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Transition Metal-Catalyzed Direct Nucleophilic Addition of C-H Bonds to Carbon-heteroatom Double Bonds

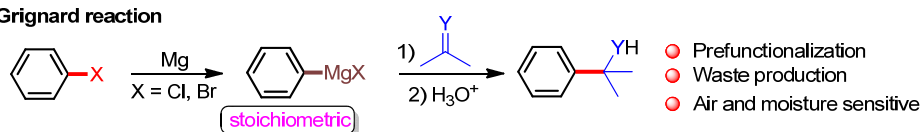
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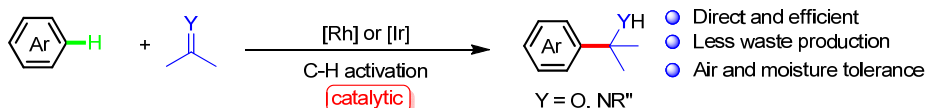
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CONSPECTUS

Grignard reaction



Catalytic Grignard-type reaction direct from C-H bonds



Transition-metal catalyzed direct C-H functionalization has drawn great attention in the past several decades owing to its advantages compared to conventional organic transformations, including higher atom-, step- and cost- economy and the avoidance of the tedious prefunctionalization and the waste emission. At current stage, to make the C-H functionalization more applicable, chemists devoted themselves to expanding the substrate and reaction scope. In the past decade, we exerted ourselves to develop new transformations based on direct C-H functionalization. In this article we accounted our recent achievements on the addition of C-H bonds to carbonyls and imines.

The addition of organometallic reagents, such as Grignard reagents, toward carbon-heteroatom double bonds is one of the most powerful reactions in organic synthesis to produce secondary and tertiary alcohols and amines. This chemistry is broadly used in both laboratory and industry. Whereas, this powerful transformation still suffers from some drawbacks: (1) the preparation of initial organohalides is tedious and sluggish from easily available fossil feedbacks; (2) plentiful metal halides salts were emitted as wastes; (3) at last but not the least, the manipulation of organometallic reagents is complicated due to its sensitivity to air and moisture. In contrast, direct insertion of polar double bonds to C-H bonds via transition metal catalysis is ideal arising from satisfying atom-, step- and cost- economy and the avoidance of the waste emission as well as of the complex manipulation of the sensitive reagents. Starting from this point, we made a commitment to this project years ago and have made credible achievements in this field.

We first carried out Ir-catalyzed addition of pyridinyl C-H bond with aldehydes promoted by silane, showing an unusual C-3 selectivity. Later on, we developed the Rh-catalyzed addition of aryl C-H bonds with aldimines in the absence of any additives with directing strategy with highest atom- and step- economy. The mechanism was investigated in depth by the isolation of key intermediates and systematical thermodynamic and kinetic studies. Such a concept was expanded to the coupling of aryl/alkenyl C-H bonds with aldehydes and imines. Notably, a tandem process of relayed C-H activation/alkyne insertion /cyclization between benzoates/benzimide and alkynes was developed, indicating the potential of the direct coupling of esters and amides with C-H bonds. Ideally, this strategy opens a new window to approach the ideal reactions to produce amines and alcohols from hydrocarbons.

Introduction

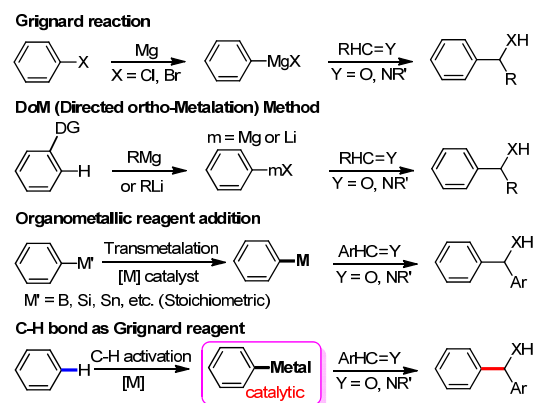
C-H bonds are widely existed in natural and synthetic chemicals. Undoubtedly, the use of C-H bonds as a surrogate of functional group to carry out organic transformations is the most efficient by avoiding tedious prefunctionalizations. Numerous achievements have been made in direct C-H functionalizations in recent years.¹ In the past decades, our researches in this field were mainly focused on oxidative coupling and insertion of carbonyls and imines to C-H bonds to expand the classification of reactions.² Recently we have reviewed our efforts in oxidative coupling.³ In this account, we narrated the transition-metal catalyzed addition of C-H bonds to carbonyls and imines. Although we are mainly focused on the work of our own research group, work from other groups are also properly summarized and described. Till now, there are another two important reviews in the important field of transition metal-catalyzed C-H bond coupling of with polar multiple bonds.⁴ In this article, we summarize the recent discoveries and developments in this field from different views, especially illustrating the difficulties we faced and the strategies we adopted to solve the difficulties.

The Background of the Addition of C-H Bonds toward Carbon-heteroatom Double Bonds

Nucleophilic addition of Grignard reagents to carbonyl compounds and their derivatives is important for the synthesis of alcohols and amines, thus won the Nobel Prize in 1912. The use of aryl halides as starting materials makes it environmentally unfriendly due to their tedious and sluggish preparation. The DoM strategy partially solves this problem while more than stoichiometric amount of organometallic reagents is necessary.⁵ It is important to note that, both these strategies suffered from complex manipulations of main group organometallic reagents due to their air- and moisture- sensitivities. Development of transition metal-catalyzed addition of more stable and air and moisture tolerant organometallic reagents (RM', M' = B, Si, Sn, etc.) to carbonyls and imines partially solved this

problem and expanded the reaction scope to some extent.⁶ In all these transformations, the organometallic reagents need tedious prefunctionalizations, thus lowering the atom- and step- economy. Obviously, transition metal-catalyzed addition of C-H bonds toward carbon-heteroatom double bonds is free of such pitfalls and highly desirable (Scheme 1).

Scheme 1. Comparing direct C-H bond addition with the Grignard reaction



Although transition-metal catalyzed coupling of C-H bonds toward alkenes and alkynes (hydroarylation, oxidative Heck reaction, cyclization and so on) were well investigated,⁷ the C-H addition to polar unsaturated carbon-heteroatom bonds *via* exact C-M intermediates was relatively rare, other than the conventional Friedel-Crafts reaction.⁸ The difficulty of transition metal-catalyzed direct C-H addition to C=X (X = O, N) bonds mainly arises from the inescapable challenges: (1) The weak nucleophilicity of C-M (M = transition metal) bonds derived from C-H bonds makes the addition untoward; (2) The X-M bond in the metal alkoxide or metal alkylamide resulting from C=X bond insertion was thermodynamically stable and the catalytic cycle is difficult to proceed.

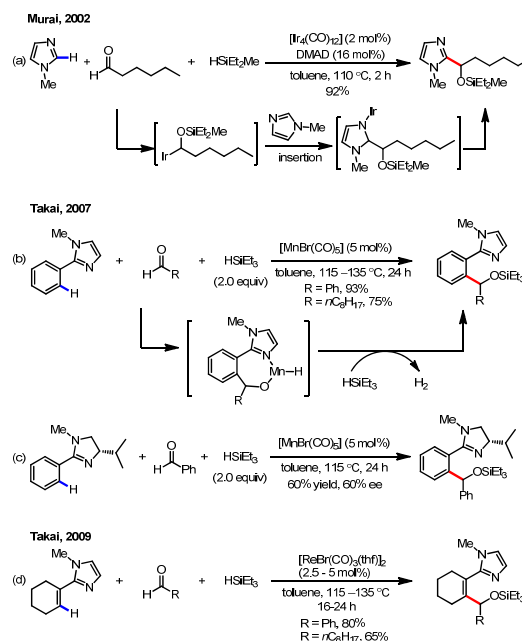
The Motivation of Direct Coupling of C-H Bonds with Carbon-Heteroatom Double Bonds

In the past several decades, chemists have never halted their steps to pursue the goal to carry out the C-H addition to carbonyl compounds. The first beautiful

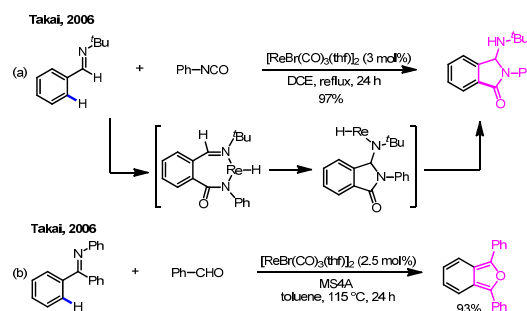
example was reported by Murai and co-workers on an iridium-catalyzed coupling of the relative acidic C-H bonds of imidazole to aliphatic aldehydes with the silane as an essential additive (Scheme 2, a).⁹ Indeed, the authors themselves proposed the alternative way initiated from the reduction of aldehyde rather than direct C-H bond activation. Later on, the similar strategy was well extended to inert aryl C-H addition to aldehydes *via* Mn-catalysis through directing strategy by Takai (Scheme 2, b).¹⁰ The hydrosilane promoted reductive elimination of manganese by silylation of an alkoxy moiety. It should be noted that an asymmetric transformation was also realized when a chiral imidazoline was used (Scheme 2, c).^{10a} Later on, they further realized the alkenyl C-H addition to aldehydes (Scheme 2, d).¹¹ With a smart design, Takai and co-workers synthesized fused rings by quenching Re-O/N intermediates (formed from C=O/N insertion) through tandem intramolecular capture in the absence of silane (Scheme 3).¹² This observation gave a side proof to support the insertion pathway. The other beautiful examples have been demonstrated by Lu¹³ and Shibata¹⁴ (Scheme 4). In their cases intramolecular C-H coupling with ketones were achieved. In 2011, Shibata further developed a Ir(III)-catalytic system.¹⁵ However, those cases were also lack of strong evidences to support the involvement of C-H activation.

Significant contribution has also been made by Larock and coworkers as early as 2004 to carry out the addition of aryl C-H bonds to nitriles to produce ketones and ketimines, supposedly undergoing Pd-catalyzed C-H activation.¹⁶ However, mainly electron-rich arenes were used and no direct evidence strongly supported the C-Pd key intermediate formation and subsequent additions (Scheme 5, a).¹⁶ In 2009, Murahashi also reported the rhenium-catalyzed addition of carbonyl α -C-H bonds to carbon-nitrogen triple bonds of nitriles (Scheme 5, b).¹⁷ Very recently, Wang reported the Pd-catalyzed indole C-3 C-H bond addition to nitriles to synthesize 3-acylindoles (Scheme 5, c).¹⁸

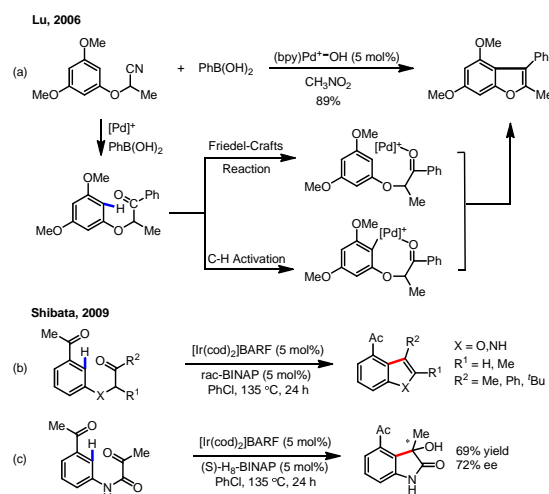
Scheme 2. Insertion of aldehyde C=O bond to sp^2 aryl and alkenyl C-H bonds assisted by silane.



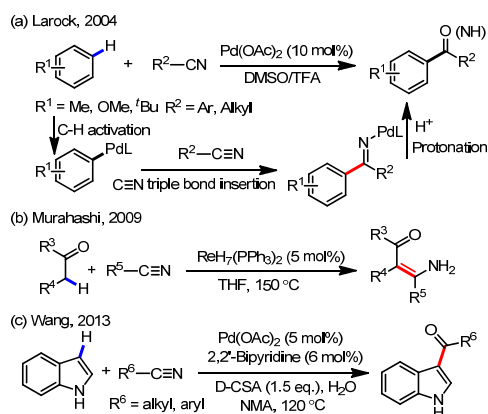
Scheme 3. C-H addition to isocyanates and aldehydes by intramolecular cyclizative trapping



Scheme 4. Intramolecular C-H addition to ketones

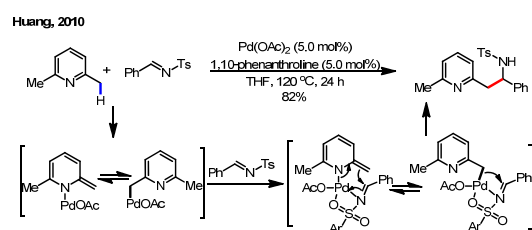


Scheme 5. C-H bond addition to nitriles



In 2010, Huang and coworkers made significant contributions to carry out the direct addition of benzylic C-H bonds to aldehyde *via* Pd catalysis (Scheme 6).¹⁹ Although some preliminary mechanistic studies supported the existence of C-Pd intermediate, the other arguable aldol-type pathway could not be rooted out at the current stage, in which Pd(II) may play a role as Lewis acid. It should be noted that after that, there have been great research interest and the additions of aza-benzylic C-H bond addition to aldimines, aldehydes, ketones and azodicarboxylate using different kinds of Lewis acids and Brønsted acids and even catalyst-free conditions have been reported.²⁰

Scheme 6. Benzylic C-H addition to aldimines

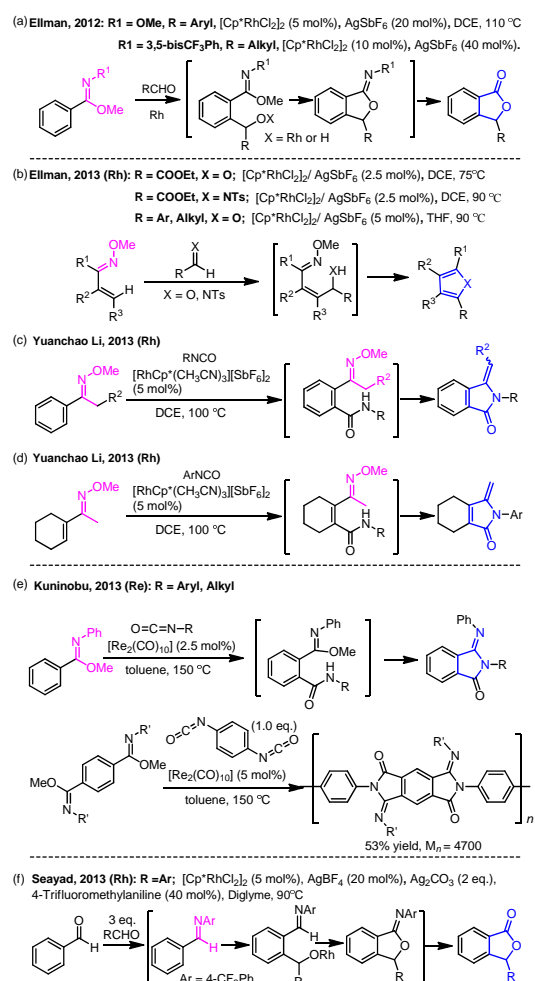


By analyzing above mentioned successful examples, it is not difficult to conclude that there are three strategies applicable to push forward the transition metal-catalyzed C-H addition to polar carbon-heteroatom double bonds: (1) using silane as additive; (2) intramolecular trapping to form a stable product; (3) intramolecular addition.

Recent Developments on C-H Addition toward C=X Bonds

Tandem C-H bond nucleophilic additions/cyclizations: Intramolecular capture to synthesize heterocycles

Inspired by Takai's pioneering work of the C-H bond addition to isocyanates and aldehydes with imine as intramolecular trapping group,¹² this field has shown bloom in recent two years to synthesize heterocycles.

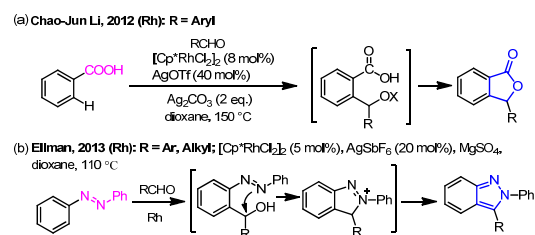
Scheme 7. C-H bond additions *via* intramolecular capture with imines and its derivatives as capturing groups

The most widely used capturing groups are imines and its derivatives. The first example after Takai's report with imine derivatives as directing group and capturing group was reported by Ellman for the Rh-catalyzed coupling of benzimidates with aldehydes to synthesize phthalides (Scheme 7, a).¹⁹ By careful tuning the substituent on the *N*-atom of imine directing group, both

aromatic aldehyde and aliphatic aldehyde can be used as electrophiles. Later, they expanded the nucleophile from aryl C-H bond to alkenyl C-H bond and both aldehyde and active imines can be used as electrophiles by changing the directing group to oxime group (Scheme 7, b).²⁰ With a similar Rh-catalytic system, Li developed the coupling of *o*-alkyl oximes with isocyanates to synthesize 5-ylidenepyrrrol-2(5H)-ones and 3-methyleneisindolin-1-ones (Scheme 7, c and d).²¹ Re-catalysts were also successful for the coupling of benzimidates with isocyanates to synthesize 3-Imino-1-isindolinones (Scheme 7, e).²² Polyimide derivatives can also be synthesized by using multi-functional group containing starting materials. A beautiful coupling of two different aldehydes to synthesize phthalides *via* imine intermediates by rhodium(III)-amine dual catalysis was reported by Seayad and coworkers (Scheme 7, f).²³

Apart from the imine group and its derivatives, other groups like carboxylic acids and diazobenzenes have also been utilized as efficient directing groups and intermolecular capturing groups for the synthesis of phthalides and indazoles (Scheme 8).²⁴

Scheme 8. C-H bond additions *via* intramolecular capture with carboxylic acid and diazo as capturing groups.

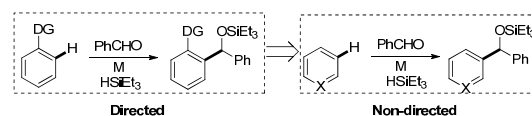


Above mentioned directing groups mainly capture the intermediate to form more stable heterocyclic products by nucleophilic additions and eliminations. In addition, the intermediate can also be trapped by oxidation²⁵ or dehydrations²⁶.

Ir-catalyzed non-directed pyridinyl C-H addition to aldehydes promoted by silane. As mentioned above, direct coupling of C-H bonds toward aldehydes *via* low-valent transition-metal catalysis could be promoted by silanes.⁹⁻¹¹ However, the current successes

were only limited to the acidic C-H bond of heterocycles and some aryl systems with directing groups. Thus, transition-metal catalyzed direct C-H addition of simple (hetero)arenes to aldehydes without directing groups is highly desirable.²⁷ (Scheme 9)

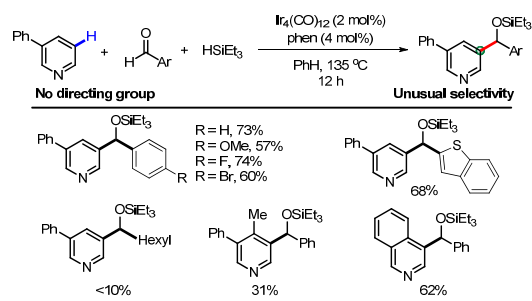
Scheme 9. Non-directed aryl C-H coupling with aldehydes



Our first glimpse was focused on the pyridinyl derivatives due to their potential application in drug discovery and material chemistry. Although many methods have been reported for the functionalization of pyridines,^{5c, 28} the intermolecular C-H activation/C-C formation at C-3 position of pyridine without activating or directing groups has been rarely achieved. With our efforts, we achieved a non-directed pyridine C-H coupling with aldehyde with an unusual C3-selectivity for the first time in the presence of silanes.²⁹

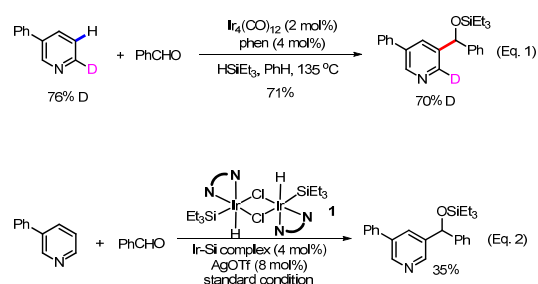
With Ir₄(CO)₁₂ as catalyst and phenanthroline as ligand, the addition of C5-H in 3-phenylpyridine toward benzaldehyde occurred to give the product in 73% yield. Electron deficient aldehydes gave better yields. Bromo- and heterocycle could be well tolerated. Unfortunately, aliphatic aldehydes showed unsatisfied efficiency (Scheme 10).

Scheme 10. Ir-catalyzed non-directed pyridine C-H coupling with aldehydes promoted by silane

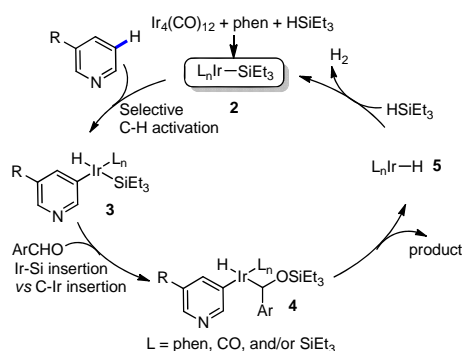


Preliminary mechanistic studies were conducted to understand the C3-selectivity. When 2-*D*-labeled 3-phenylpyridine was surveyed, no significant deuterium

loss was observed at C-2 position, indicating that the migration of C-Ir intermediate from C-2 to C-3 was unlikely (Eq. 1). In addition, a silyl iridium complex **1** was synthesized and showed great catalytic activity, suggesting that it may be a possible intermediate in this transformation (Eq. 2).³⁰ Therefore, we considered that, starting from Ir-Si species **2**, oxidative addition of pyridinyl C-H bond took place to produce the intermediate **3**. The steric and electronic property of active catalyst may play the key role to control the C3-selectivity. Due to the stability of O-Si bond, C=O bond insertion selectively to Ir-Si bond (vs. C-Ir bond) is preferred and subsequent reductive elimination led to the final product, accompanying with the generation of an iridium hydride species **5**. Finally, the active iridium catalyst **2** was regenerated by reaction of **5** with the silane. (Scheme 11)



Scheme 11. Mechanism for the Ir-catalyzed non-directed pyridine C-H coupling with aldehydes promoted by silane



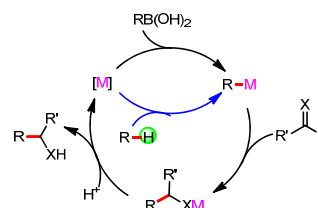
The Direct Intermolecular Addition of C-H Bonds toward C=X.

Although above mentioned three strategies showed great developments, transition metal-catalyzed direct intermolecular nucleophilic addition of C-H bonds to carbonyls or imines without additives was unknown

when we jumped into this field and it became our dream since then on.

We set out our dream to conceive such an insertion reaction in late 2004 since we initiated our independent career. Considering important transformations including the transition-metal catalyzed addition reactions of arylboronic acids to aldehydes^{6a, 6c}, the carbon-metal bond addition to polar unsaturated bonds (like aldehydes³¹, nitriles³² and CO³³) developed by Larock³⁴ and the direct C-H activation to generate C-M key intermediate through electrophilic substitution or oxidative addition^{1a, 1h}, theoretically, the proposed catalytic cycle could be drawn as Scheme 12 and we do believe that such a design is applicable under the proper conditions. After a long time of efforts, now we have made several contributions in this field.

Scheme 12. The initial design of the direct insertion of polar double bonds to C-H bonds



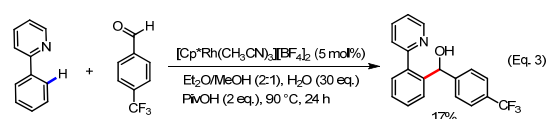
Rh-catalyzed aryl C-H bond coupling with sulfonylaldimines directed by pyridinyl group.

Combining the catalytic addition of arylboronic acid to aldehydes and current studies on C-H activations, Pd catalysts were the first choice in our mind. We chose the most common candidates of the arenes, such as 2-phenylpyridine, acetanilide, benzoic acid, indole, and so on, to investigate such a transformation with aldehydes, imines and other potential partners. Although the directing strategy or electronic control was applied, we could not observe a trace amount of desired product, albeit in some cases interesting products were observed, for example, the acylation and decarbonylation. As a result, we thought we need to find other efficient catalytic systems.

Our later research was inspired by the progress on the Rh-catalyzed addition of aryl boronic acid to carbonyl compounds, in which the aryl-Rh species formed by transmetalation was proposed to be similar with the

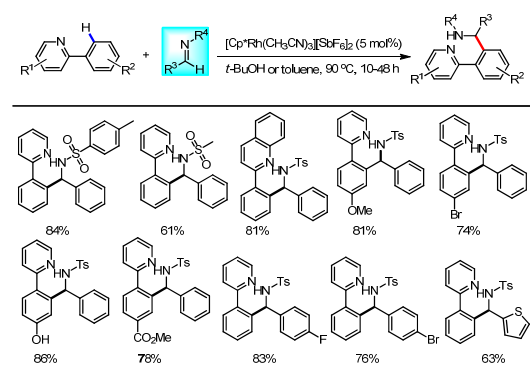
intermediate obtained by C-H activation, although generally the low valent metal catalyst is better for addition of boronic acids and high valent metal catalyst is better for C-H bond activation. (Scheme 12).

Initially, we investigated the pyridinyl directed insertion of C=O double bond in 4-trifluoromethylbenzaldehyde to aryl C-H bond and the desired product was obtained in 17% yield. (Eq. 3) Although the yield is not ideal and even could not be improved, this observation is of great importance to prove our concept and gave us the encouragement for further investigations.



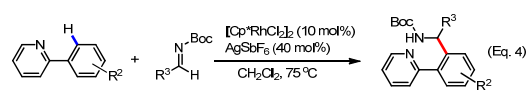
To our delight, when the reaction partner was changed from aryl aldehyde to sulfonylaldimine, the yield was dramatically enhanced. After systemic screening we found that pyridinyl directed phenyl C-H coupling with aldimines underwent smoothly with cationic Rh(III) species as catalyst in the absence of any additives and without the emission of undesirable wastes (Scheme 13).³⁵ Indeed, it seems an ideal transformation with 100% atom economy.

Scheme 13. Rh-catalyzed pyridinyl directed aryl C-H coupling with aldimines



The substrate scope for this transformation was very broad (Scheme 13). In general electron-rich arenes and electron-deficient aldimines gave better yields, because electron-rich arenes undergo electrophilic C-H activation more efficiently and electron-deficient aldimines are

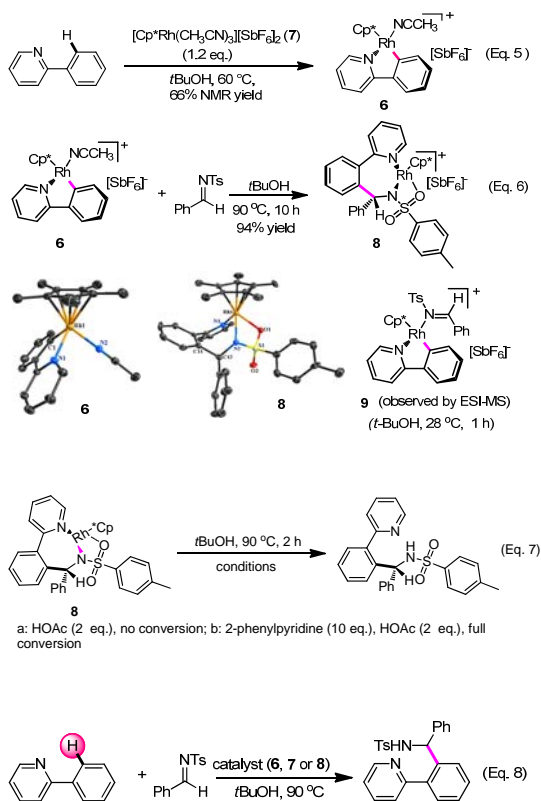
more favorable for nucleophilic attack of the C-M intermediate. Notably, directing groups other than pyridinyl were also feasible. Compared to the traditional nucleophilic addition by main group metal reagents, the sensitive substituents, for example, halo-, hydroxyl- and ester were well tolerated. Moreover, heterocyclic motifs were also compatible. Notably, almost simultaneously, Ellman and Bergman's group reported the similar observations with N-Boc arylaldimine as the partner and CH₂Cl₂ as the solvent and a combination of [Cp*RhCl₂]₂ and AgSbF₆ as the catalyst, although in relatively higher catalyst loadings (Eq. 4).³⁶



Systematic mechanistic studies on Rh-catalyzed aryl C-H coupling with sulfonylaldimines.

To get insights into the mechanism and provide suggestions for further design of other reactions, we conducted the intermediate isolation and kinetic study of this transformation.³⁷

We first synthesized the cationic C-H activation intermediate **6** using a condition similar as our standard reaction (Eq. 5). Stoichiometric reaction between compound **6** and sulfonylaldimine afforded the insertion intermediate **8** in 94% isolated yield (Eq. 6). Fortunately, we obtained the X-ray structure of both these two important intermediates **6** and **8**. Although the coordination intermediate **9** could not be isolated, it was clearly detected by *in-situ* ESI-MS and NMR spectroscopy, proving that the transformation from **6** to **8** went through coordination and then insertion. Notably, the product releasing step, the protonation of intermediate **8**, did not proceed in the presence of HOAc (Eq. 7, a). After careful analysis and investigation, we found that the presence of 2-phenylpyridine as ligand was essential to destroy the coordination of the O-atom to Rh in **8** and releases the final product. Both **6** and **8** could catalyze the standard reaction, showing their possibility as active intermediates in the catalytic cycle (Eq. 8).



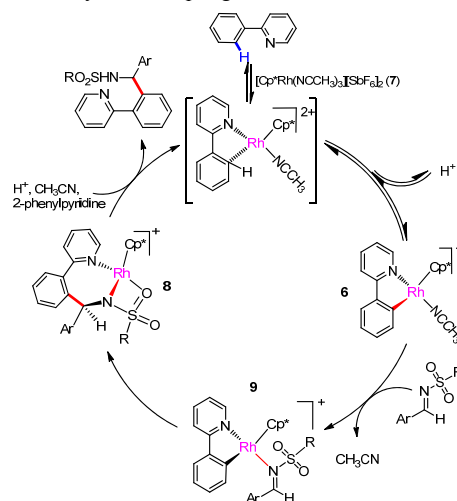
In addition, we also conducted the kinetic characterization and found that the reaction showed first-order to 2-phenylpyridine and aldimine, while less than the first-order (0.62) to the precatalyst **7**, respectively. The first order of 2-phenylpyridine and aldimine showed that they were possibly involved before the rate-determining step in the catalytic cycle. The broken reaction order for the precatalyst **7** was proposed to be resulted from the equilibrium between the precatalyst **7** and the active catalytic species. This was further supported by the exact first order of the intermediate **6** and **8**. Initial rates (k_{obs}) of 2-phenylpyridine, 2-[d1]-phenylpyridine, 2-[d5]-phenylpyridine revealed a ratio of $k_{\text{HH}}/k_{\text{HD}}/k_{\text{DD}} = 1.11 : 1.00 : 1.05$, showing that the C-H activation was not involved in the rate-determining step.

And the protonation step from intermediate **8** to product in the presence of HOAc and 2-phenylpyridine was found to finish within 1 min even at 30 °C, showing that this protonation step was very fast and was not involved in the rate-determining step.

Based on these results, we proposed the mechanism in Scheme 14. Pyridinyl directed reversible C-H

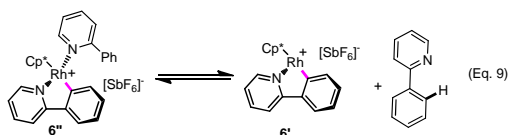
activation *via* electrophilic substitution initiated the catalytic cycle by forming the 5-membered rhodacycle intermediate **6**. Coordination of aldimine to the intermediate **6** and C=N bond insertion to the C-Rh bond gave the seven-membered rhodacycle intermediate **8**. Protonation of **8** in the presence of 2-phenylpyridine as ligand released the final product. The insertion of the C=N double bond to the C-Rh bond was the rate determining step. This transformation was conducted under mild conditions without any additives or wastes and no special technique was required, the reaction can be conducted under air atmosphere. We would say that, the inert aryl C-H bonds worked as a surrogate for aryl Grignard reagent.

Scheme 14. Mechanism for Rh-catalyzed pyridinyl directed aryl C-H coupling with aldimines

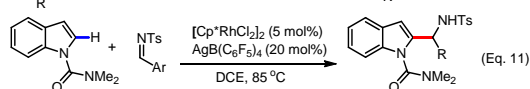
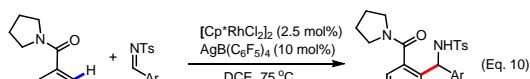


The mechanistic study for the Rh(III)-catalyzed addition of C-H bonds to imines was also conducted by Ellman and Bergman's group based on their system.³⁸ They also concluded that the insertion step was the rate-determining step. They found that compound **6'** was the active catalytic species and compound **6''** was the resting state and equilibrium was existed between them (Eq. 9). They determined the reaction order for imine and compound **6'** to be first order while reverse first order to 2-phenylpyridine. The reverse first order was proposed to result from the substrate inhibition effect in the equilibrium (Eq. 9). The difference of the reaction order for 2-phenylpyridine between this system and our system may be attributed to the lack of the substrate inhibition

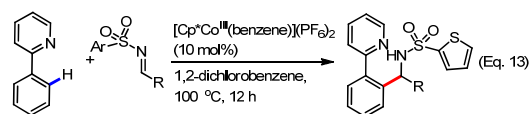
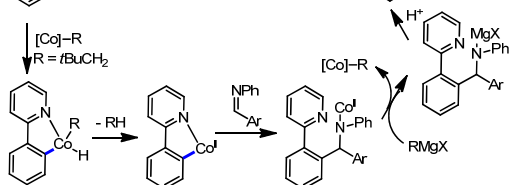
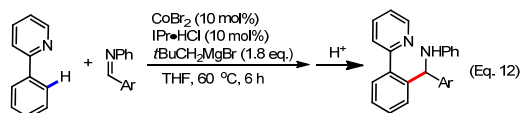
effect of 2-phenylpyridine in our system, for compound **6** was the active catalytic species (first order for **6**). In addition, they found that in their system the C-C bond formation was reversible by changing the protecting groups, which was further strongly evidenced by our later studies in C-C cleavage.³⁹



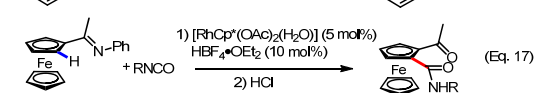
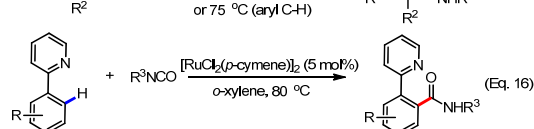
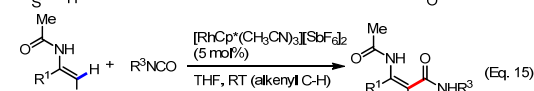
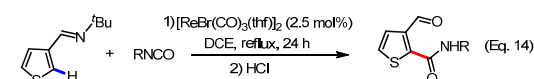
Later on, Ellman and Bergman also achieved the transformation with amide as directing group instead of pyridine to highly extend this chemistry (Eq. 10).⁴⁰ A amide directing group has also been used in the Rh-catalyzed direct C-H coupling of electron rich indoles to *N*-sulfonylaldimines by Li and co-workers (Eq. 11).⁴¹



Excitingly, a similar reaction between phenylpyridine and imine was also realized by Yoshikai and Kanai with non-precious Co catalyst (Eq. 12 and 13).⁴² In the former system of Yoshikai's, the reaction went through a Co(I)/Co(III) catalytic cycle. While the later system of Kanai's used a high valent Co-species and went through a pathway similar with our above stated Rh(III)-catalysis.

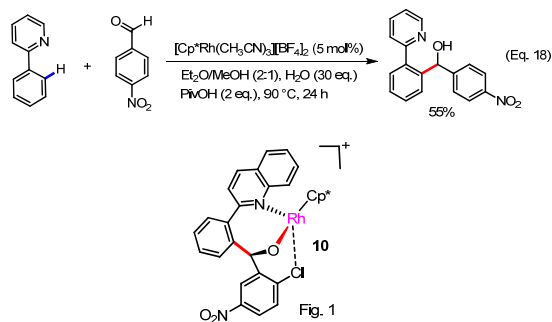


Ellman and Bergman further reported the Rh-catalyzed aryl and alkenyl C-H coupling with isocyanates with amide as directing groups (Eq. 15).⁴³ Similar transformations were also realized by Cheng and Shibata recently (Eq. 16 and 17).⁴⁴ Actually, the earlier example of the thiophene C-H bond addition to isocyanate directed by imine group was reported by Takai and coworkers (Eq. 14).⁴⁵

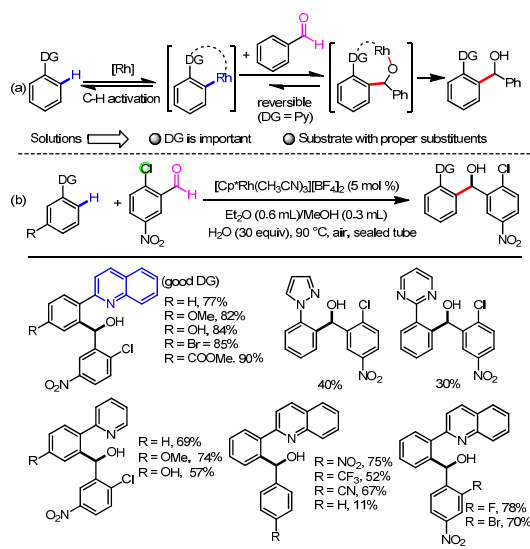


Rh-catalyzed N-heterocycle directed aryl C-H coupling with aldehydes. Meanwhile, we made our full attempts to illustrate the reason for the low yield of the aryl C-H addition to aldehydes and to improve the efficiency. Finally, we found that the insertion of the C=O bond to C-Rh bond was reversible, which decreased the efficiency of the reaction.³⁹ To solve this problem, we chose the proper substrates to tune the balance between the insertion and elimination reactions in equilibrium. Indeed, the use of active electron-deficient aldehyde as substrate and proper directing groups are feasible (Scheme 15, a).

When we performed this reaction with 4-nitrobenzaldehyde, the reaction with 2-phenylpyridine gave the product in 55% yield (Eq. 18). To our delight, when the directing group was changed to quinolinyl, the yield was improved to 75% (Scheme 15, b).⁴⁶ Unfortunately, other heterocyclic directing groups gave inferior results. Further attempts indicated that 2-chloro-5-nitro-benzaldehyde gave the best reactivity, presumably resulting from both its high electrophilicity and the weak coordination ability of the *ortho*-Cl in the substrate to stabilize the 7-membered intermediate **10**, analogous to intermediate **8** (Fig. 1).

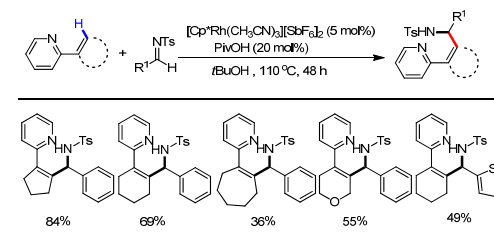


Scheme 15. Rh-catalyzed N-directed C-H coupling with aryl aldehyde

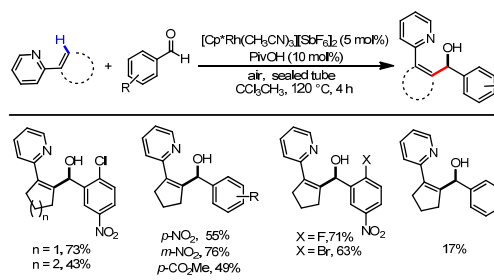


(Scheme 16). It should be noted that a higher yield was obtained with higher concentration. The reaction was proposed to go through the similar pathway as mentioned above.

Scheme 16. Rh-catalyzed alkenyl C-H coupling with aldehydes

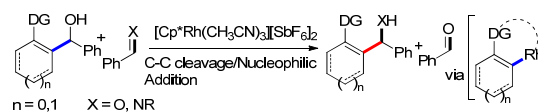


Scheme 17. Rh-catalyzed alkenyl C-H coupling with aldimines

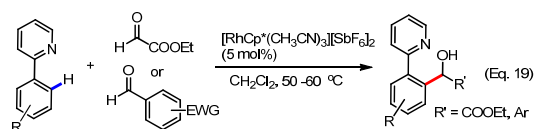


Rh-catalyzed aryl C-C cleavage and subsequent coupling to aldehydes and aldimines. During our studies to pursue the desired reactions, we observed the equilibrium between the coupling and C-C cleavage.³⁹ Based on this results, we also developed a C-C bond cleavage/insertion cascade process to realize the transformation from benzyl or allyl alcohols to amines or another alcohol (Scheme 18).⁴⁹ This reaction expanded the scope of the nucleophiles for the addition reaction toward carbonyl compounds and their derivatives. In addition, this transformation also provided a new concept for the construction of complex structures by reorganization of the carbon skeleton through C-C bond activation.

Scheme 18. Coupling of C-C bonds with aldehydes and aldimines



It is important to note that, during our studies, Li and co-workers reported the first beautiful example of pyridinyl directed C-H coupling with highly active aldehydes (Eq. 19).⁴⁷



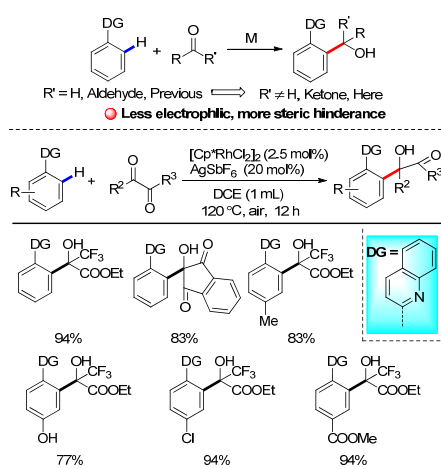
Rh-catalyzed alkenyl C-H coupling with aldehydes and aldimines. To continue our success in this field, we further extended the transformation from aryl C-H bonds to alkenyl C-H bonds.⁴⁸

With this method, allylic alcohols and amines could be constructed (Scheme 16 and 17). The addition of PivOH can promote the efficiency to some extent, acting as activation reagent for C=X bond and a proton source. The yield decreased with the increase of the ring size

Rh-catalyzed aryl C-H coupling with ketones.

Compared with aldehydes, ketones are much less electrophilic and more steric hindered, which makes the addition more difficult. Although some examples of addition to ketones of C-M bond derived from halides or boronic acids^{25a, 43} and several intramolecular addition^{13-15, 50} were presented, no intermolecular C-H addition to ketones has been realized. To explore such chemistry, we further investigated the C-H coupling with ketones *via* Rh-catalysis.

Scheme 19. Rh-catalyzed aryl C-H coupling with ketones



With previous success, we believed that the directing group played a vital role. After screening, we found that quinolinyl gave the best result as directing group and others like carbonyl, amide, imine, pyridine, carboxylic acid all gave less or no product. In addition, the presence of a coordinating atom beside the reacting carbonyl group was essential to stabilize the inserting intermediate, thus promoted the reaction. The intermolecular hydrogen bonding between the products also played a critical role in stabilizing the product to improve the yield. Gratifyingly, substrate scope for aryl partner is wide and many functional groups could be tolerated very well, for example, hydroxyl, halide and ester (Scheme 19).⁵¹ Both electron-rich and electron-deficient arenes can react very efficiently, ruling out the possibility of a Friedel-Crafts pathway. However, at the present stage, only relatively active ketones can be used while this observation unveiled the potentialities. Supposedly, this transformation went through the same

pathway as previous reported. Recently, Yang reported the Sc(OTf)₃-catalyzed intramolecular aryl C-H bond addition to ketoamide to synthesis 3-hydroxy-2-oxindoles *via* a Friedel-Crafts pathway.⁵²

Notably, the alternative Rh(III)-catalyzed C-H addition to nitrosobenzene was recently reported by Li under mild conditions.⁵³

In addition, a very beautiful example of unactivated aryl C-H bond addition was reported by Iwasawa in 2011 by directing approach and using AlMe(OMe)₂ as an additive to keep the Rh(I)/Rh(III) cycle⁵⁴, although transition metal-catalyzed C-H bond addition to CO₂ was mainly limited to the acidic C-H bonds of heterocycles, polyfluoroarenes and alkynes in the assistance of base.⁵⁵

Rh-catalyzed relayed C-H coupling with esters and amides by intramolecular annulation with alkynes.

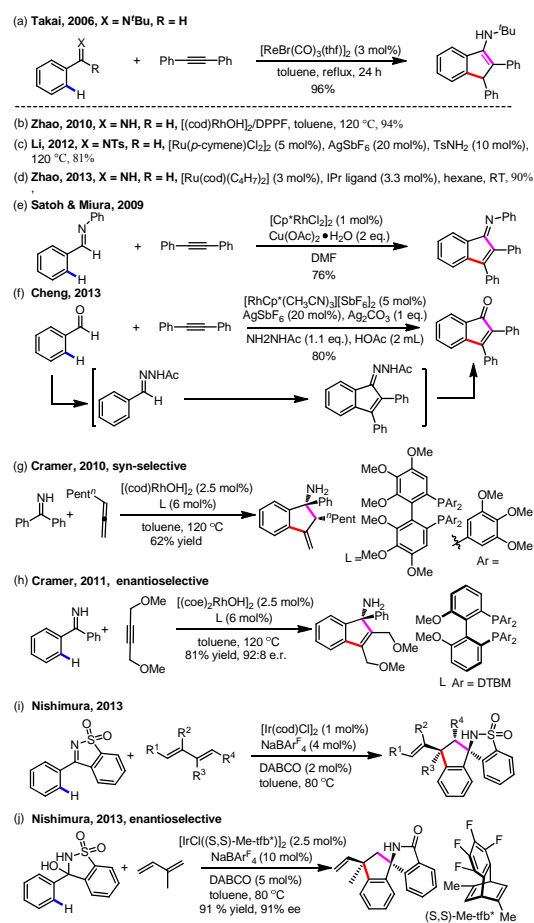
After our success of the direct C-H bond addition to aldehydes, aldimines and ketones, we further tried to investigate the more challenging C-H bond addition to esters and amides, which have much lower electrophilicity.⁵⁶ Although some successful examples of C-M bond addition to esters or amides have been reported, they are usually initiated from halides, organoboronic acids or alkenes, or went through an intramolecular pathway.⁵⁷

Firstly, we designed an intramolecular addition reaction with alkyne as a coupling partner, inspired by the beautiful examples of the transition-metal catalyzed intramolecular addition of C-H bonds to imines and ketones by coupling with alkynes or alkenes.

The first beautiful example was reported by Takai and coworkers in 2006 with imine as electrophile *via* a Re(I)/Re(III) catalytic cycle (Scheme 20, a).^{12a} Later, Zhao and Li developed the Rh- and Ru-catalytic systems of this similar reaction (Scheme 20, b and c).⁵⁸ Recently, Zhao further developed a highly efficient system at room temperature with [Ru(cod)(C₄H₇)₂] as catalyst (Scheme 20, d).⁵⁹ In the presence of oxidant, the oxidative cyclization product, imine (or ketone), will be formed with β-H elimination as terminal step (Scheme 20, e and f).⁶⁰ An enantioselective version was realized by Cramer by using alkynes containing coordinating OMe

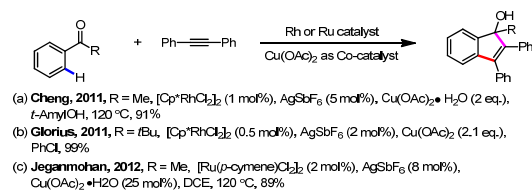
groups (Scheme 20, h).^{50c} In addition, coupling of imines with allenes and dienes other than alkynes were also investigated by Cramer and Nishiruma with Rh- and Ir-catalysis respectively (Scheme 20, g and i)⁶¹, including an enantioselective version with chiral diene ligand (Scheme 20, j).⁶²

Scheme 20. Intramolecular addition of C-H bonds to imines



In addition, C-H bonds intramolecular additions to ketones coupled with alkynes were also realized by Cheng and Glorius in 2011 with Rh-catalysis with the assistance of AgSbF₆ salt (Scheme 21, a and b).^{50a, 50b, 63} Later, a Ru-catalytic system was developed by Jeganmohan (Scheme 21, c).⁶⁴ In these systems, Cu(OAc)₂ was used as a stoichiometric or catalytic additive (co-catalyst) to facilitate the reaction by transmetalation with Rh-O species to release the Rh-catalyst.

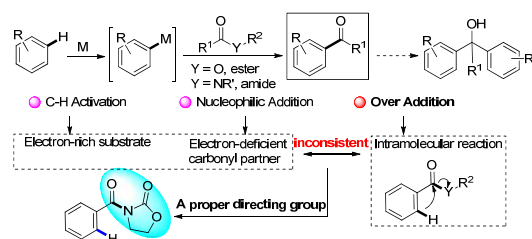
Scheme 21. Intramolecular C-H bond addition to ketones



Although above success of the intramolecular addition of C-H bonds to imines and ketones by coupling with alkynes or alkenes, the transition-metal catalyzed C-H coupling with esters was unknown at that time. We finally realized this transformation after our much efforts.⁵⁶

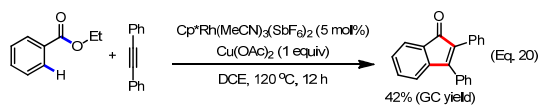
To solve this problem, two challenging points must be solved. First of all, the electronic demanding of the C-H activation (generally electron-rich system favors the electrophilic metallation) and the nucleophilic addition (generally more electron-deficient nucleophiles have higher reactivity) are not consistent (Scheme 22). On the other hand, the addition of the C-M bond to the ester or amide also produces a more reactive ketone, thus making the desirable transformation difficult. We proposed that a proper directing group (a proper substituent of the N-atom of amide) may be selected to tune the electronic factor of the system finely to balance the above mentioned inconsistency (Scheme 22).

Scheme 22. Difficulties of the coupling of C-H bond with esters and amides



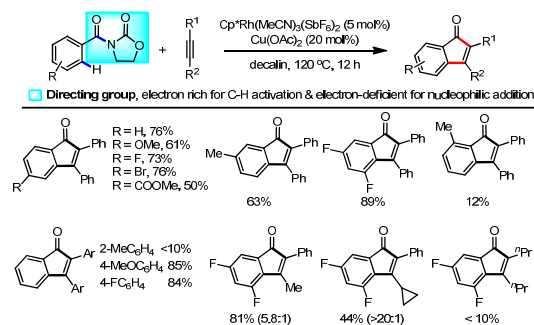
After optimization, benzoic ester could be annulated with alkynes catalyzed by Rh with Cu(OAc)₂ as co-oxidant in DCE to give the product in 42% GC yield. (Eq. 20) This was the first example of direct annulations of benzoic ester with alkynes through directed C-H functionalization. Unfortunately, the efficiency could not be promoted for this present system. Thus, we set out to explore other amide directing groups and its annulation

reactions.

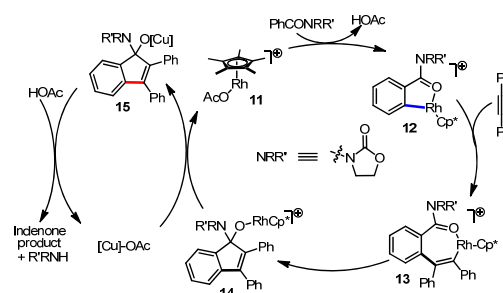


To our delight, we finally found that the *N*-acyloxazolidinone was the best directing group to give 76% yield with Rh and Cu as a co-catalyst system in decalin. Various substituents were tolerated and electron deficient benzimide gave better yields than electron rich ones, indicating a possible CMD process. *Meta*-substituted benzimide gave a single isomer. Asymmetric alkynes gave moderate selectivity and it was controlled by steric hindrance. Unfortunately, alkyl alkynes showed very low reactivity (Scheme 23).

Scheme 23. Rh-catalyzed C-H activation/coupling with amide to synthesize Indenones.



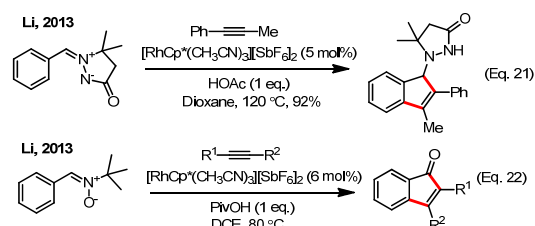
Scheme 24. Mechanism for the Rh-catalyzed C-H activation/annulation reaction.



The intramolecular and intermolecular kinetic isotopic effects were 1.9 and 2.2, indicating that the C-H activation was involved in the rate-determining step. For the proposed mechanism, C-H activation formed intermediate **12**, alkyne insertion and nucleophilic

addition gave intermediate **14**. Transmetalation between **14** and Cu species generated the copper alkoxide intermediate **15** and β -N elimination released the final product (Scheme 24).

Very recently, the intramolecular addition to azomethine ylides and nitrones were realized by Li and coworkers with Rh-catalysis in the presence of acid as additive (Eq 21 and 22).⁶⁵



Conclusion and Outlook

Based on our understanding of the mechanism, we have realized aryl and alkenyl C-H coupling with C=X (aldehydes, aldimines and ketones) with assistance of directing groups. A challenging coupling of aryl C-H bonds with amides and esters have also been realized in a tandem reaction in the presence of alkyne and a proper directing group. In addition, a non-directed pyridinyl C-H coupling with aldehydes with unusual *C3*-selectivity was also reported, albeit with the silane additive as a promoter.

With full efforts from ourselves and other leading groups, many exciting results have been achieved in this coupling reaction of C-H bonds to aldehydes and aldimines. At current stage, several directing groups have been applied and thus expanded the scope of the substrates, with aryl aldehyde and the corresponding imines showed the great reactivity. In some cases, this addition reaction can be successfully extended to the active ketones as well as the aliphatic aldehydes. With the tandem intramolecular capture version, several beautiful core structures can be constructed with this strategy. Obviously, although such a concept was proved successful, the pitfalls of such transformations highly limited their applications. There are still vast challenges and problems to be solved: (1) as mentioned above, the reversibility of the addition reaction to aldehydes is one of the main problems that limiting the scope of this

reaction and as a result new catalytic systems other than Rh-catalyzed ones should be developed; (2) C-H coupling with normal aldehydes and ketones is another goal in this field; (3) just like other C-H transformations, the coupling of sp^3 C-H bonds to popular unsaturated bonds is another important and challenging aspect. Last but not the least, the efforts to apply the developed chemistry in this field is highly desirable. We will continuously devote ourselves to unveiling the inner feature of the C-H bonds and developing new transformations from this starting point.

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BIOGRAPHICAL INFORMATION

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Zhang-Jie Shi obtained his BS at East China Normal University in 1996, and PhD with Professor Sheng-Ming Ma in the Shanghai Institute of Organic Chemistry (SIOC) in 2001. After his postdoctoral work with Professor Gregory L. Verdine at Harvard University and Professor Chuan He at the University of Chicago, he joined the chemistry faculty of Peking University in 2004, where he was promoted to a full Professor in 2008. His current research interests focus on transition metal catalyzed functionalization of inert chemical bonds and small molecules.

FOOTNOTES

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