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# Selective Catalytic Synthesis of $\alpha$ -Alkylated Ketones and $\beta$ -Disubstituted Ketones via Acceptorless Dehydrogenative Cross-Coupling of Alcohols

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**ABSTRACT:** Herein, a phosphine-free pincer ruthenium(III) catalyzed  $\beta$ -alkylation of secondary alcohols with primary alcohols to  $\alpha$ -alkylated ketones and two different secondary alcohols to  $\beta$ -branched ketones are reported. Notably, this transformation is environmentally benign and atom efficient with H<sub>2</sub>O and H<sub>2</sub> gas as the only byproducts. The protocol is extended to gram-scale reaction and for functionalization of complex vitamin E and cholesterol derivatives.

ransition-metal-catalyzed carbon—carbon bond formations are the key motif in organic synthesis.<sup>1</sup> Among various methods,  $\beta$ -alkylation of the secondary alcohols for synthesizing  $\alpha$ - or  $\beta$ -branched ketones represents the most efficient synthetic approach.<sup>2-6</sup> Traditionally, these have been synthesized in a multistep process, such as stoichiometric oxidation of alcohol, followed by the formation of lithium enolate species by using a strong base under cryogenic condition, and then alkylation with mutagenic alkyl halides,<sup>7</sup> as a result copious amount of waste has been generated during the reaction.<sup>8</sup> Moreover, alkylation with secondary alkyl halides is relatively challenging because of the occurrence of competitive side reactions, for instance, elimination. Therefore, it is desirable to develop an alternative method where these hazardous and toxic reagents can be replaced by inexpensive, biorenewable alcohols.<sup>5</sup>

The acceptorless dehydrogenative coupling (ADC) of alcohols<sup>10,11</sup> is one of the prominent synthetic strategies in contemporary chemistry. The process does not require any external hydrogen acceptor or oxidant source, H<sub>2</sub> and H<sub>2</sub>O are the only side products, which makes the process green, atom-economical, and environmentally benign. Using this concept, selective  $\alpha$ -substituted ketone formation is described via metal-catalyzed cross-coupling of primary and secondary alcohols.<sup>2</sup> Among various homogeneous transition-metal catalysts, ruthenium(II) complexes<sup>2e-h</sup> have performed very well in this transformation, as described by the group of Archard,<sup>2f</sup> Song,<sup>2g</sup> and others (Scheme 1). As the reaction produces H<sub>2</sub> as one of the byproducts, the formed ketones could further be hydrogenated to alcohols,<sup>2n,12</sup> leading to a challenge in the

Scheme 1. Ruthenium-Catalyzed  $\beta$ -Alkylation of Secondary Alcohol with Primary Alcohols (a) and Secondary Alcohols (b) to Ketones



selectivity.<sup>2f,n,12i</sup> In contrast, the reports on  $\alpha$ -alkylation of ketones using secondary alcohols to generate  $\beta$ -branched ketones are very scarce, as self-coupling<sup>3</sup> of secondary alcohols

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is one of the common undesired side products which reduce the atom economy in an overall process. Recently, Donohoe, <sup>5a</sup> Sundararaju,<sup>5b</sup> Renaud,<sup>5c</sup> and Maji<sup>5d</sup> have independently reported the synthesis of  $\beta$ -branched carbonyl compounds, where bulky ketones (e.g.,  $Ph^*COCH_3$ ,  $Ph^* = pentamethyl$ phenyl, mesityl) were used as coupling partner, and the reaction requires an equivalent or excess amount of base (2 equiv) and a superstoichiometric amount of alcohol ( $\geq 1.5$ equiv). The introduction of the substituent in the aromatic ring, specifically at the ortho and ortho' positions, proved to be the critical factor for the success of this strategy as it prevents the self-condensation of the starting ketones. Gratifyingly, Gunanathan and co-workers explored catalytic cross-coupling of two different secondary alcohols by well-defined phosphine based Ru-MACHO system, leading to  $\beta$ -branched aromatic ketones in moderate to excellent yield (30-90%).<sup>4,6a</sup> The protocol was not limited to the use of bulky substituted benzylic alcohol and does not require the excess amount of base and alcohol substrate. Despite this pioneering work, some limitations are still present from a sustainable chemistry point of view. The reaction requires anaerobic reaction conditions, the phosphine-supported ligand, and ruthenium(II)-based metal complexes. Given the well-known air and moisture sensitivities and the expensive nature of phosphine ligands, the development of a phosphine-free ruthenium complex to catalyze cross-coupling of alcohols via ADC reaction would be inevitably significant. Herein, we have synthesized new bench stable tridentate {NNN} pincer ligands outlined in Scheme S1, using cyanuric chloride as a starting precursor. The ligands feature a central triazine ring with potentially tridentate pockets, the pyrazolyl group is located at one side, and the NH functionality containing pyridyl group is situated on the other side. Complexation was performed by refluxing a solution of the NNN ligands ( $HL^1$  and  $HL^2$ ) and  $RuCl_3 \cdot xH_2O$  in methanol, which afforded the corresponding bench-stable pincer ruthenium(III) complexes as brown solids (Ru-1 and Ru-2) in good yields (Scheme 2). Among them, single crystals

Scheme 2. Synthesis of New Triazine-Based Ru-NNN Pincer Complexes Ru-1, Ru-2, and ORTEP Structure of  $Ru-2^a$ 



<sup>*a*</sup>Thermal ellipsoids are drawn with 50% probability level.

of complex **Ru-2** suitable for X-ray diffraction were obtained by slow evaporation of the saturated solution of the complex in  $CH_3CN/CH_3OH (v/v 9/1)$  at room temperature.

To inspect the catalytic applicability of the as-prepared ruthenium complexes **Ru-1** and **Ru-2**, we initiated the optimization studies with 1-(4-methoxyphenyl)ethanol (**5**c) and benzyl alcohol (**6**a) as model substrates for the catalytic  $\beta$ -alkylation of secondary alcohol with primary alcohol (see Table S1). **Ru-2** showed better activity compared to **Ru-1**, and ketone 7**ca** was obtained in 93% yield using **Ru-2** (Scheme 3). Notably, we did not observe any fully reduced alcohol, 1-(4-methoxyphenyl)-3-phenyl-1-propanol 7**ca**', reflecting excellent

Scheme 3. Ruthenium(III)-Catalyzed  $\beta$ -Alkylation of 1-(4-Methoxyphenyl)ethanol Using Benzyl Alcohol



product selectivity. With the optimized conditions in hand, we next explored the substrate scope of both secondary and primary alcohols (Scheme 4). Substrates having both electron-





"General conditions: secondary alcohol (1 mmol), primary alcohol (1 mmol), catalyst **Ru-2** (1 mol %), KO'Bu (10 mol %), and toluene (2 mL) were heated at 120  $^{\circ}$ C under air for 12 h. <sup>b</sup>Isolated yield. 'Yield in gram-scale reaction after 24 h.

donating (e.g., Me, OMe, OCH<sub>2</sub>Ph) and electron-withdrawing (e.g., Cl, Br) groups at the para position of the secondary alcohols were reacted with 6a to obtain the desired ketones 7aa-7fa, and 7ha in excellent yields (86-94%). The reducible functional groups such as -CN and  $-C\equiv CPh$  can survive the current reaction to give the desired products 7ga and 7ia selectively. Meta-substituted substrate 7ja also showed good activity. Furthermore,  $\alpha$ - and  $\beta$ -naphthylethanol were reacted with 6a to obtain the corresponding ketones in excellent 90-91% yields. Gratifyingly, the heterocyclic substrate 5m is also well-tolerated. Next, we investigated the scope of primary alcohols. The electron-donating methoxy group substituted at the different positions of the primary aromatic alcohol furnished the corresponding ketones in good yields. Notably, electron-withdrawing groups such as -Cl (6d), -CF<sub>3</sub> (6e), and reducible -OCH2CH=CH2 (6f) groups present at the para position in the benzyl alcohol afforded the desired ketones in 83-86% yields. Intriguingly, when 1,4-phenylenedimethanol (6g) was used as an alkylating agent the single  $\alpha$ -alkylated ketone 7ag was obtained with excellent selectivity. Aliphatic primary alcohols **6h** and **6i** and aliphatic secondary alcohol **5n** were also amenable to this method.

We next explored the catalytic cross-coupling of two different secondary alcohols to synthesize  $\beta$ -disubstituted ketones. The major challenge is to overcome the unwanted self-coupled aldol product, while selectivity is also another issue.<sup>4</sup> Investigation started with the reaction of **5c** and cyclohexanol in the presence of **Ru-1** (2 mol %) and KO'Bu (20 mol %) in toluene at 150 °C (see Table S2). To our delight, we observed the desired product **9ca** in 83% yield after 12 h. Notably, no self-coupled product or fully hydrogenated product **9ca'** was found. Employing **Ru-2** under similar conditions led to a better yield of **9ca**, 89% (Table S2, entry 2). Thus, the scope of the reaction was pursued with **Ru-2**. As displayed in Scheme 5, a wide variety of secondary alcohols

Scheme 5. Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols $^a$ 



<sup>*a*</sup>General conditions: 1-arylethanol (1 mmol), secondary alcohol (1 mmol), catalyst **Ru-2** (2 mol %), KO<sup>t</sup>Bu (20 mol %), and toluene (2 mL) were heated at 150 °C under air for 12 h. <sup>*b*</sup>Isolated yield. 'Yield in gram-scale reaction after 24 h. <sup>*d*</sup>Aliphatic secondary alcohol (6 mmol) was used.

was examined to synthesize  $\beta$ -disubstituted ketones. An array of diverse functionalities such as 4-methyl, 4-tert-butyl, 4methoxy, 4-dimethylamine, and 4-phenyl on the 1-phenylethanol (5b-f) were efficiently reacted with 8a to obtain  $\beta$ disubstituted ketones 9ba-fa in good to excellent yields (78-90%). Likewise, meta-substituted 5g also produced the corresponding ketone in high yield. Remarkably, sterically hindered ortho-substituted substrate was well tolerated as witnessed from the 82% yield of 2-cyclohexyl-1-(o-tolyl)ethanone (9ha). However, chloro-substituted aromatic secondary alcohol showed diminished activity. It was interesting to note that substitution on a cyclohexyl ring such as 4-tertbutylcyclohexanol 8b (or 4-methyl-butylcyclohexanol 8c) gave a mixture of diastereomers with a diastereomeric ratio of 81:19 as determined from the <sup>1</sup>H NMR of the reaction mixture. The major isomer is 1,4-cis conformation of the cyclohexyl ring,

which was consistent with the reported literature.<sup>4</sup> The result suggests a cross-coupling reaction occurred in a selective manner with substituted cyclohexanol. Gratifyingly, the scope of the methodology was expanded to a variety of other higher analogues of cyclic alcohols such as cycloheptanol and cyclooctanol. Finally, the highly challenging acyclic aliphatic secondary alcohol was found to be amenable to this method, giving 9cf-df, 9lf, and 9cg in good yields. Synthetic application of the catalytic protocol was demonstrated by reacting cholesterol with 5c and derivative of  $(\pm)$  tocopherol (6j) with 5a. These reactions can also run on gram scale, highlighting the practical utility.

To validate the homogeneous catalytic system for this Calkylation, the mercury drop test was conducted, showing no inhibition of the reaction or reduction of the product yield (Scheme S5). The liberation of  $H_2$  in ADC reaction was probed by the Pd/C catalyzed hydrogenation of styrene (Scheme S6). The impact of the NH functionality was examined by using complex Ru-2<sup>Me</sup> as the precatalyst, leading to lower yields of 7ca and 9ca and thereby indicating the importance of the NH functionality through a metal-ligand cooperative (MLC) pathway (see the Supporting Information). 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<sup>t</sup>Bu (Figure S3). It infers that 4 mol % of KO<sup>t</sup>Bu (compared to Ru-2) is necessary for activation of precatalyst. As the resulting active species (I) is diamagnetic, the NMR analysis was executed in CD<sub>3</sub>OD (see the Supporting Information). For further clarity, the experiment has been performed in the presence of PPh<sub>3</sub>. A singlet at 28.5 ppm was observed in <sup>31</sup>P{<sup>1</sup>H} NMR, indicating the phosphine ligand is coordinated to the ruthenium(II) center. Besides, species I was also confirmed by mass spectrometry analysis (see the Supporting Information). Based on this experimental evidence, we can reasonably conclude that an in situ generated ruthenium(II) species was the active species in this catalytic cycle. The resulting intermediate I can react with alcohol 5c to provide reactive ruthenium hydride species II, which was supported by mass spectrometry analysis showed in Figure S7. Despite several attempts, we failed to isolate metal hydride species under the reaction condition. Next, in the presence of KO<sup>t</sup>Bu, the base mediated cross-aldol condensation of **5**c' with **6a**' (or with **5a**' and **8a**') afforded  $\alpha_{\beta}$ -unsaturated ketone **7ca**-I (or 9aa-I), suggesting the formation of a ketone or aldehyde in situ as the intermediates. The reaction of 7ca-I with 6a under optimized condition afforded desired ketone 7ca in good yield. Likewise,  $\beta$ -branched ketone **9aa** was obtained by using intermediate 9aa-I and cyclohexanol (Scheme S8, S11). Similar results were observed with molecular H<sub>2</sub> in its place of alcohol (See ESI). These data suggest that in both cases,  $\alpha_{\beta}\beta_{\beta}$ unsaturated ketone (7ca-I or 9aa-I) is the reaction intermediate and the reaction likely proceeds via a ruthenium hydride species, either derived from dehydrogenation of alcohol or molecular H<sub>2</sub>. Furthermore, deuterium labeling experiment was performed in both cross-coupling reactions to validate the involvement of hydrogen-borrowing methodology. Under the standard conditions, the reaction of 5c-D with 6a or with 8a yielded expected H/D scrambled product 7ca-D or 9ca-D in 85% and 78% yields, respectively (Scheme S15). The

# Scheme 6. Proposed Mechanism for Cross-Coupling of Alcohols



above results demonstrated that the dehydrogenative step takes place in the ADC reaction sequence and the involvement of the cooperative bifunctional mechanism. The kinetics analysis for the cross-couple product 7ca or 9aa was carried out under optimized conditions. As shown in the kinetic profile in Figures S1 and S2, the consumption of alcohol 5a or 5c declines rapidly in the first 2 h and then gradually decreases over the remaining time. Interestingly, the corresponding aldehyde **6a**', ketone (**5a**' or **5c**'), and  $\alpha,\beta$ -unsaturated ketone (7ca-I or 9aa-I) were found as intermediates. In order to understand the rate of dehydrogenation of aliphatic secondary alcohol vs aromatic secondary alcohol by catalyst Ru-2, the investigation has been illustrated with 8a and 5c under the standard conditions for 2 h. A higher yield of 8a' (18%) was obtained with respect to 5c' (11%) by GC analysis, which revealed that dehydrogenation of the aliphatic secondary alcohol was faster than the benzylic ones under the reaction conditions (see the Supporting Information).

On the basis of these experimental findings, taking earlier reports into account,  $2^{2f,4,12a,13-15}$  and with the help of DFT calculations, a plausible catalytic cycle has been proposed as shown in Scheme 6. Since the calculation of cross-coupling of secondary alcohols is not well explored,<sup>15</sup> we commence our study with 1-phenylethanol 5a and cyclohexanol 8a as the model substrates. All calculations were performed at the M06-L level of theory (see the Supporting Information for details). The calculated free energy result and some key optimized structures are depicted in Table S4. At first, the precatalyst Ru-2 is reduced in situ to form the Ru(II) species under the reaction conditions. The resultant active species I is then reacted with alcohol (5a or 8a) converted into ruthenium hydride intermediate II in a downhill process ( $\Delta G = -19.7$ kcal/mol for **5a** and  $\Delta G = -22.7$  kcal/mol for **8a**) via an outer sphere MLC pathway and proton shuttle type of TS (O-TS-1A or **O-TS-1B**). The energy barrier for 8a ( $\Delta G^{\ddagger} = 9.7 \text{ kcal/mol}$ ) is slightly lowered with respect to dehydrogenation of **5a** ( $\Delta G^{\ddagger}$ = 13.3 kcal/mol), which supports the above experimental

observation (see Scheme S15). It was also found that the aromatized intermediate VIII ( $\Delta G = -14.7 \text{ kcal/mol}$ ) could be easily formed by the addition of an -OH bond of alcohol with the proton shuttle type of mechanism via the MLC pathway (see Scheme S18). Subsequently,  $\beta$ -hydride elimination takes place and yields ketone-coordinated intermediate **X** ( $\Delta G = -10.9$  kcal/mol). To release the corresponding ketone 5a' from X requires higher energy (X  $\rightarrow$  XI;  $\Delta G = 14.6$ kcal/mol) compared to the energy barrier for  $\beta$ -hydride elimination step ( $\Delta G^{\ddagger}$  = 11.5 kcal/mol) (see Scheme S18). Isomerization can lead to ruthenium hydride intermediate II in a downhill process of 25.7 kcal/mol (XI  $\rightarrow$  XII). Further, NICS (0) calculation was performed to evaluate the change in the aromaticity during  $I \rightarrow II$  or vice versa (see the Supporting Information). A base-mediated cross-aldol reaction between in situ generated ketones 5a' and 8a' gives  $\alpha_{,\beta}$ -unsaturated ketone compound 9aa-I, which inserts into the Ru-H bond of II in an uphill process ( $\Delta G = 2.4 \text{ kcal/mol}$ ) while crossing a barrier (R-TS-1) of only 3.3 kcal/mol to give III. Complex III undergoes  $\sigma$ -bond metathesis with molecular H<sub>2</sub> with slightly higher energy barrier (**R-TS-2**,  $\Delta G^{\ddagger} = 5.5$  kcal/mol), leading to the desired product **9aa** in exothermic fashion ( $\Delta G = -27.2$ kcal/mol) and regeneration of the active metal hydride intermediate II.

The alternative alcoholysis of III involves coordination of **5a** to the ruthenium center to give IV via molecular complex (III...5a). This process is an endothermic ( $\Delta G = 10.6 \text{ kcal/} \text{ mol}$ ), followed by  $\sigma$ -bond metathesis of Ru–C with the O–H of **5a** in IV, giving product **9aa** and intermediate V. Complex V undergoes  $\beta$ -hydride elimination, liberation of ketone, and isomerization to regenerate intermediate II. The process (V  $\rightarrow$  II) is thermodynamically downhill ( $\Delta G = -17.6 \text{ kcal/mol}$ ). These observations open up the possibility of both the alcoholysis and hydrogenation pathways giving rise to the formation of product **9aa**. Lastly, the Ru–H and N–H cooperation involving the metal hydride intermediate II and the –OH group of the alcohol (**5a** or **8a**) to yield H<sub>2</sub><sup>16</sup>

regenerates active catalyst I via the transition state O-TS-2A with energy barrier  $\Delta G^{\ddagger} = 32.8 \text{ kcal/mol}$  (for 5a) or O-TS-2B with energy barrier  $\Delta G^{\ddagger} = 28.6 \text{ kcal/mol}$  (for 8a).

In summary, a phosphine-free pincer ruthenium-catalyzed cross-coupling of primary and secondary alcohols to  $\alpha$ -substituted ketones and two different secondary alcohols to  $\beta$ -disubstituted ketones were demonstrated. The preliminary mechanistic studies indicated that the dehydrogenation of alcohol follows a proton shuttle type of TS and the involvement of "borrowing hydrogen" catalysis. The use of air-stable catalyst, a catalytic amount of base, aerobic reaction conditions, and high selectivity in C–C bond formation are the important practical features.

#### ASSOCIATED CONTENT

# Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04098.

Experimental procedures, spectroscopic data for all new compounds, theoretical calculations, crystallographic data for **Ru-2**, and computational data (PDF)

FAIR data, including the primary NMR FID files, for compounds 3a, 3b, 4a, 4b, 6k, 6k', 7aa-aj, 7ca-D, 7ba-na, 9aa-ha, 9lf, 9ca-D, HL<sup>1</sup>, HL<sup>2</sup>, and I (ZIP)

## **Accession Codes**

CCDC 2047904 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### **Author Contributions**

D.B. performed all of the experimental work. B.S. and H.K.S. performed the computational calculations. D.B., S.N., and A.D. wrote the manuscript.

#### Notes

The authors declare no competing financial interest.

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