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# Transition metal-catalyzed C-H functionalization of *N*-oxyenamine internal oxidants

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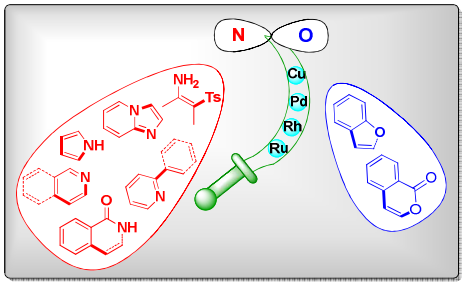


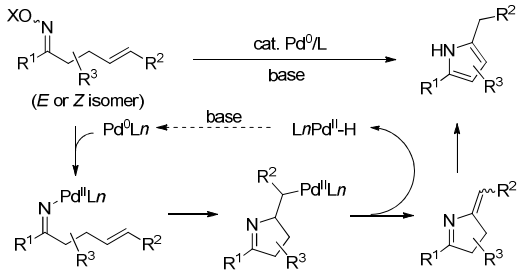

**Abstract:**

The transition metal-catalyzed C-H functionalization with hydroxylamine derivatives serving as both reactants and internal oxidants has attracted a lot of interest. These reactions obviate the need for external oxidants and therefore find high reactivity and selectivity, as well as excellent functional group tolerance under mild reaction conditions, and moreover, water, methanol or carboxylic acid is generally released as the by-product, thus leading to reduced waste. This review focuses on the transition metal-catalyzed oxidative C–H functionalization of *N*-oxyenamine internal oxidants, with an emphasis on the scope and limitations, as well as the mechanisms of these reactions.

## 1. Introduction

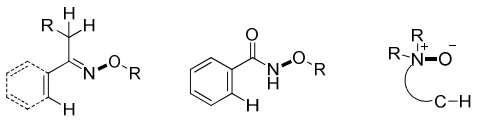
Hydroxylamines are very important compounds in organic chemistry, and have been widely applied in organic synthesis.[1] The structures bearing an *N*-oxyenamine moiety are considered as quite unstable due to the weak N−O σ bond with an average energy of ~57 kcal/mol, which is much less than the energies of the $\sigma_{C-X}$

(X = C, N, O) (69−91 kcal/mol) bonds.[2] As a consequence of the low strength, the N-O bond cleavage of hydroxylamine derivatives was generally favored, thus frequently being utilized to initiate further transformation for constructing a range of functionalized molecules. An ingenious synthetic strategy is to design hydroxylamine derivatives as both reactant and oxidant towards transition metal-catalyzed oxidative C-H functionalization, which is often called "internal oxidant". Internal oxidant is an emerging concept which has been introduced initially as oxidizing directing groups in C-H activation reactions. In a broad sense, however, transition metal-catalyzed reactions using *N*-oxyenamine internal oxidants had been developed over the years far before the concept emerged. Typical examples include Pd-catalyzed intramolecular *aza*-Heck cyclization (Scheme 1) and Cu-catalyzed amination with ketone oximes as the internal oxidant, which was seminally studied by Narasaka and co-workers in the late 20th century.[3] Indeed, some elegant amino-Heck reactions and intermolecular aminations based on *N*-oxyenamine derivatives and Pd or Cu catalysis were disclosed in the last decade. However, we consider these being rather a competent application than a fundamentally new concept, which therefore will not be discussed in this review. Notably, as a variant of *N*-oxyenamine internal oxidants, using N-N bond as internal oxidant has also attracted certain attention in recent years.[4-6] While high reactivity and selectivity are observed in these transformations, the starting materials are often not easily available, and moreover, the *N*-moiety released would more seriously cause environmental issues.




Scheme 1

This review is dedicated to showcase and discuss recent progress in the field of transition-metal catalyzed C-H functionaliztion[7-13] of the molecules bearing an *N*-oxyenamine internal oxidant. Among them, the N-O bond reductive cleavage directly leads to the generation or regeneration of the active metal catalyst. So to that extent three types of hydroxylamine derivatives were generally utilized as internal oxidants in transition metal-catalyzed C-H functionalization: oximes, hydroxamic acids, and *N*-oxides (Scheme 2). As shown, ketoxime $\alpha$ $C_{sp3}$-H functionalization or neighboring group-oriented $C_{sp2}$-H activation would be triggered by the united effort of a metal catalyst and the *N*-oxyenamine moiety. Likewise in the cases of hydroxamic acids and *N*-oxides, neighboring group-oriented $C_{sp2}$-H activation generally occurred to initiate directly oxidative C-C bond coupling or heterocyclization with final N-O bond cleavage under transition metal catalysis.



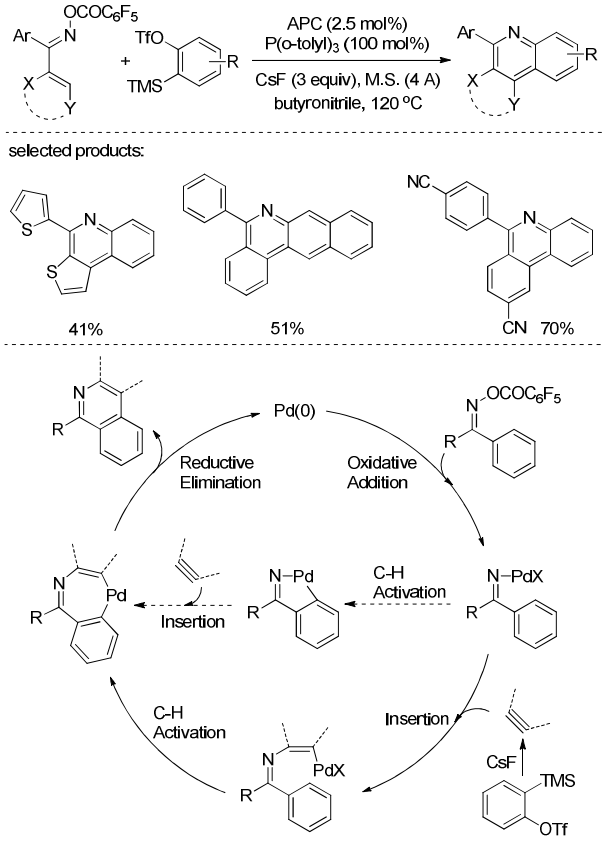

Scheme 2

## 2. Oximes as internal oxidants

### 2.1 Pd-catalyzed reactions

For the facile and highly efficient elaboration of *N*-heterocycles, Narasaka-Heck cyclization generally refers to palladium-catalyzed intramolecular processes.[3] On the other hand, the high activity of the imino-$Pd^{II}$ intermediate derived from the oxidative addition of an *N*-oxyenamine to $Pd^0$ would enable intermolecular transformations through traping the imino-$Pd^{II}$ intermediate by external reaction partners. In 2009, Neuville and Zhu *et al.* found benzynes and electron-deficient alkynes could efficiently trap the imino-$Pd^{II}$ intermediate from the oxidative insertion of Pd(0) species into the N-O bond of an acyloximes (Scheme 3).[14] The synthetic significance of this discovery is well documented with the fact that a range of phenanthridine and isoquinoline derivatives were prepared in moderate to good yields by the

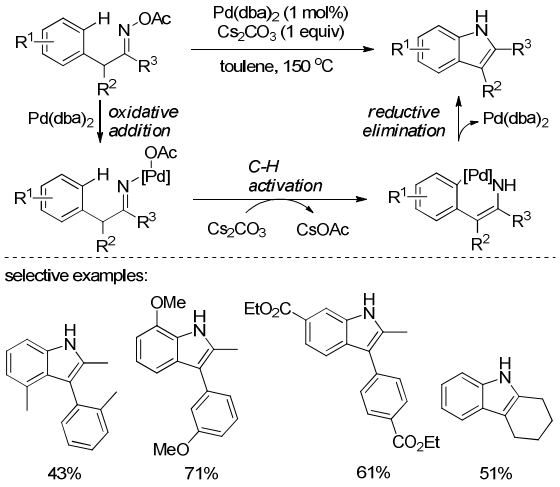
intermolecular reaction of biaryl oximes and benzynes (alkynes). Notably, the oximes bearing an aryl and an alkyl group proved to be poor substrates, affording the expected products in rather low yields. The authors hypothesized that imine-enamine tautomerization would lead to some unproductive reaction pathways. As shown, two reaction pathways were proposed for the final products with predominantly different sequence between the *ortho* C-H activation process and the benzyne (or alkyne) insertion.




Scheme 3

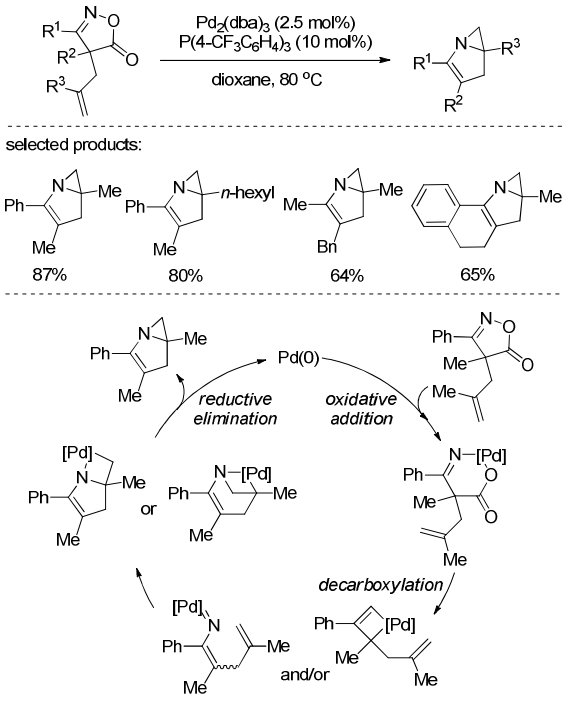
One year later, Hartwig *et al.* reported a method for palladium-catalyzed intramolecular aromatic C-H bond amination for the synthesis of 3-arylated and annulated indoles, albeit in moderate yields (Scheme 4).[15] The oxime ester moiety as firstly an internal oxidant initiates the generation of the imino-$Pd^{II}$ intermediate, and then as a directing group assists the *ortho* C-H metalation, with a subsequent reductive elimination/C-N bond formation to afford the final indoles. Remarkably, the authors isolated an imino-$Pd^{II}$

complex when treating the pentafluorobenzoyl oxime ester with a stoichiometric amount of $Pd(PCy_3)_2$. The structure was confirmed by X-ray diffraction. It was shown positively either to catalyze the cyclization reaction or to convert directly to the final indole products. Moreover, this imino-$Pd^{II}$ complex is the first isolated complex formed by oxidative addition of an N-X bond (X = N, O, halide) to Pd(0), which would inspire other Pd(0)-catalyzed transformations from oximes.




Scheme 4

Cyclic oxime esters such as 4*H*-isoxazol-5-ones were judiciously designed for Pd(0) catalytic systems by Ohe *et al.*, and found high activity in the decarboxylation-involved aziridination reaction (Scheme 5).[16] This method provides a novel and facile entry to diversified polycyclic aziridine derivatives, which can be conveniently converted to other novel functionalized products by simple addition/ring-opening reactions. Furthermore, the cyclic oxime esters can be readily prepared from *β*-ketoesters and are generally thermally stable. These all make Pd-catalyzed oxime transformations particularly fascinating and attractive. In this particular case, the authors proposed that the cyclic imino-Pd(II) formed through oxidative addition would be rapidly converted to a vinylnitrene/palladium complex and/or four-membered azapalladacyclobutene intermediate, which would undergo cycloaddition with the tethered alkene, with a subsequent reductive elimination to produce the bicyclic aziridine products (Scheme 5).

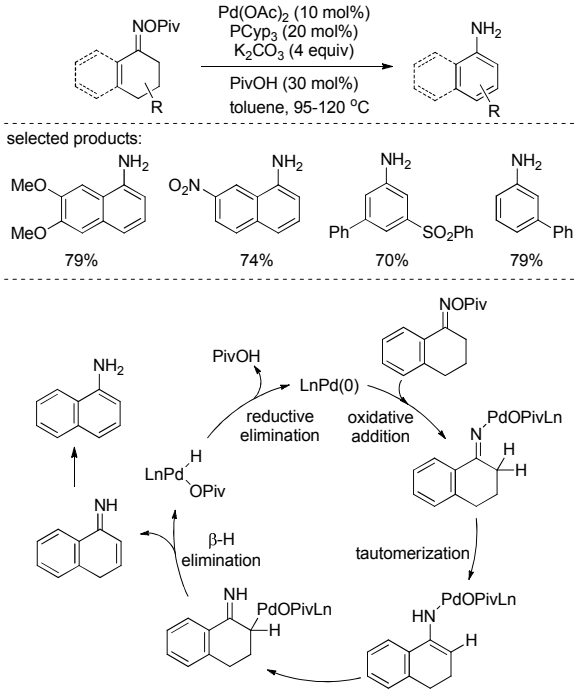



Scheme 5

The Semmler−Wolff reaction is a classic but rarely used method for the synthesis of aromatic primary amines from cyclohexenone- and tetralone-derived oximes due to the inevitability of harsh reaction conditions. In 2013, Stahl *et al.* developed a Pd(0)-catalyzed Semmler−Wolff reaction for the conversion of substituted cyclohexenone oxime esters to primary anilines (Scheme 6).[17] Initially, *O*-pentafluorobenzoyl and *O*-pivaloyl oxime derivatives were found to lead to the highest yield of the desired products, and the authors opted to proceed with pivaloyl oxime derivatives rather than the more expensive pentafluorobenzoyl derivatives. In the present system, a broad range of primary aniline and 1-aminonaphthalene derivatives were prepared in moderate to excellent yields, which were generally much higher than those obtained by traditional methods. Moreover, several pharmaceutically active compounds were successfully achieved from the resultant 1-aminonaphthalenes with considerable yields.

The oxidative addition of the oxime N−O bond to Pd(0) species in this work has been confirmed by the isolated imino-Pd(II) intermediate, which simply resulted from a stoichiometric reaction. Based on this

observation and previous studies on cyclohexanone dehydrogenation, a plausible mechanism was proposed for this Pd-catalyzed Semmler−Wolff reaction. The oxidative addition and subsequent tautomerization afford enamine-derived amido-Pd(II) species. Further isomerization of this species results in the coversion of this *N*-bound enamido−Pd(II) species to its *C*-bound isomer. *β*-Hydride elimination and subsequent tautomerization generate the final 1-aminonaphthalenes. Additionally, the authors speculated that the additional pivalic acid in the system could facilitate the proton-transfer process involved in the tautomerization step.

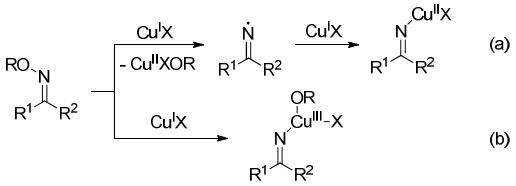



Scheme 6

## 2.2 Cu-catalyzed reactions

Based on Narasaka's pioneering works involving copper-catalyzed transformations of oximes, we can summarize herein two interactive patterns between Cu(I) complex and oximes: (1) radical reduction of oxime N-O bond by Cu(I) to form imine radical intermediate, which would further associate Cu(I) to form Cu(II) complex (Scheme 7a); (2) oxidative insertion of Cu(I) species into the N-O bond to afford Cu(III)

intermediate (Scheme 7b). Both copper complexes are highly active and enable to initiate further transformation for direct bond formation or *N*-heterocycle synthesis. Recently, a number of elegant works have been reported to prepare various nitrogen-containing motifs. Simultaneously, they have in turn proved the rationality of the two patterns.

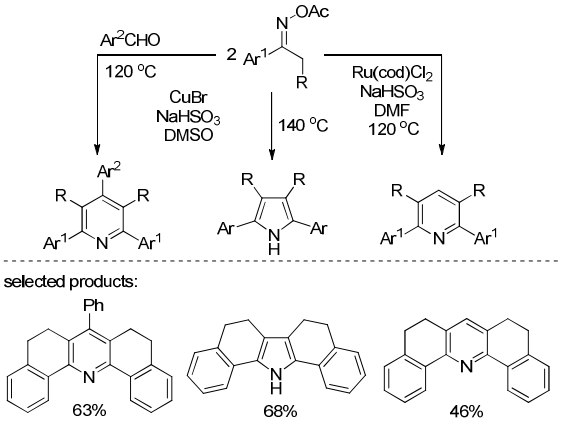



Scheme 7

### 2.2.1 Cu-catalyzed heterocyclization reactions from oximes

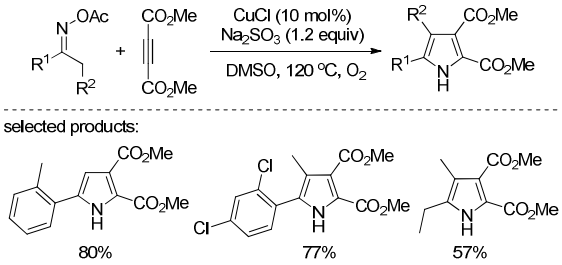
Cu-catalyzed transformations of oximes could provide facile methods for direct C-heteroatom bond formation in a redox manner, which has been well established by early developed amination.[3] These transformations are of great potentials for the construction of nitrogen-containing heterocyclic compounds. In recent years, Guan *et al.* developed a series of methods for the synthesis of symmetrical N-heterocycle compounds from two molecules of oxime acetates (Scheme 8). Treated with aldehydes under the catalytic CuBr/$NaHSO_3$/DMSO system, oxime acetates afford highly substituted pyridines.[18] This method tolerates a wide range of functional ketone oximes and aryl aldehydes, and allows rapid and efficient elaboration of oxime acetates into highly substituted pyridines. Notably, the authors disclosed that $NaHSO_3$ as an additive in the reaction could efficiently inhibit the hydrolysis of oxime acetates into ketones. Recently, under the same CuBr/$NaHSO_3$/DMSO catalytic system, Guan *et al.* developed an efficient synthetic protocol for symmetrical pyrroles from aryl alkyl ketoxime acetates in the absence of aldehydes.[19] Elevated reaction temperature (140 $^{o}$C) is required for this system. All the same, methyl ketoxime acetates show very low reactivity. For example, acetophenone oxime affords 2,5-diphenyl pyrrole only in 10% yield. Not long afterward, Ru-catalyzed cyclization of two molecules of ketoximes with DMF was described for the synthesis

of tetrasubstituted symmetrical pyridines.[20] In this case, *N*-acyliminium ion, which derived from DMF by initially $Ru^{II}$-mediated oxidation, displaces aryl aldehyde to serve as a source of a one carbon synthon. Despite the overall efficiency of these methods, it would be more practical if the authors designed the synthesis of asymmetrically substituted heterocycles based upon the proposed inspiring mechanism.



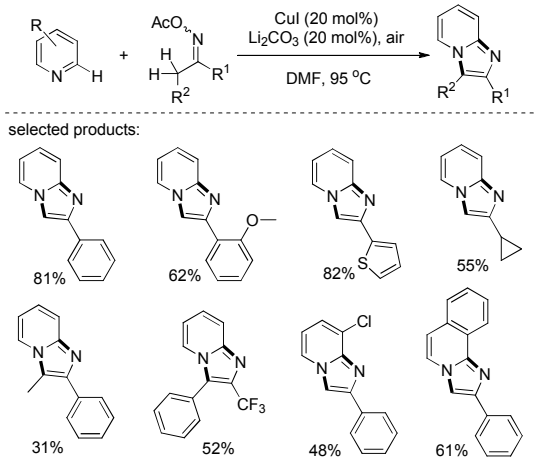

Scheme 8

To develop a more practical method for pyrrole synthesis from oximes, Jiang and co-workers described a $CuCl/Na_2SO_3$/DMSO catalytic system, in which asymmetrically substituted pyrroles have been accessed via a formal oxidative [3 + 2] cycloaddition of ketoximes and electron-deficient alkynes.[21] Generally, the reaction of oxime acetates with dimethyl acetylenedicarboxylate (DMAD) smoothly give the desired products in moderate to good yields (Scheme 9). Methyl and non-methyl ketoximes feature the same high reactivities. It is worth mentioning that dialkyl oxime acetates such as 3-pentanone oxime acetate are also fruitful, affording the corresponding alkyl-subsituted pyrroles. Oxygen atmosphere is critical to the present transformation. That prompts us to speculate that a $Cu^{III}$ intermediate may be involved in the reaction process.




Scheme 9

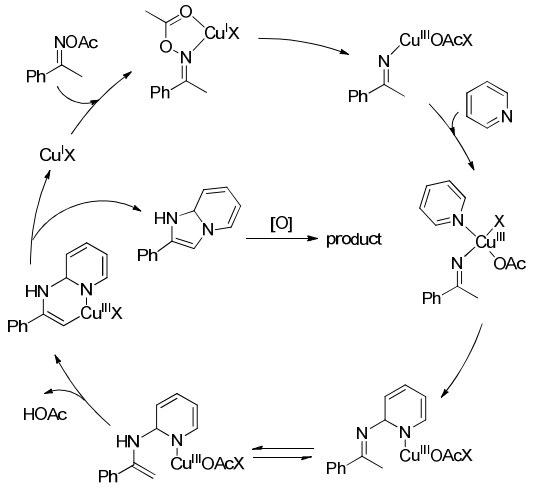
Direct functionalization of unactivated pyridine remains a significant challenge. In 2013, the same group discovered that the highly active intermediate derived from oxime ester and copper catalyst could activate the pyridine C-N double bond. This seminal discovery provides an opportunity to ideal access to pyridine-fused compounds.[22] With a crucial additive $Li_2CO_3$, the oxidative cyclization affords a broad range of substituted imidazo[1,2-*a*]pyridines in moderate to good yields (Scheme 10). Aryl, alkyl, methyl, and non-methyl oximes are all fruitful substrates. Isoquinolines also react well with oximes to give imidazo[1,2-*a*]isoquinolines in moderate yields. This protocol features advantages including high efficiency, inexpensive catalyst, economic and environmentally friendly oxidant, and water as the byproduct. Moreover, it might open up a new way to construct complex molecules through direct conversion of unactivated pyridines.




Scheme 10

With the fact that the addition of a free radical scavenger TEMPO or ethene-1,1-diyldibenzene could

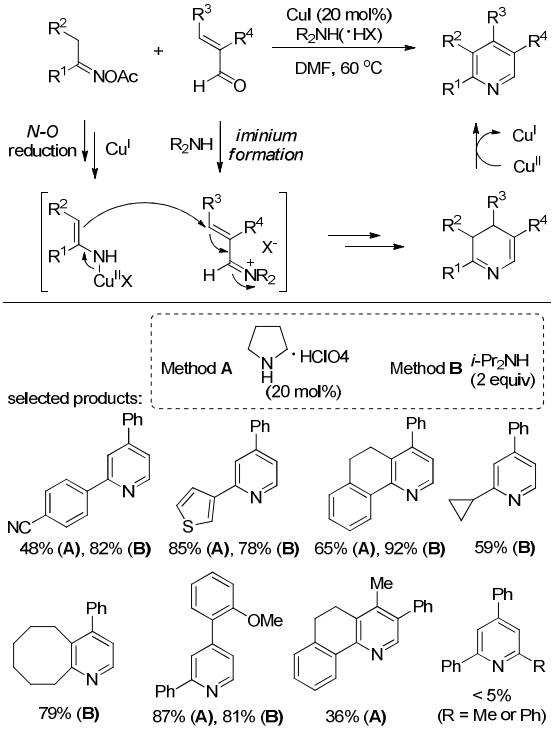
not prohibit the cyclization, they proposed a organometallic or $Cu^{I}/Cu^{III}$ catalytic system (Scheme 11), in which the oxidative insertion of a Cu(I) species into the N-O bond would be the first step. The resulting Cu(III) intermediate would undergo migration insertion into pyridine C-N double bond. Then intramolecular H-abstraction and subsequent reductive elimination afforded the cyclized intermediate, with an oxidative aromatization to give the final imidazo[1,2-*a*]pyridines. Notably, such a reaction pathway probably provides the basis for the high regioselectivity observed when C3-subsituted pyridines were used.




Scheme 11

For the copper-catalyzed heterocycle synthesis from oximes, Yoshikai *et al.* designed a cascade reaction for modular pyridine synthesis from oximes and enals through synergistic copper/iminium catalysis.[23] After optimization study, the authors defined the methods using pyrrolidinium salt (20 mol%) and *i*-$Pr_2NH$ (2 equiv) as methods A and B, respectively (Scheme 12). Generally, the desired products were obtained in moderate to good yields with a wide range of ketoxime esters well tolerated, including those derived from aryl, heteroaryl, alkenyl, and alkyl ketones and even cyclic ketones. And *β*-aryl enals led to the final pyridines with higher efficiency than alkyl substituted reactants. As for the reaction mechanism, a synergistic catalytic system was proposed to clarify the reaction pathway, in which the copper(I) catalyst activates oximes to form a key copper(II) enamide intermediate, and simultaneously an iminium ion is

afforded from enal and secondary ammonium salt. Then Michael addition and subsequent condensation cyclization lead to dihydropyridine products, with a rapid oxidation by copper(II) to furnish the final pyridines and release the catalytically active Cu(I) species. In addition to Yoshikai's pyridine synthesis, very recently, Cui and co-workers reported an efficient Cu(I)/piperidine/DCE catalytic system for the preparation of 2-aminonicotinonitriles from oximes and enenitriles.[24]

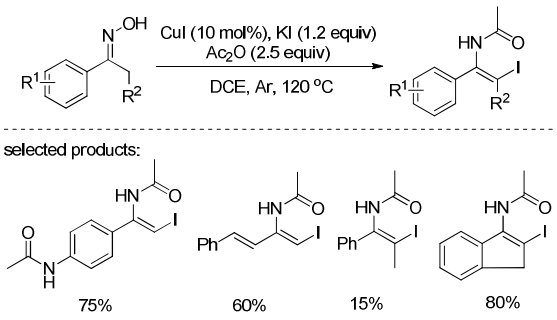



Scheme 12

### 2.2.2 Direct *α*-functionalization of ketoximes

The cross coupling reactions of ketone oximes could proceed at the ketone *α*-position under copper catalytic systems because of the high level of activity of the *α* C-H bonds. Guan *et al.* reported, in 2013, copper-catalyzed direct synthesis of iodoenamides from ketoximes by oxidative C-I bond formation.[25] With CuI being the best calalyst and inorganic KI providing an iodine source, this reaction is successful with various methyl ketone-derived oximes bearing different functional groups, such as methoxyl, halogen, acetylamino, and even nitro group, leading to the corresponding iodoenamide products with complete

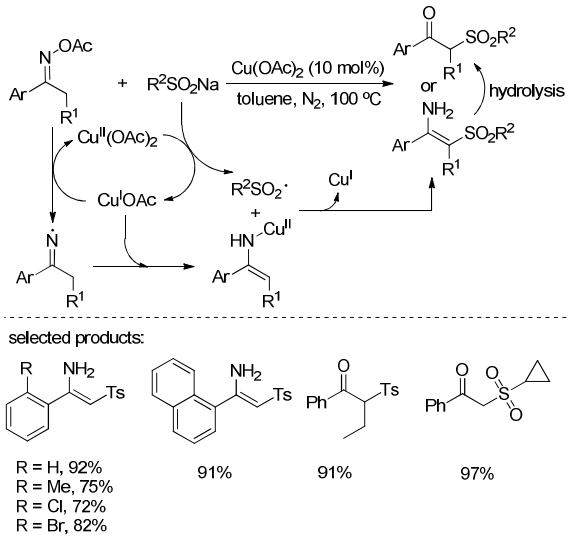
(*Z*)-stereoselectivity and moderate to good yields (Scheme 13). This oxidative coupling is gram-scalable with a considerable yield. Moreover, the resultant *Z*-iodoenamide products are flexible building blocks. The authors proposed a single electron-transfer pathway based on a series of control experiments including radical-trapping reaction with TEMPO adding into the system.




Scheme 13

Jiang and co-workers recently applied ketone oximes bearing an alkyl group in direct oxidative C-S bond formation at the ketone $\alpha$ position with sodium sulfinates as the coupling partner, providing a novel entry to $\beta$-sulfonylvinylamines (Scheme 14).[26] $\beta$-Ketosulfones are important synthetic intermediates for the construction of a broad range of useful molecules. Thus in this work, $\beta$-ketosulfones were defined as the target molecules through a simple hydrolysis of the $\beta$-sulfonylvinylamine products. A number of *para*- and *meta*-substituted acetophenone oxime acetates coupled well with aryl and alkyl sodium sulfinates, affording the desired $\beta$-ketosulfones in good to excellent yields by two-step operation. Interestingly, while *ortho*-F- or OMe-substituted acetophenone oxime as the substrate afforded the desired $\beta$-ketosulfone product, oximes with *ortho*-Cl, Br, and Me functional groups gave $\beta$-sulfonylvinylamines. The corresponding $\beta$-ketosulfones were obtained only after a treatment with strong acid. Although a radical mechanism would be involved with sodium sulfinates, the results from mechanistic experiments can not rule out an organometallic pathway in this transformation. Therefore, alternatively the C-S bond reductive elimination of a Cu(III) intermediate is proposed to be an reaction pathway. With oximes as internal

oxidants, this work shows advantages including simple and mild conditions, reduced waster formation, and more importantly very high efficiency of this transformation.

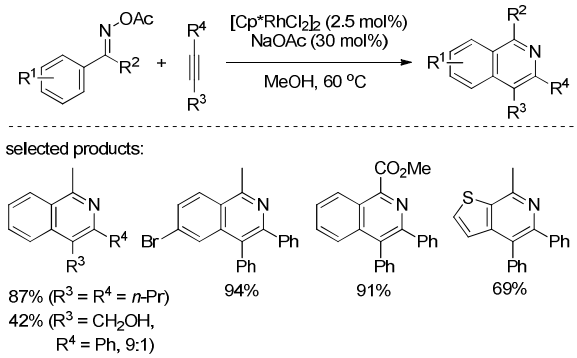



Scheme 14

### 2.3 Rh-catalyzed C-H activation of oximes

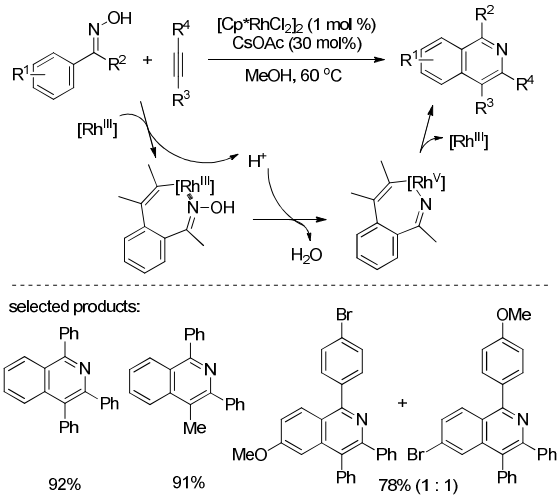
In 2010, Chiba *et al.* reported the first example of Rh(III)-catalyzed synthesis of isoquinolines from aryl ketone *O*-acyloxime derivatives and internal alkynes.[27] The use of $[Cp^*RhCl_2]_2$ catalyst makes this transformation occurs under rather mild conditions (60 °C), and inorganic base NaOAc as an additive is required[28] for this transformation. The present methodology shows wide substrate tolerance with aryl ketone *O*-acyloxime derivatives and internal alkynes, affording the desired products in moderate to excellent yields (Scheme 15). Unsymmetrical alkynes give isoquinolines with high regioselectivity, albeit in moderate yields. Mechanistically experimental data suggests that C-H rhodation initiates the catalytic cycle and is believed to be the rate-determining step, and a 6$\pi$-electrocyclization-based mechanism is most likely ruled out. However, problems related to the C-N bond coupling and N-O bond cleavage remain unsolved, and both stepwise and synergistic pathways are possible. One year later, the same group disclosed Cu-Rh bimetallic relay catalysts for the synthesis of azaheterocycles from aryl ketone *O*-acetyl

oximes and internal alkynes. In this system, $Cu(OAc)_2$ as a redox-active additive improved the overall activity level of bulky aryl ketoxime acetates, and a large number of pyridine-fused heterocycles have been efficiently accessed.[29]




Scheme 15

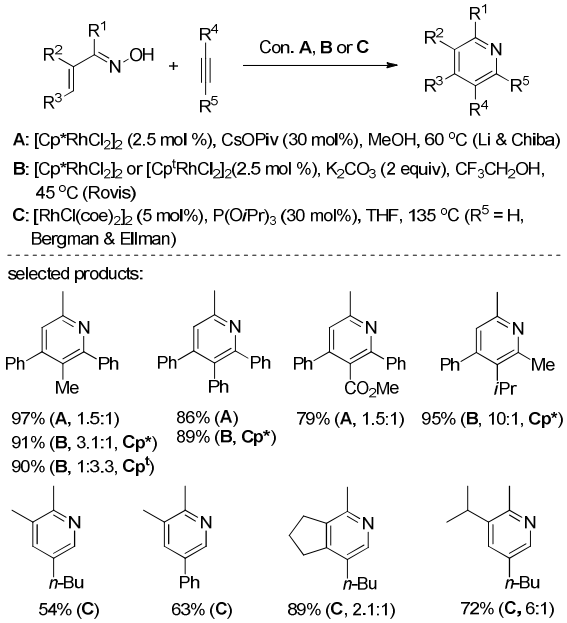
Li *et al.* also described, in 2011, isoquinoline synthesis from aryl ketone oximes and internal alkynes with a slightly lower loading of the $[Cp^*RhCl_2]_2$ catalyst (1 mol %) and CsOAc (30 mol %) as an efficient additive.[30] This method shows high synthetical efficiency (15 examples being given in 35-95% yields). Moreover, for the first time a novel C-N reductive elimination from Rh(V) intermediate was proposed based upon mechanistically experimental results (Scheme 16).




Scheme 16

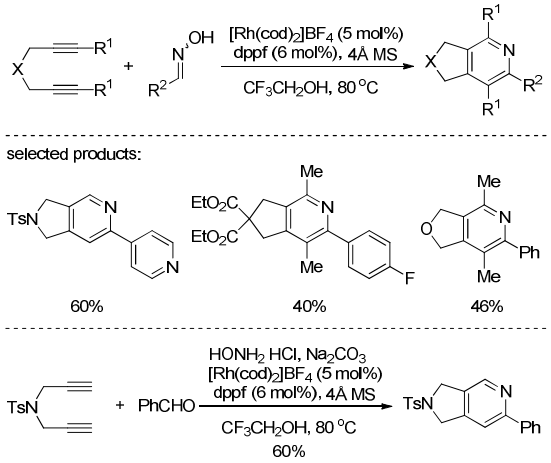
In the same year, Li and Chiba collaboratively applied $\alpha,\beta$-unsaturated ketoximes and internal alkynes

to the synthesis of pyridine derivatives via Rh(III)-catalyzed C-H activation reactions.[31] CsOPiv was found superior to other additives in this case, and under the optimal conditions various functionalized pyridines were prepared in moderate to excellent yields, however, with poor regioselectivity when using asymmetric internal alkynes (Scheme 17). Several months later, a similar pyridine synthesis was introduced by Rovis *et al.* under the catalytic $[Cp^tRhCl_2]_2$ (or $[Cp^*RhCl_2]_2$)/$K_2CO_3$/2,2,2-trifluoroethanol (TFE) system.[32] The regiochemistry of asymmetric internal alkynes was investigated. Both electronic and steric effects arised from two coupling partners were found influential. Moreover, $[Cp^tRhCl_2]_2$ and $[Cp^*RhCl_2]_2$ were found conversely regioselective in some cases. In addition to the works of internal alkynes, in 2012, Bergman and Ellman studied the synthesis of pyridines from ketoximes and terminal alkynes under Rh(I) catalytic system (Scheme 17).[33] By the use of triisopropyl phosphite as a simple and inexpensive ligand, this protocol affords substituted pyridines in moderate to excellent regioselectivities, and simultaneously the undesired competitive dimerization of terminal alkynes is efficiently suppressed. Also, this catalytic system is suitable for internal alkynes.




Scheme 17

Recently, Rh-catalyzed [2+2+2] cycloaddition of diynes and aldehyde oximes has been developed by Wan *et al.*, in which aldehyde oximes served as formal internal oxidants for this pyridine synthesis.[34] Solvent and ligand seem to be critical for a successful transformation, and the screening revealed an catalytic $[Rh(cod)_2]BF_4$/dppf/$CF_3CH_2OH$ system to be optimal. A range of *C*-, *N*-, and *O*-tethered diynes and various (hetero)aryl oximes are tolerated to afford the corresponding products in moderate to high yields (Scheme 18). Moreover, the one-pot pyridine synthesis from aldehyde, hydroxylamine and diyne has been achieved, which makes this methodology more practical.



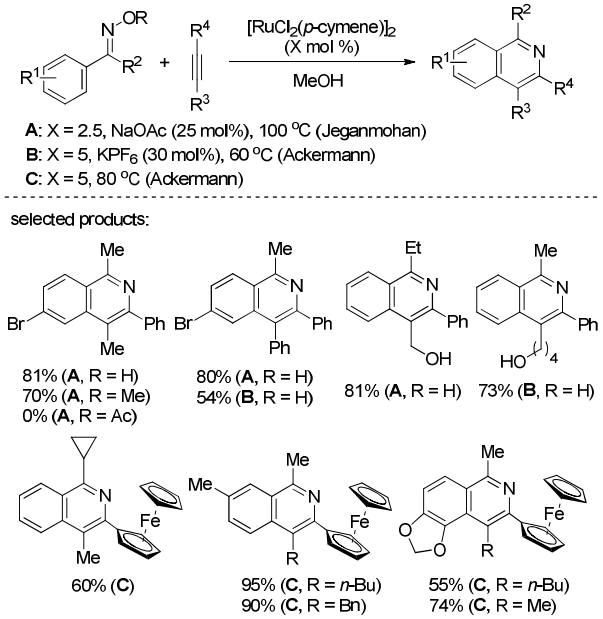

Scheme 18

**2.4 Reactions with oximes as internal oxidants under Ru, Ni, and Fe catalysis**

The reductive cleavage of oxime N-O bond could occur under other metal catalysts such as Ru, Ni, and Fe complexes. Generally, these reactions shed no more light on the reaction mechanism, and seem to be somewhat complementary to that of Pd, Cu, and Rh-catalyzed reactions previously described. For example, the reaction pertain of oximes as oxidizing directing groups in Ru-catalyzed C-H activation for isoquinoline synthesis is very similar to that of Rh catalysis, with a simple displacement of metal salt. However, in some cases the observed reaction regioselectivity would vary when different transition metal catalysts were used.

In 2012, Jeganmohan[35] and Ackermann[36] independently reported the Ru-catalyzed cyclization of

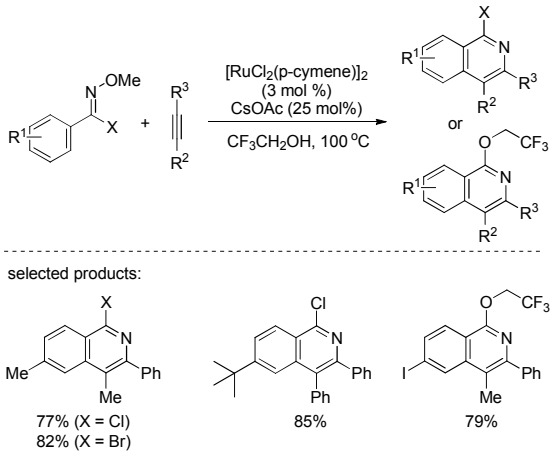
aromatic ketoximes with alkynes for practical synthesis of substituted isoquinolines (Scheme 19). The two reaction systems were carried out under slightly different conditions. Notably, Jeganmohan disclosed that while oxime and oxime ether were fruitful for this transformation, no cyclization product was detected when using oxime ester, which was inexplicably varied from the case of Rh-catalytic systems. This phenomenon can not obscure the virtues of this protocol. With less-expensive Ru catalyst compared to Rh catalyst, the cyclization features the same high yielding and broad functional group tolerance in both systems. Moreover, isoquinoline products were generally obtained in a highly regioselective manner when using unsymmetrical internal alkynes as the substrates. In addition to common alkynes, recently Ackermann discovered that ferrocenylalkynes showed very high level of activity under Ru-catalyzed additive-free conditions.[37]




Scheme 19

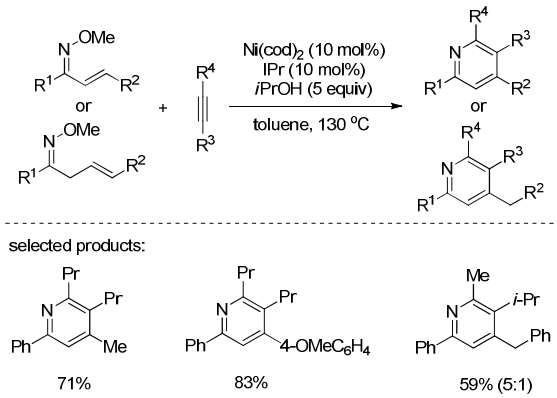
In 2013, Jeganmohan *et al.* designed *O*-methylbenzohydroximoyl halides towards Ru-catalyzed cyclization with alkynes, providing efficient access to 1-haloisoquinolines (Scheme 20).[38] Very high regioselectivities are also observed with all screened unsymmetrical internal alkynes. However, the substrate scope is limited since this reaction is very sensitive to the electronic and steric effects of the functional

groups on benzene ring.



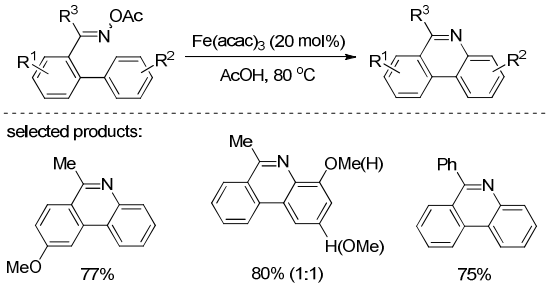

Scheme 20

In 2012, Ni-catalyzed cyclization of unsaturated oximes with alkynes was described by Kurahashi and Matsubara.[39] *α*,*β*-Unsaturated oximes as well as *β*,*γ*-unsaturated oximes were investigated to react with alkynes in the presence of Ni(0)/IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), furnishing 2,3,4,6-tetrasubstituted pyridines in good yields (Scheme 21). Differed from Rh-catalyzed reactions, Ni(0) complex is unlikely to initiate a C-H activation process, thus, the authors proposed that the oxidative addition of an oxime N-O bond to the Ni(0) catalyst would be the first step. Moreover, mechanistically experimental data indicated that *i*PrOH as an additive would facilitate ligand exchange to form the more active *i*PrONi(II) species from the MeONi(II) intermediate.




Scheme 21

The phenanthridine synthesis through iron-catalyzed intramolecular *N*-arylation of *O*-acetyl oximes was reported by Yoshikai *et al.* in 2013 (Scheme 22).[40] Various substituted phenanthridine derivatives were prepared in moderate to excellent yields (51-93%) from 2-biarylketone oximes via direct C-N bond formation. Copper salts such as CuI and $Cu(OAc)_2$ could also lead to the generation of phenanthridine products, which may becloud the real reaction mechanism in the case of iron(III) catalysis. However, a Friedel-Crafts type mechanism is preferred based upon some experimental observation.




Scheme 22

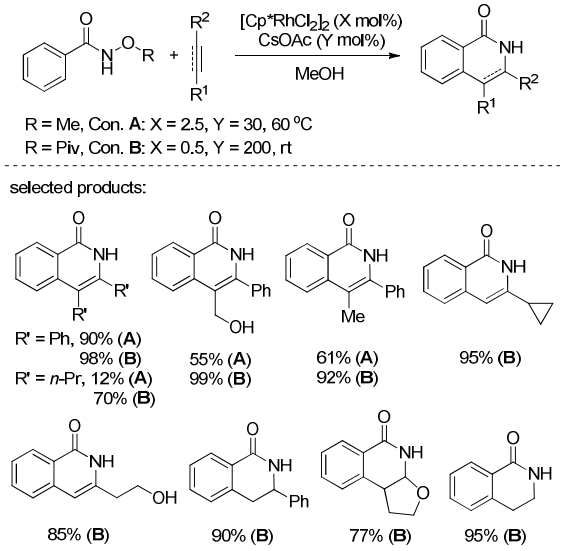
## 3 Hydroxamic acid as oxidizing directing group for C-H activation

The virtues of Pd- and Rh-catalyzed C–H activation reactions using oximes as oxidizing directing groups have indeed inspired chemists to explore more oxidizing directing groups based upon *N*-oxyenamines to construct diversified molecules. Hydroxamic acid is such an outstanding representative, which has led to a series of elegant reports of Rh- and Ru-catalyzed C-H functionalization in an overall redox neutral manner. The reactions complement well to those external oxidant-involved C-H activation reactions of primary benzamides. Furthermore, they feature obvious advantages in synthetic aspect.

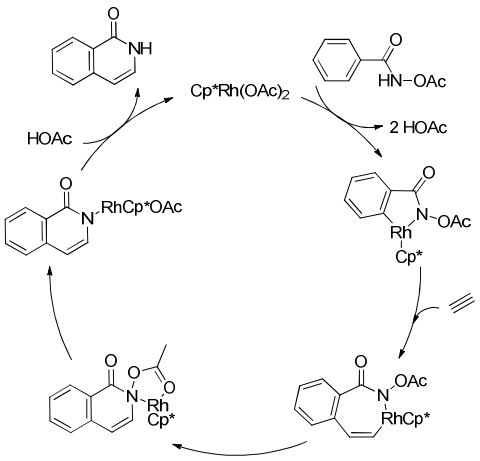
### 3.1 Rh-catalyzed C-H activation reactions

In 2010, Guimond and Fagnou *et al.* applied benzhydroxamic acids for the first time as oxidizing directing groups, which was introduced to Rh(III)-catalyzed *ortho* C-H activation for isoquinolone synthesis.[41] The described catalytic $[Cp^*RhCl_2]_2$/CsOAc/MeOH system is slightly different from that for isoquinoline

synthesis from oximes and alkynes (Scheme 23). However, when an aryl-alkyl disubstituted alkyne was employed in this hydroxamic acid-based system, excellent regioselectivity was observed with the aryl group being closed to the N moiety. One year later, the authors utilized *N*-pivalate benzamides in place of *N*-methoxy benzamides and found that the reactions with this internal oxidant could be performed at room temperature even with 0.5 mol% loading of the $[Cp^*RhCl_2]_2$ (Scheme 23).[42] With this activity-improved reaction partner, simple dialkyl alkynes, sterically hindered alkynes, alkynes bearing heteroatoms, and even terminal alkynes are all high yielding to deliver a wide range of isoquinolone products with exceptional regioselectivities (asymmetrical alkynes). Moreover, instead of alkynes, both internal and terminal olefins are effective coupling partners, which readily react with *N*-pivalate benzamides, giving dihydroisoquinolone products in good to excellent yields. A plausible mechanism was proposed on the basis of experimental data and DFT studies, where a stepwise C-N bond reductive elimination/N-O bond oxidative addition pathway is supported by DFT calculations (Scheme 24).

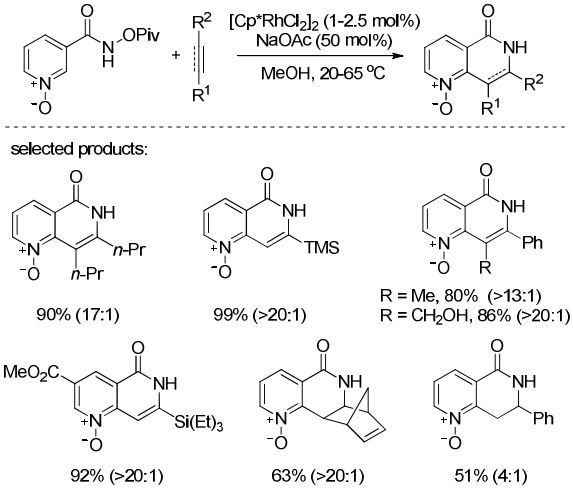



Scheme 23




Scheme 24

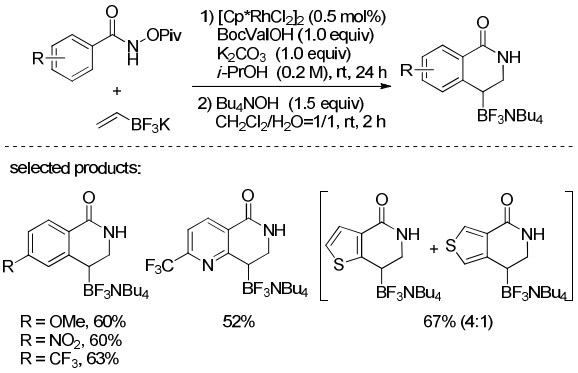
Huckins and Bercot developed, in 2013, Rh(III)-catalyzed C−H activation for the regioselective synthesis of naphthyridinones by the use of double directing group strategy.[43] The employment of nicotinamide N-oxides enables perfect regioselectivity on the pyridine C2 position. Also, high regioselectivity for the insertion of asymmetric alkenes or alkynes was observed. Generally, high yields of naphthyridinone N-oxides can be achieved using low catalyst loadings and mild conditions (room temperature) in the couplings with alkynes, while alkenes require slightly more elevated temperatures to afford dihydronaphthyridinone N-oxide products. (Scheme 25)




Scheme 25

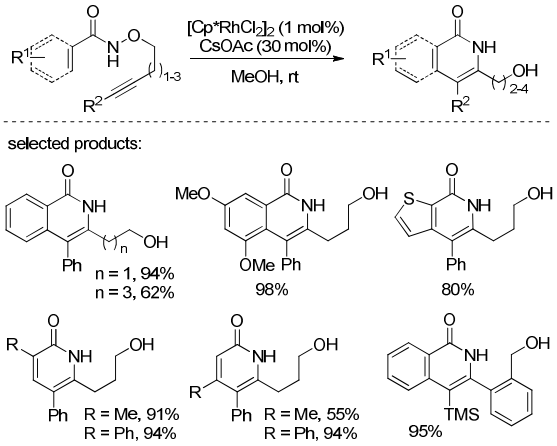
In the same year, collaborative studies by Rombouts and Molander revealed that potassium

vinyltrifluoroborate could serve as an efficient partner with *N*-pivalate benzamides for Rh(III)-catalyzed annulations.[44] As a regioisomerically complementary substitution pattern to other alkenes in related reactions, this method affords 4-trifluoroboratotetrahydroisoquinolones under mild reaction conditions. In general, the desired products in a tetrabutylammonium salt were obtained in moderate yields, which subsequently could be derivatized by *N*-arylations, retaining the boron substituent for further elaboration. (Scheme 26)



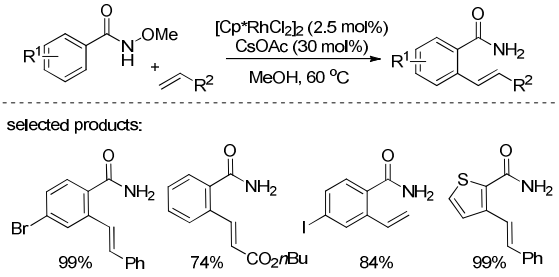

Scheme 26

In 2012, Park *et al.* designed benzhydroxamic acids bearing an alkynyl group under Rh catalysis, which could undergo intramolecular annulation to prepare hydroxyl isoquinolones (Scheme 27).[45] The previously established intermolecular reaction conditions is suitable for this intramolecular variant with high levels of reactivity and regioselectivity. Further screening indicates a reduced catalyst loading (1 mol%) and reaction temperature (rt) to be optimal for the desired products. A broad range of hydroxyl isoquinolones were prepared in good to excellent yields. Acrylic acid-derived internal oxidants also showed very high reactivity to transfer into hydroxyl 2-pyridone products. Furthermore, by use of this method as the key transformation the total synthesis of (±)-antofine, (±)-septicine, (±)-tylophorine, and rosettacin has been successfully achieved.



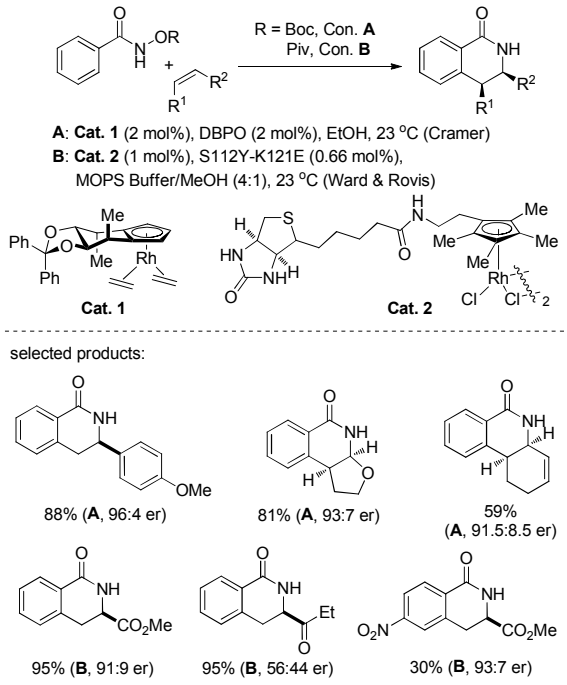

Scheme 27

In 2011, Glorius *et al.* reported the same catalytic $[Cp^*RhCl_2]_2$/CsOAc/MeOH system for the *ortho* C-H olefination of *N*-methoxy benzamides, affording *trans*-olefinated benzamides.[46] This highly active system was found to allow high yields (up to 99%) and a remarkably broad substrate scope with 1 mol% loading of the $[Cp^*RhCl_2]_2$ catalyst (Scheme 28). Many important functional groups such as iodides, bromides, methoxy, nitro, ester, and acetyl were well tolerated. While acyclic olefinated products generated in the case of *N*-methoxy benzamides, the authors also disclosed the formation of 3,4-dihydroisoquinolones when *N*-pivalate benzamides were used under a slightly changed condition. Later, the chemoselectivity observed with both substrates of *N*-OMe and *N*-OPiv internal oxidants were pragmatized by DFT calculations by Xia *et al.*[47] Moreover, When *N*-OPiv is involved, a cyclic Rh(V) nitrene intermediate is supported by the calculation of the energy barrier.




Scheme 28

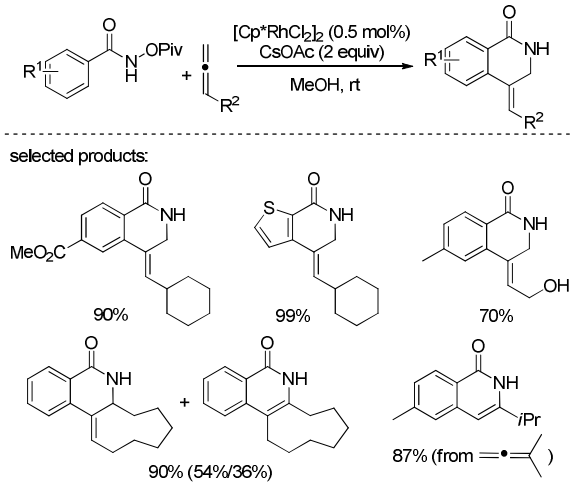
In 2012, independent studies by Cramer[48] and the collaborative studies of Ward and Rovis[49] revealed at the same time Rh-catalyzed C-H activation for the asymmetric synthesis of 3,4-dihydroisoquinolone from benzhydroxamic acids and olefins (Scheme 29). With a biotinylated analog Rh catalyst incorporated within streptavidin, while several asymmetrically synthetic examples were given with moderate to good enantioselectivities, Ward and Rovis have demonstrated the chirality derived from a supramolecular assembly of a Cp* fragment and a protein. Meanwhile, Cramer utilized a more common and simple strategy by the introduction of a chiral cyclopentadienyl ligand. In this case, a broad range of styrenes and cyclic olefins coupled smoothly with Boc-derived benzhydroxamates, affording the corresponding 3,4-dihydroisoquinolones in high yields with exceptional regioselectivities and consistently excellent enantioselectivities. Thus in the synthetic aspect, apparently the latter features more advantages.




Scheme 29

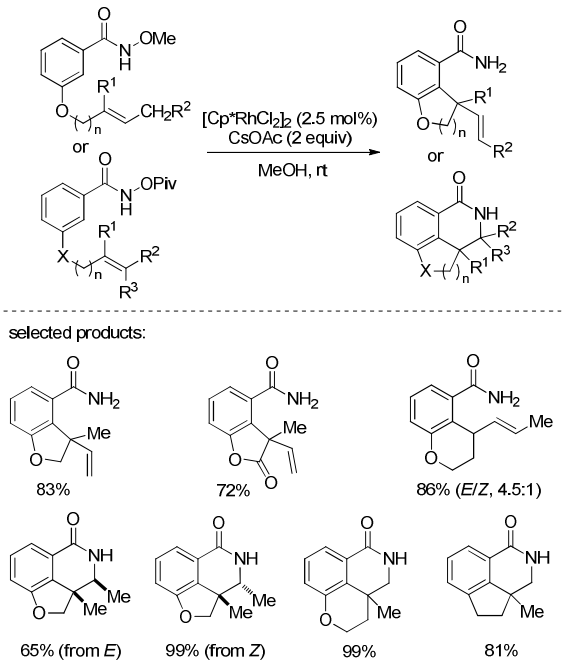
In addition to normal olefins, Glorius *et al.* developed Rh(III)-catalyzed C-H activation of benzhydroxamates with allene compounds for the synthesis of 3,4-dihydroisoquinolones (Scheme 30).[50] Also

an OPiv-derived substrate is required for this intermolecular annulation. The regioselectivity of the allene coupling partners was controlled by the steric factors of both the two substrates, with the fact that isoquinolone products were furnished with a vinyl migration when 3-substituted benzhydroxamates or 1,1-disubstituted allenes were subjected to the catalytic system.



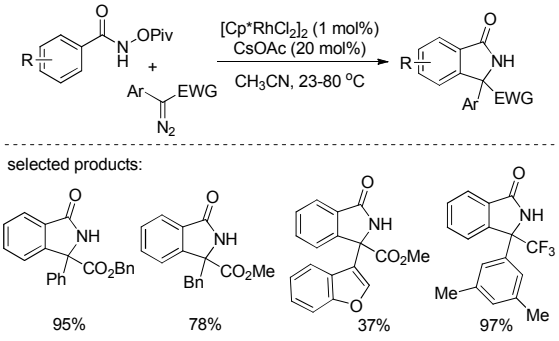

Scheme 30

In 2013, Rovis *et al.* discovered intramolecular C-H activation reactions of benzhydroxamates bearing an alkenyl moiety.[51] Three distinct reaction pathways occurred when different amide directing groups attached to the reactants, with a wide variety of tethered alkenes cyclized to give five- or six-membered products in good to excellent yields. With an oxidizing directing group, *N*-OMe amides and *N*-OPiv amides selectively resulted in dehydrogenative Heck-type products and amidoarylation products, respectively, consistent with the overall observation from previous works (Scheme 31).

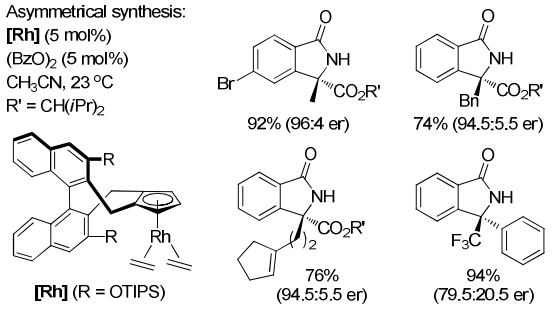



Scheme 31

Donor/acceptor diazo compounds were readily supposed introducing to Rh-catalyzed C-H functionalization with an internal oxidant. In a typical Rh(III)-catalyzed system for C-H activation of benzhydroxamates, diazo compounds were found by Rovis *et al.* in 2013 to be efficient coupling partners as a one-carbon component for $\gamma$-lactamization.[52] Generally, a wide range of substrates are tolerated to give the corresponding isoindolones in high yields (Scheme 32). This methodology would be well extended to asymmetrical synthesis because of the products bearing a tetrasubstituted carbon as well as the rather mild reaction conditions. Significantly that has been achieved by Cramer very recently.[53] The Rh complex comprising a $C_2$-symmetric disubstituted Cp ring with a chiral backbone is employed to enable the asymmetric synthesis, affording a broad range of isoindolones in good yields and excellent enantioselectivities (Scheme 33).

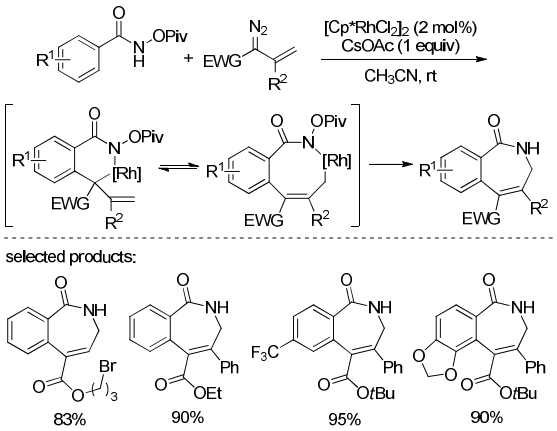



Scheme 32



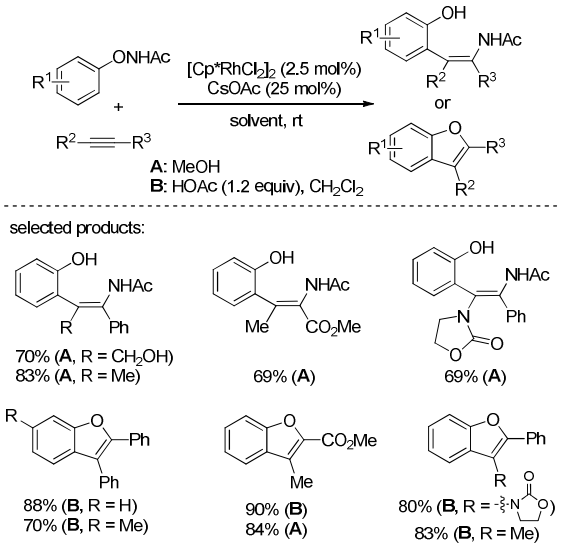

Scheme 33

Subsequently, vinyl diazo compounds were judiciously designed as a three-carbon component for Rh(III)-catalyzed C–H activation/[4 + 3] cycloaddition with benzhydroxamates, which provided convenient access to azepinones (Scheme 34).[54] Since azepines and their derivatives are well-known seven-membered nitrogen-containing heterocycles in natural and pharmaceutical compounds, this method represents an elegant entry to these compounds with advantages in terms of simple starting materials, mild reaction conditions, broad substrate scope and high efficiency. As a supplementary application, very recently, Cui *et al.* also designed heterocyclic hydroxamates, which coupled well with diazo compounds or alkynes to afford pharmacologically privileged pyrrole-fused products.[55]

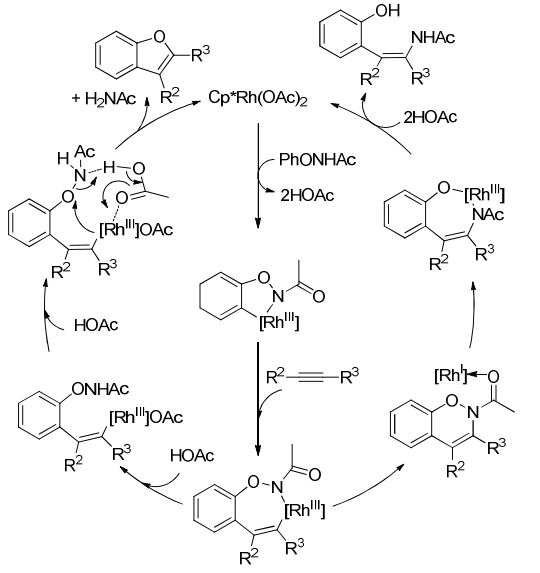



Scheme 34

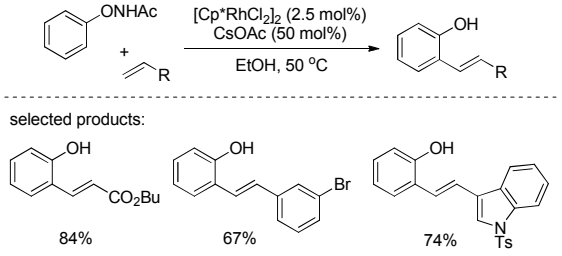
In 2013, Liu and Lu applied *N*-phenoxyacetamides as oxidizing directing groups to Rh(III)-catalyzed C–H activation reactions (Scheme 35).[56] While a highly atom-economical aminoarylation of alkynes results in *ortho*-hydroxyphenyl-substituted enamides, an unexpected synthesis of valuable benzofuran derivatives through C-C/C-O bond formation has been achieved by slightly switching the reaction conditions. It is shown that both the solvent effect and the type of alkyne partner are of critical importance to the chemoselectivity. In contrast to general pattern that the oxy component of internal oxidants served as a leaving group in previous works, in this oxidative benzofuran synthesis, the amido component was released. An electrophilic oxygenation was proposed for the new C-O bond formation (Scheme 36). With the same strategy, the authors also developed *ortho* C-H olefination of *N*-phenoxyacetamides under Rh(III) catalysis, providing novel access to *ortho*-alkenyl phenols (Scheme 37).[57]




Scheme 35



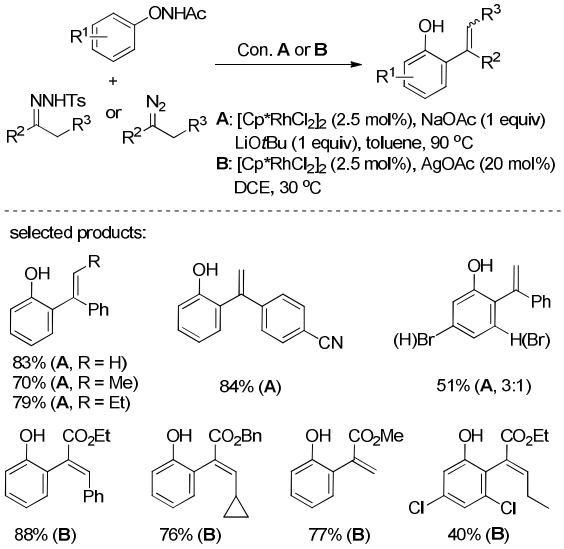

Scheme 36




Scheme 37

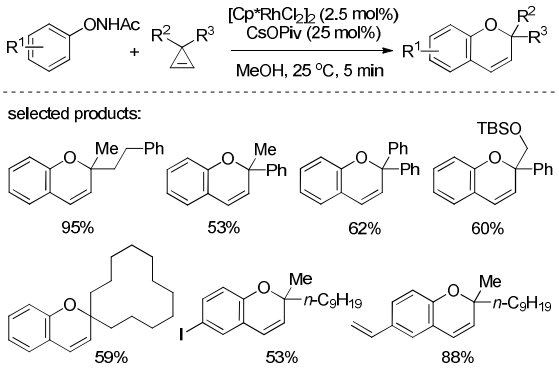
Recently, *N*-phenoxyacetamides as internal oxidants were used to couple with *N*-tosylhydrazones and

diazoesters by Wang *et al.*, also leading to *ortho*-alkenyl phenols.[58] A large number of active substrates have been subjected to the Rh(III)-based conditions to give the coupled products in good yields and with excellent regio- and stereoselectivity (Scheme 38). Rather than heterocyclization in the reactions of benzhydroxamates and carbenoids previously reported,[52-55] in this case, $\beta$-hydride elimination of the cyclic Rh intermediate readily occurred to ultimately afford the *ortho*-alkenylation products.



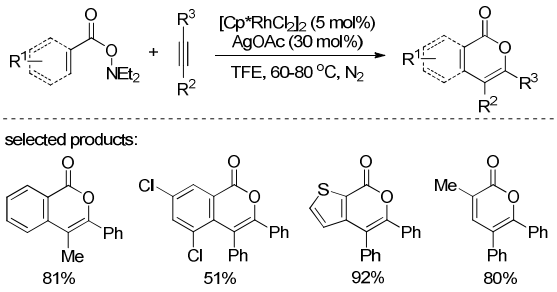

Scheme 38

Very recently, Wang *et al.* expanded *N*-phenoxyacetamide internal oxidants to the coupling reaction with cyclopropenes, disclosing a rhodium(III)-catalyzed transannulation through C-H activation (Scheme 39).[59] This protocol represents the first example of using cyclopropenes as a three-carbon unit in rhodium(III)-catalyzed C(sp2)-H activations. It is probably due to the highly strained ring system of cyclopropenes that the coupling reaction proceeds under mild reaction conditions at room temperature and features very high efficiency towards a wide range of substrates.




Scheme 39

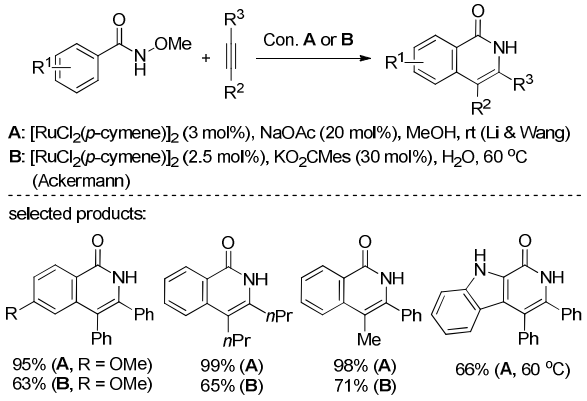
Likewise, *O*-benzoylhydroxylamines can serve as internal oxidants as well as oxygenating agents for sequential *ortho* C-H activation/C-O bond formation with amino moiety as a leaving group. Very recently, Liu *et al.* described a Rh(III)-catalyzed C-H activated annulation of *O*-benzoylhydroxylamines with internal alkynes to prepare isocoumarins and $\alpha$-pyrones.[60] The solvent effect was found crucial for the desired reaction. Under the optimal $[Cp^*RhCl_2]_2$/AgOAc/TFE catalytic system, the coupling of benzoates and alkynes was smoothly achieved to construct oxygen-containing heterocycles in moderate to excellent yields (Scheme 40). Moreover, high level of regioselectivity was obtained when asymmetric alkynes were employed. Since almost all of works using *N*-oxyenamine internal oxidants mentioned above are dedicated to nitrogen-containing molecules, the present results might support the development of new strategies for constructing useful oxygen-heterocycles.




Scheme 40

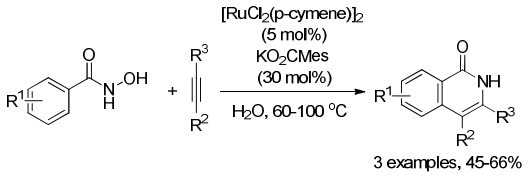
### 3.2 Ru-catalyzed C-H activation reactions

As above mentioned, C-H activation reactions of benzhydroxamates were frequently conducted under Rh(III) catalysis. Like the case of oxime internal oxidants, Ru catalysts were also participated in this crowd, albeit with few examples. In 2011, subsequent collaborative studies of Li and Wang[61] and independent studies by Ackermann[62] disclosed Ru-catalyzed isoquinolone synthesis through the C-H activation of *O*-Me benzhydroxamates with alkynes in organic media and water, respectively (Scheme 41). It is gratifying that $[RuCl_2(pcymene)]_2$ seems to behave higher active than $[Cp^*RhCl_2]_2$ since this transformation smoothly occurs under a lowered temperature (i.e. room temperature vs 60 $^oC$), leading to the same high yielding. On the other hand, compared to the case of *O*-Piv benzhydroxamates under room temperature, this Ru-catalyzed C-H activation of *O*-Me benzhydroxamates also features advantage in terms of atom economy because of MeOH being leaving group rather than PivOH.



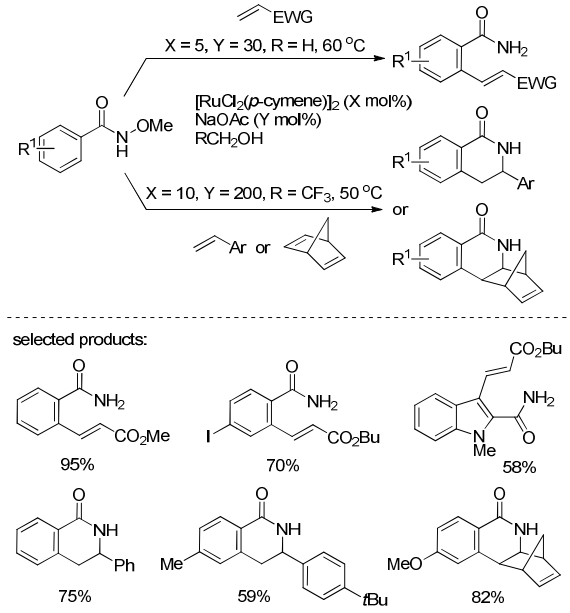

Scheme 41

Notably, in a further investigation, Ackermann found that free hydroxamic acids also proceeded well in the ruthenium-catalyzed annulations of alkynes by C-H/N-O bond cleavages (Scheme 42). Considering the use of water as the reaction media in the system, this method represents a promising sustainable chemical process with high atom-economy.




Scheme 42

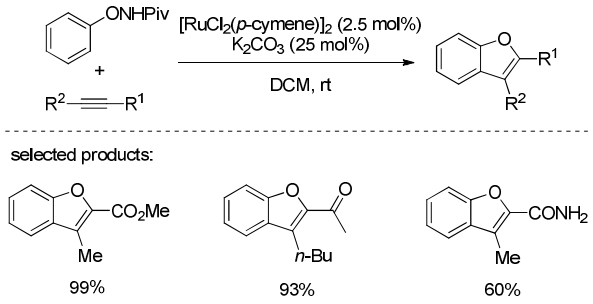
Also, the C-H activation of benzhydroxamates with olefins was studied under Ru catalysis. In 2012, Li and Wang *et al.* reported a switchable synthesis of *ortho*-olefinated benzamides and 3,4-dihydroisoquinolinones from *N*-methoxybenzamides, where the chemoselectivities were generally obtained due to different olefins utilized, rather than the nature of benzhydroxamates.[63] This observation is quite different from the case of Rh-catalyzed transformation. While the reactions using acrylic activated alkenes in MeOH afford olefinated benzamides, styrenes or norbornadiene in TFE provide an efficient entry to 3,4-dihydroisoquinolinone derivatives (Scheme 43).




Scheme 43

Very recently, Lu and Liu developed benzofuran synthesis from N-phenoxypivalamides using a less expensive catalytic system including ruthenium catalyst and $K_2CO_3$ as the additive compared their previous reported catalytic [Rh]/CsOAc system. With the fact that N-phenoxyacetamide was inevitably

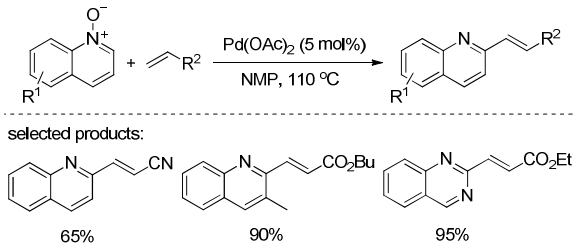
decomposed to phenol as a side product, N-phenoxypivalamide was found to furnish good to nearly quantitative yields of the desired benzofurans (Scheme 44).[64]



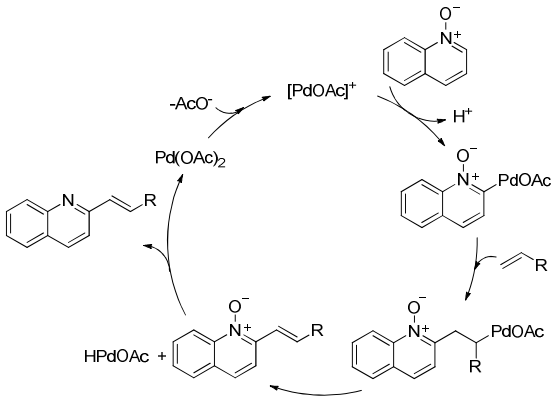

Scheme 44

## 4 *N*-Oxides as Oxidizing Directing Groups

*N*-oxides such as pyridine-*N*-oxides were generally utilized as an activated pyridine motif for C2-functionalization under transition metal catalysis. An external oxidant is generally necessary for the regeneration of the metal catalyst. Furthermore, reducing agents are needed to reduce the resultant *N*-oxide products. Dehydrogenation coupling using *N*-oxides as an internal oxidant therefore features significant advantages: synthetic step is reduced and water is the sole by-product. In 2009, Cui and Wu have pioneered Pd-catalyzed C-H functionalization with quinoline-*N*-oxides as both substrates and internal oxidants.[65] With a very facile catalytic system, the present reactions provided a convenient access to a range of 2-alkenylated quinolines and 1-alkenylated isoquinolines in chemo- and regioselective manners under external-oxidant-free conditions (Scheme 45). The authors proposed a possible reaction sequence involving oxidative Heck coupling and N-O bond reduction of the *N*-oxide products by Pd(0) species (Scheme 46). Although more general pyridine-*N*-oxides were unfruitful and highly excess acrylates (5 equiv) were required for a desired conversion, this protocol is of great significance due to its inspiring insights into transition metal-catalyzed C–H functionalization with the concept of green oxidizing directing group.

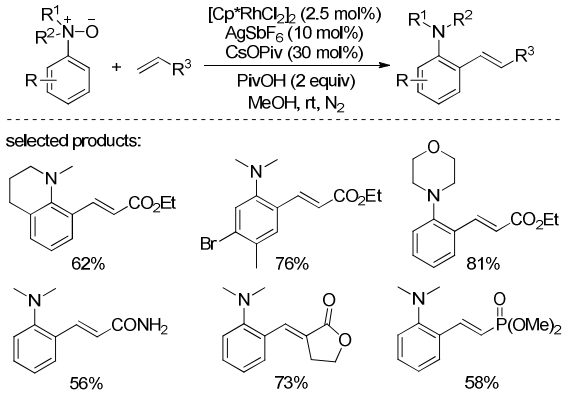



Scheme 45




Scheme 46

Ingeniously, aniline *N*-oxide was designed as a variant for oxidizing directing C-H olefination by You *et al.* in 2013.[66] The efficient catalytic system comprises $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), CsOPiv (30 mol%), and PivOH (2.0 equiv) in MeOH under room temperature, which furnished a series of 2-alkenylated tertiary anilines in moderate to good yields (Scheme 47). Moreover, the elongated $\pi$-conjugated skeletons of the resultant tertiary dianilines exhibit significant fluorescence emission in both the solid state and in solution, therefore illustrating potential applications in organic functional materials. Mechanistically experimental results and the isolation of a five-membered cyclometalated $Rh^{III}$ complex support a plausible mechanistic pathway, where the N-O bond cleavage occurs in the final step associating with the regeneration of the $Rh^{III}$ catalyst. Interestingly, this is very similar to the $Rh^{III}$-catalyzed *ortho* C-H olefination of benzhydroxamates.




Scheme 47

## 5 Conclusions

In past years, various powerful metal-catalyzed methods for oxidative C-H functionalization have been developed, with most methods operating with strong or harsh oxidants. This review focused on transition metal-catalyzed C-H functionalization involving internal oxidant strategy and related mechanistic insights. Compared to conventional transformations with external oxidants, these reactions generally found higher levels of reactivity and selectivity and a broader reactant scope, and more importantly obviating the need for an external oxidant could lead to reduced amount of waste formed. Besides, the substrates with an internal oxidant have been utilized to easily bring the metal to the proximity of the desired reaction site, which would lead to a successful conversion under relatively mild reaction conditions. These advantages make the strategy of *N*-oxyenamine internal oxidant particularly practical and fascinating for transition metal-catalyzed C–H oxidative functionalization. The transformations presented will continue to drive the field forward towards the development of ideal oxidative bond formation processes.

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