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Transition-Metal-Catalyzed C−C Bond Formation from C−C Activation

Feijie Song, Biqin Wang, and Zhang-Jie Shi*

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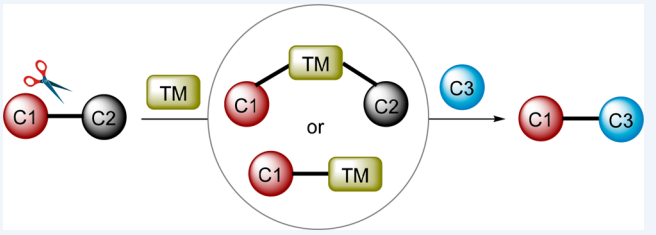
CONSPECTUS: C−C single bonds are ubiquitous in organic compounds. The activation and subsequent functionalization of C−C single bonds provide a unique opportunity to synthesize conventionally inaccessible molecules through the rearrangement of carbon skeletons, often with a favorable atom and step economy. However, the C−C bonds are thermodynamically and kinetically inert. Consequently, the activation of C−C bonds is particularly attractive yet challenging in the field of organic chemistry. In the past decade, we sought to develop efficient strategies to carry out transition-metal-catalyzed diverse C−C cleavage/C−C forming reactions and to obtain some insights into the intrinsic reactivities of different C−C bonds. With our efforts, readily available alcohols, carboxylic acids, and ketones served as suitable substrates for the catalytic C−C coupling reactions, which are reviewed in this Account. In 2009, we observed a Ni-catalyzed cross coupling of aryl nitriles with arylboronic esters through C−CN cleavage. Encouraged by these results, we are interested in transition-metal-catalyzed C−C bond activation. Due to their broad availability, we then turned our attention to C−C cleavage of carboxylic acids. Rhodium-catalyzed decarbonylative coupling of carboxylic acids with (hetero)arenes was then achieved through oxidative addition of *in situ* formed, more reactive mixed anhydrides to Rh(I) without the need for oxidants that are commonly required for the decarboxylative coupling of carboxylic acids. Subsequently, the decarbonylation of more challenging unstrained aryl ketones was realized under Rh catalysis assisted by *N*-containing directing groups. Following this work, a group exchange of aryl ketones with carboxylic acids was achieved through 2-fold C−C bond cleavage. By employing the chelation strategy, Rh-catalyzed C−C bond activation of secondary benzyl alcohols was also accomplished through *β*-carbon elimination of the rhodium alcoholate intermediates. The competing oxidation of secondary alcohols to ketones via *β*-hydrogen elimination of the same intermediates was suppressed as thermodynamically favorable five-membered rhodacycles are formed after *β*-carbon elimination. Different types of transformations of alcohols, including the Heck-type reaction with alkenes, cross coupling with arylsilanes, and Grignard-type addition with aldehydes or imines, have been achieved, showing the great potential of secondary alcohols in the formation of C−C bonds. These C−C bond-forming reactions are complementary to traditional cross couplings of aryl halides with organometallic reagents. However, these transformations produce small molecules as byproducts. To improve the atom economy, we then investigated C−C bond transformations of strained-ring cyclic compounds. Ni-catalyzed intermolecular cyclization of benzocyclobutenones with alkynes was recently achieved via the uncommon cleavage of the C1−C8 bond by employing a removable blocking strategy. Rh-catalyzed intramolecular annulation of benzocyclobutenols with alkynes was also achieved. In summary, our developments demonstrate the great potential of transition-metal-catalyzed C−C bond activation for the formation of new C−C bonds. To further expand the synthetic utility of C−C bond activation, more efforts are required to expand the substrate scope and to achieve earth-abundant metal-catalyzed transformations.



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a Pyridine Group. *Angew. Chem., Int. Ed.* **2012**, *51*, 2690−2694.[2] *In this work, we realized a novel Rh-catalyzed decarbonylation reaction of unstrained ketones through N-containing-group-assisted C−C cleavage.*

- Lei, Z.-Q.; Pan, F.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Li, Y.-X.; Sun, J.; Shi, Z.-J. Group Exchange between Ketones and Carboxylic Acids through Directing Group Assisted Rh-Catalyzed Reorganization of Carbon Skeletons. *J. Am. Chem. Soc.* **2015**, *137*, 5012−5020.[3] *In this work, we realized an unprecedented Rh-catalyzed group exchange of carboxylic acids with unstrained ketones assisted by directing groups via 2-fold C−C bond activation and obtained a deep understanding of the mechanism through in-depth investigations.*
- Guo, J.-H.; Liu, Y.; Lin, X.-C.; Tang, T.-M.; Wang, B.-Q.; Hu, P.; Zhao, K.-Q.; Song, F.; Shi, Z.-J. Site-Selective C−C Cleavage of Benzocyclobutenones Enabled by a Blocking Strategy Using Nickel Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 19079−19084.[4] *In this work, Ni-catalyzed intermolecular annulation of benzocyclobutenones with alkynes was achieved through an uncommon cleavage of the C(sp^3)−C(CO) bond by using a removable blocking strategy.*

1. INTRODUCTION

C−C single bonds are ubiquitous structural units of organic compounds. Direct C−C functionalizations have attracted great interest from chemists because this strategy provides the possibility to construct conventionally inaccessible molecules through the tailoring of molecular skeletons. However, the activation of C−C single bonds has always been challenging for the following reasons: (1) the high average bond energy of C−C bonds (90 kcal/mol) makes their cleavage difficult, (2) their sterically protected nature and high orbital directionality keep C−C bonds inaccessible, and (3) the presence of multiple C−C bonds in the molecule renders selective C−C bond cleavage difficult.[5]

In the past two decades, significant progress has been made in transition-metal-catalyzed C−C activation. To overcome difficulties associated with C−C activation, two strategies have been developed, which rely on increasing the energy state of substrates, decreasing the energy state of organometallic intermediates, or both. Among the two strategies, the first one is more widely used by introducing strained small-membered rings into substrates (Figure 1a). The release of strain energy provides significant driving force for the cleavage and further transformations of C−C bonds.[6] However, additional driving forces are needed for the reaction of unstrained molecules. Pioneering studies of Jun and Suggs have shown that *N*-containing groups are suitable directing groups to assist the oxidative addition of C−C bonds (usually ketones) to transition metals.[7] The coordination of the metal center to the directing group places the metal at a proximal position for C−C activation and generates thermodynamically stable five-membered metallacyclic intermediates after C−C cleavage, which further undergo various transformations (Figure 1b).[8] In addition, metal-catalyzed C−C activation of unstrained tertiary aryl, allyl, and alkynyl alcohols has been achieved via β-carbon elimination, which is significantly driven by the formation of stable ketone byproducts and relatively stable alkynyl, allyl, and aryl metallic species (Figure 1c).[9]

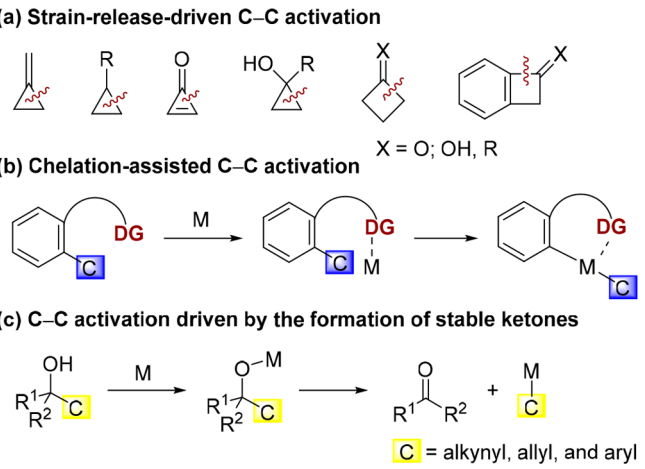

Figure 1. Strategies for the transition-metal-catalyzed activation of C−C bonds.

In the past decade, our group continuously pursued novel transformations based on transition-metal-catalyzed C−C activation (Figure 2). In 2009, we first realized Ni-catalyzed cross coupling of aryl nitriles with boronic ester.[10] Afterward, the C−C bond functionalization of carboxylic acids was achieved by their *in situ* conversion to anhydrides and subsequent Rh-catalyzed decarbonylative coupling of anhydrides with heteroarenes. Subsequently, more challenging substrates, including unstrained ketones and secondary benzyl alcohols, participated in diverse C−C activation/C−C forming reactions with the assistance of chelation groups. Last but not least, strained benzocyclobutene-derived ketones or alcohols were applied to C−C bond functionalizations, driven by the release of ring strain. In this Account, we focus on the C−C bond cleavage of carbonyl compounds as well as alcohols.

2. C−C BOND ACTIVATION WITH THE LOSS OF SMALL MOLECULES

2.1. Decarbonylative Coupling of Carboxylic Acids with Arenes

We were interested in transition-metal-catalyzed C−C coupling of carboxylic acids for their structural diversity, commercial availability, and nontoxicity. Undoubtedly, the coupling between carboxylic acids and (hereto)arenes is a promising protocol for constructing C−C bonds by combining the advantages of both coupling partners.[11] Although significant progress has been made in the decarboxylative coupling of carboxylic acids with arenes, complicated catalytic systems and the requirement of expensive oxidants limited their applications.[12] Inspired by pioneering studies that anhydrides could undergo decarbonylative transformations under redox-neutral conditions,[13,14] we envisioned that *in situ*-formed anhydrides from carboxylic acids may undergo sequential oxidative addition with low-valent transition metals and decarbonylative coupling with arenes. Although this protocol would produce environmentally unfriendly CO as a byproduct, it has the advantage of obviating the use of external oxidants.

Optimization studies showed that the reaction was achieved by using 2.5 mol % $[Rh(CO)_2Cl]_2$ as a catalyst, pivalic anhydride as an activator, and toluene as a solvent at 140 °C for 24 h (Figure 3a).[15] Pyridyl directing group was necessary to assist the regioselective C−H activation of arenes. Under the optimal conditions, aryl, heteroaryl, and alkyl carboxylic acids success-

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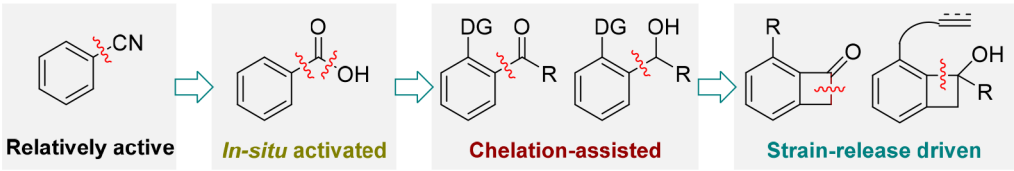

Figure 2. General overview of research programs.

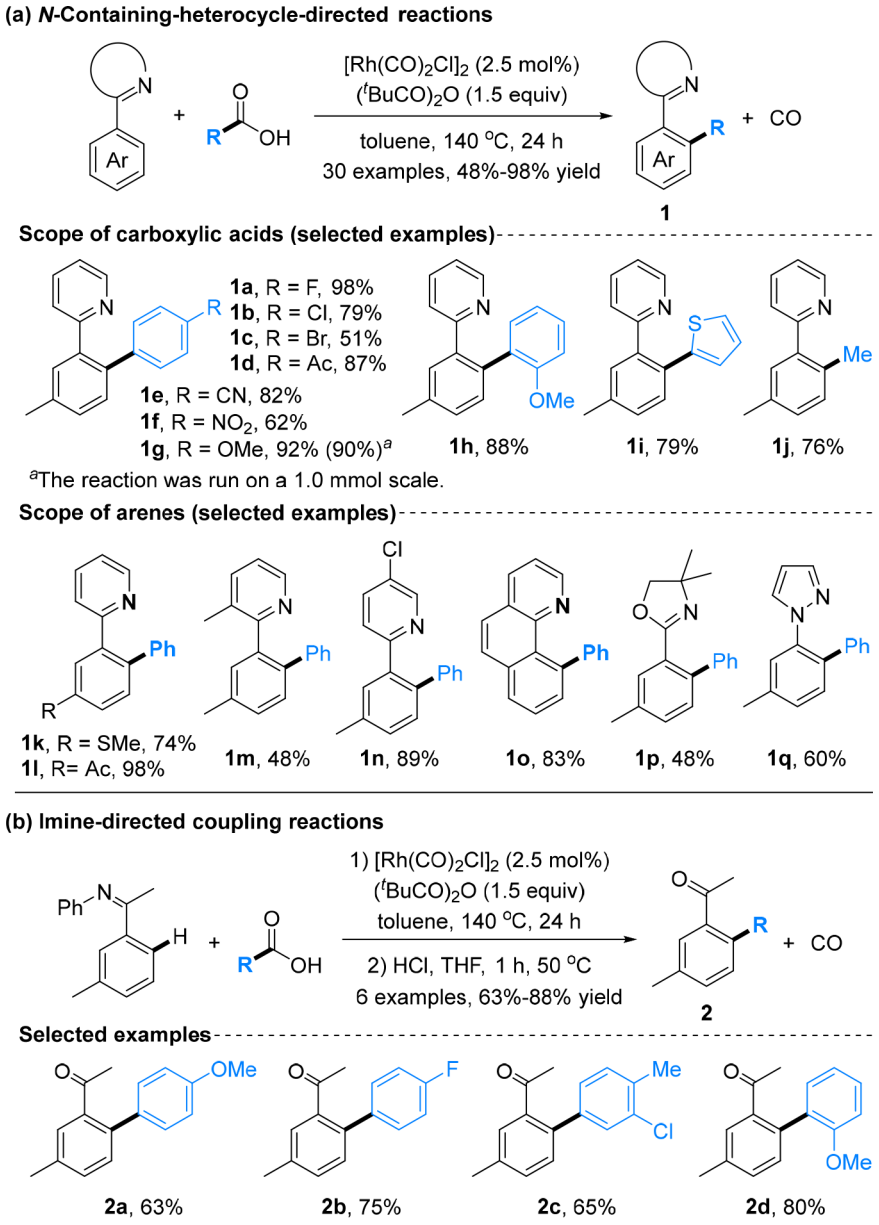

Figure 3. Rh-catalyzed decarbonylative coupling of carboxylic acids with arenes.

fully participated in the coupling reactions to afford the desired products **1** in 48−98% yield. Electron-donating and electron-withdrawing groups on carboxylic acids and 2-arylpyridines were all very compatible with the above-mentioned catalytic conditions. The reaction could be scaled up to 1.0 mmol without a loss of efficiency. Besides the pyridyl group, substituted pyridyl, benzo[h]quinolone, 2-oxazolyl, pyrazolyl, and 2-quinolinyl groups could also direct the reaction (Figure 3a, **1m**−**1q**). More importantly, imine could serve as the directing group to deliver substituted ketones **2** in 63−88% yield after hydrolysis, showing potential applications of this chemistry (Figure 3b).

Furthermore, decarbonylative arylation of indoles with carboxylic acids was realized under the same conditions as the reaction of arenes (Figure 4).[16] In this case, the *N*-(2-pyrimidyl) group, which could be easily removed upon treatment with EtONa in DMSO at 100 °C, was found to be the best choice of directing group. As a consequence, various 2-arylindoles **3** resulting from the selective C2-arylation of indoles were synthesized in 72−96% yield. A C7-arylation product was not

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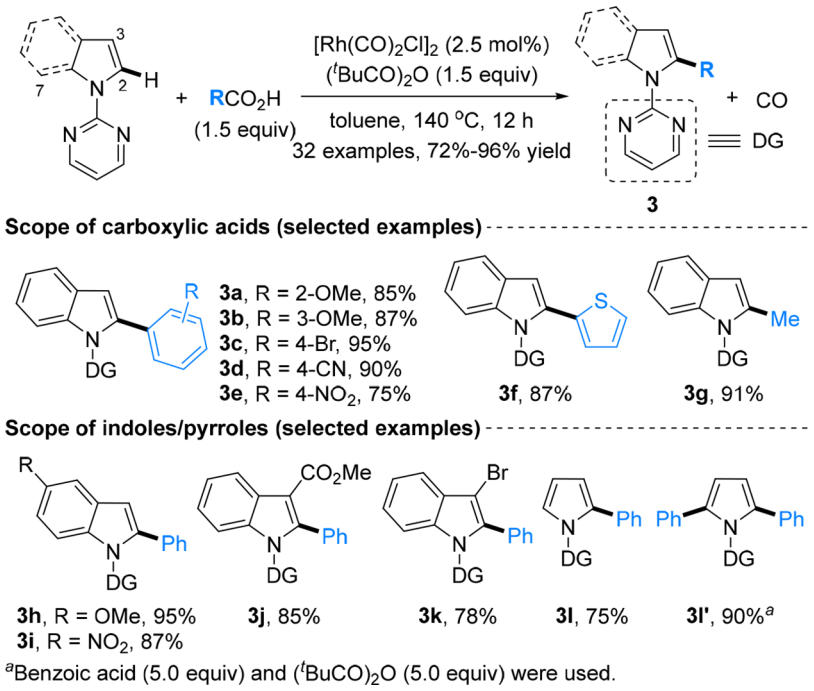
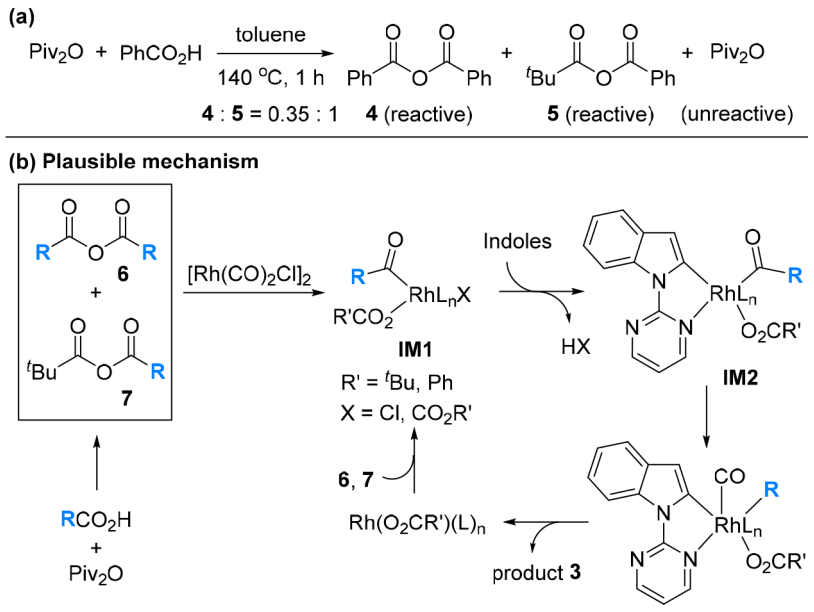


Figure 4. Coupling of carboxylic acids with indoles/pyrroles.

Scheme 1. Mechanistic Studies for the Coupling of Indoles with Carboxylic Acids



observed even with sterically hindered C3-substituted indoles (Figure 4, **3j** and **3k**). *ortho*-, *meta*-, and *para*-substituted benzoic acids were all successfully engaged in the reaction (Figure 4, **3a**–**3e**), which were in sharp contrast to the previously reported decarboxylative arylation of indoles that was applicable only to *ortho*-substituted benzoic acids.[17] Besides, pyrroles could undergo selective mono- and diarylation reactions by tuning the amount of carboxylic acids (Figure 4, **3l** and **3l′**).

Several experiments were conducted to gain some insight into the mechanism. NMR spectroscopy analysis of the reaction mixture of equimolar amounts of $(^{t}BuCO)_2O$ and benzoic acid stirred in toluene at 140 °C for 1 h delivered benzoic anhydride **4** and benzoic pivalic anhydride **5** in a ratio of 0.35:1, which both underwent decarbonylative coupling with indole in the presence of $[Rh(CO)_2Cl]_2$ catalyst (Scheme 1a). In contrast, $(^{t}BuCO)_2O$ was completely unreactive under the same conditions probably due to the steric hindrance of the bulky *tert*-butyl group. GC-MS analysis of the gas phase of the reaction mixture revealed the formation of carbon monoxide, which confirmed the decarbonylative pathway. On the basis of these experimental results and mechanisms reported in the literature, a catalytic pathway different from the originally proposed one is shown in Scheme 1b. The reaction of pivalic anhydride with carboxylic acids in the absence of rhodium catalysts produces anhydrides **6** and **7**, both of which undergo oxidative addition with the Rh^{I} complex at the less hindered C(CO)−C bond to initiate the catalytic cycle, producing Rh^{III} species **IM1**. Electrophilic C−H activation of indoles with **IM1** assisted by a 2-pyrimidyl group affords the

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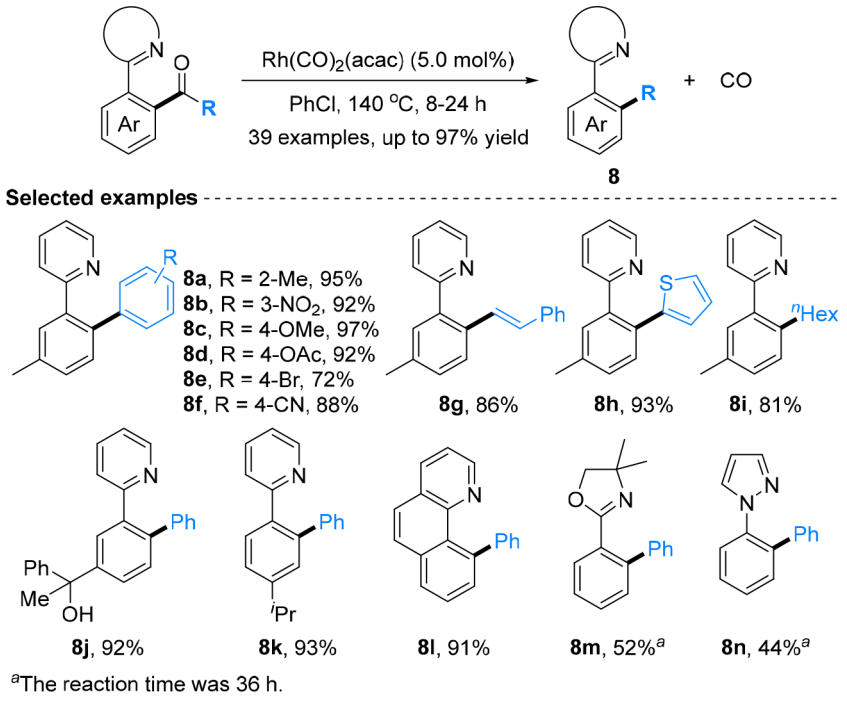
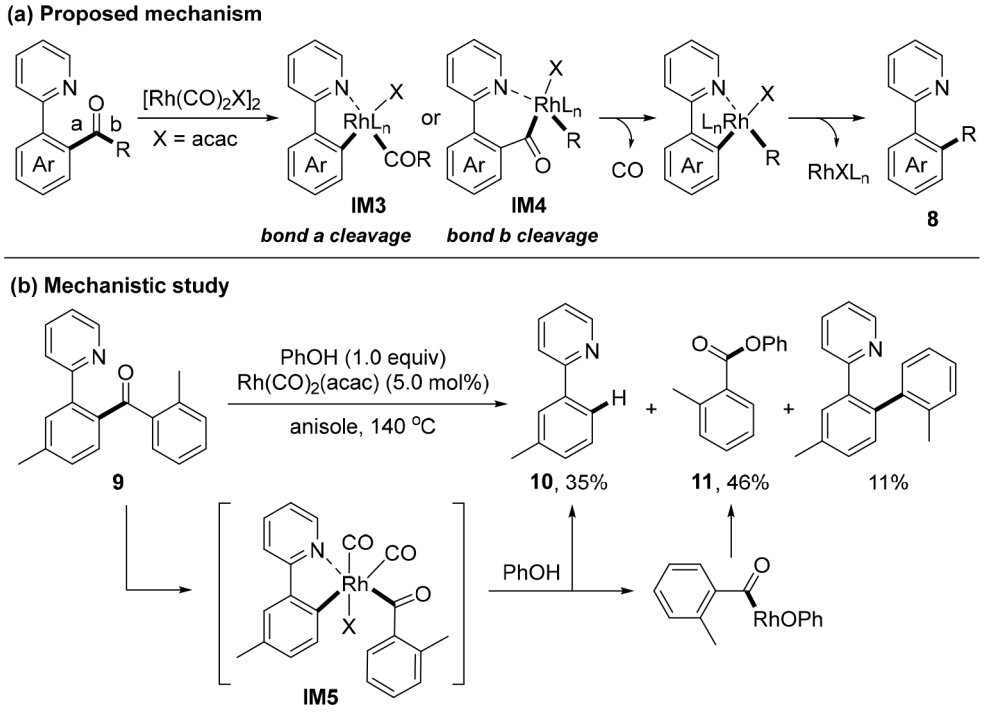


Figure 5. Rh-catalyzed decarbonylation of ketones.

Scheme 2. Proposed Mechanism for the Rh-Catalyzed Decarbonylation of Ketones



rhodacycle **IM2**. Decarbonylation and subsequent reductive elimination of **IM2** deliver final products and regenerate the Rh^{I} catalyst.

2.2. C−C Bond Activation of Linear Ketones

2.2.1. CO Extrusion of Aryl Ketones. Ketones are another important type of carbonyl compounds. The development of the decarbonylative transformation of ketones would expand their synthetic utilities, such as serving as a removable activating group or a novel carbon source. In comparison with the decarbonylation of aldehydes,[18] the decarbonylation of ketones is more challenging. Before our studies, successful examples mainly relied on strained ring systems.[19] For unstrained ketones, only one example of the Rh-catalyzed decarbonylation of diarylketones was reported by Brookhart, which suffered from high catalyst loading, limited substrate scope, and low product yields.[20]

Owing to the successful experience in C−H activation with a directing strategy,[21] we envisioned that the same strategy might be effective for the decarbonylation of unactivated ketones to

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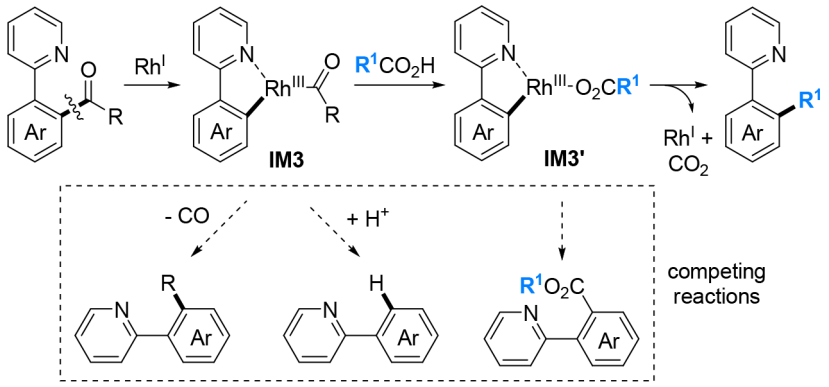
Scheme 3. Proposed Group Exchange Reaction between Ketones and Carboxylic Acids



prepare substituted arenes **8** (Figure 5). Considering the good performance of the pyridyl group, we attempted the pyridyl-directed decarbonylation of arylketones and found that the optimal conditions were 5.0 mol % $(CO)_2Rh(acac)$ as catalyst and chlorobenzene as solvent at 140 °C.[2] Under these conditions, biaryl ketones, aryl heteroaryl ketones, alkenyl aryl ketones, and alkyl aryl ketones were successfully engaged to afford the decarbonylation products in 72−97% yield. Biaryl ketones with *ortho* substituents, electron-donating groups, or electron-withdrawing groups all smoothly underwent the decarbonylation reaction (Figure 5, **8a**−**8f**). Notably, an alkyl ketone bearing a long-chain alkyl group was converted to the desired product **8i** without the formation of branched alkylarene byproducts, showing the complementary feature of the present protocol to traditional Friedel−Crafts reactions. Other nitrogen-containing groups such as pyrazolyl and oxazolyl groups were also applicable directing groups, albeit with lower efficacies (Figure 5, **8m** and **8n**).

A plausible mechanism is shown in Scheme 2a. The reaction originates from the chelation-assisted oxidative addition of Rh^I with a C(CO)−C bond (bond a or bond b) to afford five- or six-membered acylrhodium metalacyclic species **IM3** or **IM4**, respectively. The decarbonylation of either **IM3** or **IM4** followed by reductive elimination delivers the final products **8** and regenerates the Rh^I catalyst. To determine which bond (bond a or bond b) is cleaved in the catalytic cycle, phenol was added to the reaction system of ketone **9** to intercept the rhodacyclic species (Scheme 2b). Besides the desired decarbonylation product, 2-arylpyridine **10** and phenyl 2-toluoyate **11** resulting from the reaction of the five-membered rhodacycle **IM5** with phenol were formed in comparable yields. These results support the cleavage of bond a, although the cleavage of bond b could not be completely ruled out at this stage.

2.2.2. Group Transplant between Aryl Ketones and Carboxylic Acids. We speculated that a group exchange might take place between biaryl ketones and carboxylic acids if acylrhodium species **IM3** could undergo decarboxylative coupling with carboxylic acids (Scheme 3). Consequently, a novel group-transfer reaction could be developed to provide an unprecedented approach to substituted arenes from readily available starting materials. Undoubtedly, great challenges have to be overcome to prevent many competing processes, including the decarbonylation, protonation, and transfer carboxylation of aryl ketones (Scheme 3).

To prove our concept, pyridyl-assisted reactions of different aryl ketones with 4-methoxylbenzoic acid were tested.[3] The group exchange reaction did occur in the presence of 10 mol % $Rh(CO)_2(acac)$, although in all cases byproducts **14** from the intramolecular decarbonylation of ketones were obtained in variable yields (Figure 6a). Ketones with bulky aryl or alkyl groups gave better selectivity for intermolecular arylation over intramolecular decarbonylation, and the best result was obtained with isobutyl ketone **12e** (85% yield, >20/1 ratio). Further optimizations showed that the best conditions were 5.0 mol % $Rh(CO)_2(acac)$ as a catalyst and 2.0 mL of chlorobenzene as a solvent at 140 °C for 24 h (Figure 6b). Under these conditions, a variety of aryl, heteroaryl, alkenyl, and alkyl acids successfully participated in the reaction to afford the desired products **13** in 48−90% yield (Figure 6b, **13a**−**13i**). However, electron-deficient benzoic acids gave lower yields than electron-rich ones due to the formation of more protonation byproducts (Figure 6b, **13b** vs **13f**). With respect to ketones, 5-substituted aryl ketones delivered only monoarylated products no matter whether the substituents were electron-donating or electron-withdrawing (Figure 6b, **13j** and **13k**). In contrast, 5,6-unsubstituted aryl ketones afforded a small quantity of diarylated products along with the desired monoarylated products (Figure 6b, **13m**), suggesting that pyridyl-directed C−H arylation was involved due to the release of steric hindrance. Besides pyridyl, pyrazolyl and oxazolyl groups also directed the reaction, although the desired monoarylated products were obtained in low yields owing to the incomplete conversion of starting materials (Figure 6b, **13n** and **13o**). Interestingly, diarylated products were not observed in these cases.

GC-MS analysis of the reaction of ^{13}C-labeled benzoic acid with ketone **12e** showed that ^{13}CO rather than $^{13}CO_2$ was released (Scheme 4a). Treating the remaining reaction mixture with 4-phenylphenol resulted in ^{13}C-unlabeled 2-methylbutanoate **15** and ^{13}C-labeled benzoate **16**. These results suggested that CO came from carboxylic acid and the carbonyl moiety of ketone was converted to carboxylic acid. When sterically demanding *o*-toluic acid was employed as the coupling partner to study the steric effect on the reaction, the reaction showed very low conversion and produced several products, including the desired arylation product **17**, exchanged ketone **18**, protonation product **19**, and decarbonylation product **20**, all in trace amounts (Scheme 4b). The observation of ketone **18** implied the presence of acylrhodium(III) species in the catalytic cycle, which may undergo decarbonylation to furnish **17**. In addition, a trace amount of mixed anhydride ($PhCO_2CO^iPr$) was detected by HRMS analysis of the reaction mixture, hinting at the possibility of anhydride as an intermediate. Therefore, crossover experiments related to anhydride were then investigated (Scheme 4c). Both ketone and arylpyridine coupled

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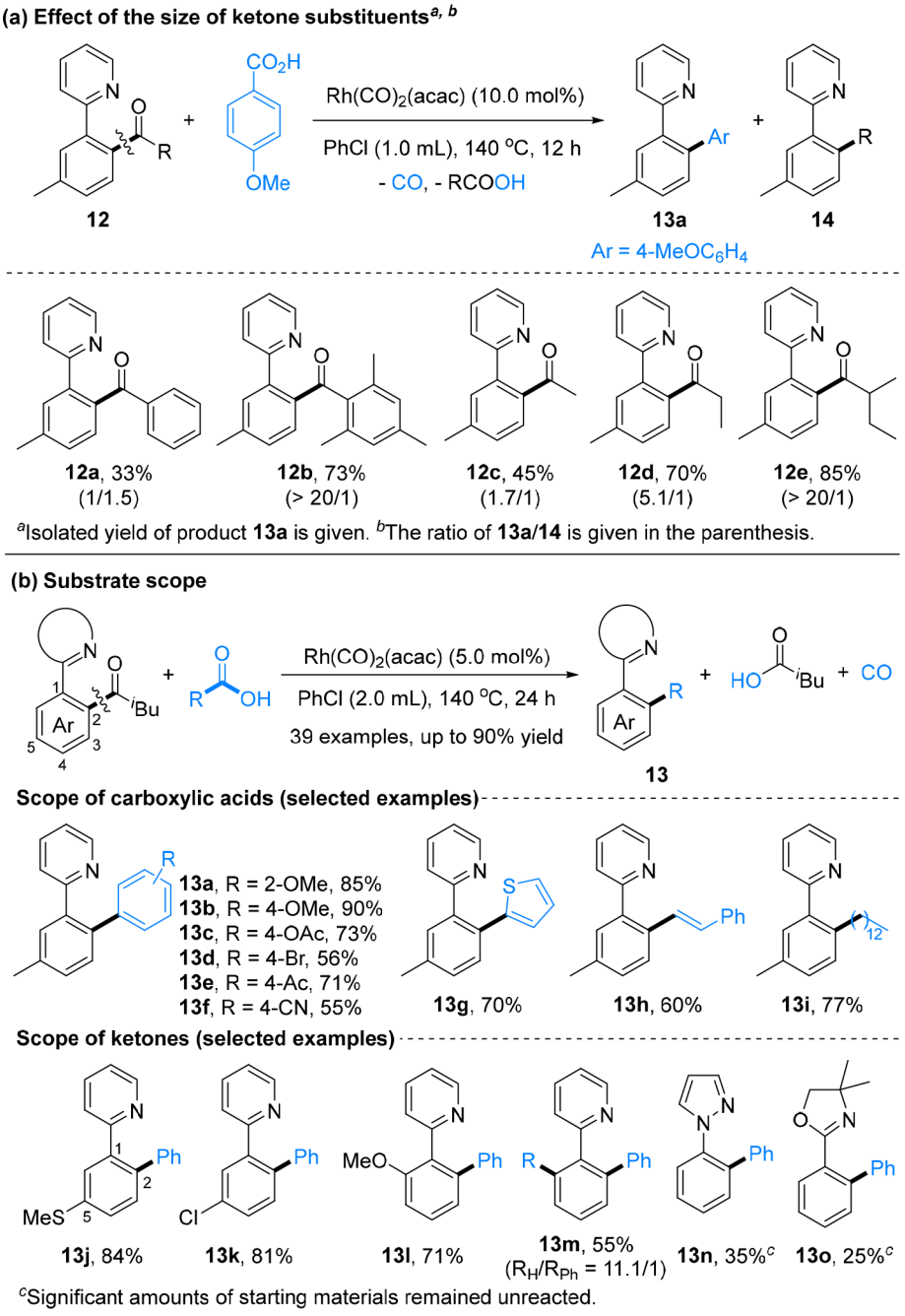

Figure 6. Rh-catalyzed group exchange between ketones and carboxylic acids.

with carboxylic acids, although ketone delivered the desired product in a much higher yield than arylpyridine. In contrast, the competition reaction between two arenes afforded the corresponding products in comparable yields. These results suggested that both C−C activation/arylation and C−C cleavage/protonation/C−H arylation pathways were involved in the catalytic cycle, although the former one was preferred.

Therefore, a plausible mechanism is proposed in Scheme 5, which is further supported by density functional theory (DFT) calculations. First, the rapid ligand exchange of benzoic acid with $Rh(CO)_2(acac)$ affords $Rh(CO)_2(CO_2Ph)$ **IM6**, which then coordinates with a pyridyl ketone substrate to deliver intermediate **IM7**. **IM7** undergoes pyridyl-assisted C−C bond activation via oxidative addition to form **IM8**, which overcomes an activation energy of 10.9 kcal/mol. C−O reductive elimination from **IM8** with an energy barrier of 12.7 kcal/mol delivers anhydride-rhodium complex **IM9** (3.5 kcal/mol), which is transformed to the more stable **IM10** (0.6 kcal/mol) through ligand slipping. Oxidative addition of the less hindered acyl C−O bond to the Rh center in **IM10** forms **IM11**, which requires a moderate energy barrier of 8.7 kcal/mol (Scheme 5, path a). The decarbonylation of **IM11** leads to unstable rhodium(III) species **IM12** (10.4 kcal/mol) with a 21.9 kcal/mol energy barrier. Then one CO molecule is released from the rhodium center of **IM12** to form the more stable intermediate **IM13** (4.8 kcal/mol). C−C reductive elimination from **IM13** with an energy barrier of 18.6 kcal/mol followed by ligand exchange with ketone and benzoic acid produces the desired product **13** and regenerates **IM7**. These calculations reveal that decarbonylation is involved in the turnover-limiting step (**IM11**

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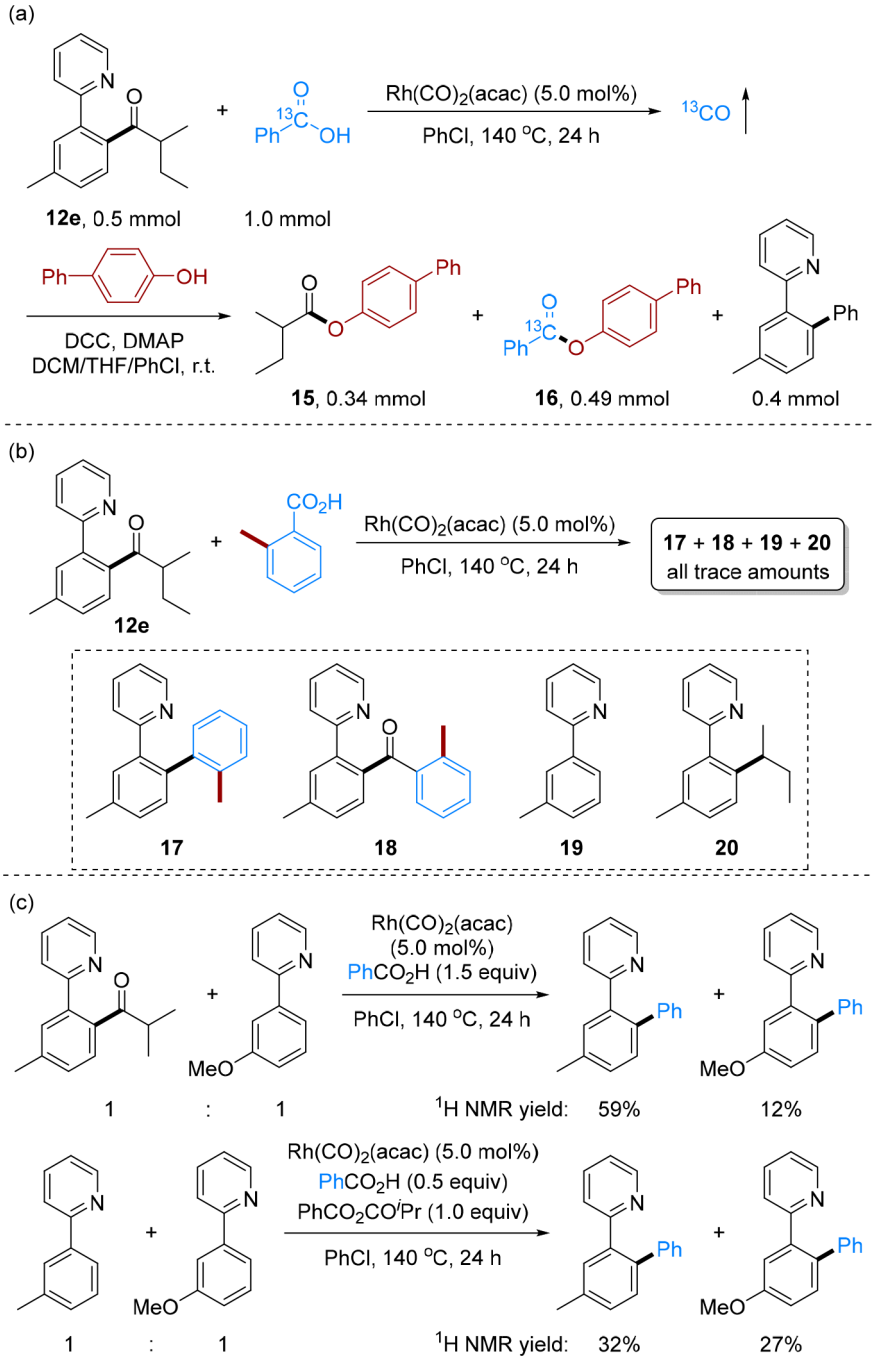
Scheme 4. Mechanistic Studies on Decarbonylative Coupling of Carboxylic Acids with Ketones



→ **IM12**), which is consistent with $^{12}C/^{13}C$ kinetic isotopic studies based on the Singleton method. Complexes **IM6**, **IM7**, and **IM13** were observed by ^{1}H NMR or *in situ* IR analysis, solidifying the proposed mechanism. On the other hand, **IM9** and **IM10** may be protonated by carboxylic acids to produce arylpyridine and anhydride, which then enter the catalytic cycle through Rh-catalyzed C−H activation (path b). When electron-deficient benzoic acids with strong acidity were employed, the protonation step became important. As a result, more protonation byproducts were formed.

2.3. C−C Activation of Secondary Alcohols

β-Carbon elimination of alcohols is different from oxidative addition in the following aspects: (1) *β*-C elimination is an intramolecular process while oxidative addition is an intermolecular one, (2) *β*-C elimination produces one weak M−C bond (20−30 kcal/mol) while oxidative addition produces two, and (3) the formation of stable carbonyl compounds via *β*-C elimination could offer additional driving force for C−C activation. Therefore, the C−C functionalization of alcohols via *β*-C elimination has a chemistry distinct from that of ketones via oxidative addition. Although transition-metal-catalyzed C−C cleavage of tertiary alcohols has been well studied,[6c,9] challenges remain when applying to secondary alcohols due to competing *β*-H elimination (Scheme 6a). We conceived that C−C activation of secondary alcohols may be achieved with the assistance of a chelation group by the formation of

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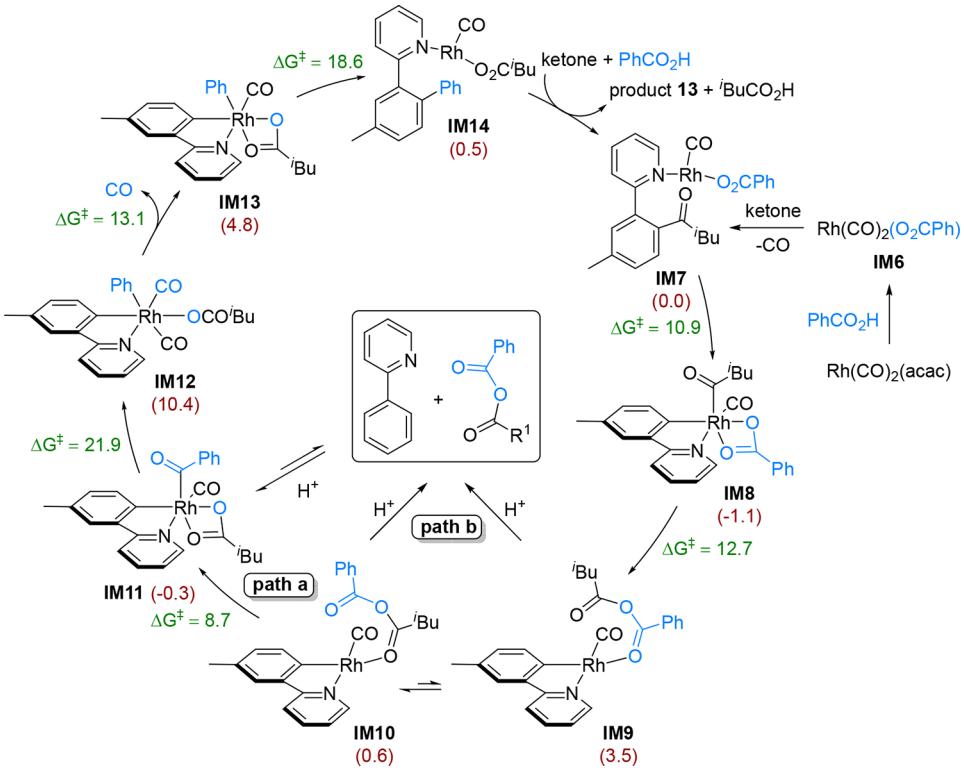
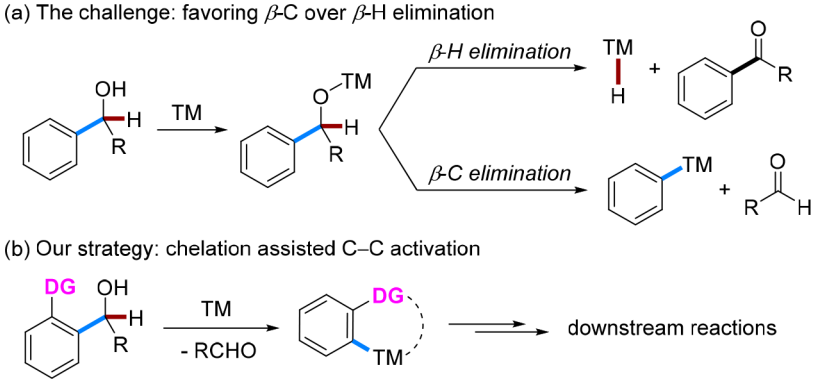
Scheme 5. Plausible Mechanism for the Decarbonylative Coupling of Carboxylic Acids with Ketones[a]



[a]DFT calculations were performed with the Gaussian 09 program using the M06 method. Energies and energy barriers are shown in kcal/mol.

Scheme 6. Our Design for C−C Bond Activation of Secondary Alcohols



thermodynamically stable metallacyclic intermediates and aldehydes (Scheme 6b).

2.3.1. Alkenylation. Pyridyl-directed alkenylation of secondary alcohols **21** with alkenes was first investigated (Figure 7).[1] It was found that the best result was obtained by using α-phenyl alcohol **21a** (1.0 equiv) as the substrate in the presence of 2.5 mol % $[Cp^*RhCl_2]_2$ and 1.2 equiv of Ag_2CO_3 in EtOH at 70 °C (Figure 7a). The reaction could be scaled up to 1.0 mmol without any loss of efficiency. Besides secondary aryl alcohol, secondary alkyl alcohols (**21b** and **21c**) and tertiary alcohol **21d** also participated in the reaction, although affording the products in lower yields. However, the primary alcohol **21e** did not deliver any desired product. The alcohol motif at the nonchelating position remained intact (Figure 7b, **22a**), indicating that the chelation group was critical to the reaction. 4-Substituted alcohols afforded only monoalkenylated products (Figure 7b, **22b** and **22c**), while 4-unsubstituted alcohols delivered monoalkenylated products along with a small amount of dialkenylated ones (Figure 7b, **22d**−**22f**), suggesting that the steric demand of the 4-substituent significantly hindered the second C−H alkenylation. With respect to alkenes, alkylalkenes and arylalkenes with a variety of functional groups such as acetyl, cyano, halogen, and methoxy groups were all suitable partners for furnishing alkenylarenes **22** in up to 94% yield. Notably, the reaction of alkyl alkenes delivered alkenylation products that have undergone double bond migration (e.g., in product **22l** the double bond is unconjugated to the phenyl ring) (Figure 7b, **22l**).

The competitive experiment between alcohol **21a** and 2-phenylpyridine **23** showed that arylalkene **24** resulting from the alkenylation of **21a** was formed as the major product. Other products, including the protonation product of **21a** and the mono- and dialkenylation products of **23**, were afforded in low yields (Scheme 7a). These results indicated that C−C activation

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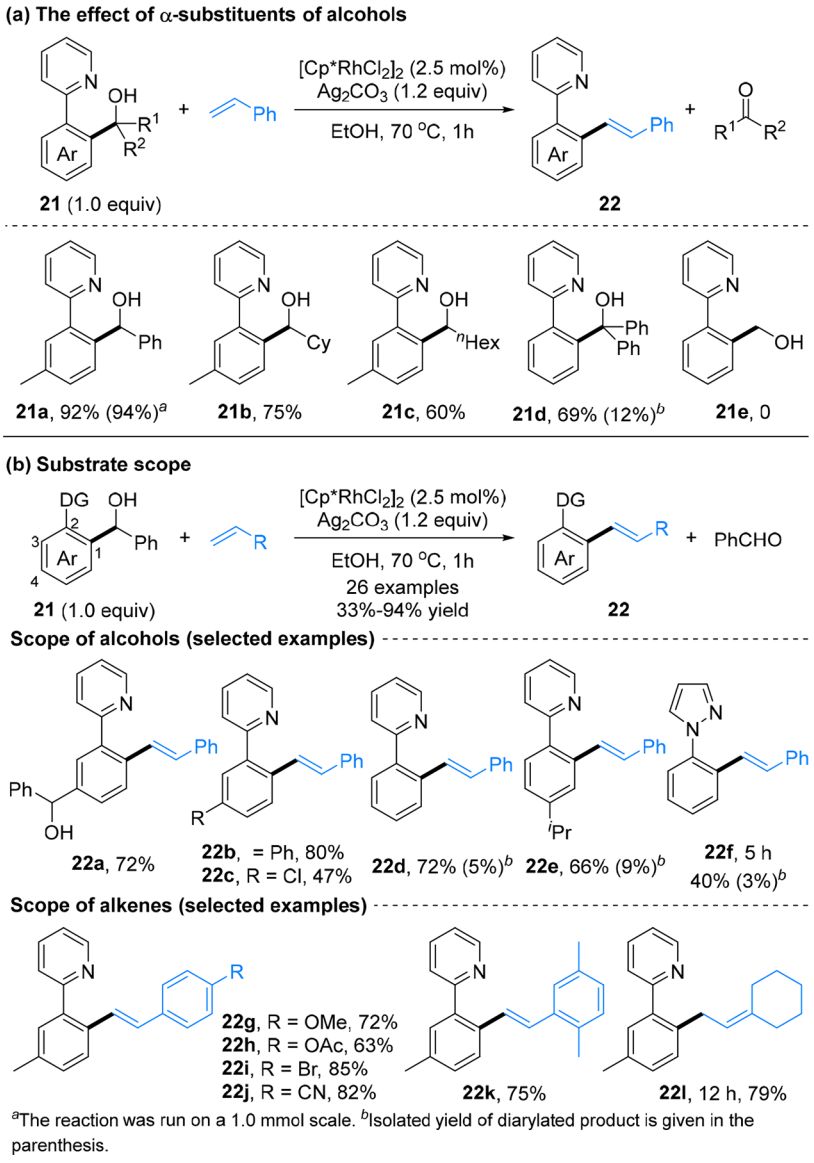

Figure 7. Substrate scope of the Rh-catalyzed alkenylation of secondary alcohols.

of alcohols was the predominant pathway, although C−H activation also existed in the catalytic cycle. Consequently, the following mechanism is proposed (Scheme 7b): substitution of alcohols with Rh(III) followed by β-C elimination delivers **IM15**, which then undergoes migratory insertion with alkenes and β-H elimination to afford the final products and Rh(I) species (path a, major pathway). On the other hand, intermediate **IM15** could be protonated to afford arylpyridine, which is then involved in the catalytic cycle via C−H activation (path b, minor pathway). Oxidation of Rh(I) by Ag_2CO_3 regenerates the catalytically active Rh(III) complex.

2.3.2. Arylation with Arylsilanes. It was proposed that **IM15** could undergo transmetalation with organometallic reagents such as arylsilanes to afford biaryls **25** after reductive elimination (Figure 8a).[22] Biaryls were indeed obtained in 26−96% yield by using 5.0 mol % cationic $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as the catalyst and 4.0 equiv of AgF as an oxidant in a mixed solvent composed of 1:1 ^{t}BuOH/THF at 90 °C for 16 h. The reaction showed wide substrate scope and high functional group tolerance. Aryl and heteroarylsilanes were suitable coupling partners (Figure 8a, **25a**−**25d**). The *ortho* group on arylsilanes did not block the reaction (Figure 8a, **25a**). Alcohols bearing a substituent at the *ortho* or *meta* position relative to the pyridyl group afforded monoarylated products only (Figure 8a, **25e** and **25f**). However, alcohols having a *para* substituent or no substituent on the aryl ring delivered a small quantity of diarylated products in addition to the monoarylated ones (Figure 8a, **25g** and **25h**). The competitive experiment between alcohol **21a** and arylpyridine **26** suggested that the arylation reaction proceeded through two distinct pathways involving direct C−C arylation and C−C protonation/C−H arylation, although C−C arylation was more favorable (Figure 8b).

2.3.3. Group Exchange with Imines and Aldehydes. Traditional methods for the conversion of secondary alcohols to amines usually require multistep reactions (Scheme 8a). Undoubtedly, the development of the one-step transformation of alcohols to amines would significantly improve the synthetic efficiency. In recent years, several examples of the metal-catalyzed conversion of alcohols to amines via the hydrogen borrowing strategy were reported.[23] We envisioned that the nucleophilic addition of arylrhodium species **IM15** with imines may provide an alternative approach to amines (Scheme 8b). In

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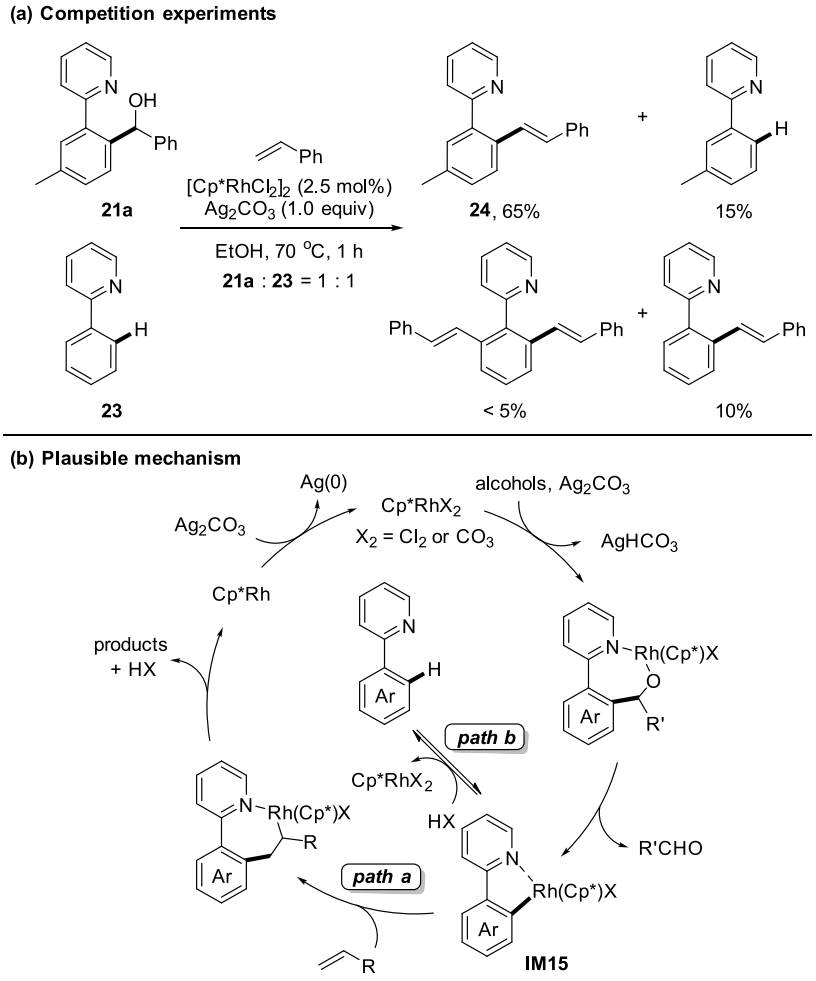
Scheme 7. Mechanistic Studies for Alkenylation of Secondary Alcohols



comparison with the insertion of **IM15** with alkenes, the reaction with polar double bonds is more challenging since two coordination modes (σ and π) with the metal center are present to complicate the reaction. In addition, aldehyde byproducts may compete with imines to participate in the reaction.

After screening various conditions, the reaction was achieved by using pyridyl as the directing group, 5.0 mol % $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as the catalyst, and ^{t}BuOH as the solvent at 90 °C (Figure 9a).[24] Under the optimal conditions, a variety of secondary benzylic alcohols could undergo a substitution reaction with imines to afford the desired products **28** in 24−88% yield. Similar to the reactions of alcohols with alkenes and arylsilanes, tertiary alcohol was also applicable (Figure 9a, **27e**), while primary alcohol could not deliver any desired product (not shown here). However, the reaction with imines showed some distinct characteristics, including the following: (1) 4-unsubstituted alcohols did not undergo diamination reactions, (2) alkylaryl alcohol showed poor reactivity (Figure 9a, **27d**), and (3) the pyrazolyl group did not direct the reaction. With respect to imines, the reaction of aryl imines bearing electron-withdrawing groups showed higher reactivity than those with electron-donating groups, probably due to the higher electrophilicity of electron-deficient imines (Figure 9b, **28a**−**28e**). A variety of electron-withdrawing groups, such as halogen, nitro, and trifluoromethyl groups, were well tolerated. The *ortho* substituent of aryl imines diminished the efficiency (Figure 9b, **28g**). The reactions of α-phenyl alcohol **27f** with electron-deficient aldehydes were also realized (Figure 9b). In these cases, the competing reaction of alcohol with *in situ*-formed benzaldehyde was largely inhibited due to its weaker electrophilicity (Figure 9b, **28h**−**28j**). Furthermore, the reaction of allylic alcohol **29** with imines was achieved at a higher temperature of 110 °C, which represented the first example of the metal-catalyzed C(alkenyl)−C(alkyl) cleavage of alcohols (Figure 9c).

Mechanistic studies showed that Rh^{III} complex **30** catalyzed the reaction, suggesting that the five-membered rhodacycle may be a catalytically active species (Scheme 9a). To obtain some information on the intermediates, the reaction of alcohol with imine was studied by *in situ* NMR in a dilute solution of **27f** in d_8-toluene (Scheme 9b). It was found that **27f** was quickly consumed in the initial stage with the concomitant formation of 2-phenylpyridine and benzaldehyde. After 1.5 h, the yield of 2-phenylpyridine reached the highest value of 92% and the desired product was formed in 10% yield. With the extension of time, 2-phenylpyridine was gradually consumed, which was accompanied by the formation of amine. These results clearly showed that 2-phenylpyridine was an important intermediate. The competitive reaction between alcohol **27a** and 2-phenylpyridine showed that products resulting from C−C and C−H activations were obtained in comparable yields (Scheme 9c). These observations suggested that the sequence involving C−C activation → protonation → C−H activation → nucleophilic addition was the main reaction pathway, although C−C

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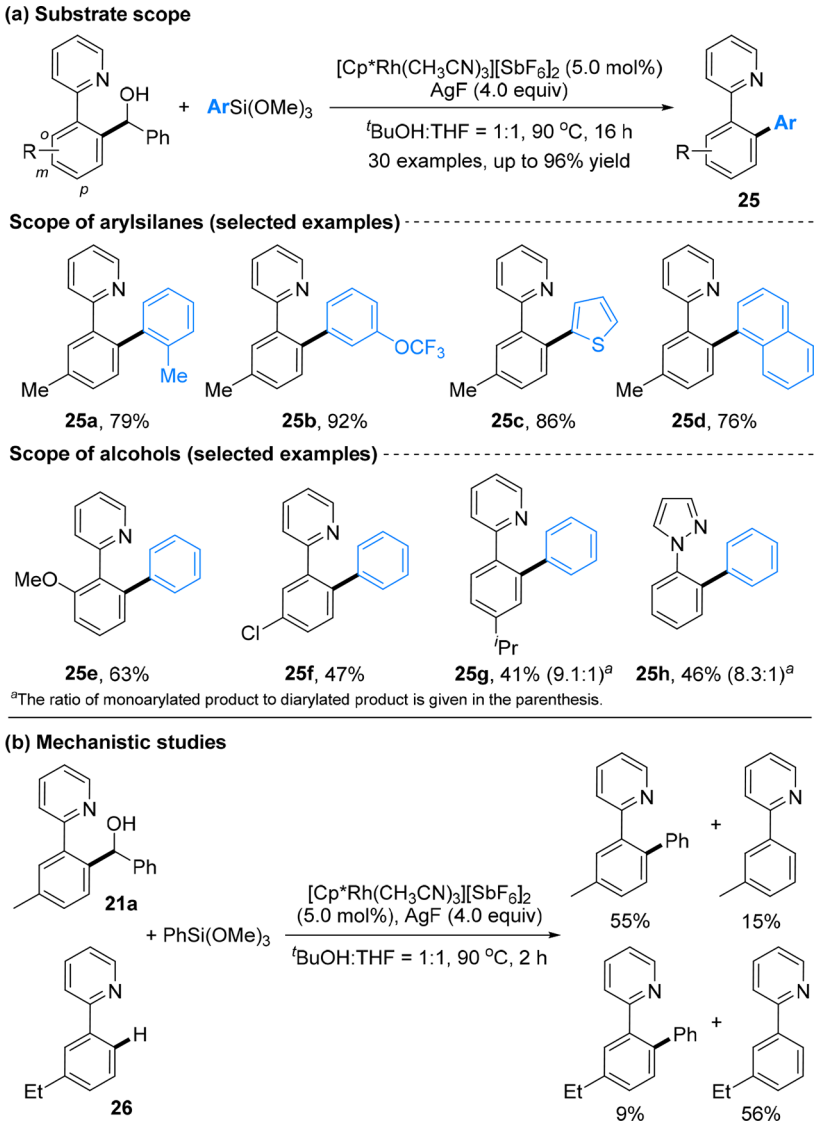
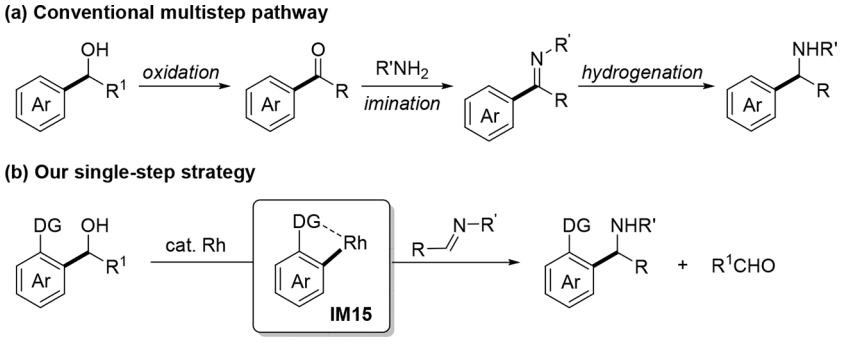


Figure 8. Rh-catalyzed arylation of secondary alcohols.

Scheme 8. Conversion of Secondary Alcohols to Amines



cleavage/nucleophilic addition could not be excluded. Very recently, a more atom-economical Rh-catalyzed substitution of secondary benzyl alcohols with sulfonamides was reported. The reaction proceeded through a pathway similar to our methodology except that imines were generated *in situ* from amines and *in situ*-formed aldehydes.[25]

2.3.4. Reductive C−C Bond Cleavage. Besides C−C forming reactions, **IM15** was also engaged in C−H formation by using clean H_2 as a reductant in the presence of 5.0 mol % $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ at 80 °C for 36 h.[26] As a result, the reductive cleavage of the unstrained C−C bond of benzyl alcohols was achieved for the first time. Notably, arenes **31** and primary alcohols **32** were often obtained in quite different yields (Figure 10).[27] Both pyrazolyl and pyridyl groups were effective directing groups. Diaryl and alkylaryl methanols with a variety of

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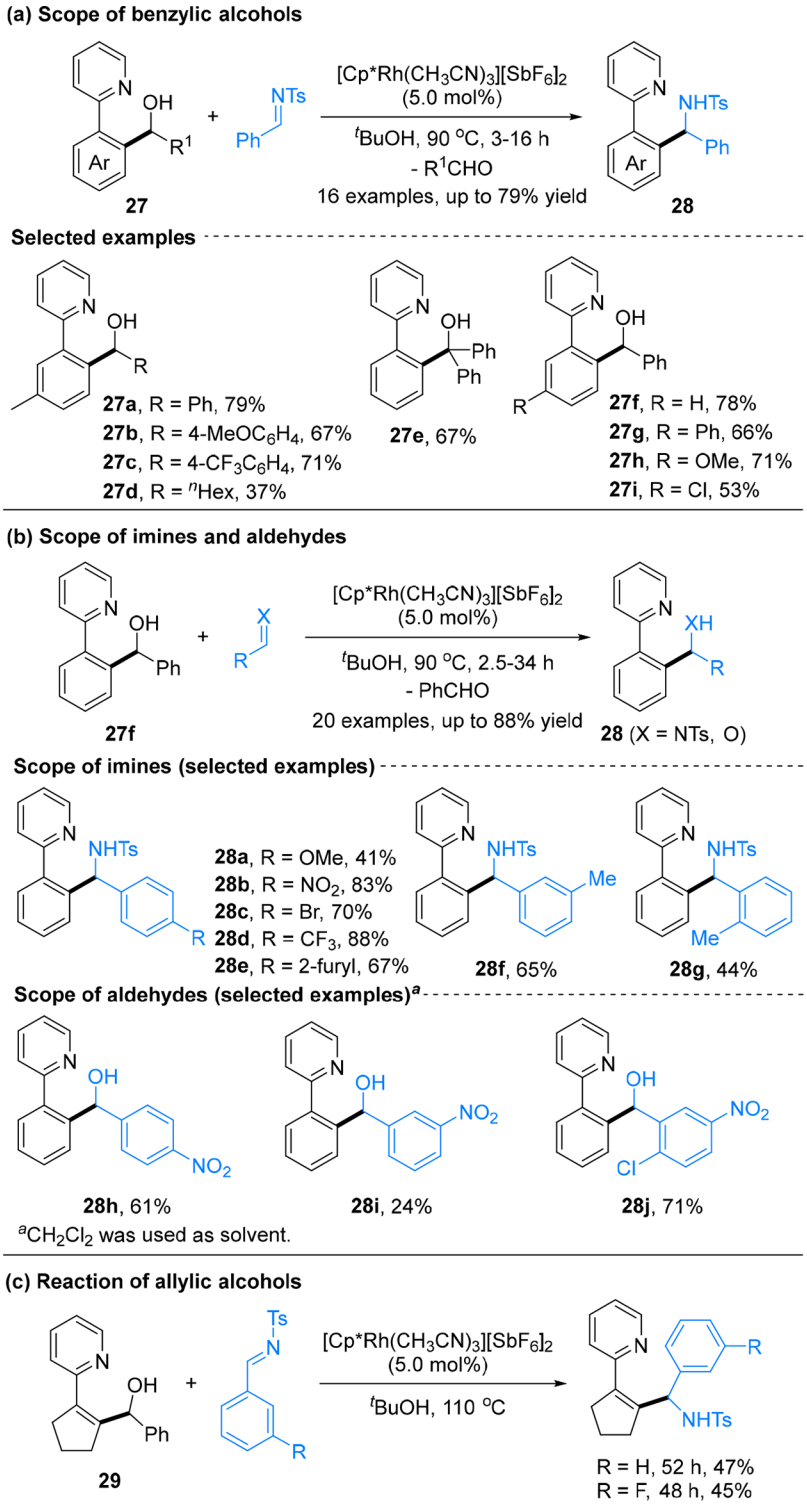

Figure 9. Rh-catalyzed reactions of secondary alcohols with imines/aldehydes.

functional groups, such as bromo, chloro, and ester, were all suitable substrates.

The reaction of **33** with D_2 in ethanol and with H_2 in d_6-EtOH in the presence of 5.0 mol % $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ at 80 °C both delivered *ortho*-deuterated phenylpyridine and α-deuterated alcohol, although deuteration ratios were different, illustrating that both H_2 and ethanol served as hydride sources (Scheme 10a). ^{1}H NMR analysis of the crude reaction mixture obtained from alcohol **33** under the above-mentioned catalytic conditions at different time intervals showed that 2-phenylpyridine, 1-naphthaldehyde, and 1-naphthylmethanol were generated during the reaction process, although 1-naphthylmethanol was formed at a lower rate than 2-phenylpyridine (Scheme 10b). These results suggested that the Rh^{III} complex did not catalyze C−C cleavage and reduction of aldehyde in the same catalytic cycle because it would produce arene and alcohol at the same rate. Besides $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$, Rh^{III} complex **30** also catalyzed the reductive cleavage of **33**. The

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Scheme 9. Mechanistic Studies on the Reaction of Secondary Alcohols with Imines

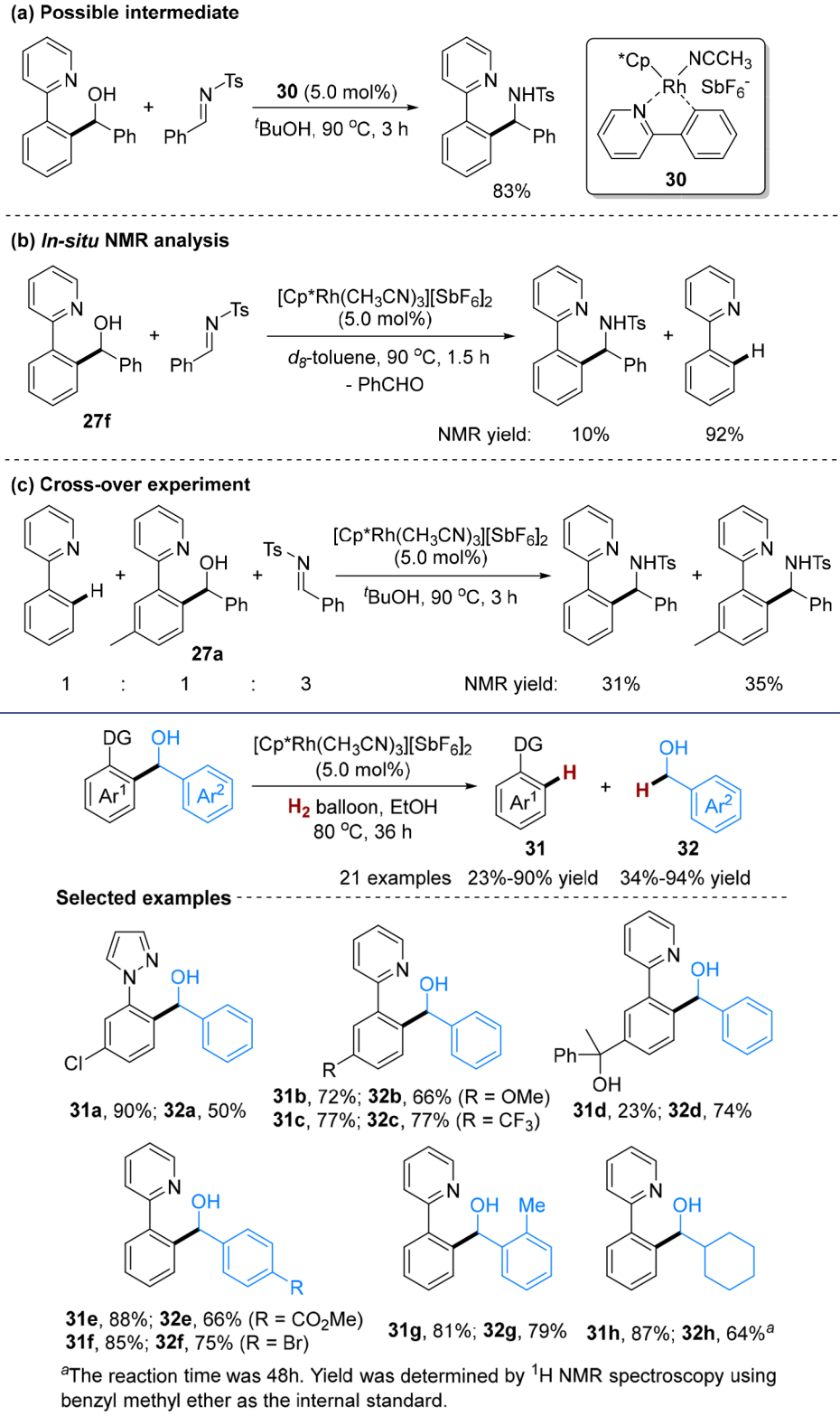

Figure 10. Reductive cleavage of secondary alcohols.

stoichiometric reaction of **30** with H_2 in the absence of **33** produced 2-phenylpyridine with the observation of the signal for Rh−H species in the ^{1}H NMR spectrum. Based on these results, a tentative mechanism is proposed in Scheme 10c. The substitution of the Rh^{III} complex with a secondary alcohol followed by chelation-assisted β-carbon elimination delivers aldehyde and the five-membered rhodacycle **IM16**. Hydrogenation of **IM16** affords arene products **31** and rhodium hydride species **IM17**, which then reduces *in situ*-generated aldehydes to alcohols (path a). Alternatively, **IM16** could be

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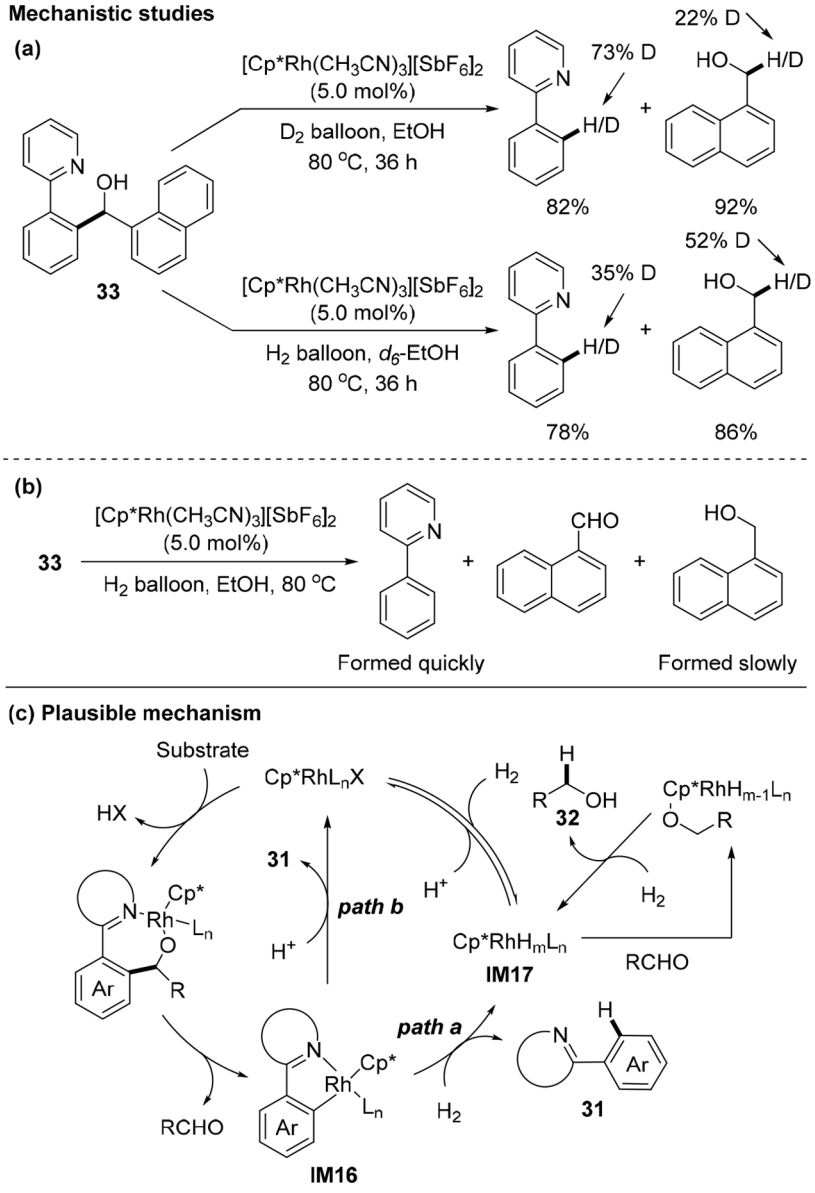
Scheme 10. Mechanistic Studies for the Reductive Cleavage of Secondary Alcohols



protonated by ethanol to deliver **31** and a Rh^{III} catalyst, which is engaged in the next catalytic cycle or reduced to rhodium hydride to further reduce aldehyde (path b). This mechanism could rationalize the discrepancy between the yields of arenes and alcohols since they are generated through the hydrogenation of different intermediates, namely, complex **IM16** and aldehyde, respectively.

3. C−C BOND ACTIVATION OF STRAINED-RING COMPOUNDS

To overcome the difficulty associated with C−C bond activation, employing small-membered rings as substrates has proven to be effective, being significantly driven by the release of ring strain. However, the reaction of highly strained benzocyclobutene derivatives that would offer the opportunity to synthesize structurally diverse aryl compounds has been underrepresented in the literature. Stimulated by the pioneering work in this field,[6e,28] we turned our attention to study the reactivity of benzocyclobutenones and benzocyclobutenols.

3.1. C−C Bond Activation of Benzocyclobutenones

In recent years, Rh-catalyzed intramolecular reactions of benzocyclobutenones with 2π units via C−C bond activation have been well developed by Dong and co-workers with a "cut and sew" strategy.[28,29] More challenging intermolecular transformations of benzocyclobutenones were scarce, and successful examples usually involved the cleavage of the $C(sp^2)$−C(CO) bond due to the formation of thermodynamically more stable arylmetal species.[30] Inspired by the theoretical studies of Li[31] and Huang,[32] we assumed that introducing a substituent at the C3 position of benzocyclobutenones may block the adjacent $C(sp^2)$−C(CO) bond and facilitate the cleavage of the $C(sp^3)$−C(CO) bond. As a proof of concept, the intermolecular reaction of benzocyclobutenones with alkynes was investigated.[4] As shown in Figure 11, annulation product **34** resulting from the cleavage of $C(sp^3)$−C(CO) bonds was obtained in good to excellent yield by using 5−20 mol % $Ni(cod)_2$ as a catalyst and 5−20 mol % $(p\text{-}MeOC_6H_4)_3P$ as a ligand in toluene at 80−120 °C for 16 h. Only a trace amount of products resulting from $C(sp^2)$−C(CO) bond cleavage was produced under these

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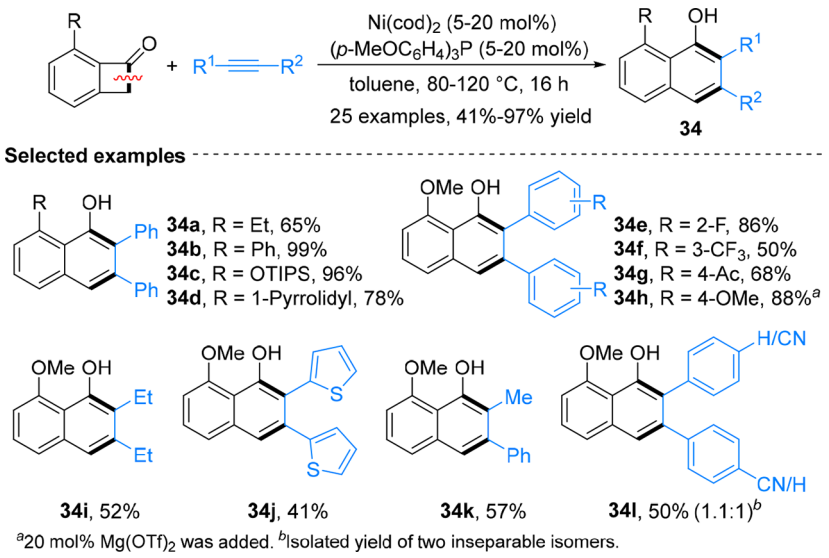
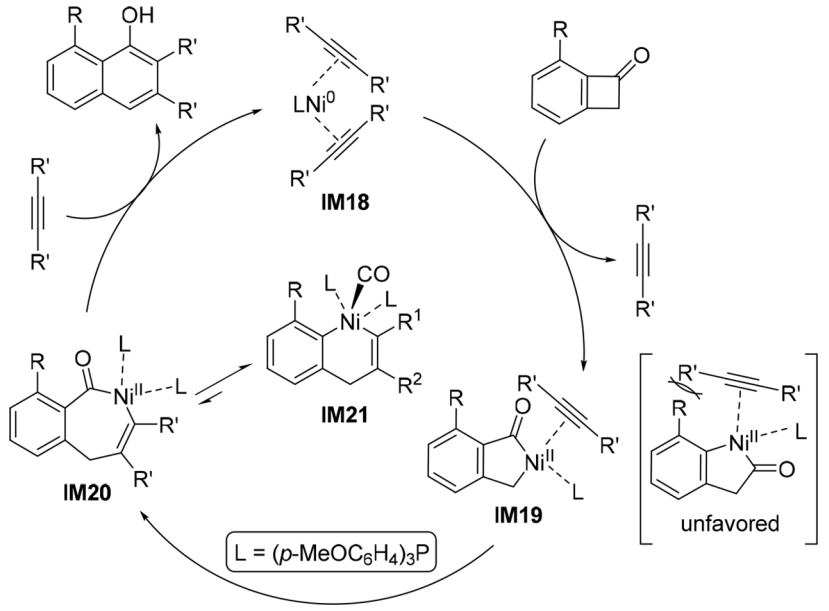


Figure 11. Ni-catalyzed annulation of benzocyclobutenones with alkynes.

Scheme 11. Proposed Mechanism for Ni-Catalyzed Annulation of Benzocyclobutenones with Alkynes



conditions. Benzocyclobutenones with alkoxyl, amino, alkyl, and phenyl groups at the C3 position were all suitable substrates (Figure 11, **34a**−**34d**). Symmetrical dialkyl and di(hetero)aryl alkynes successfully participated in the reaction, although 20 mol % $Mg(OTf)_2$ was necessary for the reaction of electron-rich diaryl alkynes (Figure 11, **34h**). $Mg(OTf)_2$ may serve as a Lewis acid to coordinate with alkynes or benzocyclobutenones to increase the reactivity. The reaction of alkyl aryl alkynes showed excellent regioselectivity, affording products with the alkyl group next to the hydroxyl group (Figure 11, **34k**). However, unsymmetrical diaryl alkynes delivered two regioisomers in comparable yields (Figure 11, **34l**). Notably, the blocking alkoxyl group could be easily removed after the transformation by $Co(acac)_2$ and $LiAlH_4$ to afford 1-naphthol derivatives.

Control experiments showed that the C3 substituent was critical to control the regioselectivity, as C3-unsubstituted benzocyclobutenone delivered the product from $C(sp^2)$−C(CO) bond cleavage. A tentative mechanism is proposed in Scheme 11. Ni(0) coordinates with alkynes to afford intermediate **IM18**, which undergoes oxidative addition with the $C(sp^3)$−C(CO) bond of benzocyclobutenones to produce **IM19**. Migratory insertion of **IM19** with alkynes delivers seven-membered nickelacyclic intermediate **IM20**, which is in equilibrium with thermodynamically more stable six-membered nickelacycle **IM21**. C−C reductive elimination from **IM20** furnishes the final products and reproduces Ni(0) species. The formation of intermediates **IM18**−**IM21** was supported by HRMS and ReactIR studies.

3.2. C−C Bond Activation of Benzocyclobutenols

As discussed in Figure 11, the intermolecular reaction of benzocyclobutenones with alkynes suffered from poor regioselectivity when unsymmetrical diaryl alkynes were employed. It was envisioned that the regioselectivity issue could be addressed through a two-step protocol involving a regiodefined intramolecular transformation and subsequent removal of the tethering group. Then we first studied the transition-metal-

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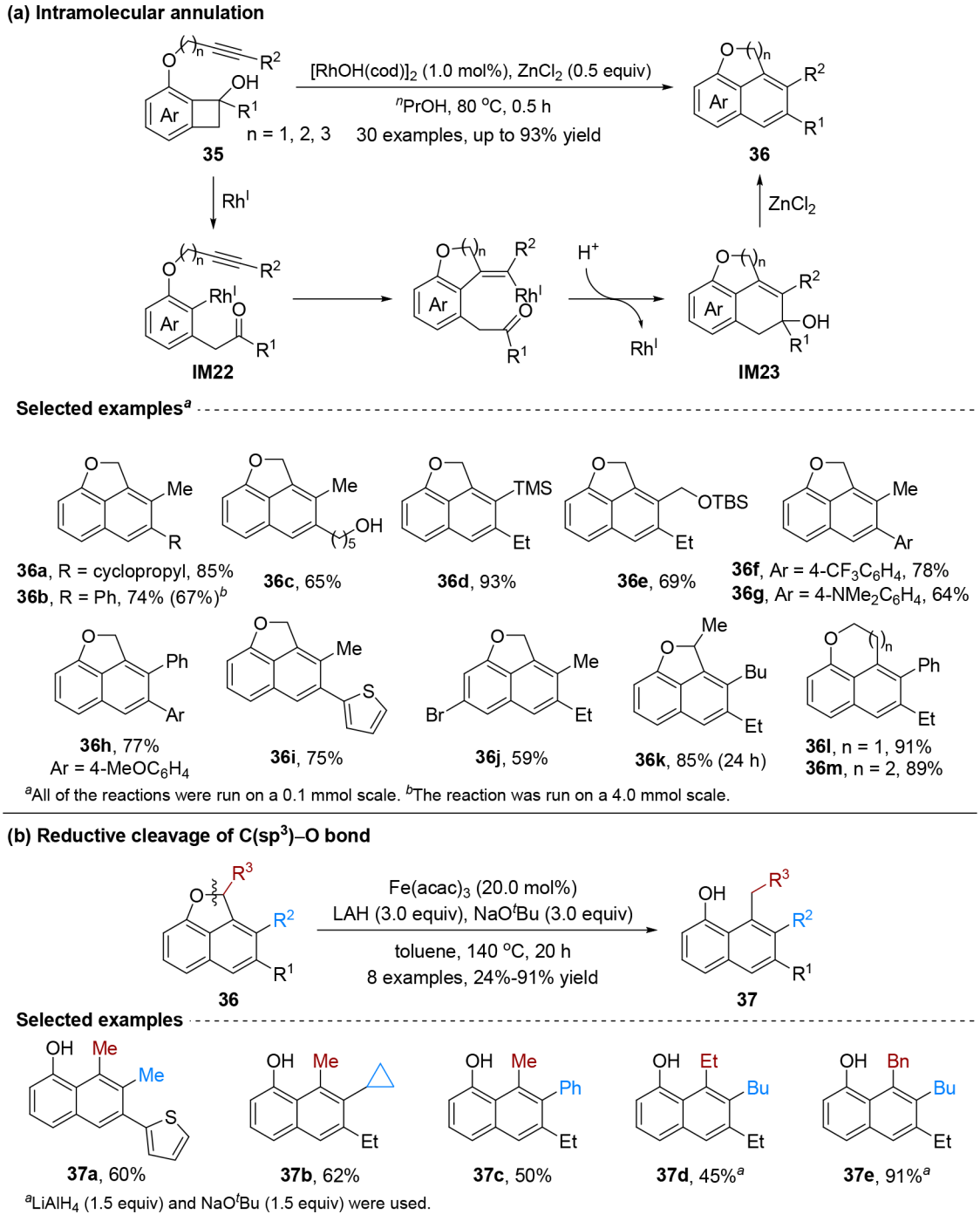

Figure 12. Rh-catalyzed annulation of benzocyclobutenols with alkynes.

catalyzed intramolecular transformation of *O*-bearing alkyne-tethered benzocyclobutenols **35**. The reaction was realized by using 1.0 mol % $[Rh(OH)(cod)]_2$ as a catalyst, 0.5 equiv of $ZnCl_2$ as a Lewis acid, and ^{n}PrOH as a solvent at 80 °C (Figure 12a).[33] Mechanistically, the reaction proceeds through β-carbon elimination of rhodium alcoholates **IM22** resulting from the substitution of benzocyclobutenols **35** with a rhodium catalyst. Subsequent intramolecular migratory insertion of alkenes into Rh−C bonds, nucleophilic addition, and protonation deliver alcohol intermediates **IM23**. The dehydration of **IM23** in the presence of $ZnCl_2$ produces final products **36**. Under the above-mentioned catalytic conditions, annulated naphthalenes **36** bearing dialkyl, diaryl, and alkyl aryl groups were synthesized in a regiocontrolled manner. A variety of functional groups, including alkenyl, alkoxyl, amino, halogen, siloxyl, silyl, trifluoromethyl, and free hydroxyl groups, were all compatible. In most cases, the annulation reactions could go to completion within 0.5 h to afford the desired products in >50% isolated yield. Benzocyclobutenols with a substituent at the propargylic position were also suitable substrates, although a longer reaction time was required (Figure 12a, **36k**). The reaction could be scaled up to a 4.0 mmol scale (Figure 12a, **36b**, 67% yield). Furthermore, the C(sp^3)−O bond of 2*H*-naphtho[1,8-*bc*]furans **36** was selectively cleaved by iron catalysis to afford 1-naphthol derivatives **37** (Figure 12b). Thus, a highly regioselective

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intermolecular annulation of 2-hydroxybenzocyclobutenols with alkynes was achieved through a "two-step" protocol.

4. CONCLUSIONS AND OUTLOOK

We commenced our studies on metal-catalyzed C−C bond activation from an unexpected Ni-catalyzed cross coupling of aryl nitriles with aryl boronic esters. Since then, a series of C−C forming reactions via the activation of different types of C−C bonds were realized, including the decarbonylative coupling of carboxylic acids with C−H bonds of (hetero)arenes and with C−C bonds of ketones, the decarbonylation of ketones, the coupling of secondary alcohols with alkenes, aryl silanes, and imines, and the ring-opening/ring-forming reactions of benzocyclobutene-derived alcohols and ketones with alkynes. Different strategies such as a directing strategy and a blocking strategy in combination with the development of novel catalytic systems were employed to control the reactivity and the chemo- and regioselectivity of C−C bonds. In-depth investigations of these transformations revealed some detailed mechanisms.

Despite notable progress, the reactions still suffer from many limitations. First, most of the cleavable C−C bonds are those that are adjacent to the hydroxyl or carbonyl group. Second, *N*-containing directing groups, which often need additional steps to install and are difficult to remove, are usually required for the cleavage of unstrained C−C bonds. Third, the reactions usually employ rhodium complexes as catalysts, which have the disadvantages of high cost and low sustainability. In recent years, several elegant examples have been reported that addressed these issues to some extent. For example, chelation-assisted functionalizations of allylbenzenes have been achieved via the activation of nonpolar C−C bonds.[34] Our group achieved a Ag-catalyzed 1,4-aryl migration of γ,γ-disubstituted triflic amides from carbon to the nitrogen center, which cleaved the C−C bond far from the polar group through a radical pathway.[35] By using photocatalysis, unstrained aliphatic alcohols were applicable starting materials for C−C cleavage without the need of directing groups.[36] With respect to cheap metal-catalyzed C−C bond activation, Ni complexes are the most promising catalysts,[6a,37] although a few examples of Co[38]- and Mn[39]-catalyzed transformations have been reported very recently. Further developments of different concepts and strategies that could achieve (1) temporary, removable, or transformable directing-group-assisted or even nondirected C−C bond activation of unstrained molecules, (2) transformations of structurally more diverse compounds other than alcohols and ketones, and (3) earth-abundant metal-catalyzed transformations are highly desirable. We hope that this Account will attract more interest from the organic chemistry community to C−C bond transformations and inspire chemists to think about the reactivity of C−C bonds in a different way.

AUTHOR INFORMATION

Corresponding Author

Zhang-Jie Shi − *Department of Chemistry, Fudan University, Shanghai 200433, P. R. China;* orcid.org/0000-0002-0919-752X; Email: zjshi@fudan.edu.cn

Authors

Feijie Song − *College of Chemistry and Materials Science, Sichuan Normal University, Chengdu, Sichuan 610066, P. R. China;* orcid.org/0000-0002-6782-1175

Biqin Wang − *College of Chemistry and Materials Science, Sichuan Normal University, Chengdu, Sichuan 610066, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.3c00230

Author Contributions

CRediT: **Zhang-Jie Shi** conceptualization, formal analysis, funding acquisition, project administration, supervision, validation, writing-review & editing.

Notes

The authors declare no competing financial interest.

Biographies

Feijie Song obtained her B.Sc. in chemistry from Beijing Normal University in 2003 and Ph.D. from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in 2008 under the supervision of Prof. Yuanhong Liu. Then she successively worked at Duke University and the University of North Carolina, Chapel Hill as a postdoctoral research fellow between 2008 and 2011. After that, she joined Sichuan University and was promoted to associate professor in 2014. She moved to Sichuan Normal University in 2016 and was promoted to a full professor in 2021. Her current research interest is transition-metal-catalyzed C−C bond activation and functionalization.

Biqin Wang was born in Sichuan Province, China. She earned her B.Sc. degree in chemistry from Sichuan Normal University in 1986 and has been working at the same university since then. She was a visiting scholar at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in 1999 and at Peking University in 2007. She was promoted to full professor in 2008 and is currently the director of discipline construction division at Sichuan Normal University. Her research mainly focuses on transition-metal-catalyzed C−H and C−C bond activations.

Zhang-Jie Shi was born in July 1974 in Anhui, China. He received his bachelor's degree in chemical science from East China Normal University in Shanghai, China, in 1996. He obtained his Ph.D. degree in 2001, supervised by Professor Shengming Ma from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. Following his graduate research, he moved to the Department of Chemistry and Chemical Biology at Harvard University as a postdoctoral fellow in the laboratory of Professor Gregory L. Verdine (2001 to 2002). He then joined Professor Chuan He's group as a research associate at the University of Chicago. He joined the faculty at Peking University at the end of 2004. In 2008, he was promoted to full professor. In 2017, he moved to Fudan University. His research interest is transition-metal-catalyzed inert bond (C−H, C−C, C−O, C−N, etc.) activation.

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