Account

Transition Metal-Catalyzed Ortho-Functionalization in Organic Synthesis

Young Jun Park and Chul-Ho Jun*

Center for Bioactive Molecular Hybrid (CBMH), Department of Chemistry, Yonsei University, Seoul 120-749, Korea
**E-mail: junch@yonsei.ac.kr*
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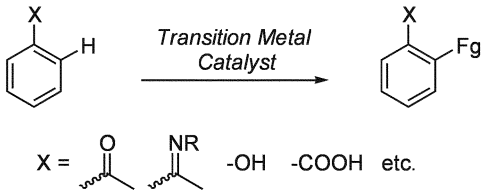
Recent progress in the filed of transition-metal mediated C-H bond activation has had a great influence on organic synthesis. Among such transition-metal catalyzed reactions, ortho-functionalization via the chelation-assisted strategy has been paid great attentions as one of the powerful methodologies for converting aromatic compounds into ones that are more functionalized at the exclusively ortho-position. In this context, various transition metal-catalyzed ortho-functionalizations such as alkylation, alkenylation, silylation and carbonylation are described briefly and their prospects are suggested.

Key Words : Transition metal, Ortho-functionalization, Chelation-assistance, C-H bond activation, Catalysis

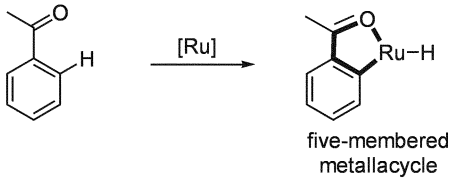
Introduction

Over the last few decades there have been many attempts to develop C-H bond activation by using a transition metal catalyst, since it is possible to functionalize a nonreactive C-H bond with synthetically valuable groups in a selective and atomically economical way.[1] As a result, various noble organic transformations have been reported to date that are usually difficult to achieve by classical organic reaction. One of the most useful classes of such catalytic reactions is the "functionalization" of aromatic C-H bonds ortho to certain coordinating groups such as acyl, imine, hydroxy and the carboxylic group (Eq. 1).[2]



Fg = functional groups: alkyl, alkenyl, silyl, etc. (1)

This intriguing reaction, originally reported by Murai as an ortho-alkylation in 1993,[3] opened up new synthetic methodologies for converting aromatic compounds into ones that are more substituted at the exclusively ortho-position, unlike other aromatic substitution reactions using stoichiometric amounts of metal salts, as in Friedel-Crafts alkylation.[4] The observed high regioselectivity and high efficiency in this reaction greatly benefits from the chelation assistance by the coordinating groups in substrates to form a stable five-membered metallacyclic intermediate (Eq. 2; details are in the main text).



(2)

Because C-H bonds are usually kinetically inert and their bond dissociation energy is high in the range of 105-110 kcal/mol,[5] the additional energy being released from the formation of a stable five-membered cyclic system via the coordination of a hetero atom to metal center is believed to be responsible for the observed high efficiency and selectivity.[6] Initially, many stoichiometric C-H bond activations were developed, and further applications of these strategies were applied to the catalytic reactions. The C-H bond activations are divided into two main categories: chelation-assisted and non-chelation activations, and have been reviewed in several important papers.[1] In this paper we will

Young Jun Park (b. 1971) received his B.S., M.S. and Ph. D degrees in Chemistry from Yonsei University in 1995, 1997, and 2003, respectively. He is currently working as a postdoctoral associate in the Department of Chemistry and the Center for Bioactive Molecular Hybrid at Yonsei University under the guidance of Professor Chul-Ho Jun.

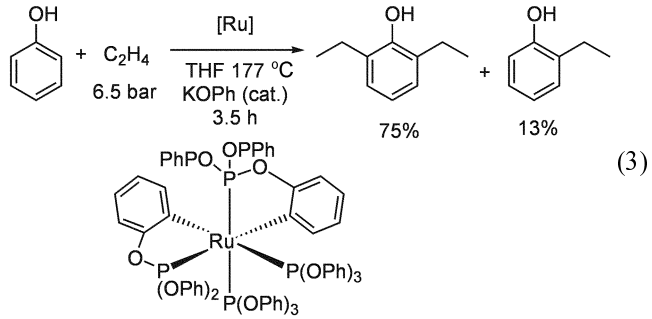
Chul-Ho Jun (b. 1953) received his B.Sc. degree in Chemistry at Yonsei University (1976), and Ph.D. from Brown University (1987) under the supervision of Professor J. W. Suggs. From 1991-1992, he worked at Yale University as a post-doctoral research fellow under Professor R. H. Crabtree. Between 1976 and 1993, he worked as a research scientist at the Agency for Defence Development in Korea. In 1993 he moved to Yonsei University as an Associate Professor, and then, in 1995 he was promoted to full Professor. He is one of NRL directors (2000-2005) and a recipient of the Korean Chemical Society Award (2004).

focus on the catalytic ortho-functionalization of aromatic compounds using the chelation assisted strategy in terms of synthetic utility.

Catalytic Ortho-Functionalization

The ability to functionalize ortho C-H bonds of aromatic compounds selectively and catalytically has very useful potential applications in organic synthesis. For example, derivatives of aromatic compounds such as alkylbenzenes, phenols, and anilines are very important chemicals to pharmaceutical applications and the fine chemical industry. A large number of methods have been reported in the literature and many chemists continue to improve this methodology. Beginning with ortho-alkylation among the ortho-functionalizations of aromatic compounds, various functional groups such as alkenyl, silyl and carbonyl can be introduced selectively and catalytically at the ortho-position. In addition, an enantioselective version of this kind of reaction has been developed. As described above, the important step in ortho functionalization is the formation of a metal-carbon bond through an oxidative C-H bond cleavage at the ortho-position. This process is facilitated by the coordinating groups, which exert a directing and stabilizing effect on the five-membered metallacyclic intermediate. The resulting intermediate reacts with an incoming substrate to yield the ortho functionalized product followed by a subsequent insertion into a metal-carbon bond and reductive elimination. In this chapter, we will briefly survey several categories of catalytic ortho-functionalization of aromatic compounds.

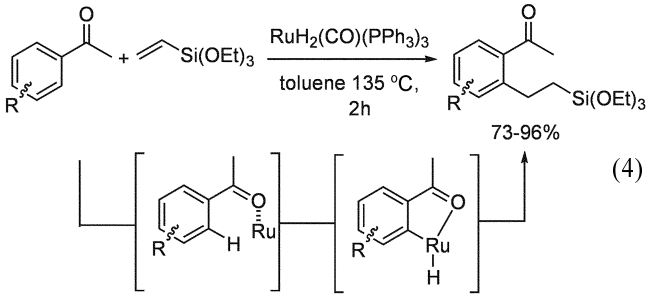
Ortho-Alkylation. The first example of ortho-alkylation was achieved with regioselective double and mono ethylations of phenol in the presence of an ortho-metalated phosphite-ruthenium complex acting as a catalyst (Eq. 3).[7]



(3)

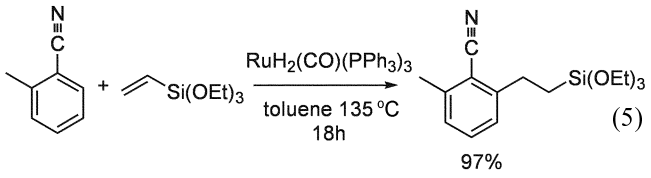
The ethylations occur at the ortho position to the hydroxy group and the double ethylation is predominant. Without phenol, ortho-ethylation on a phosphite ligand was observed. From this observation, the substitution of the phosphite ligand on ruthenium by ethylene molecules was suggested as a prerequisite stage before insertion of ethylene into the metal-carbon bond. Although this is the first case that used an ortho-metalated complex in the carbon-carbon bond forming catalytic reaction, the substrate scope was restricted to ethylene.

In 1993, Murai and his co-workers reported highly efficient and selective ruthenium-catalyzed ortho-alkylation using acetophenone derivatives and vinyl silanes as substrates (Eq. 4).[2]



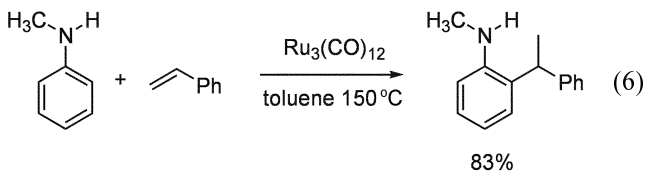
(4)

This result was a breakthrough demonstrating that ortho-alkylation could be utilized in practical organic synthesis because of its relatively broad scope of ketones. Though various aromatic ketones containing functional groups such as ester, amide, amine and ether can be used in this reaction, the olefins are strictly limited to those containing silicon such as triethoxyvinylsilane. On the other hand, in terms of ortho-selectivity and efficiency, this catalytic system is quite remarkable. Most reactions are completed within two hours and their regioselectivities can be controlled by the steric and electronic effect of substituents on aromatic ketones. In addition, the functional group tolerance of substituted ketones is also relatively good. A mechanistically interesting feature of this reaction is the chelation assistance of the carbonyl group in hydrido metallacyclic intermediate formation *via* oxygen coordination on ruthenium. Among the various coordinating groups examined by Murai, the nitrilie group is interesting to note because it used a π orbital of nitrile as a coordinating functional group (Eq. 5), though the exact mechanism is not yet clear.[8]



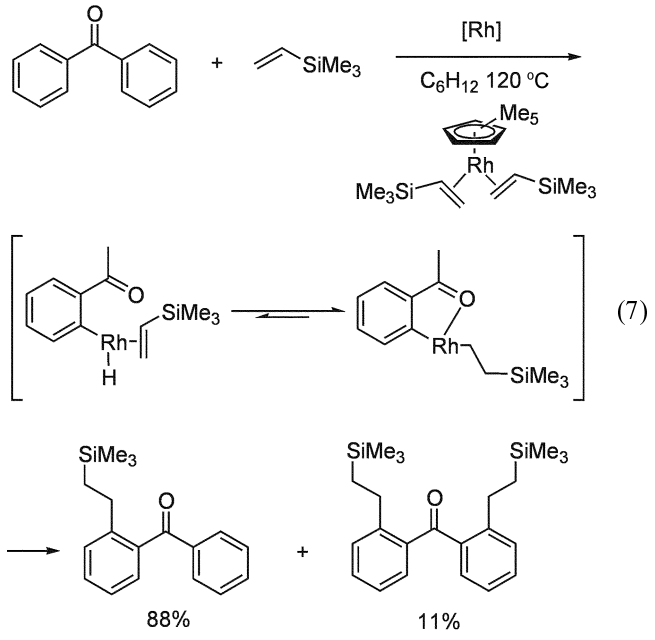
(5)

As observed in Murai's ortho-alkylation, most alkylated products are anti-Markovnikov's couplings contrary to Markovnikov's case of conventional Friedel-Crafts alkylation of aromatic compounds with olefins. Uchimaru reported that a $Ru_3(CO)_3$-catalyzed reaction of N-methylaniline with styrene could produce Markovnikov's adduct exclusively, when an amine group was used as a directing group (Eq. 6).[9]



(6)

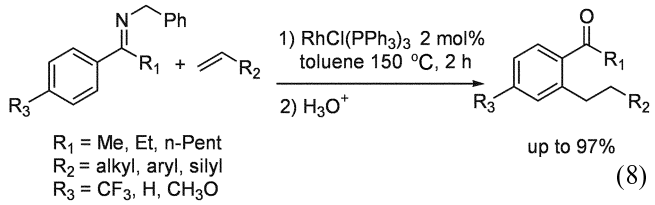
From the mechanistic point of view, a half-sandwich rhodium-catalyzed ortho alkylation shows somewhat different feature, though the reaction products are almost identical (Eq. 7).[10]



(7)

Similar to Murai's reaction, this system also exhibit high ortho-selectivity and efficiency. However, contrary to the ruthenium-catalyzed system in Eq. 5, the coordinating step of rhodium to an oxygen atom in the carbonyl group seems to be anticipated to occur prior to reductive elimination rather than C-H activation. This mechanistic proposal is supported by additional kinetic experiments and the H/D isotope exchange between aromatic ketone and vinyl silane.

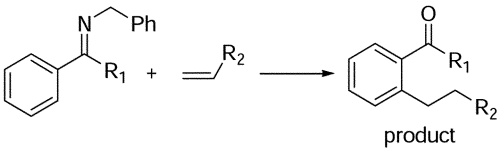
While ortho-alkylation reactions described so far show high efficiency, there still remains the limitation of choosing olefins. Most olefins should contain silane or the siloxane group. In 2000, during our experiments on transimination-assisted hydroacylation, we also found that Wilkinson complex could catalyze ortho-alkylation of aromatic imines with regioselectivity and high efficiency (Eq. 8).[11]



(8)

In contrast to Murai's ruthenium-catalyzed ortho-alkylation, with our Wilkinson complex and benzyl imine system, even terminal olefin with or without allylic protons were used successfully (Table 1). Remarkably, even dienes and internal olefins were also applicable. Another feature differing from Murai's result is that electron-withdrawing groups at para-position in the imine largely enhance the reactivity of this

Table 1.



R_1	R_2	Yield (%)	R_1	R_2	Yield (%)
CH_3	t-C_4H_9	97	CH_3CH_2	$(CH_3)_3Si$	93
CH_3	C_6F_5	91	n-C_5H_{11}	$(CH_3)_3Si$	73
CH_3	Cy	65			
CH_3	n-C_4H_9	94		Olefin	
CH_3	n-C_6H_{13}	71	CH_3		95[a]
CH_3	n-$C_{10}H_{25}$	82	CH_3		42[b]
CH_3	$(CH_3)_3Si$	92	CH_3		35[c]

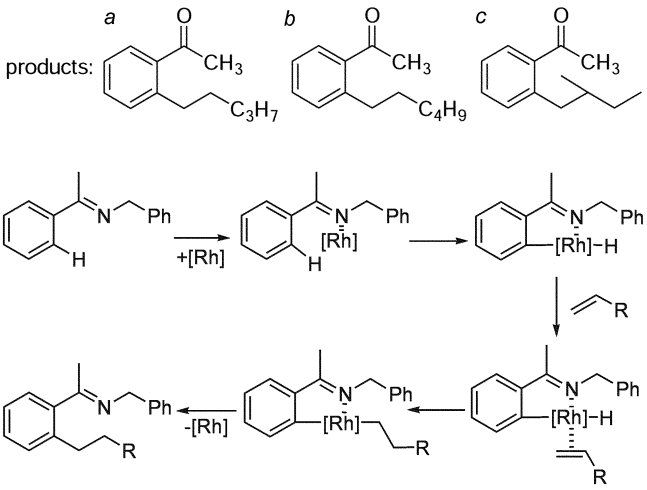
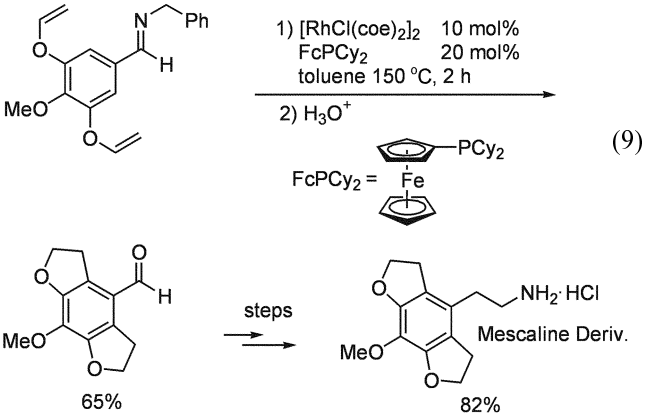


Figure 1

system. From a mechanistic point of view, our system exhibits a similar reaction pathway scenario (Figure 1). The precoordination of the imine group, through the nitrogen atom to the rhodium center, assist cleavage of the ortho C-H bond in the selective activation of an aromatic C-H bond. And then, olefin coordination leads to the insertion of the metal-hydride bond into olefin. Finally, reductive elimination gives the ortho-alkylated products.

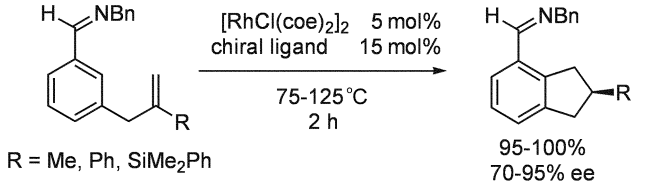
The usefulness of our ortho-alkylation system consisting

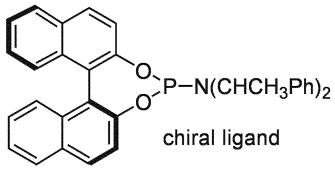


(9)

of benzyl imine and a rhodium catalyst was further proved separately by Bergman *et al.* in 2003 (Eq. 9).[12] They demonstrated that an intra-molecular version of ortho-alkylation could be utilized in a synthesis of bio-active molecules such as mescaline derivatives.

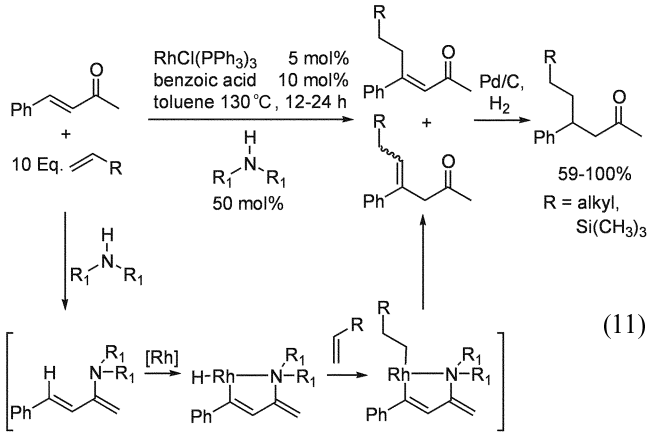
Bergman also reported in 2004 highly efficient and enantioselective intramolecular cyclization of aromatic imines of benzylamine (Eq. 10).[13] Though various ortho-alkylation reactions through chelation assistance have been developed as described so far, enantioselective transformation using this strategy is extremely rare. To achieve a high yield with enantioselectivity, a bulky monodentate chiral phosphoamidite ligand was used. It is remarkable that very good enantioselectivties are observed even under a relatively high reaction temperature.





(10)

This chelation-assisted cyclometalation strategy could be extended to β-alkylation of aliphatic sp^2 C-H bond (Eq. 11).[14] When enone reacted with excess olefin in the presence of Wilkinson complex, benzoic acid and secondary amine at 130 °C for 12 h, β-alkylated products were obtained in good yields. From some experimental results, the following mechanism was proposed: dienamine might be a key intermediate of the reaction since β-alkylation did not occur at all in the absence of secondary amine. Thus, the simple chelation of a rhodium type to the nitrogen atom is an important factor for the efficiency of the reaction.



(11)

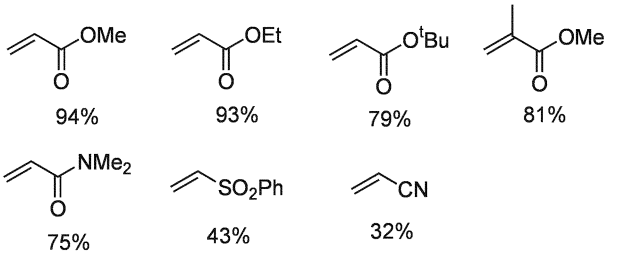


Figure 2

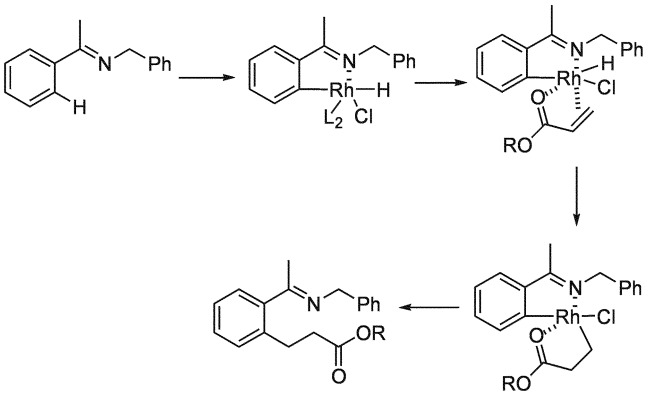
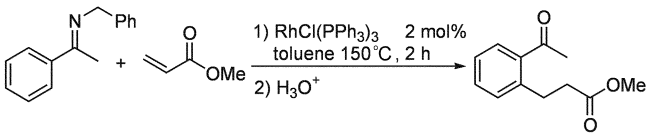


Figure 3

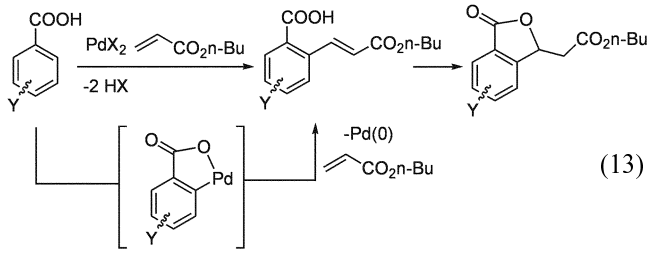
The most notable progress in ortho-alkylation was made by our group in 2004 (Eq. 12).[15] By that time many improvements for the scope of olefin were achieved by us and others, but olefin bearing functional groups could not be introduced to aromatic compounds through an ortho alkylation method. Fortunately, we found that our Wilkinson complex and benzyl imine system could tolerate various functional groups in olefin substrates. For example, olefins containing ester, amide, sulfonate and nitrile groups are effectively applied to our ortho alkylation system with a good efficiency outcome (Figure 2). By closer inspection of this interesting olefin substrate, we suggested that there might be chelation effects of substrates during the olefin coordination process (Figure 3). Indeed, these functionalized olefins are much more reactive than "nonfunctionalized" olefins. On the other hand, when rhodium cationic species were employed as a catalyst, much higher yields of ortho-alkylated products could be obtained, even at lower temperatures.



(12)

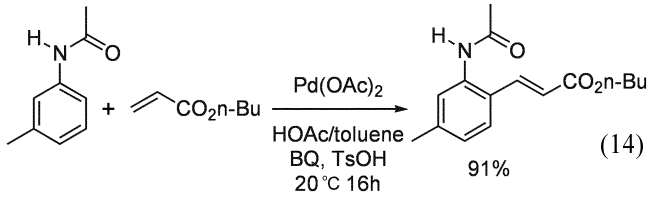
Ortho-Alkenylation. Catalytic alkenylation reactions are useful methods for producing styrene derivatives, which are versatile starting materials in organic synthesis such as polymer production. One of the most popular methods is the catalytic coupling of aromatic halide with olefins, a Heck

reaction. However, a Heck reaction should be accompanied by large halide salts as a by-product. Thus, it would be preferable if this kind of transformation could be accomplished *via* a C-H bond activation rather than a carbon-halide one. In 1998, a palladium-catalyzed oxidative coupling reaction using a carboxylic group as an ortho directing group was reported by Miura (Eq. 13).[16]



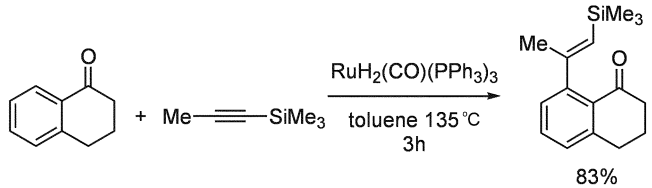
(13)

In this reaction, the carboxylic group plays an important role in cyclopalladation through chelation assistance. Consequently, most substitutions occur regiospecifically. A similar reaction was reported using chelation assistance with the amide group (Eq. 14).[17] This reaction can be performed without directing functional groups, however, the previous regioselectivity could not be conserved. This example is interesting in that it shows that chelation assistance could be applied to electrophilic C-H bond activation.



(14)

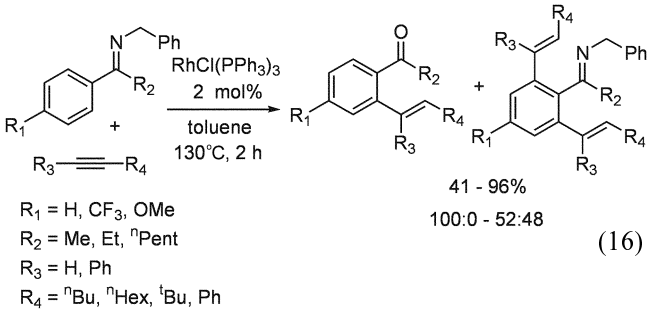
Ortho-alkenylation using the same protocol as Murai's ortho-alkylation is rare. Only a few examples are reported to date. One such example is the ruthenium-catalyzed reaction of a specific ketone such as α-tetralone with a silyl group containing internal alkynes (Eq. 15).[18] However, in this case also, the limitations in olefin choice still remains.



(15)

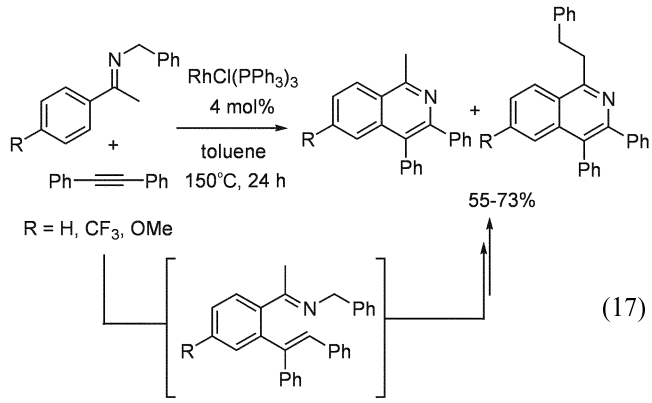
In 2003, based on our ortho alkylation strategy using Wilkinson complex and benzyl imines, we reported the rhodium-catalyzed direct ortho-alkenylation of common aromatic benzyl imine with terminal alkynes as well as internal alkynes (Eq. 16).[19]

The reaction of benzyl imine of acetophenone with several terminal alkynes afforded mono- and double-alkenylated



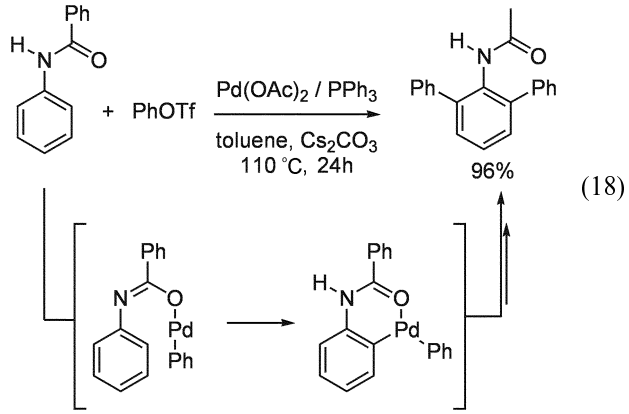
(16)

products, depending on both substituents of alkyne and aromatic imine. Interestingly, when more vigorous conditions were employed, we found that two isoquinoline derivatives were unexpectedly formed from the reaction of benzyl imine with diphenylacetylene (Eq. 17). At present, the mechanism for the formation of such isoquinoline derivatives is not clear, but it is believed that mono alkenylated species might be a key intermediate for this tandem-alkenylation cyclization.



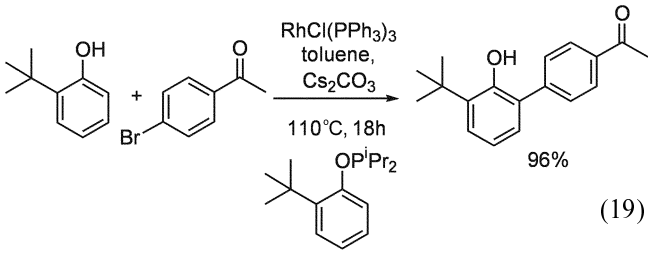
(17)

Ortho-Arylation. Catalytic arylation through C-H bond activation is very interesting because such a transformation could be an alternative synthetic methodology for an aryl-aryl coupling reaction such as Suzuki reaction. One of the important advances in this regard is the palladium-catalyzed aryl-aryl coupling between benzanilide and aryl triflate (Eq. 18).[20]



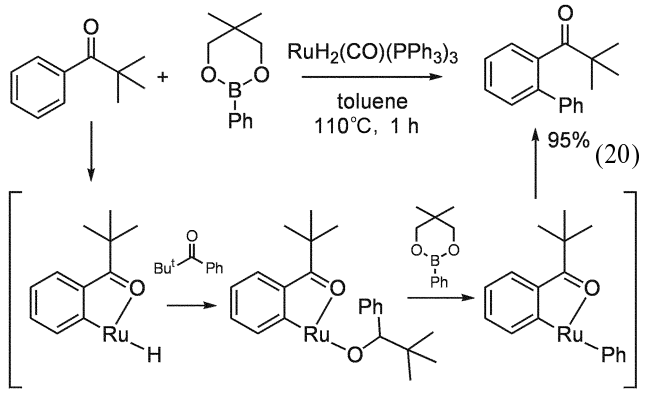
(18)

Also in this case, an oxygen atom of the amide group is responsible for the observed selective double ortho-arylation. Recently, a rhodium-catalyzed aryl-aryl coupling reaction of aryl halide with phenol was also reported (Eq. 19).[21] In this reaction, the additional co-catalyst, phosphinite, played a significant role in the electrophilic substitution at the ortho position.



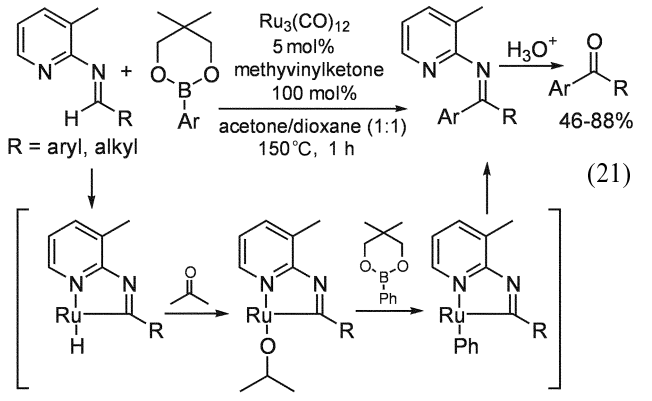
(19)

Another interesting class of ortho-arylation was reported by Kakiuchi (Eq. 20).[22] The mechanism of this reaction is very similar to Murai's ortho-alkylation in that a hydrido ruthenacyclic intermediate is involved. The ruthenium-hydride inserts into the carbonyl group of another ketone substrate instead of olefins. The resulting alkoxoruthenium species are transmetalated with a boron reagent to form the intermediate aryl-ruthenium. Finally, reductive elimination furnishes ortho arylated ketones.



(20)

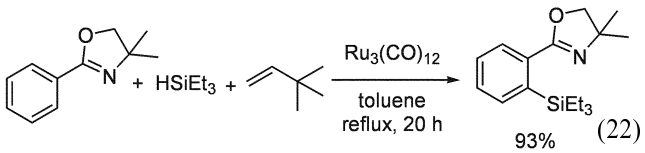
Very recently, we reported that aromatic imines of 2-amino-3-picoline could undergo an efficient $Ru_3(CO)_{12}$-catalyzed coupling reaction with various aryl boronates through chelation-assisted C-H bond activation (Eq. 21).[23]



(21)

The alkoxoruthenium species derived from the reaction of hydrido ruthenium with acetone is believed to be a key intermediate as found in Kakiuchi's ortho-arylation. The most important feature of this novel imine-aryl coupling reaction is that aliphatic imines are also effective substrates.

Ortho-Silylation. For catalytic dehydrogenative silylation of arenes and alkanes, additional hydrogen acceptors are necessary since this process is thermally disfavored reaction. Once this requirement is fulfilled, selective ortho silylation can be accomplished via chelation assistance (Eq. 22 and 23).[24,25] In these cases, various directing groups are applicable such as imine, amine, pyridyl, azoles and ester functions.



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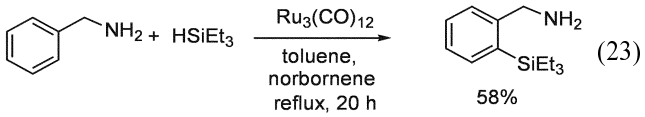
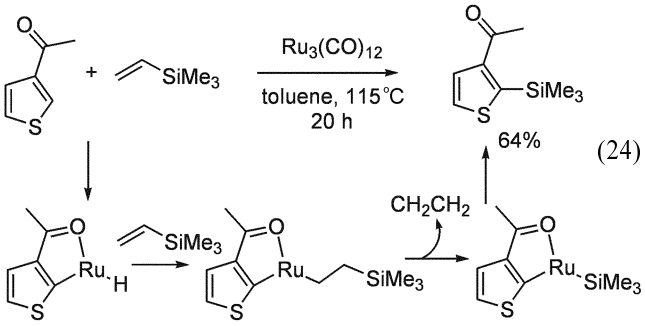


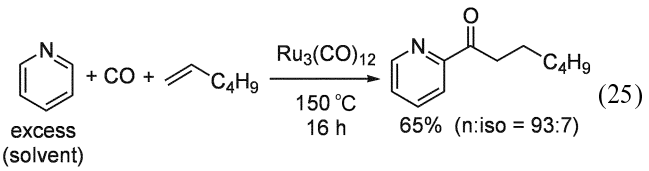
(23)

From the mechanistic point of view, vinylsilane is a unique silylating reagent since additional hydrogen acceptors are not necessary in this system (Eq. 24).[26] During the reaction, vinylsilane serves as both a hydrogen acceptor and a silylating reagent with the generation of ethylene.



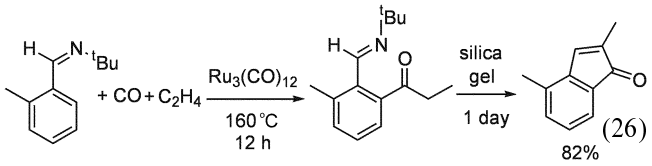
(24)

Ortho-Carbonylation. Carbonylation leading to ketone as a product can be performed in thermal conditions because it is an exothermic reaction. In 1992, Moore reported that the reaction of pyridine with carbon monoxide and olefin in the presence of $Ru_3(CO)_{12}$ produces an acylated product at α position (Eq. 25).[27] In this case, the existence of the chelation assistance of pyridine is not clear but the observed regio selectivities are interesting. On the other hand, Murai reported that aromatic aldimine gave indenones through a



(25)

chelation-assisted carbonylation reaction at the ortho-position followed by an intramolecular aldol reaction (Eq. 26).[28]



(26)

Concluding Remarks

Since the seminal report by Murai in 1993, significant advances have been made in the area of ortho function-alization reaction using a chelation-assisted strategy. While the history of this transformation is relatively short, various high yielding reactions with a variety of substrate classes have been accomplished by many synthetic chemists, including an enantioselective version. Of particular useful-ness is the ability to perform these reactions in a highly regio-selective fashion, which will makes this transfor-mation valuable to fine chemical and novel materials synthesis. We believe that this reaction will become increasingly more important due to its potential and the fact that many challenges such as enantioselective reaction still remain.

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