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Group Exchange between Ketones and Carboxylic Acids through Directing Group Assisted Rh-catalyzed Reorganization of Carbon Skeletons

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ABSTRACT: The Rh(I)-catalyzed direct re-organization of organic frameworks and group exchanges between carboxylic acids and aryl ketones was developed with the assistance of directing group. Biaryls, alkenylarenes, and alkylarenes were produced in high efficiency from aryl ketones and the corresponding carboxylic acids by releasing the other molecule of carboxylic acids and carbon monoxide. A wide range of functional groups were well compatible. The exchanges between two partners were proposed to take place on the Rh-(III) centre of key intermediates, supported by experimental mechanistic studies and computational calculations. The transformation unveiled the new catalytic pathway of the group transfer of two organic molecules.

Introduction

Traditional organic synthesis basically depends on the transformations between different functional groups. The scaffold re-organization of organic compounds through C-C bond cleavage could be a conceptually different, straightforward and efficient strategy to build up new skeletons from existing structural units.[1] Transition-metal catalyzed selective C-C bond activation (cleavage) is currently of great interest to organometallic chemists, due to not only its fundamental academic interest to carry out the re-organization of organic molecule skeletons, but also its potential application in organic synthesis.[2] However, the cleavage of C-C bonds faces several challenges from both thermodynamic and kinetic issues, including high bond dissociation energy (BDE) of C-C bonds while relatively lower BDE of forming C-M bonds, steric hindrance of attacked C-C bonds, and selectivity among various C-C bonds in the same molecule.[3] Over the past few decades, significant progress has been made to cleave C-C bonds through different strategies, for example, by relieving the strain of small rings,[4] forming small molecules,[5] inducing aromatic stabilization,[6] forming stable metallacyclic complexes,[7] cleavage of C-CN bond[8] and others.[9] Another successful strategy is to use directing group to assist the C-C cleavage, as shown in pioneer works by Suggs,[10] Jun[2c,2e,11] and others.[12] With this strategy, our group recently reported the Rh-catalyzed selective cleavage of C-C bonds of secondary benzyl alcohols and following transformations.[5f,5h,12e]

Among many type of organic molecules, ketones were seriously regarded as an objective due to their unique reactivity in the field of C-C activation (Figure 1)[4e,4h,4k,4p,4q,7b,9b,9c,9f,9j-l,12h]. For example, with directing strategy in the presence of Rh(I), either one of the acyl C-C bond was cleaved through oxidative addition (path a and path b in Figure 1). Through path a, the carbonyl group was remained and new C-C bonds were formed through the exchange with another molecular of unsaturated species[2e,10b,12c,12d,12g] (i) or the cross coupling with organometallic reagents[12e] (ii). With the same strategy, we conducted the extrusion of carbon monoxide of ketones to form the new C-C bond by cleaving the other acyl C-C bond of ketones[13] (path b, iii). Based on this observation, the intermolecular decarbonylation coupling between arenes and in-situ formed mixed anhydrides was also achieved.[14] In this article, we developed a novel group exchange transformation between ketone and carboxylic acids to form new C-C bond by releasing one molecule of new carboxylic acid and carbon monoxide through the same intermediate in our previous studies (iv).

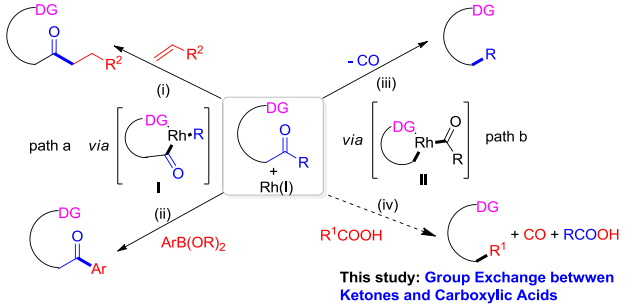


Figure 1. Directed C-C Cleavage of Ketones via Rh(I) Catalysis

Results and Discussion

Serendipity and Further Design on Group Exchange

In our previous studies on the CO extrusion of arylketone, we found a credible amount of protonated 2-phenylpyridine **3aa** as byproduct if the ketone substrate **1aa** in the absence of *meta*-substituent was submitted (Eq 1). To catch the proposed intermediate of Rh(III)-acyl species in catalytic cycle, PhOH was added to the system and indeed the corresponding phenyl ester **2zz** was observed in 46% NMR yield (Eq 2). Thus, we envisaged that, if another molecule of carboxylic acid was introduced into the reaction system, two acyl groups might be exchanged on Rh centre by releasing the other molecule of carboxylic acid if matched. New acyl-Rh species may undergo the decarbonylation to form new substituted arenes. If this chemistry applied, new concept to realize the group exchanges between two independent organic molecules can be proved.

With this idea in mind, we set out to test the proposed group exchange between biaryl ketone **1b** in the presence of 1.0 equiv of *p*-methoxylbenzoic acid **2a**. As designed, both intramolecular and intermolecular decarbonylative products **3a** and **3b** were detected, companying with the formation of benzoic acid **2b** and carbon monoxide (Eq 3). Since the protonation of ketone was also observed, the possibility to produce the group-exchanging product **3a** through the sequence of C-C cleavage/ protonation/ C-H activation/ decarboxylative coupling with carboxylic acid could not be rooted out from this transformation. To clearly understand the pathway to produce the cross coupling product, the control experiment was conducted with the corresponding arylpyridine **3z** in the presence of acid **2a** under the same condition (Eq 4). The recovery of both starting materials (**2a** and **3z**) supported the group exchange pathway rather than the sequence initiated from the protonation without other additives.

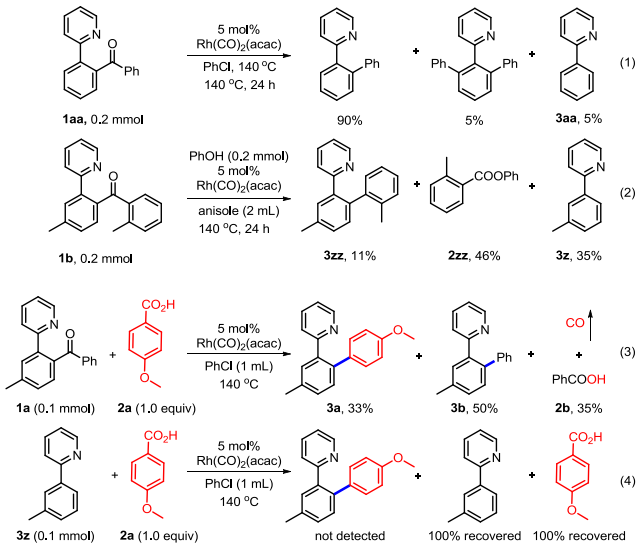


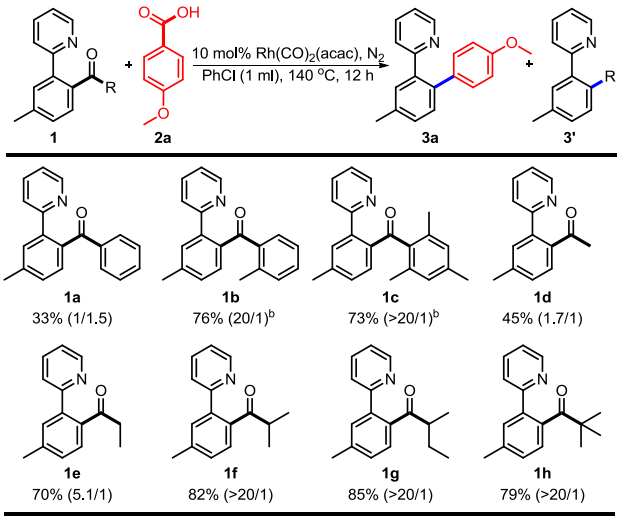
Figure 2. The initial results and control experiments

Investigation on Substrates Compatibility

To further prove our concept of group exchange and evaluate the proper substrates for this process, we first investigate the reactivity of different aryl ketones with the same acid **2a** (**Table 1**). Considering that the steric effect might enhance the chemoselectivity, *o*-toluyl ketone **1b** was selected as a substrate. To our delight, the desired product **3a** was obtained in 76% yield with an excellent selectivity between intramolecular and intermolecular arylation (ratio = 20/1). Owing to the steric effect to slow down the C-C cleavage, a longer reaction time was required to reach the complete conversion. Predictably, more hindered substrate **1c** gave better selectivity with a comparable yield. We concluded that the steric hindrance was the most critical factor to control the chemoselectivity in this transformation. Indeed, the yield was not significantly improved with further optimization of reaction parameters, such as temperature, solvent, catalyst set, or the amount of catalyst and the partner of other carboxylic acids.

To further explore the diversity of the substrates, various alkyl aryl ketones were also investigated (**Table** 1). From the results we can see, alkyl acyl groups are better for both efficiency and selectivity to form the biaryls, although less hindered acetyl and propionyl substrates were not ideal, which may arise from easy reductive elimination to form alkylarenes from C-Rh-C intermediates. With more hindered alkyl ketones as substrates, the selectivity and yields also increased to some extent and the best result was given by **1g**.

Table 1. Substrate-controlled selectivity[a]



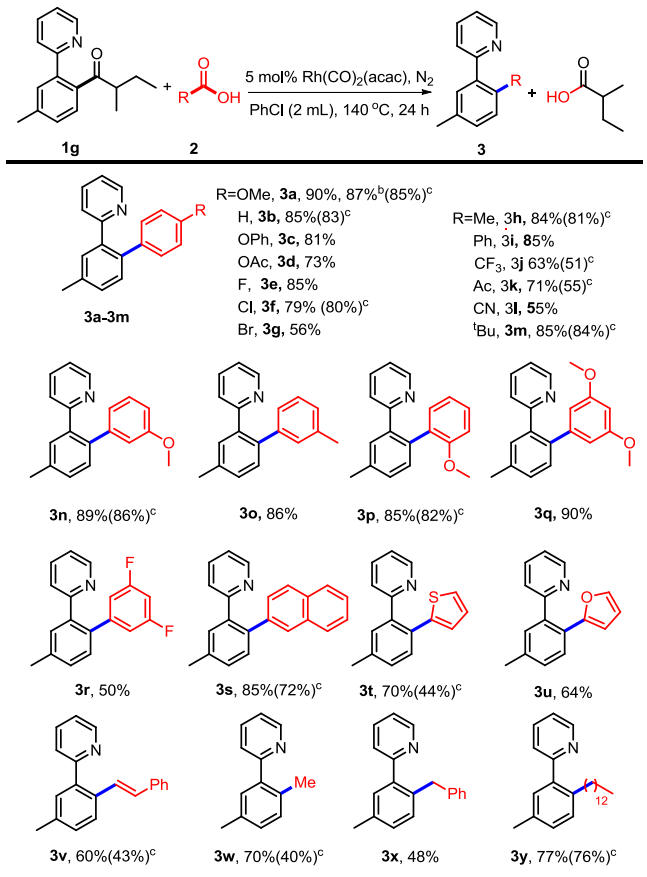
Note: a. reaction conditions: 0.1 mmol of **1**, 2.0 equiv of **2a** in PhCl at 140 °C for 12 h; isolated yield; ratio of **3a/3'** was determined by crude ^{1}HNMR in parenthesis; b. reacted for 24 h.

Based on the balance of reactivity, efficiency, selectivity and availability of the substrates, we chose **1g** as a standard model. After the systematic condition screening (**Table S1**), we found that the reaction reached the best efficiency and selectivity with 4.0 equiv of **2b** in the presence of 5.0 mol% of $Rh(CO)_2(acac)$ as catalyst. The 90% isolated yield was obtained at 140 °C for 24 h under N_2 atmosphere with a trace amount of both direct decarbonylative and protonated byproducts.

With the optimized reaction condition in hand, various acids were investigated (**Table 2**). The results indicated that the electron-donating groups are beneficial for this group exchange (**3a**, **3h**, **3i, 3m**). In contrast, the electron deficient groups, such as trifluoromethyl (**3j**), acetyl (**3k**), and nitrile

(**3l**), decreased the yields, and more protonated byproducts were detected. Other disubstituted acid substrates, such as 3,5-dimethoxyl- (**3q**) and 3,5-difluoro- (**3r**), also gave good yields. Various functionalities, including PhO- (**3c**), AcO- (**3d**), and different halides (**3e**-**g**), survived well, providing opportunities for further functionalization.[15] The steric hindrance obviously decreased the efficiency although *ortho*-methoxylbenzoic acid (**3p**) showed the credible efficiency. Notably, heteroaromatic carboxylic acids, such as 2-thienylcarboxylic acid (**3t**) and 2-furic acid (**3u**), showed the acceptable reactivity and the desired products were isolated in good yields. It was important to note that, cinnamic acid (**3v**) and various aliphatic acids (**3w**-**3y**) were also the proper partners for this transformation. The corresponding alkenyl- and alkyl- arenes were produced in moderate to good yields. To our interest, the isomerisation of long chain aliphatic acids to branched product was not observed, which partially ruled out cationic and radical intermediates. Thus, this method can serve as a supplement to Friedel-Crafts reaction. It should be noted that, in many reactions, the amount of acid **2** could be reduced to 1.5 equiv with comparable yields (**3a**, **3b**, **3f**, **3h**, **3m**, **3n**, **3p**, **3y**);

Table 2. Pyridinyl-directed Rh(I)-catalyzed decarbonylation-coupling of acid[a]

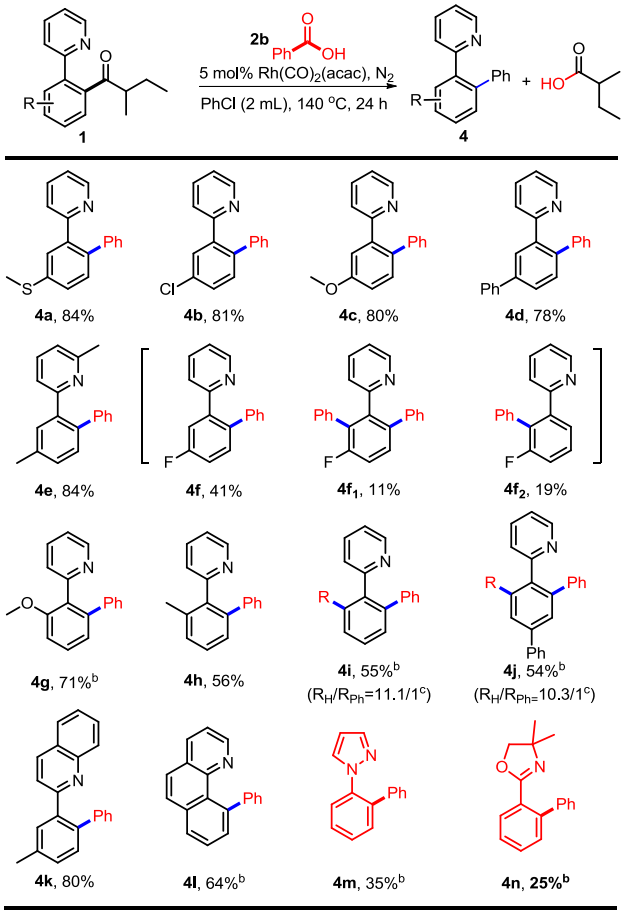


Note: a. reaction condition: 0.2 mmol of **1g**, 4.0 equiv of **2**, 140 °C for 24 h, isolated yield; b. in the atmosphere of O_2, trace starting material remained by TLC; c. 0.2 mmol of **1g**, 1.5 equiv of **2**, 140 °C for 24 h, isolated yields in the parenthesis.

while for electron poor and short chain alkyl carboxylic acids with low boiling points (**3j**, **3k**, **3s**, **3t**, **3v**, **3w**), 1.5 equiv amount of acid **2** resulted in decreased yields.

To explore the effect of substituents on ketone, we investigated a variety of 2-phenylpyridine derivatives (**Table 3**). We found that, electron-neutral and electron-rich groups promoted the efficiency and the desired cross decarbonylative coupling products were produced in good yields (**4a**, **4c**). In contrast, electron-poor groups reduced the efficiency and more protonation byproducts were detected (**4d**). It should be noted that, 2-methyl on pyridine (**4e**) and *ortho*-methoxyl-(**4g**), *ortho*-methyl-(**4h**) groups on phenyl did not show strongly steric or chelating effects and the yields were retained, or slightly decreased. To our interest, for 2-(3-fluorophenyl-)pyridine (**4f**), both *ortho*- isomers and diphenylated products were observed, which might be attributed to the fluoride effect.[16] According to this result, the phenyl group scrambling was proved.[13,17] Such an aryl scrambling was also observed on 2-phenylpyridine or 4-substituted substrates, which indicated that the potential pathway through C-H activation was involved, accompanying with the group exchange. Other than pyridyl group, 2-phenylquinolinyl, benzo[h]quinoliyl, pyrazolyl and oxazolyl gave desired products in credible yields, while with starting material remaining when **4l**-**n** served.

Table 3. N-containing heterocycles-directed Rh(I)-catalyzed decarbonylation-coupling of acid[a]



Note: a. reaction condition: 0.2 mmol of **1**, 4.0 equiv of **2b**, 140 °C for 24 h; b. some started materials remained; c. ratio of R_H/R_{Ph} was detected by crude ^{1}H NMR (400 MHz).

Isotopic Tracing Studies and Control Experiments

Further experiments have been conducted to unveil the reaction pathway. To identify the source of CO, a ^{13}C-labeled acid was submitted (**Figure 3**). The ^{13}C-labelled CO was detected by GC-MS in the presence of ^{13}C-labeled benzoic acid in both reactions with aryl ketone and alkyl ketone as substrates (Eqs 5 and 6). To further prove that CO came from the ketone, both remained acid **2b** and newly generated *o*-toluic acid were quenched by esterification with 4-phenylphenol.[18] The results confirmed that the released acid did not contain the ^{13}C-labelled motif, which was consistent with our conclusion.

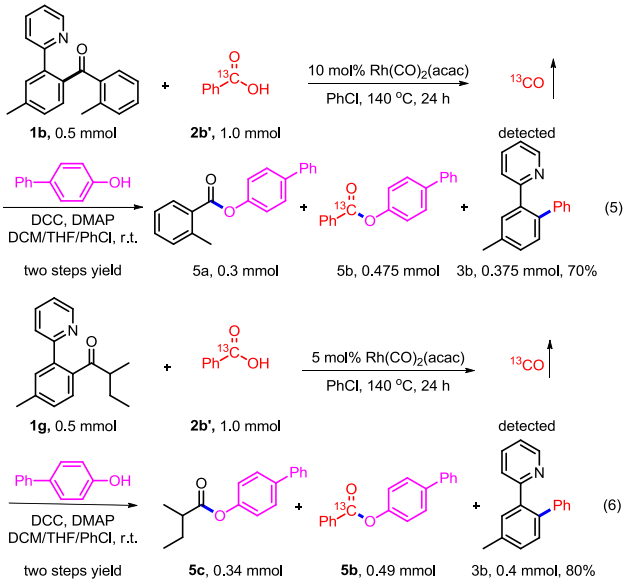


Figure 3. Isotope-tracing Studies

While investigating the steric effect of the acid partner, we found that a trace amount of exchanged ketone **1b** companying with a small amount of protonated byproduct **3z** were observed when steric hindered *o*-toluic acid **2z** was subjected to the reaction with a very low conversion (Eq 7). It is of great importance to imply that the decarbonylation might take place after the group exchange on Rh centre since in the cases a trace amount of exchanged ketone was observed after the group exchange. We tried to inhibit the decarbonylation in the atmosphere of CO (1 atm) from **1g** with **2z** or **2a** as starting materials. However, the similar results were observed and only a trace amount of exchanged ketone **1b** was observed with a very poor conversion when a steric aromatic acid **2z** applied as above results (Eq 8), while only the decarbonylative cross coupling product **3a** was observed in an excellent yield when high reactive aromatic acid **2a** was applied (Eq 9). These results indicated that the presence of CO was not a key issue for this transformation.

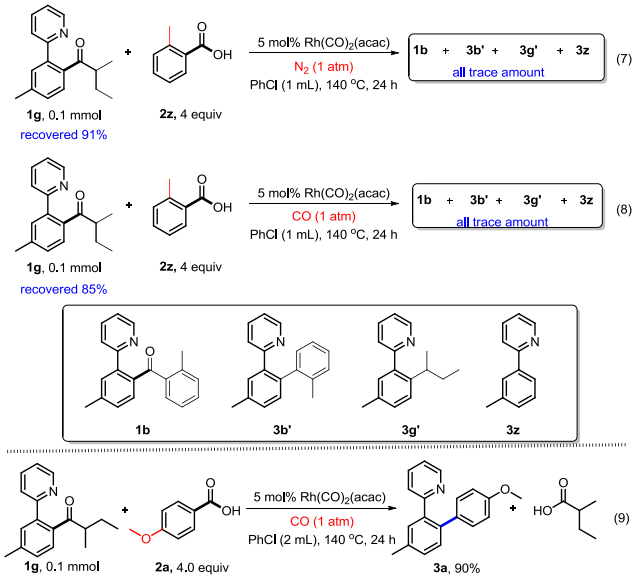


Figure 4. Control experiments under different atmosphere

To clearly rationalize the mechanism, we must answer how the intermediate ketone **1b** is formed? Was it generated from the mixed anhydride?[14,19] To our delight, a trace amount of mixed anhydride was detected by HRMS in the reaction system, which indicated that the anhydride might be a key intermediate to facilitate such a group exchange.[18] Several control experiments related to the mixed anhydride were investigated (**Figure 5** and **Figure 6**). The efficiency of desired group exchange process is higher than the direct arylation through C-H activation starting from the corresponding 2-arylpyridine, thus provide the proof to support that the "intramolecular" group exchange was preferred to the sequence of C-C cleavage/ protonation/ direct C-H arylation with mixed anhydride, which was supposedly produced *in-situ* from substrates and additional acid (Eqs 10 and 11). Comparing the results from the crossover experiments with the same benzoic acids (Eqs 12 and 13), we observed that the exchange product **3b** was preferred, thus also indicating that the "intramolecular" reaction is dominated (if it was produced, the mixed anhydride was not dissociate from the catalytic Rh centre). However, the "intermolecular" process by dissociation was also supported from these control experiments albeit in the relatively lower efficacy.

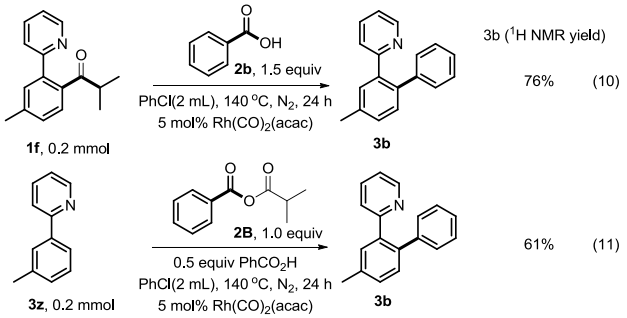


Figure 5. Comparison with mixed anhydride

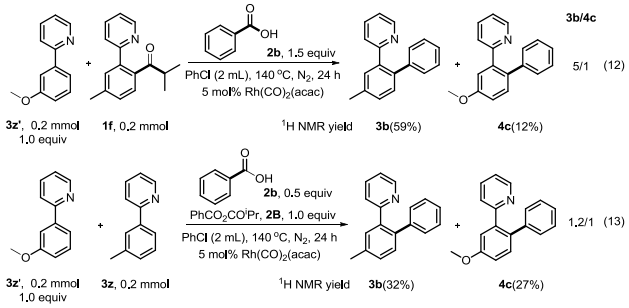
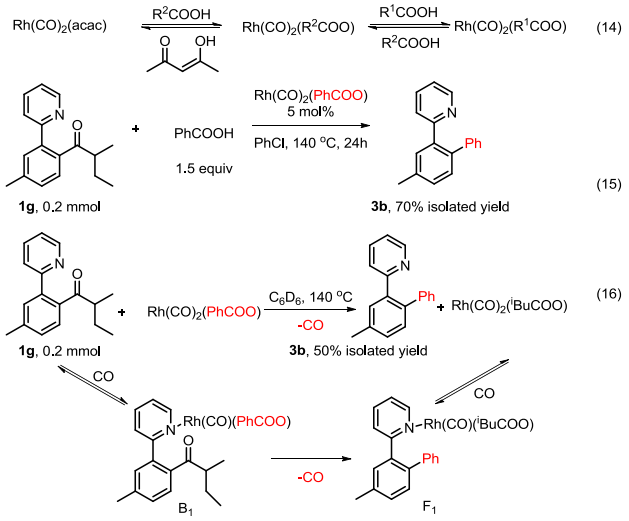


Figure 6. Crossover experiment

Detecting of Active Catalytic Species

Next, we intended to explore the role of acid **2,** which is might not only play a role as a partner. As the acidity of benzoic acid was stronger than that of acetylacetone (acac), the rapid ligand exchange of $Rh(CO)_2(acac)$ to form the new complex $Rh(CO)_2(PhCOO)$ was observed *in-situ* and confirmed by ^1H NMR, which was considered the real active species in this transformation (Eq 14). Indeed, the preformed complex $Rh(CO)_2(PhCOO)$ showed comparable efficiency as $Rh(CO)_2(acac)$ (Eq 15). Stoichiometric experiment with $Rh(CO)_2(PhCOO)$ as starting material in the absence of additional benzoic acid could also afford the desired product with 50% yield (Eq 16). The released acid was found as a ligand to facilitate the group exchange. During this process, the additional acid is not required, so-called "intramolecular" process, which was consistent with the crossover experiments (**Figure 6**). Indeed, the rapid equilibriums between precatalyst **I** with species **B** and **F** as resting states were observed by in-situ IR[18] (**Figure 7**). Thus, we confirmed that the carboxylic acid **2** also acted as the ligand of Rh catalyst and took part in the group exchange at the initiating stage. For $[Rh(CO)_2Cl]_2$ catalyst, the acidity of hydrogen chloride is much stronger than that of benzoic acid. Thus the ligand exchange is more slow, probably resulting in the background decarbonylative coupling of the starting material.[18]



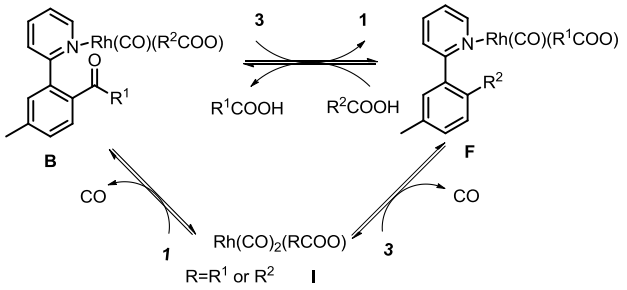


Figure 7. Ligand exchange of catalyst and resting states of catalyst

Electronic Effect of Benzoic Acid

Although this transformation is well controlled by steric hindrance, we also intended to study the electronic effect of substituted benzoic acids. Two competition reactions were explored under the typical conditions as shown in Tables 2 (Eqs 17 and 18). A 1:1 molar ratio mixture of **2a** and **2b**, **2b** and **2j** were reacted with **1g**, affording the arylation products **3a** and **3b** in a 44: 40 molar ratio (Eq 17), **3b** and **3j** in a 50:20 molar ratio (Eq 18), which further demonstrates that an electron-donating substituent in the benzoic acid favored the arylation while electron-withdrawing substituent in the benzoic acid was less reacted. This result is opposite of reactivity to aromatic aldehydes in Rh-catalyzed decarbonylation,[20] which could be explained that strong electron withdrawing group on the benzoic acid causes the increase of protonation byproduct.

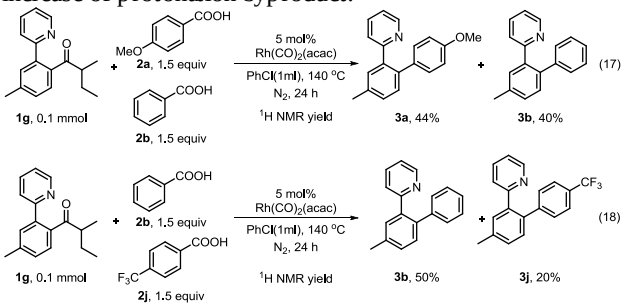


Figure 8. Competition study for the decarbonylative coupling of benzoic acid and substituted benzoic acid

Based on these experiments, the whole catalytic cycle was proposed as **Figure 9**. After the ligand exchange with acid partner, the Rh complex **I** coordinated to the substrate **1** to afford **B**. The oxidative addition of alkyl ketone to Rh centre occurred to form the Rh(III)-acyl species **C**. After forming a tight coordinated anhydride complex **D** and ligand slipping to form the other complex **E**, the oxidative addition took place at the acyl C-O bond to form another Rh(III)-acyl species **F** (path **a**). Followed by the decarbonylation, the complex **G** was formed. Finally the reductive elimination on Rh centre took place to afford the desired product **3**, regenerating the active catalyst by ligand exchange with benzoic acid. On the other hand, the dissociation of anhydride from the Rh centre could also take place. Depending on the acidity of benzoic acid, this pathway might become important through the protonation of the Rh-complex, which was consistent with the observation of the protonated byproducts[21] (path **b**). Since electron

withdrawing benzoic acid exhibited stronger acidity, the portion of path **b** might become an unignorable pathway.

Proposed Catalytic Cycle

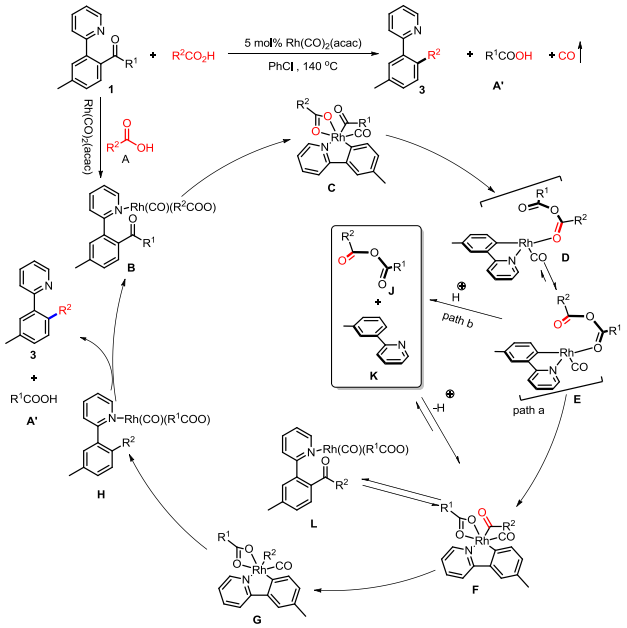


Figure 9. Catalytic Cycle of Cross Decarboxylative Coupling of Aryl Ketone with Carboxylic Acid

$^{12}C/^{13}C$ Kinetic Studies

To prove the proposed pathway of the reaction, we followed Singleton method[22] to measure the $^{12}C/^{13}C$ kinetic isotopic effects. We hoped that such studies ascertained the potential involvement of the oxidative addition, the exchange of Rh(III)-acyl process, decarbonylative and reductive elimination into the turnover-limiting step of catalysis. Obviously, there were four carbons involved in the reaction, and two of these four carbons participated in two different processes. Thus, two independent experiments were conducted for ketone **1g**[23] and acid **2y**. Four gram scale reactions were run to approximately 80% conversion, and the recovered starting material was examined for ^{13}C content by using quantitative ^{13}C NMR spectroscopy. 4-(*tert*-butyl)benzoic acid was converted to methyl 4-(tert-butyl)benzoate for easy isolation. The $^{12}C/^{13}C$ kinetic isotope effects were determined for a number of carbons, including the carbonyl and adjacent aromatic and alkyl carbons, and carbonyl of aromatic acid and adjacent aromatic carbons, with the results summarized in **Figure 10**. Significant large isotopic effects were synchronously observed at the carbonyl of aromatic acid (1.032 ± 0.003 and 1.031 ± 0.003) and adjacent aromatic carbons of (1.024 ± 0.003 and 1.027 ± 0.004), indicating the rate-limiting step of decarbonylation; while negligible isotopic effects on the carbonyl of ketone and adjacent aromatic carbons (more than 0.998 and less than 1.004 in all experiments) suggested the lack of involvement in the rate limiting step of oxidative addition. In conclusion, these results suggested that the decarbonylation is the turnover-limiting step of the reaction. Similarly, in Madsen's studies, they also observed that the decarbonylation was the rate limiting step for the decarbonylation of aromatic aldehyde.[20]

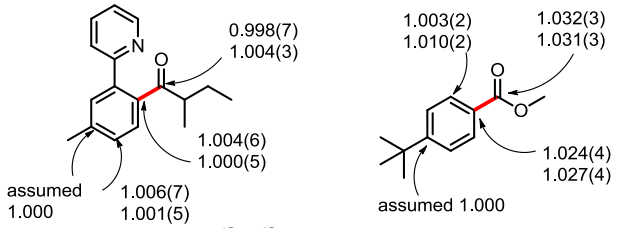


Figure 10. Observed $^{12}C/^{13}C$ kinetic isotope effects for select carbons during the decarbonylative coupling of acid.

Computational Studies

To further rationalize the reaction mechanism, density functional theory (DFT)[24] studies have been performed with GAUSSIAN09 program[25] using the M06[26] method. For Rh atom the SDD basis set with Effective Core Potential (ECP)[27] was used; for the rest atoms, the 6-31+G** basis set was used. Except for the CO molecule, geometry optimization was performed in chlorobenzene (ε=5.697) using the SMD[28] method. Harmonic vibration frequency calculations were carried out at 413.15K, the optimized structures are all shown to be either minima (with no imaginary frequency) or transition states (with one imaginary frequency). The calculation starts from complex **B** (**Figure 7**), and the typical substrates **1g** and **2b** were used in the caculation.

As shown in **Figure 11**, in the first step, the oxidative addition of the reactant complex **B** via transition state **TS-OA-BC** (10.9 kcal/mol) leads to Rh(III)-acyl species **C**. Subsequently, the reductive elimination of the acyl group and the benzoic acid anion in **C** over transition state TS-RE (11.6 kcal/mol) yields the mixed anhydride-Rh complex **INT1**. The dissociation/recoordination of **INT1** forms **INT2**, in which the carbonyl coming from substrate **1g** coordinates with the Rh centre, like communicating on the Rh centre. Then, oxidative addition of the mixed anhydride at the C-O bond coming from benzoic acid via transition state **TS-OA** (9.3 kcal/mol) leads to a new Rh(III)-acyl species **D**, in which the acyl groups has been exchanged compared with **C**. The reductive elimination of **D** over transition state **TS-RE-DH** (18.1 kcal/mol) leads to the slightly unstable exchanged ketone **H** (2.0 kcal/mol). Based on the calculated barriers, under the reaction condition of 140 °C, the equilibrium of the intermediates shown in **Figure 11** can be easily set up, and the acyl group can be exchanged easily via **R.E./O.A.** and dissociation/recoordination processes of the mixed anhydride intermediate. This mechanism is strongly supported by the experiments shown in **Figure 5** and **Figure 6**. A concerted σ-bond metathesis transition state was located. However, the barrier is as high as 86.8 kcal/mol. Therefore, this mechanism can be safely excluded.

As shown in **Figure 12**, the decarbonylation of intermediate **D** via transition state **TS-DeCO-D** (21.6 kcal/mol) forms **E-2CO** which has two coordinated CO molecules. On the attacking of the 2-methylbutanoic acid anion (**TS-E-CO-D'**, 23.5 kcal/mol), one CO molecule is driven out leading to intermediate E. Subsequently, the reductive elimination of **E** over transition state **TS-RE-EF-D** (23.4 kcal/mol) affords the desired product **3**. The

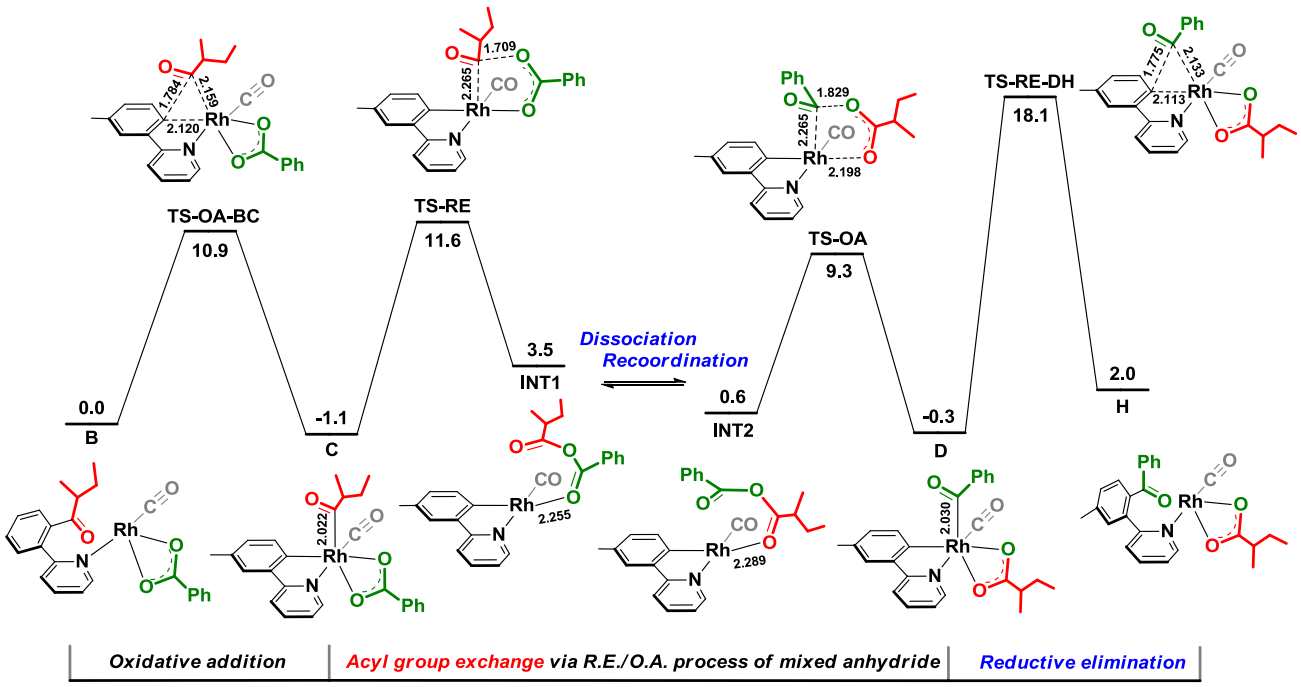


Figure 11. The equilibrium of intermediates B, C, INT1, INT2, D and H. The acyl group can be exchanged easily via R.E./O.A. and Dissociation/Recoordination processes of the mixed anhydride intermediate. The selected bond lengths are in angstroms, and the relative free energies in chlorobenzene Gsol (413.15 K, 1.0 atm) are in kcal/mol. Calculated at M06/6-31+G/SDD level**

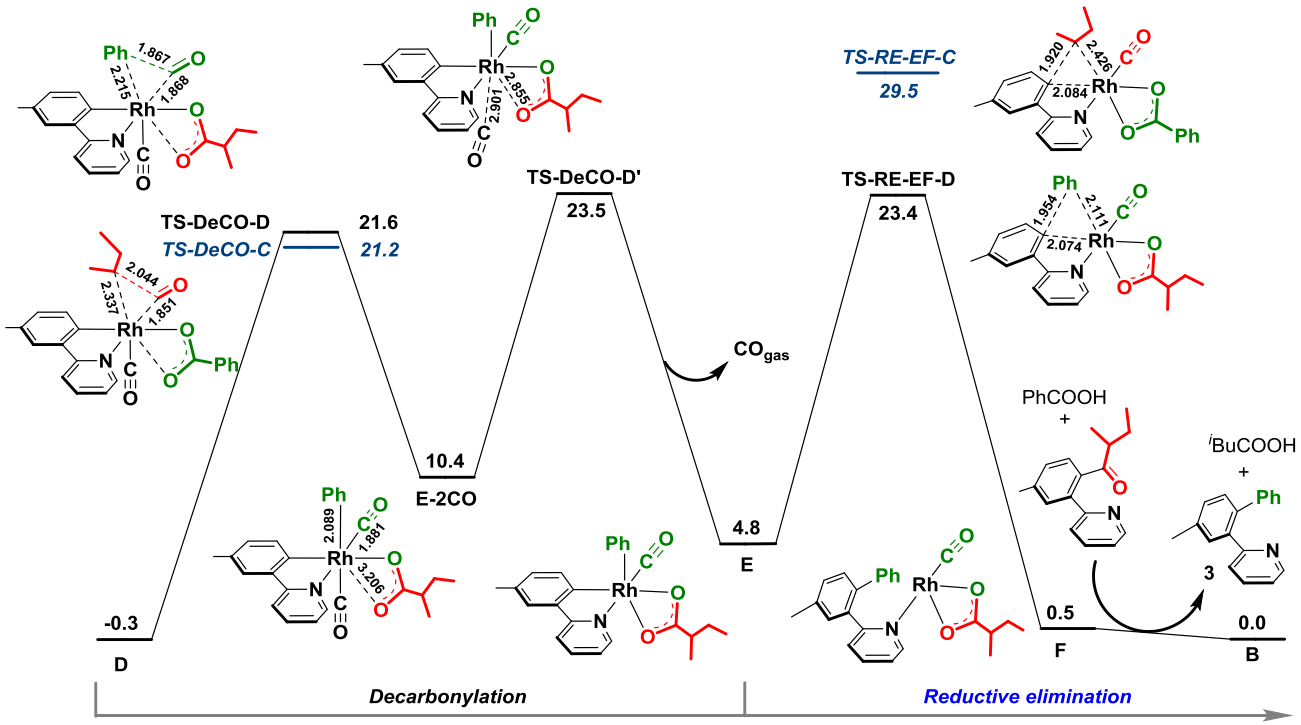


Figure 12. The decarbonylation, CO emission and reductive elimination steps of intermediate D. The decarbonylation and reductive elimination transition states for intermediate C were also shown (in italic). The selected bond lengths are in angstroms, and the relative free energies in chlorobenzene Gsol (413.15 K, 1.0 atm) are in kcal/mol. Calculated at M06/6-31+G/SDD level.**

decarbonylation is the rate-determining step. However, the barrier of the reductive elimination of intermediate **E** is just slightly lower. These results are consistent well with the observed large $^{12}C/^{13}C$ kinetic isotope effects at both the aromatic acid and adjacent aromatic carbons (**Figure 10**).

The barrier of decarbonylation of intermediate **C** (**TS-DeCO-C**, 21.2 kcal/mol) is similar to that of intermediate **D**. Whereas the barrier of the reductive elimination of the decarbonylative intermediate form **C** is much higher (**TS-RE-EF-C**, 29.5 kcal/mol). This may account for the chemoselectivity. From the calculation, we also confirmed the decarbonylation is involved in the rate determining step, which consistent with the $^{12}C/^{13}C$ kinetic studies.

Conclusion

In conclusion, we have developed an unprecedented process to carry out the group exchange of two separated carbonyl compounds. Two parts have been well proved shaking their hands on the Rh(III) centre through two different acyl-Rh intermediates. Isotopic-tracing studies and by-product identification strongly supported the hypothesis of group exchange via Rh catalysis. Systematic kinetic experiments were conducted to find that decarbonylative is the rate determining step. The calculation ascertained the proposed mechanism and kinetic results. This study extensively opens an eye to reconsider the organic synthesis through completely new channel based on the reorganization of the structural skeletons and group exchange. Further investigations to explore new chemistry with this strategy are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Details for calculation and experimental procedures, including spectroscopic, analytical data of the new compounds are reported in supporting information. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interests.

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