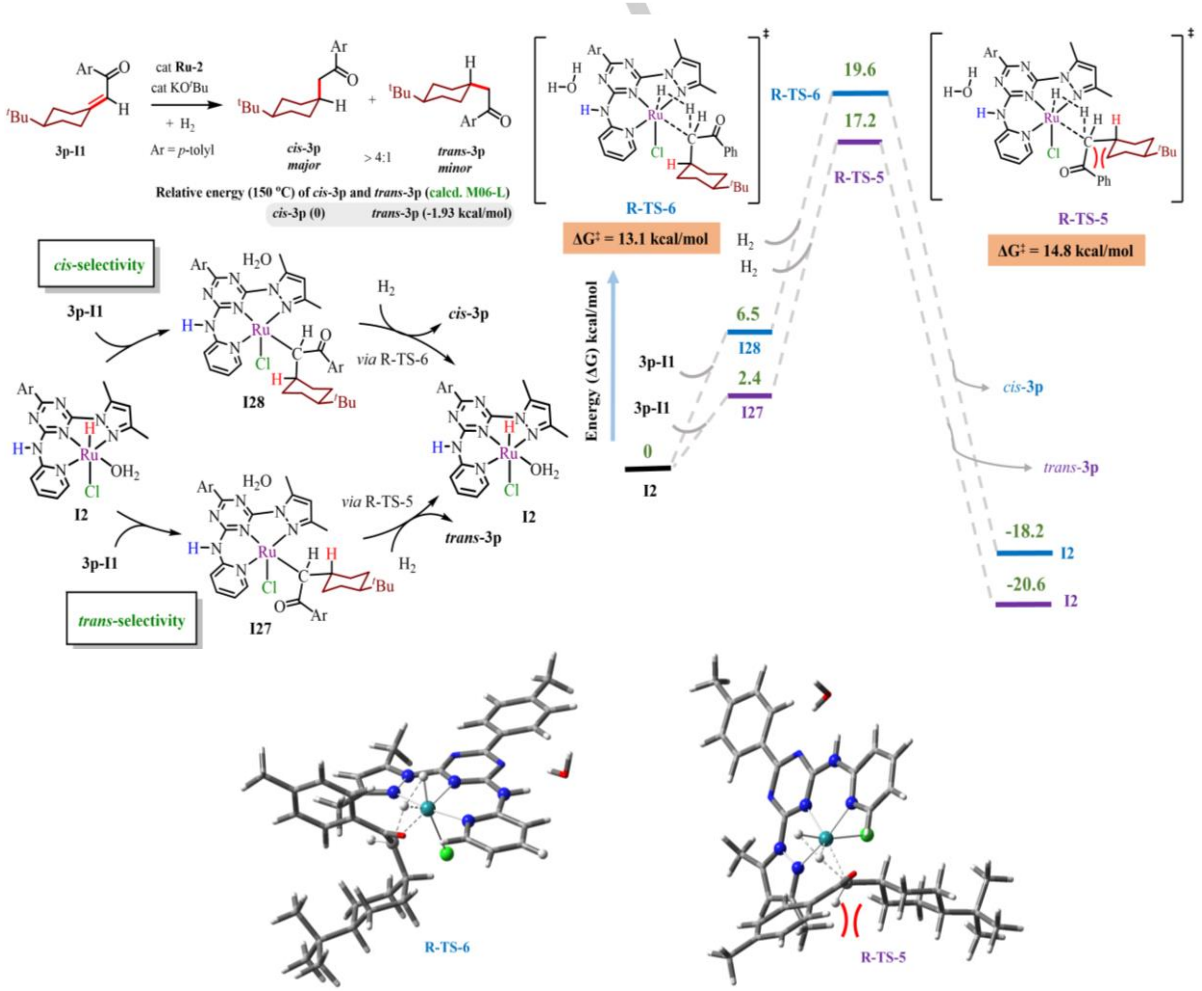


Scheme 9. Reduction of *β*, *β*-disubstituted *α*, *β*-unsaturated ketone



Scheme 10. Origin of the diasteroselectivity

On the other hand, *β,γ*-enone **3a-I2** can be formed *via* E2 mechanism, which includes endergonic protonation of **I17** with ^{t}BuOH to form enolate **I19** (ΔG = 30.9 kcal/mol), followed by hydroxyl elimination *via* **D-TS-2** ($\Delta G^{\ddagger}$ = 18.5 kcal/mol) or otherwise *via* direct **D-TS-3** ($\Delta G^{\ddagger}$ = 37.9 kcal/mol). These results suggested that unsaturated ketone is kinetically favored and *β,γ*-unsaturated ketone is thermodynamically favoured. Notably, α,β-unsaturated ketone 3a-I1 is a conjugated one, likely to be less stable with respect to β,γ-enone 3a-I2. They may in equilibrium under the reaction conditions and is predicted in favor of the β,γ-isomer with the minimal 1,3-diaxial interactions and relief of ring strain/allylic strain with flattened cyclohexene conformation (see Scheme 8, insight).

Step-IV: Since the formation of α,β-enone **3a-I1** is the kinetically favorable process, we have examined the reduction of **3a-I1** with alcohol **3a** to obtain the hydrogenated product **3a** *via* alcoholysis pathway (Scheme 9). In this, first the unsaturated ketone **3a-I1** is inserted into the Ru-H bond of **I2** through **R-TS-1** to provide complex **I22**. The energy barrier required for this step is of only 3.3 kcal/mol. Then, complex **I22** gives the product **3a** and metal-alkoxo intermediate **I24** *via* the coordination of **2a** and subsequent σ-bond metathesis of Ru-C with the O-H of **2a**. The process is an exothermic (**I22** → **I24**, ΔG = -14 kcal/mol) and requires the energy barrier **R-TS-2**, $\Delta G^{\ddagger}$ = 8.7 kcal/mol. Complex **I24** then undergoes β-hydride elimination, releases the ketone **2a'**, and subsequent isomerization to regenerate complex **I2**. The process (**I24** → **I2**) is thermodynamically downhill (ΔG = -16.8 kcal/mol). The alternative reaction of **3a-I1** with molecular hydrogen can give the product **3a** *via* hydrogenation pathway as previously described.[12b]

To gain more insight into the origin of *cis*-selectivity in the *C*-alkylation process, we have performed the computational study for the hydrogenation of **3p-I1** (Scheme 10). The result suggests that stereoselectivity is likely to be kinetically controlled. Since a higher energy barrier is involved in the molecular H_2 addition step with respect to alkene **3a-I1** insertion step in the hydrogenation of **3a-I1** (in Scheme 9, **R-TS-1,** $\Delta G^{\ddagger}$ = 3.3 kcal/mol; **R-TS-4,** $\Delta G^{\ddagger}$ = 5.5 kcal/mol), we have focused the 2nd step involving σ-bond metathesis of Ru−C with the H_2. Calculated data suggests that a lower energy barrier (~ 1.7 kcal/mol) is required for the formation of ***cis*-3p** product ($\Delta G^{\ddagger}$ = 13.1 kcal/mol) with respect to ***trans*-3p** product ($\Delta G^{\ddagger}$ = 14.8 kcal/mol), further the process for the formation of ***cis*-3p** product (ΔG = -24.7 kcal/mol) is slightly more exothermic than ***trans*-3p** product (ΔG = -23 kcal/mol). Hence, this high stereoselectivity possibly governed by kinetic as well as theromodynamic parameters.

Conclusion

In summary, a phosphine-free pincer ruthenium-catalyzed efficient and expedient method was developed for *α*-alkylation of ketones with secondary alcohols to produce *β*–branched ketones. Pleasingly, challenging substrates such as unsubstituted and nonhindered acetophenone compounds are effectively alkylated under the ruthenium catalysis. The scope of alcohols spans from aliphatic, cyclic to acyclic secondary alcohols. A complex molecule such as cholesterol was also successfully functionalized by this method. The origin of the diastereoselectivity has been disclosed while the substituted cyclohexanol compounds was used as alkylating agent in the reaction conditions. Contrary to previously reported procedures, this strategy explored the bench-stable ruthenium(III) as the pre-catalyst, aerobic reaction condition, high selectivity in the cross-coupling reaction are beneficial. The mechanistic studies with the help of DFT calculation suggested that the involvement of ''borrowing hydrogen'' catalysis and the role of the metal-ligand cooperation was important for the success of such catalytic reaction.

Experimental Section

General procedure for synthesis of *β*-disubstituted ketones: A mixture of aromatic ketone (1 mmol, 1 equiv), aliphatic secondary alcohol (1.5 mmol, 1.5 equiv), **Ru-2** (2 mol%), KO^{t}Bu (20 mol%), 4 Å molecular sieves and toluene (2 mL) was added into a pyrex tube (50 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 150 ^{o}C with continuous stirring for 12 hours. The resulting mixture was then passed through a bed of celite, the filtrate was collected and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography over silica gel using petroleum ether or ethyl acetate/ petroleum ether mixture as an eluent.

All experimental details and characterization data could be found in the Supporting Information. [17-23]

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