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Base-controlled NHC-Ru-catalyzed transfer hydrogenation and α-methylation/transfer hydrogenation of ketones using methanol

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ABSTRACT

Herein, we report the NHC-Ru catalyst system that realizes the chemo-selective transformation of ketones with methanol. By simply changing the base, a broad range of structurally diverse ketones, could be selectively and efficiently converted to the corresponding β-methylated secondary alcohols or secondary alcohols. Remarkably, this catalytic system was very effective for the synthesis of bio-related molecules and deuterated alcohols, as well as the three-component coupling between methyl ketones, primary alcohols, and methanol. The reaction mechanism was further revealed by experiment and DFT mechanistic investigations.

Methanol is a less toxic, cheap and abundant chemical, which has shown great potential in organic transformations and energy technologies. In particular, methanol has emerged as an appealing methylation agent based on the borrowing hydrogen (BH), or hydrogen auto-transfer (HA) approach [1–4]. Compared to conventional methylation reagents such as Grignard reagents, methyl iodide and methyl sulfate, methanol is more green, sustainable and less toxic. It allows the formation of various *C*-Me or *N*-Me groups through the reaction of methanol with N or C-nucleophiles, respectively. In addition, methanol is also an excellent hydrogen carrier (*ca.* 12.5 wt% hydrogen), which has been used for the transfer hydrogenation (TH) of unsaturated bonds [5]. A wide range of substrates such as ketones, aldehydes, olefins, and alkynes could be readily reduced though transfer hydrogenation, using MeOH as the hydrogen source.

Recently, significant efforts have been devoted to the transformation of ketones with methanol. Though transfer hydrogenation, the ketones could be reduced to secondary alcohols (Scheme 1a). For examples, Sundararaju *et al.* demonstrated a Cp*Ir(III) complex with 6, 6′–hydroxyl-2,2′-bipyridyl ligand for transfer hydrogenation of ketones using methanol [6]. In 2020, Li *et al.* also reported the [Cp*Ir(2,2′-bpyO)(OH)][Na] complex for transfer hydrogenation of ketones with methanol [7]. Later, such transformation was achieved by Bagh *et al.* as well using a Ru-triazole complex [8].

In addition, ketones could also be converted to α-methylated ketones with methanol as a C1 source through the BH or HA approach. Over the past decades, the groups of Donohoe [9,10], Obora [11], Andersson [12], Morrill [13], Sortais [14], and others [15–17], have developed varieties of transition metal complexes for the synthesis of α-methylated ketones (Scheme 1b). For example, Liu's group and Morril's group independently developed the cobalt [15] and iron [13]-based catalysts for the α-methylation of ketones with methanol. Later, Sortais *et al.* reported a PN_3P-Mn complex catalyzed the α-methylation of ketones with methanol [14]. Although the amount of methanol is significantly excessive in these reactions, the further transfer hydrogenation of α-methylated ketones to the β-methylated secondary alcohols is very rare. In 2022, Xing and Wang *et al.* reported the synthesis of β-methylated secondary alcohols from non-methylated ketones with methanol utilizing a Cp*Ir complex [18]. However, this catalytic system requires two consecutive processes, and is only applicable to non-methylated ketones. While preparing this article, Kundu *et al.* reported a cyclometalated (NNC)Ru(II) complex, which catalyzed the selective functionalization of ketones with methanol [19]. In these transformations, different products could be obtained from the reaction of ketones with methanol, involving several pathways, such as transfer hydrogenation, α-methylation, and α-methylation/transfer hydrogenation (Scheme 1c). However, it is still a great challenge to control the selectivity for transfer hydrogenation and methylation using a single catalyst.

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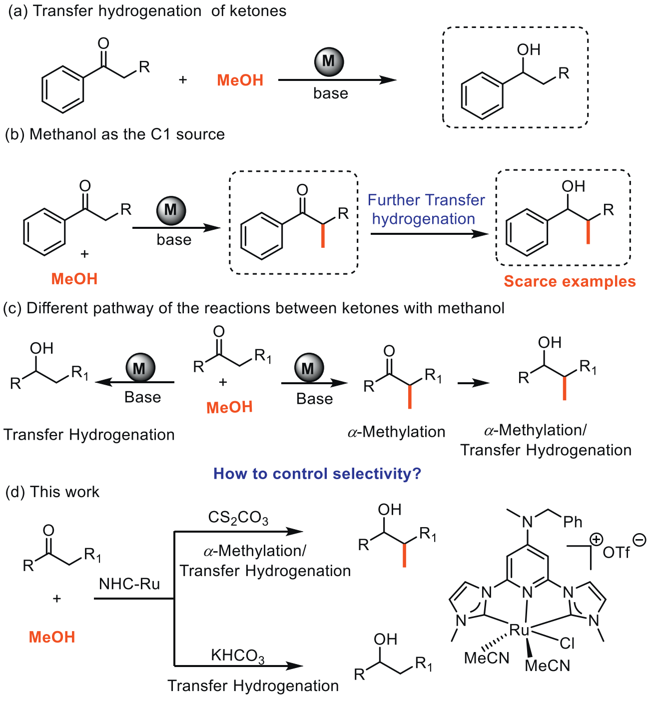


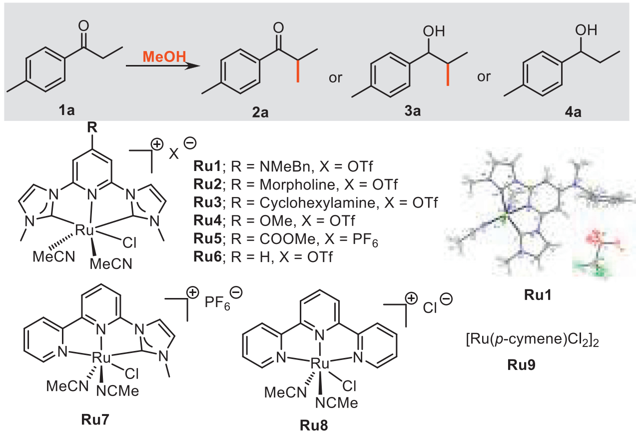
Scheme 1. The transformation of ketones with methanol and challenges.

Herein, we report the pincer-type NHC-Ru complex, which is a promising catalyst for the selective transformation of ketones with methanol (Scheme 1d). They are significant because (1) we realize the base-controlled selectivity for transfer hydrogenation and methylation; (2) we provide a green way to the transfer hydrogenation of ketones using methanol; (3) the synthesis of β-methylated secondary alcohols is now accessible; (4) the conditions are mild, and weak bases are used.

We investigated the transformation of 4′-methylpropiophenone (**1a**) with methanol in the presence of a pyridyl-based CNC ligand-stabilized Ru complex (**Ru1**) and observed a base-dependent product formation (Table 1 and Table S5 in Supporting information). When the Cs_2CO_3 (entry 1) is used as a base, the α-methylation/transfer hydrogenation pathway is preferred, and 85% yield of the β-methylated secondary alcohol **3a** was obtained with a great selectivity (**2a**:**3a**:**4a** = 7:85:0). While 82% yield of **4a** with a great selectivity (**2a**:**3a**:**4a** = 0:2:82) was achieved though the transfer hydrogenation pathway, with $KHCO_3$ as a base (entry 2). Then, a library of Ru complexes (**Ru2**-**Ru9**) was tested to investigate the effect of the structure of the catalyst on catalytic activity [20]. **Ru2**-**Ru6** bearing different R groups (R = NR_1R_2, OMe, $COOCH_3$, H) attached to the pyridyl ring, and **Ru7** with bipyridyl-based NNC ligand, were found to be slightly less reactive compared to **Ru1** (entries 3 and 4). The tris-bipyridyl-based NNN complex **Ru8** and $[Ru(p\text{-cymene})Cl_2]_2$ (**Ru9**), displayed much inferior activity compared to **Ru1** (entries 5 and 6). In the absence of the Ru complex or base, no products were observed in the control experiments (Table S7, entries 9 and 10).

Using the optimized conditions, we investigated the substrate scope for the selective synthesis of β-methylated secondary alcohols (Scheme 2). The propiophenone derivatives containing electron donating groups like methoxy and methyl gave the corresponding products **3a** and **3b**, and **3e**-**3f** in good to excellent yields (76%–96%). However, substrates bearing electron-withdrawing groups (-CF_3 and -Cl) exhibited relatively poor yields (**3c** and **3d**). In the case of 4′-fluoropropiophenone, the fluorine group was converted to the methoxy group and furnished the product **3b** in 56%

Table 1
Selected data for the screening of the optimal conditions.[a,b,c]

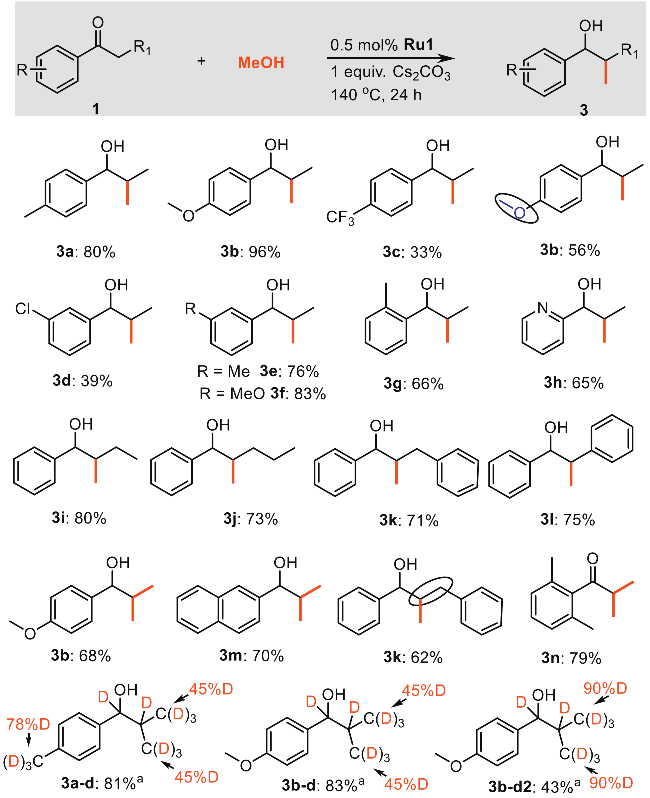


Entry	Ru	Base	**2a** (%)	**3a** (%)	**4a** (%)
1	**Ru1**	Cs_2CO_3	7	85	0
2[c]	**Ru1**	$KHCO_3$	0	2	82
3	**Ru2-Ru6**	Cs_2CO_3	7	70–81	0
4	**Ru7**	Cs_2CO_3	6	73	12
5	**Ru8**	Cs_2CO_3	20	41	0
6	**Ru9**	Cs_2CO_3	31	9	7

[a] Reaction conditions: **1a** (0.5 mmol), methanol (0.5 mL), **Ru1** (0.5 mol%), Cs_2CO_3 (1 equiv.), 140 °C, 24 h.

[b] Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

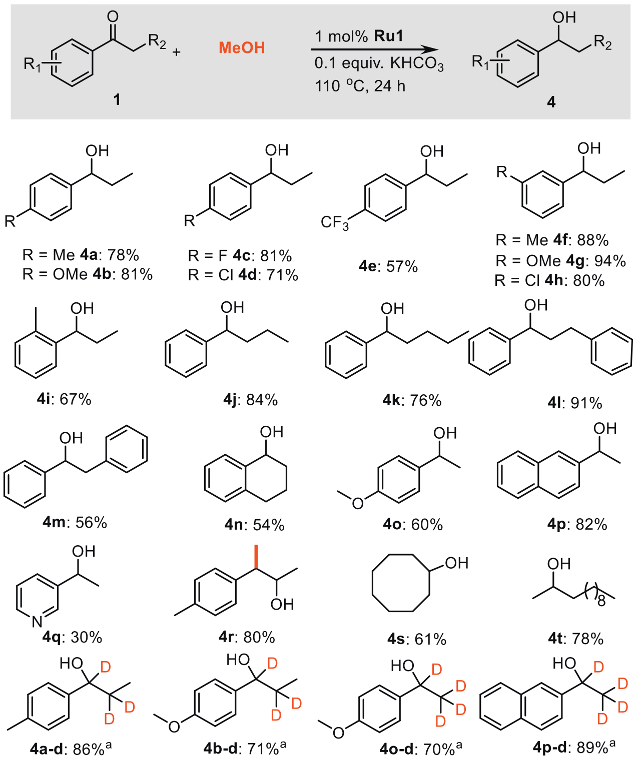
[c] Reaction conditions: **1a** (0.5 mmol), methanol (1.5 mL), **Ru1** (1.0 mol%), $KHCO_3$ (0.1 equiv.), 110 °C, 24 h.



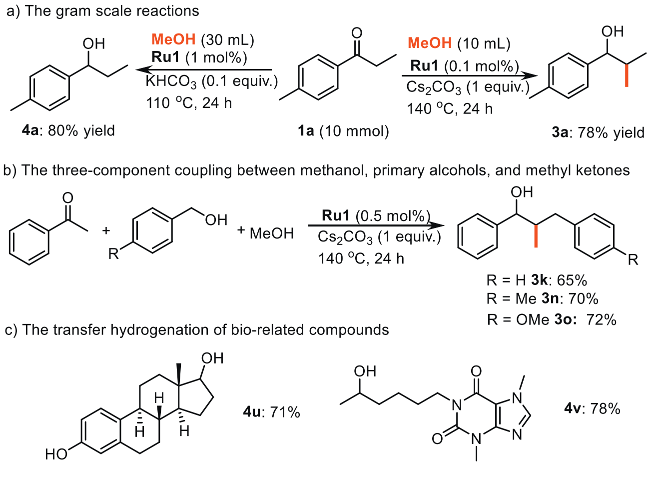
Scheme 2. Substrate scope for the synthesis of β-methylated secondary alcohols. Reaction conditions: **1** (0.5 mmol), methanol (0.5 mL), **Ru1** (0.5 mol%), Cs_2CO_3 (1 equiv.), 140 °C, 24 h. [a] CD_3OD (0.5 mL) was used.

yield. Sterically hindered 2′-methylpropiophenone and heteroaromatic 2-propionylpyridine were compatible, and generated **3g** and **3h** in 66% and 65% yields, respectively. The α-alkyl (Et, *n*-Pr, Bn), and α-phenyl substituted acetophenone derivatives undergo efficient methylation in excellent yields (**3i**–**3l**, 71%–80%). Moreover, acetophenone derivatives such as 4′-methoxyacetophenone and 2-acetonaphthone provided the di-methylated products **3b** and **3m** in 68% and 70% yields, respectively. For the sterically hindered 2,6-di-methyl acetophenone, the carbonyl group has not been reduced and the α-methylated ketone **3n** was obtained in 79% yield. Notably, the α,β-unsaturated ketone *trans*-chalcone was also well tolerated and furnished the product **3k** in 62% yield. When CD_3OD was used, a β-CD_3 group and significant deuterium incorporation at the α- and β-positions were found in the products **3a-d** and **3b-d.** Interestingly, we also observed H/D exchange for substrate with benzylic position (**3a-d**) [17]. In the case of 4′-methoxyacetophenone, the doubly deuteromethylated product **3b-d2** was obtained in 43% yields. These results indicated that methanol is the source of the methyl group and the hydrogen source.

Next, we also explored the scope of the transfer hydrogenation of ketones using methanol (Scheme 3). Propiophenone derivatives bearing either electron-donating or electron-withdrawing substituents were selectively reduced to afford the corresponding products **4a**–**4h** in 57%–94% yields. In this transformation, the halogen substituents such as fluorine or chlorine, and F_3C-group were well tolerated, and yielded the corresponding products **4c**–**4e** and **4h** in good yields. Even sterically hindered 2′-methylpropiophenone could smoothly convert to the corresponding product **4i** in 67% yield. The α-substituted acetophenones like butyrophenone, valerophenone, 3-phenylpropiophenone, and 2-phenylacetophenone afforded the desired products **4j**–**4m** in 56%–91% yields. Cyclic ketone α-tetralone and heteroaromatic 3-acetylpyridine were compatible, and the corresponding products **4n** and **4q** were isolated in 54% and 30% yields, respectively. Furthermore, 4′-methoxyacetophenone and 2-acetonaphthone were also found to be active enough to yield the corresponding products **4o** and **4p** in 60% and 82% yields, respectively. Notably, 4′-methylphenylacetone reacted efficiently with methanol to produce the β-methylated secondary alcohol **4r** in 80% yield. Aliphatic ketones, such as cyclooctanone and 2-dodecanone, showed high reactivities, achieving the corresponding products **4s** and **4t** in 61% and 78% yields, respectively. Again, the transfer hydrogenation proceeded well when CD_3OD was used, and significant deuterium incorporation at the α- and β-positions were found in the products **4a-d**, **4b-d**, **4o-d**, and **4p-d**.



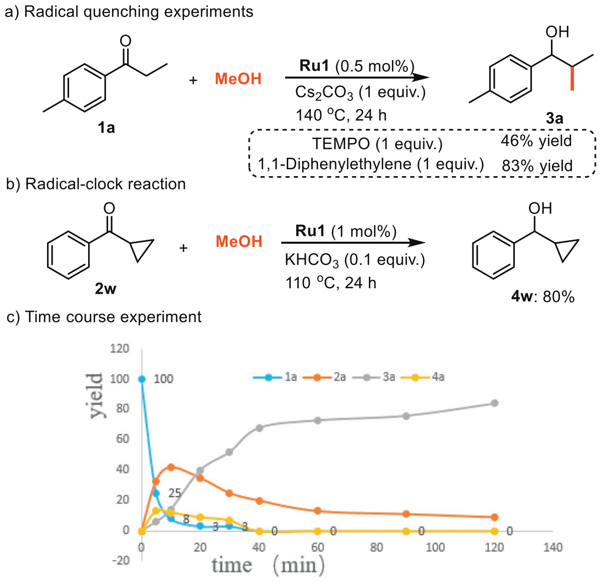
Scheme 3. Substrate Scope for the transfer hydrogenation of ketones using methanol. Reaction conditions: **1** (0.5 mmol), methanol (1.5 mL), **Ru1** (1.0 mol%), $KHCO_3$ (0.1 equiv.), 110 °C, 24 h. ^{a} CD_3OD (1.5 mL) was used.



Scheme 4. Gram-scale reactions and synthetic application.

To explore the synthetic potentials of our protocol, gram-scale reactions, and several synthetic application experiments were carried out (Scheme 4). With **1a** as a substrate in 10 mmol scale reactions, products **3a** and **4a** were obtained in 78% and 80% yields, respectively (Scheme 4a). Delightfully, the loading of **Ru1** could be reduced to 0.1 mol% for the gram-scale synthesis of **3a**. Additionally, this protocol worked smoothly in three-component coupling between methanol, primary alcohols, and methyl ketones. Moderate to good yields of doubly alkylated products **3k**, **3n**, and **3o** were obtained in this one-pot process (Scheme 4b). Moreover, the developed method was also successfully applied for the transfer hydrogenation of bio-related compounds such as estrone and pentoxifylline (**4u** and **4v**, Scheme 4c).

In order to gain mechanistic insight, we performed a series of control experiments and kinetic experiments. Firstly, the effect of the base on the reaction selectivity was studied. The strong bases such as KO*t*Bu, KOH, NaO*t*Bu, NaOH, and Cs_2CO_3 are more prone to the aldol condensation, resulting the product **3a** as a major product. The weak bases such as $KHCO_3$, K_2CO_3, $NaHCO_3$, and Na_2CO_3 cannot promote the methylation step, and transfer hydrogenation product **4a** was obtained as a major product. In the presence of radical scavengers such as TEMPO and 1,1-diphenylethylene, product **3a** was obtained in 46% and 83% yields, respectively (Scheme 5a). Additionally, a radical clock substrate, cyclopropyl phenyl ketone, offered the product **4w** in 80% yield (Scheme 5b). Therefore, the radical pathway could be ruled out in this transformation [21]. A parallel experiment revealed a $k\mathrm{H}/k\mathrm{D}$ value of 1.09 (Fig. S1 in Supporting information), indicating that the activation of methanol may not be involved in the rate-determining step (RDS). Furthermore, a time course experiment (Scheme 5c, Fig. S2 in Supporting information) using **1a** and MeOH to form the **3a** was carried out to gain further information about the mechanism [22]. We found that the progress of the reaction was very rapid during the ini-



Scheme 5. Preliminary mechanistic studies.

tial period; almost 52% of **1a** was converted to both **2a** (33%), **3a** (6%), and **4a** (13%) after 5 min. After that, there was a gradual increase of **3a** with the corresponding depletion of **2a** and **4a**, which supports the tandem α-methylation/transfer hydrogenation steps. Subsequently, kinetic studies (Figs. S3 and S4 in Supporting information) suggested a zero-order dependence on the concentration of ketone **1a**, and a first-order dependence on the concentration of Ru catalyst.

Based on the above results and literature precedents [16,18,23,24], two catalytic cycles for the α-methylation/transfer hydrogenation and transfer hydrogenation and its results of DFT calculations were depicted in Scheme 6. Both cycles are initiated by the base-mediated activation of the compound **Ru1** afforded the alkoxo complex **IM0**, from which dissociation of acetonitrile ligand provided the corresponding intermediate **IM1** (10.5 kcal/mol, Scheme S4 in Supporting information). Next, β-hydrogen elimination through transition state **TS1** (13.3 kcal/mol) generated the ruthenium hydride species **IM3** (21.3 kcal/mol). For the α-methylation steps, the aldol condensation undergoes in the presence of Cs_2CO_3, which produces the α,β-unsaturated ketones **1aa**. Afterward, the C=C bond of **1aa** was reduced *via* **TS2** (5.0 kcal/mol), giving the intermediate **2a**. For the transfer hydrogenation steps, the C=O bond of intermediate **2a** or **1a** was reduced through transition state **TS3** (31.1 kcal/mol) or **TS4** (29.2 kcal/mol) to give the alcohol product **3a** or **4a**, respectively. The low free energy barrier of the methanol dehydrogenation steps (**TS1**, 13.3 kcal/mol) suggests that alcohol dehydrogenation is not the RDS, which is in line with the results of the observed KIE values. A facile C=C bond hydrogenation step (**TS2**, 5.0 kcal/mol) was consistent with the time course experiments that 33% of **2a** was detected after 5 min.

In conclusion, we developed highly chemoselective and efficient NHC-Ru-catalyzed tandem α-methylation/transfer hydrogenation or transfer hydrogenation of ketones using methanol. A wide range of ketones bearing different functional groups were well tolerated. In this protocol, two different kinds of secondary alcohols including the deuterated alcohols were chemoselectively synthesized by simply changing the base. Moreover, this process was also successfully extended to the bio-related molecules, and the three-component coupling between methyl ketones, primary alcohols, and methanol. Experiment and DFT mechanistic investigations revealed that this catalyst system follows the α-methylation/transfer hydrogenation or transfer hydrogenation mechanism.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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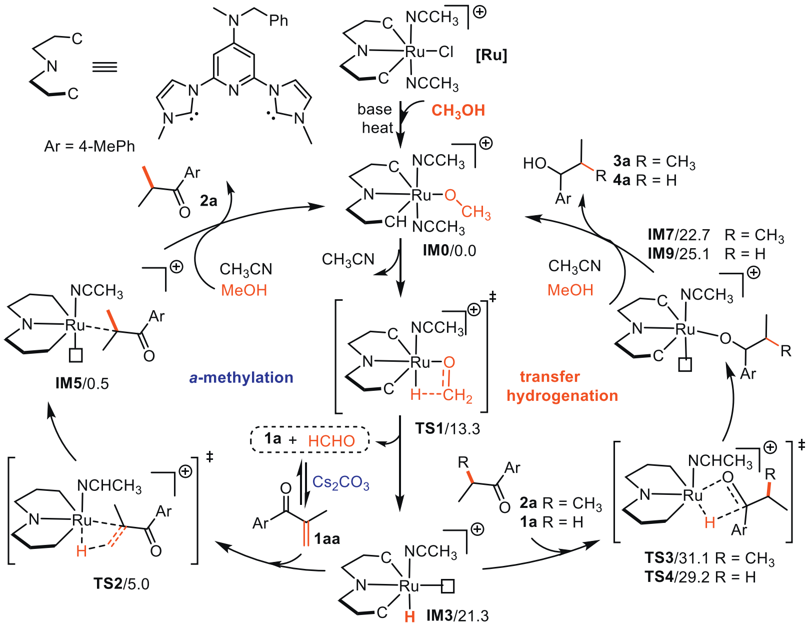

Scheme 6. Plausible reaction pathways. Free energies are given in kcal/mol.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109323.

References

[1] M. Liu, L. Xu, Y. Wei, Chin. Chem. Lett. 33 (2022) 1559–1562.
[2] V. Goyal, N. Sarki, A. Narani, et al., Coord. Chem. Rev. 474 (2023) 214827.
[3] P.Mehara Sheetal, P. Das, Coord. Chem. Rev. 475 (2023) 214851.
[4] J. Guo, J. Tang, H. Xi, S.Y. Zhao, W. Liu, Chin. Chem. Lett. 34 (2023) 107731.
[5] N. Garg, A. Sarkar, B. Sundararaju, Coord. Chem. Rev. 433 (2021) 213728.
[6] Z. Chen, G. Chen, A.H. Aboo, J. Iggo, J. Xiao, Asian J. Org. Chem. 9 (2020) 1174–1178.
[7] R. Wang, X. Han, J. Xu, P. Liu, F. Li, J. Org. Chem. 85 (2020) 2242–2249.
[8] R. Ghosh, N.C. Jana, S. Panda, B. Bagh, ACS Sustainable Chem. Eng. 9 (2021) 4903–4914.
[9] L.K. Chan, D.L. Poole, D. Shen, M.P. Healy, T.J. Donohoe, Angew. Chem. Int. Ed. 53 (2014) 761–765.
[10] D. Shen, D.L. Poole, C.C. Shotton, et al., Angew. Chem. Int. Ed. 54 (2015) 1642–1645.
[11] S. Ogawa, Y. Obora, Chem. Commun. 50 (2014) 2491–2493.
[12] X. Quan, S. Kerdphon, P.G. Andersson, Chem. Eur. J. 21 (2015) 3576–3579.
[13] K. Polidano, B.D.W. Allen, J.M.J. Williams, L.C. Morrill, ACS Catal. 8 (2018) 6440–6445.
[14] A. Bruneau-Voisine, L. Pallova, S. Bastin, V. Cesar, J.B. Sortais, Chem. Commun. 55 (2019) 314–317.
[15] Z. Liu, Z. Yang, X. Yu, et al., Org. Lett. 19 (2017) 5228–5231.
[16] K. Chakrabarti, M. Maji, D. Panja, et al., Org. Lett. 19 (2017) 4750–4753.
[17] J. Sklyaruk, J.C. Borghs, O. El-Sepelgy, M. Rueping, Angew. Chem. Int. Ed. 58 (2019) 775–779.
[18] A. Song, S. Liu, M. Wang, et al., J. Catal. 407 (2022) 90–96.
[19] K. Ganguli, A. Mandal, M. Pradhan, A.K. Deval, S. Kundu, ACS Catal. 13 (2023) 7637–7649.
[20] C. Huang, J. Liu, H.H. Huang, X. Xu, Z. Ke, Chin. Chem. Lett. 33 (2022) 262–265.
[21] A.K. Bains, A. Biswas, D. Adhikari, Chem. Commun. 56 (2020) 15442–15445.
[22] J. Tang, J. He, S.Y. Zhao, W. Liu, Angew. Chem. Int. Ed. 62 (2023) e202215882.
[23] B. Paul, S. Shee, D. Panja, K. Chakrabarti, S. Kundu, ACS Catal. 8 (2018) 2890–2896.
[24] S. Shee, B. Paul, D. Panja, et al., Adv. Synth. Catal. 359 (2017) 3888–3893.