Chem Soc Rev

REVIEW ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d0cs00447b

Recent advances in chelation-assisted site- and stereoselective alkenyl C–H functionalization

Jian Zhang, *[a] Xiunan Lu,[a] Cong Shen,[a] Liangyao Xu,[a] Liyuan Ding[a] and Guofu Zhong*[ab]

Olefinic C–H functionalization represents an atom- and step economic approach to valuable olefin derivatives from simpler ones, but controlling the selectivity remains a challenge. Remarkable progress has been made in the site-selective C–H functionalization of arenes and alkanes, but there are still limited examples of selective C–H functionalization of olefins presumably due to the lability and easy decomposition of the alkenyl moiety. Chelation-assisted C–H activation represents an efficient protocol for site- and stereo-selective construction of carbon–carbon and carbon–heteroatom bonds. This review highlights recent advances in vicinal- and geminal-group-directed olefinic C–H functionalization, including alkenylation, arylation, alkynylation, alkylation, halogenation, silylation, cyanation and annulation by the formation of *exo*-/*endo*-metallocycles. In particular, geminal-group-directed C–H functionalization is covered for the first time, as well as distal-selective alkenyl C–H functionalization under palladium/norbornene cooperative catalysis, which provides novel disconnections in retrosynthetic analysis and represents the future trend in green chemistry.

Received 25th June 2020

DOI: 10.1039/d0cs00447b

rsc.li/chem-soc-rev

[a] College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China. E-mail: zhangjian@hznu.edu.cn, zgf@hznu.edu.cn
[b] School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China

1. Introduction

Alkenes are one of the most abundant raw feedstocks to construct complex chemicals, and many efforts have been made towards developing methods for the synthesis of functionalized olefins,

Jian Zhang

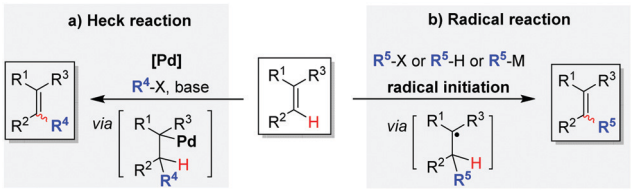
Jian Zhang was born in Zhejiang, China. He received his BS degree from Central South University in 2003 and his MS degree from Nankai University under the guidance of Professor Huailin Sun in 2006. After working in WuXi AppTec as a research scientist for 3 years, he moved to Nanyang Technological University in Singapore in 2009 and received his PhD degree in organic chemistry in 2013 under the guidance of Professor Teck-Peng Loh and Professor Soon Hyeok Hong. After working with Professor Teck-Peng Loh in Nanyang Technological University as a research associate, he joined the College of Materials, Chemistry & Chemical Engineering in Hangzhou Normal University in 2015, where he was appointed as a full professor in 2017. His research interests focus on transition metal-catalyzed C–H bond functionalization and domino reaction.

Xiunan Lu

Xiunan Lu was born in Zhejiang, China. She received her BS degree from Quanzhou Normal University in 2016. She then joined the research group of Professor Jian Zhang and Professor Guofu Zhong in the College of Materials, Chemistry and Chemical Engineering at Hangzhou Normal University in 2016. After she received her MS in 2019, she has been working as a research assistant in the College of Materials, Chemistry & Chemical Engineering in Hangzhou Normal University, working with Professor Jian Zhang. Her current research interests focus on the transition-metal-catalyzed formation of C–N and C–C bonds and their applications in organic synthesis.

including classic elimination from halides, Wittig reactions, olefin metathesis, addition to alkynes, and Heck reactions.[1] However, most of these methods employ pre-activated substrates and/or produce stoichiometric by-products which significantly reduce the reaction efficiency. Olefins are abundant and readily available raw materials; direct alkenyl C–H functionalization represents an atom- and step-economic approach to prepare valuable olefin derivatives from simpler ones, and is generally divided into two strategies: non-directed- and directed alkenyl C–H functionalization.

The Heck reaction represents a well-known approach for non-directed functionalization of alkenyl C–H bonds, and the mechanism involves insertion of alkenes and β-H elimination to provide *trans*-alkenes in most of the cases (Scheme 1a).[2–4]



Scheme 1 Non-directed C–H functionalization of alkenes by addition–elimination mechanisms: (a) Heck reaction and (b) radical alkenylation.

Cong Shen

Cong Shen was born in Zhejiang, China. He received his BS degree in applied chemistry from Hangzhou Normal University in 2018. He joined Professor Jian Zhang and Professor Guofu Zhong's research group in 2018 and now is a graduate student in the College of Materials, Chemistry & Chemical Engineering in Hangzhou Normal University. His research interests focus on transition metal-catalyzed C–H bond functionalization.

Liangyao Xu

Liangyao Xu was born in Zhejiang, China. He received his BS degree from Hangzhou Normal University in 2018. In the same year, he joined the research group of Professor Jian Zhang and Professor Guofu Zhong in Hangzhou Normal University. He is currently a graduate student in the College of Materials, Chemistry & Chemical Engineering in Hangzhou Normal University and his research interests focus on transition metal-catalyzed C–H bond functionalization.

Liyuan Ding

Liyuan Ding was born in ShanXi, China. She received her BS from Xinzhou Normal University in 2010. Then she moved to Hangzhou Normal University as a graduate student and worked on organic photoelectric materials, under the supervision of Prof. Huayu Qiu. After she received her MS, she has been working as a laboratory technician since 2013 in the College of Materials, Chemistry and Chemical Engineering in Hangzhou Normal University. Her current research interests focus on synthetic organic chemistry.

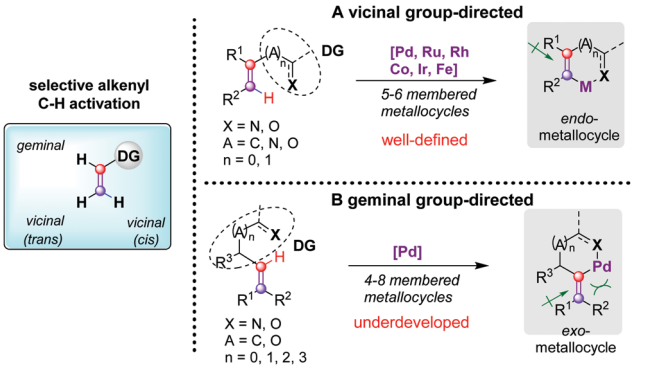
Guofu Zhong

Guofu Zhong has been a chair professor in organic chemistry at the College of Materials, Chemistry & Chemical Engineering of Hangzhou Normal University since 2011. He is a professor in the School of Chemistry and Chemical Engineering of Qufu Normal University from November 2020. He received his PhD degree in asymmetric catalysis in 1998 at The Scripps Research Institute under Professor Richard A. Lerner. Prior to his PhD, he studied organometallic chemistry with Professor Manfred Schlosser at the University of Lausanne. He obtained his BSc degree in chemical engineering at Nanjing University of Science & Technology in Nanjing and his MSc degree in organic chemistry at East China University of Science & Technology in Shanghai. He was an assistant professor at Scripps Research (1999–2004), a professor at Fudan University in Shanghai (2005–2006) and an associate professor at Nanyang Technological University in Singapore (2006–2011). He focuses on organic chemistry, asymmetric catalysis and medicinal chemistry.

Recently, remarkable efforts have also been made towards olefinic C–H functionalization using carbon/heteroatom-centered radical species which proceeded by radical addition to alkenes and the subsequent single-electron-transfer (SET) oxidation/elimination to provide alkene derivatives (Scheme 1b).[5] However, both of the non-directed alkenyl C–H functionalizations proceed by the addition/elimination mechanisms, and the site- and stereo-selectivities are largely governed by the intrinsic sterically and electronically biased properties of the alkene substrates, usually leading to *E*-alkenes using mono-substituted alkenes as the substrates. When di- or tri-substituted alkenes are employed as the substrates, controlling the site- and stereo-selectivities by these non-directed methods remains a formidable challenge, providing *Z*/*E* mixed isomeric olefins, which greatly inhibit their practical applications. Multi-substituted alkenes, widely used as versatile building blocks, are key structural motifs in countless natural and bioactive compounds. Consequently, it is highly desirable to develop site- and stereo-selective C(vinylic)–H functionalization to afford unsymmetrical tri- and tetra-substituted olefins without steric or electronic bias.

Chelation-assisted C–H bond activation generally achieves excellent site- and stereo-selectivity by using directing groups (DGs) to distinguish C–H bonds on the basis of their distance and geometry in the molecule relative to the DG.[6–24] The DGs usually play multiple roles: bringing the transition metal by chelation in close proximity to the specific C–H bond, acting as a σ-donor ligand and increasing the effective concentration of the catalyst at a specific site to improve the reaction efficiency. While directed *ortho*-selective C–H activation that proceeds by five- or six-membered cyclometallation has attracted great attention, some other elegant variants have also been demonstrated, including the rigid template strategy, catalytic σ-activation by *ortho*-C–H metalation, use of norbornene as a transient mediator, and weak hydrogen bonding, leading to *meta*- or *para*-C–H functionalization.[25–31] Owing to the diverse utilization of olefins, directed alkenyl C–H functionalization would be appealing as an efficient and selective method for the preparation of multi-substituted alkenes. However, compared with well-defined aryl C–H functionalization, alkenyl C–H bond activations are more difficult and the following challenges could be anticipated. First, the DGs (electro-donating or electro-withdrawing) attached to olefins usually make the substrates more reactive. The more reactive alkene easily undergoes π-bond breaking reactions such as electrophilic/conjugate addition, oxidation and polymerization, which are not applied to stabler aromatic substrates. Second, transition-metal-catalyzed side reactions, such as nucleophilic addition and π-bond insertion, could be competitive with alkenyl C–H activation, because olefins are usually better ligands than arenes. Third, due to the delocalization of arenes, aromatic C–H cyclometallation could be much easier than that of alkenes.

Although expanding the chelation-assisted strategy from arenes to olefins is appealing but more challenging, recent advances have demonstrated that directed C(vinylic)–H activation is feasible by careful evaluation of various reaction substrates and conditions. Incorporation of directing-groups into olefins allows site- and stereo-selective functionalization of vinylic C–H bonds, by the formation of cyclic alkenyl-metal intermediates. Remarkable efforts have been made on vicinal-group-directed alkenyl C–H bond functionalization such as alkenylation, arylation, alkynylation, alkylation, halogenation, silylation, cyanation and annulation,[32–160] and these methods lead to excellent *cis*-selectivity by *endo*-cyclometallation (Scheme 2A). However, the vicinal selectivity that originated from the formation of five- or six-membered *endo*-metallocycles severely retarded its potential applications in organic synthesis. Moreover, nearly all the directed olefinic C–H functionalizations employ conjugated olefinic substrates such as acrylamides, acrylic acids, acrylates, enamides, and enol esters, and expanding reactivity to nonconjugated olefins would be appealing. In this context, the development of chelation-assisted olefinic C–H functionalization *via exo*-metallocycle intermediates is fundamentally and complementarily important. According to previous reports, however, in comparison to the generation of *endo*-metallocycles, the requirements for additional conformational degrees of freedom and increased energy in *exo*-cyclometallation prevent the corresponding transition-metal-catalyzed reactions.[161–164] Very recently, however, there have been some new advances in geminal-group-directed olefinic C–H functionalization *via exo*-metallocycles, which greatly expands the concept of chelation-assisted alkenyl C–H functionalization (Scheme 2B).[165–174]



Scheme 2 Directed alkenyl C–H functionalization: (A) vicinal group-directed olefinic C–H functionalization and (B) geminal group-directed olefinic C–H functionalization.

Although some reviews on the topics of non-directed olefinic C–H functionalization[4,5] and vicinal-group-directed alkenyl C–H activation/functionalization[32] have already appeared, this research area is fast-growing, and remarkable advances have been made in recent years. Herein, we provide a relatively comprehensive overview in which the majority of the results on vicinal- and the geminal-group-directed olefinic C–H bond activation/functionalization are presented, and the reaction modes and mechanisms are both emphasised. In particular, geminal-group-directed C(alkenyl)–H functionalization is covered for the first time in this review, including alkenylation,[165–168] allylation,[169] iodination,[170] alkynylation,[171] arylation,[172] and distal-selective alkenyl C–H functionalization under geminal-group-directed palladium/norbornene (Pd/NBE) cooperative catalysis.[174] In this respect, the fast developing alkenyl C–H

activation/functionalization represents an efficient method for the site-/stereo-selective preparation of valuable olefinic compounds.

2. Vicinal group-directed olefinic C–H functionalization

In 1995, the Murai group reported the first olefinic C–H alkylation of α,β-enones with triethoxyvinylsilane catalyzed by $RuH_2(CO)(PPh_3)_3$.[77] After this advance, many efforts have been made on vicinal-group-directed olefinic C–H bond activation/functionalization, including alkenylation, arylation, alkynylation, alkylation, halogenation, silylation, cyanation and annulation by cascade sequences. In these protocols, excellent *cis*-selectivity was achieved under the chelation-assistance of the directing group by the formation of *endo*-metallocycle intermediates, leading to valuable *Z*-olefin derivatives.

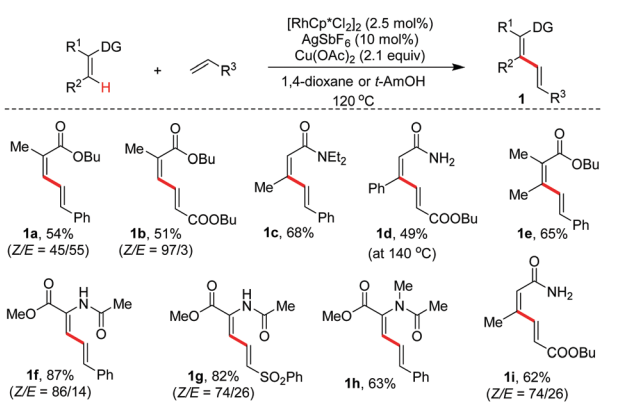
2.1 Vicinal group-directed olefinic C–H alkenylation

Electron-deficient alkenes, such as acrylates, vinyl ketones, vinyl phosphates, acrylamides and vinyl sulfones, are usually employed as C–H alkenylation reagents with the assistance of metal oxidants such as copper(II) or silver(I) salts, leading to linear 1,3-diene derivatives. Meanwhile, alkynes and allenes are also suitable coupling partners in olefinic C–H alkenylation to provide branched conjugated dienes with atom economy and excellent regio-/stereoselectivities.

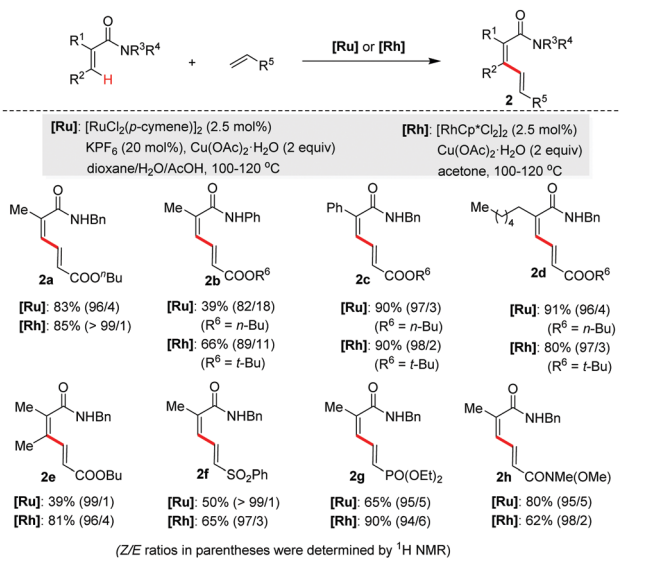
In 2011, the Glorius group reported an amide/ester directed and Rh-catalyzed oxidative C–H olefination of acrylates and acrylamides, as well as valuable di-unsaturated α-amino acid derivatives (Scheme 3). In this protocol, commercially available $[RhCp^*Cl_2]_2$ was used as the catalyst and $AgSbF_6$ as an additive together with $Cu(OAc)_2$ as an oxidant in 1,4-dioxane or *t*-AmOH to give the corresponding linear conjugated dienes **1**. Notably, *Z*,*E*-configured 1,3-dienes were commonly obtained as the major products due to the chelation-assisted olefinic C–H activation. Di-unsaturated α-amino amides led to *Z*,*Z*-dienes presumably due to the stronger directing effect of the amide than the ester group. Interestingly, the cross-coupling reaction can also be performed on a large scale using only 20 mol% $Cu(OAc)_2$ in air. This reaction represents the first example of chelation-assisted C–H/C–H cross-coupling of alkenes to afford 1,3-dienes, although moderate selectivities/yields were obtained in most of the cases.[33]

To achieve better reactivity and selectivity, the Loh group disclosed ruthenium- and rhodium-catalyzed oxidative C–H/C–H cross-coupling reactions of acrylamides with electron-deficient alkenes such as acrylates, acrylamides, vinyl sulfones, styrenes and even vinyl phosphates. The protocol provides an efficient route for the synthesis of (*Z*,*E*)-configured dienamides **2** with excellent regio- and stereo-selectivity (*Z*,*E*/*Z*,*Z* up to 99/1, up to 91% yield), using robust complex $[RuCl_2(p\text{-cymene})]_2$ or $[RhCp^*Cl_2]_2$ as the catalyst. The catalytic conditions exhibit a broad spectrum of functionality tolerance, including CO_2R, COMe, SO_2Ph, CONHBn, CN, $PO(OEt)_2$, and Weinreb amides (Scheme 4). The reaction is proposed to be initiated by directed C–H cyclometalation of an acrylamide. Coordination of the alkene to the metal center followed by insertion of the alkene bond forms a seven-membered ruthacycle or rhodacycle species. Subsequent β-H elimination occurs to afford the desired (*Z*,*E*)-dienamides **2**. An isotopically labeled experiment led to *Z*-selective olefinic H/D exchange on methacrylamide, indicating a reversible C–H cyclometallation event.[34]

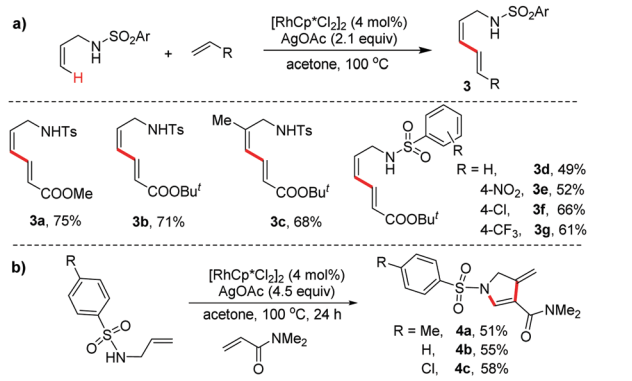
In previous cases, it was difficult for mono-substituted alkenes to undergo directed olefinic C–H activation *via* cyclometallation due to disfavoured steric and/or electronic effects. However, Li and co-workers disclosed a rhodium-catalyzed oxidative C–H/C–H coupling between *N*-sulfonyl allylamines and electron deficient alkenes such as acrylates and acrylonitrile. The C–H olefination proceeded well to provide *Z*,*E*-butadienes **3**, and no geminal C–H alkenylation product was generated (Scheme 5a).[35] Interestingly, the reaction with *N*,*N*-dimethylacrylamide that led to 2,3-dihydropyrroles **4a–4c** with an



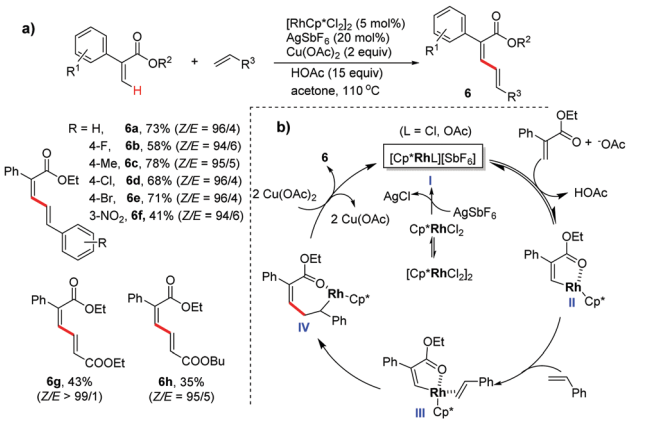
Scheme 3 Rh-catalyzed olefinic C–H alkenylation using alkenes (Glorius, 2011).[33]



Scheme 4 Rh- or Ru-Catalyzed olefinic C–H alkenylation of acrylamides using alkenes (Loh, 2012).[34]



Scheme 5 Rh-Catalyzed olefinic C–H alkenylation of NH-Ts allyl amines using alkenes (Li, 2013).[35]

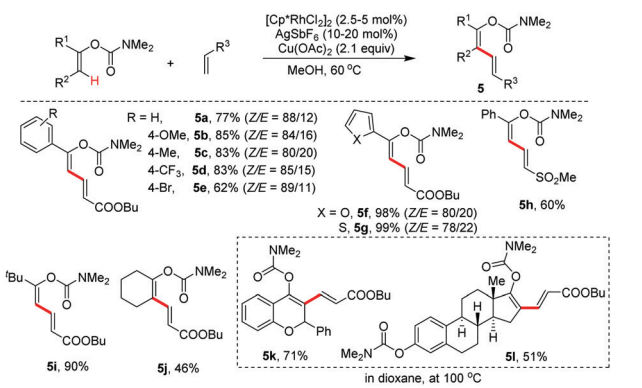


Scheme 7 Rh-Catalyzed olefinic C–H alkenylation of acrylates using alkenes (Zhang, 2014).[37]

exo-cyclized double bond proceeded *via* an intramolecular insertion of alkyl rhodium(III) species into olefins (Scheme 5b). The kinetic isotope effect experiment was performed, and k_H/k_D was determined to be 4.2, indicating the C–H activation to be involved in the turnover-limiting step.

After their previous advance in amide- and ester-directed C–H olefination,[20] Glorius and co-workers further reported a Rh-catalyzed olefinic C–H alkenylation of enol carbamates with excellent stereo-selectivity, allowing the preparation of linear 1,3-dienes **5** from aryl, alkyl, and cyclic enolates. KIE experiments suggest that the alkenyl C–H bond activation is the rate-determining step. The cleavage of the carbamate moiety enables the formation of either (*E*)-3-alkenones or various interesting products by C–O bond activation under Ni-catalysis. Notably, biologically relevant compounds such as flavanone and estrone derived enol-carbamates were also smoothly converted under optimal conditions, showing its robustness and practicality (Scheme 6).[36]

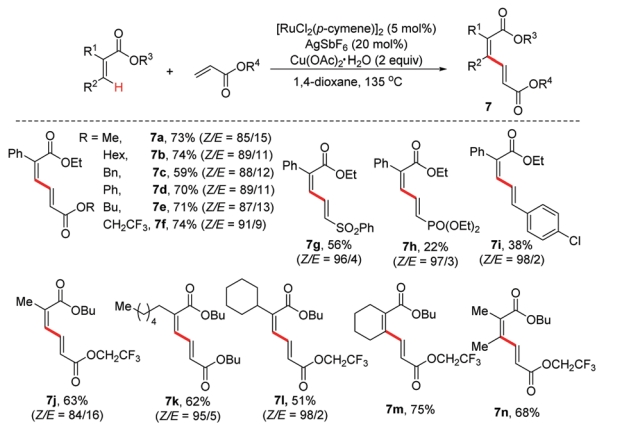
Not only amides and carbamates but weakly-coordinating esters can also act as DGs to promote C–H olefination. The Zhang group reported an ester-directed olefinic C–H olefination of 2-aryl acrylates with alkenes under rhodium(III)-catalysis. Styrenes and 2-aryl acrylates bearing electron-donating and electron-withdrawing groups on both sides reacted well to give (*Z*,*E*)-dienes **6** with high stereoselectivity and efficiency. However, cross-coupling of acrylates led to unsatisfactory results. The cross-coupling was proposed to proceed by the formation a cyclic vinyl rhodium intermediate (**II**) with the assistance of the ester group, and the subsequent alkene insertion and β-H elimination released product **6** and a Rh(I) species, which was oxidized to Rh(III) species **I** by a copper(II) salt to enter the next catalytic cycle (Scheme 7).[37]



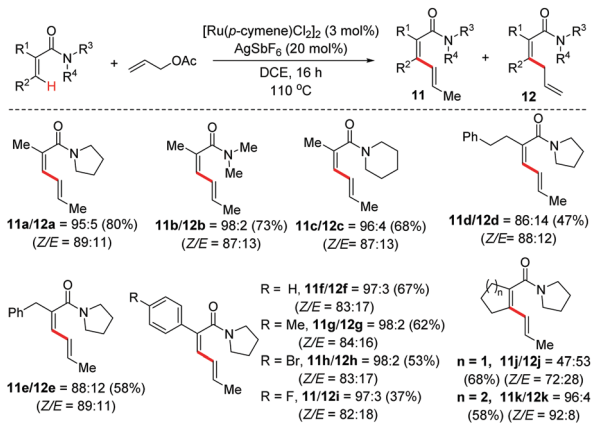
Scheme 6 Rh-Catalyzed olefinic C–H alkenylation of enol carbamates (Glorius, 2014).[36]

An oxidative C–H/C–H cross-coupling reaction of simple acrylates to generate substituted conjugated muconates is appealing but challenging due to the easy homodimerization and the weak coordination of esters. In 2015, the Loh group demonstrated a ruthenium-catalyzed ester-directed oxidative olefinic C–H/C–H cross-coupling reaction between two readily available acrylates. Herein, the substituent on the α-position of the acrylate greatly influences its reactivity and chemoselectivity to facilitate *cis*-olefinic C–H activation. By using a weakly coordinating ester as the directing group, this method efficiently provides a site- and stereo-selective approach for the preparation of valuable (*Z*,*E*)-muconates, **7**. One of the terminal ester groups on the conjugated muconates was selectively converted into the corresponding monocarboxylic acid or alcohol under mild hydrolysis and reduction conditions respectively. An intermolecular KIE value was determined to be 1.8, indicating that the C–H bond cleavage should be involved in the rate-determining step (Scheme 8).[38]

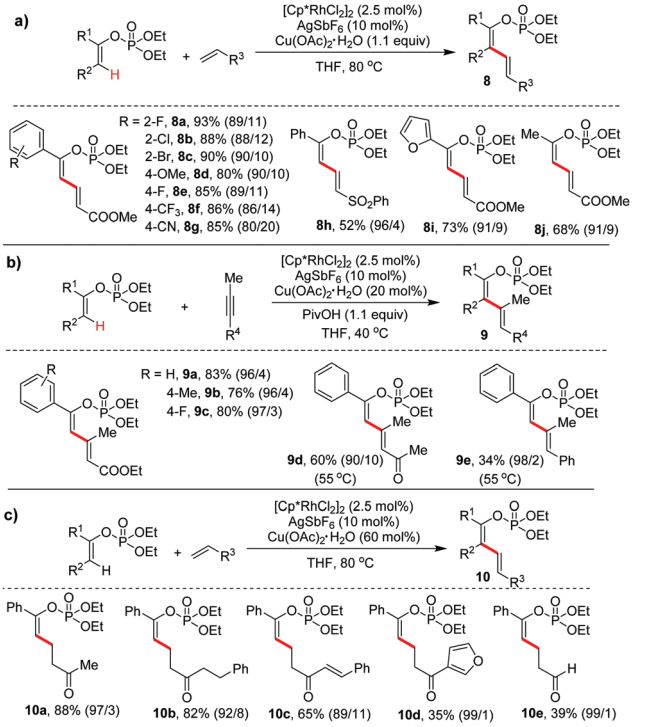
Enol phosphates usually serve as versatile intermediates in metal-catalyzed cross-coupling reactions. The Loh group further developed a rhodium-catalyzed and phosphate-directed olefinic C–H functionalization of electron-rich enol phosphates. A wide variety of coupling partners such as electron deficient alkenes, alkynes, and allenes could be used as coupling partners, leading to the formation of various valuable alkenylated and hydroalkenylated enol phosphates **8** and **9** (Scheme 9a and b). Notably, both aryl and alkyl vinyl ketones reacted with enol phosphates to provide the alkylation products **10** and a trace amount of 1,3-diene, using a decreased amount of $Cu(OAc)_2 \cdot H_2O$ (60 mol%) (Scheme 9c). Herein, β-H elimination is disfavored presumably due to the easy formation of a rhodium-*oxa*-π-allyl species, which



Scheme 8 Ru-Catalyzed cross-coupling reactions of acrylates using alkenes (Loh, 2015).[38]



Scheme 10 Ru-Catalyzed olefinic C–H alkenylation of acrylamides using allyl acetate (Zhang and Zhong, 2016).[40]



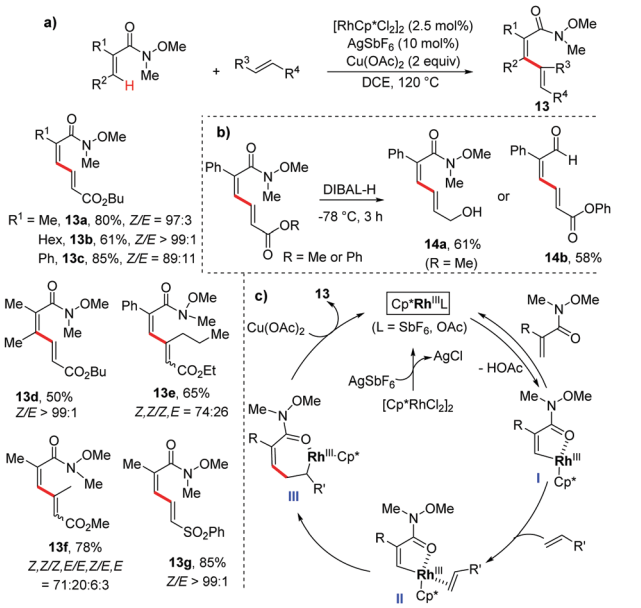
Scheme 9 Rh-Catalyzed olefinic C–H alkenylation/alkylation of enol phosphates using alkenes (Loh, 2015).[39]

is converted to conjugate addition product **10** after protonolysis. The protocol is of great importance due to the high regio- and stereoselectivity, good functional group compatibility, and versatile utility of the coupling products. Deuterium labelled experiments suggest a reversible C–H cyclometalation event, and an intermolecular KIE value of 2.2 reveals that the C–H bond cleavage might be involved in the rate-determining step.[39]

Previous methods required external metal oxidants to regenerate the active catalytic species and thus provided stoichiometric amounts of metal waste, reducing the overall "greenness" of the process. We developed a ruthenium-catalyzed cross-coupling between acrylamides and allyl acetate, with the assistance of tertiary aminocarbonyl as the directing group.[40] This protocol proceeded under external oxidant-free conditions by β-OAc elimination and resulted in (*Z*,*E*)-butadiene skeletons **11** with a trace amount of allylation product **12**. Other allyl esters were also examined in this allylation reaction, although they exhibited decreased efficiency. As unconjugated alkenes were normally inert to acrylamides, this protocol provides alternative access to 5-alkyl dienamides **11** (Scheme 10).

N-Methoxy-*N*-methylamides (Weinreb amides) represent synthetically valuable functionalities which can be easily converted into ketones and aldehydes. Our group developed a Weinreb amide directed olefinic C–H alkenylation using electron-deficient alkenes, which was performed with catalyst $[RhCp^*Cl_2]_2$, additive $AgSbF_6$ and oxidant $Cu(OAc)_2$. Mono- and di-substituted acrylamides were all converted well to afford excellent stereo-selectivity. This protocol was also applied to internal alkenes such as ethyl 2-hexenoate and methyl crotonate, providing multi-substituted 1,3-dienes **13e** and **13f** in good yields and with moderate *Z*/*E* selectivity (Scheme 11a). Notably, the Weinreb amide or ester group in the 1,3-dienes can be selectively converted into the corresponding aldehyde **14b** or allyl alcohol **14a** by simple treatment with DIBAL-H (Scheme 11b). A plausible mechanism is proposed to be initiated by anion exchange between $[Cp^*RhCl_2]_2$ and $AgSbF_6$ to afford active Rh(III) species **I**, which selectively inserts into the vicinal olefinic C–H bond and forms a five-membered rhodacycle (**II**). Subsequent olefin insertion and β-H elimination provide 1,3-diene **13** and Rh(I) species, and the latter one is converted to active Rh(III) species by oxidation with copper(II) (Scheme 11c).[41]

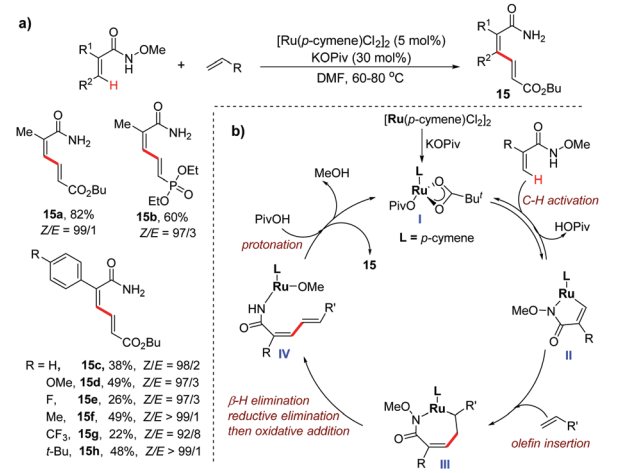
Another strategy is the application of an internal oxidizing directing group that acts as both a directing group and an internal oxidant for redox-neutral coupling reactions. In 2017, our group demonstrated a cross-coupling reaction between acrylamides and acrylates in the absence of any external oxidant, using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst and KOPiv as an additive. This protocol employs NH–OMe amide as an oxidizing directing group to afford efficient and mild synthesis of 1,3-dienes **15** with excellent stereoselectivities, liberating methanol as the sole by-product. The reaction is proposed to



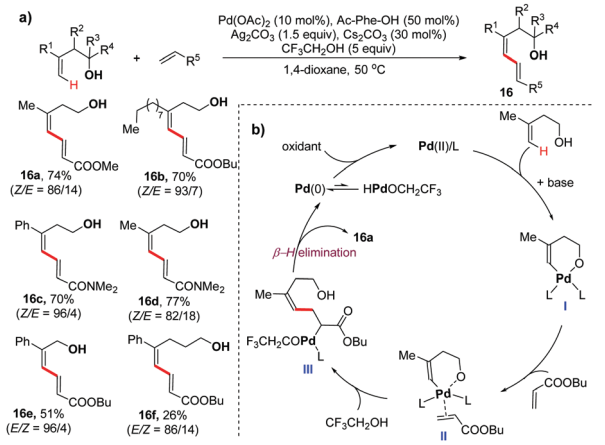
Scheme 11 Rh-Catalyzed Weinreb amide-directed olefinic C–H alkenylation (Zhang and Zhong, 2017).[41]

proceed *via* a reversible C–H bond activation process to form a ruthenacycle, **II**, with concomitant liberation of pivalic acid. Then, the electron-deficient alkene inserts into the Ru–C bond to form seven-membered ruthenacycle intermediate, **III**. Subsequent β-H elimination and reductive elimination furnish ruthenium(0), which inserts into the N–O bond to afford ruthenium(II) amide intermediate **IV**. The final protonation of **IV** releases product **15** and regenerates the active ruthenium(II) biscarboxylate catalyst **I** (Scheme 12).[42]

The Loh group continued the olefinic C–H activation and they recently developed a hydroxy group directed olefinic C–H alkenylation of homoallylic alcohols under palladium catalysis. The easily oxidative hydroxy group acts as the directing group in such directed C–H olefination and controls the stereoselectivity of



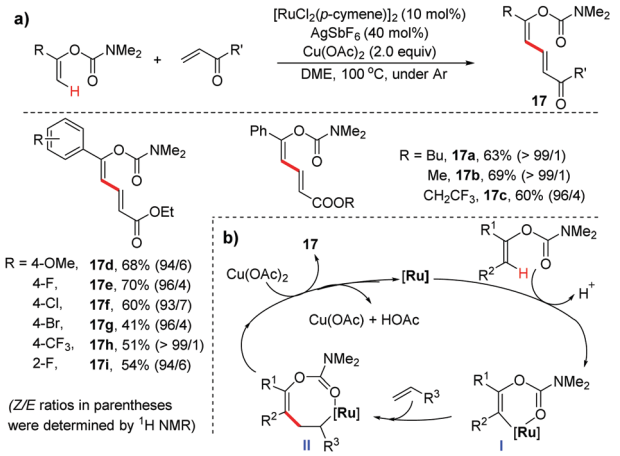
Scheme 12 Ru-Catalyzed olefinic C–H alkenylation of acrylamides using internal oxidants (Zhang and Zhong, 2017).[42]



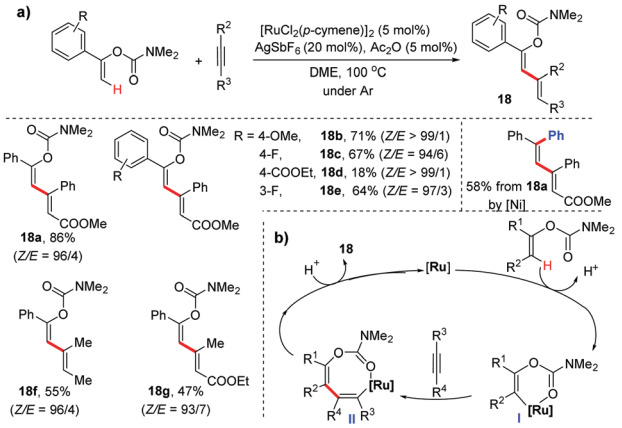
Scheme 13 Pd-Catalyzed olefinic C–H alkenylation of alkenyl alcohols (Xu and Loh, 2017).[43]

the products (Scheme 13a). In the presence of palladium catalyst and a mono-protected amino acid (MPAA) ligand, the alkenes bearing the hydroxy functionality can couple efficiently with electron-deficient alkenes such as acrylates, vinyl ketones and acrylamides to form conjugated dienes **16**. Notably, while homoallyl alcohols reacted best to proceed *via* a six-membered *endo*-metallocycle intermediate, allyl alcohols only led to moderate yields *via* a five-membered *endo*-metallocycle. In addition, alcohol 4-phenylpent-4-en-1-ol provided C–H alkenylation product **16f** in only 26% yield *via* a seven-membered *endo*-metallocycle. A plausible mechanism proposed by the authors is shown in Scheme 13b. Under the palladium catalysis, hydroxy group-directed vinylic C–H bond cleavage occurred to afford a six-membered *endo*-palladacycle, **I**. Alkene coordination followed by migratory insertion afforded intermediate **III**. Species **III** then led to the formation of the alkenylation product **16** by β-H elimination and liberated Pd(0) species which could be re-oxidized into Pd(II) with the aid of silver oxidant. The kinetic study suggested that the C–H bond cleavage could be the rate-determining step.[43]

The enol-carbamate functionality is of particular interest because of its facile preparation from ketones and easy transformations to other valuable functionalities. Our group developed an olefinic C–H alkenylation of enol carbamates using internal alkynes or electron-deficient alkenes under ruthenium catalysis. By using carbamates as the directing groups, the cross-coupling led to stereo-selective synthesis of valuable (*Z*,*E*)- and (*Z*,*Z*)-butadienes **17** and **18** (Schemes 15a and b). Plausible mechanisms are illustrated in Schemes 14 and 15. First, vinylic C–H activation of enol carbamates takes place to give six-membered alkenyl-ruthenacycle intermediates **I** with the liberation of a proton. Then, alkene insertion of **I** and the subsequent β-hydride elimination led to linear 1,3-dienes **17**, and the ruthenium hydride was re-oxidized by Cu(II) to regenerate the catalytically active species (Scheme 14b). In contrast, alkyne insertion of **I** followed by protonolysis produced branched 1,3-dienes **18** (Scheme 15b). Treatment of product **18a** with phenyl boronic acid led to an arylated product in good yield by C–O bond cleavage under Ni-catalysis.[44]



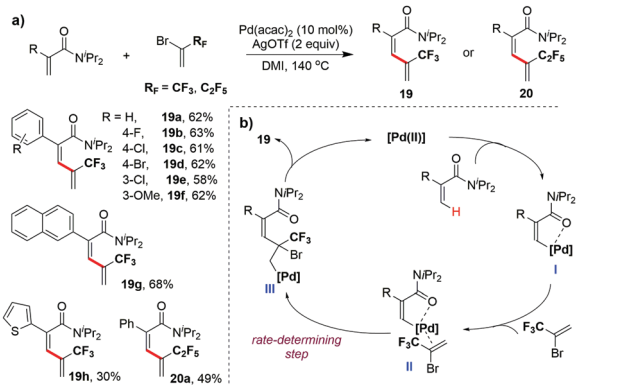
Scheme 14 Ru-Catalyzed olefinic C–H alkenylation of enol carbamates using alkenes (Zhang and Zhong, 2017).[44]



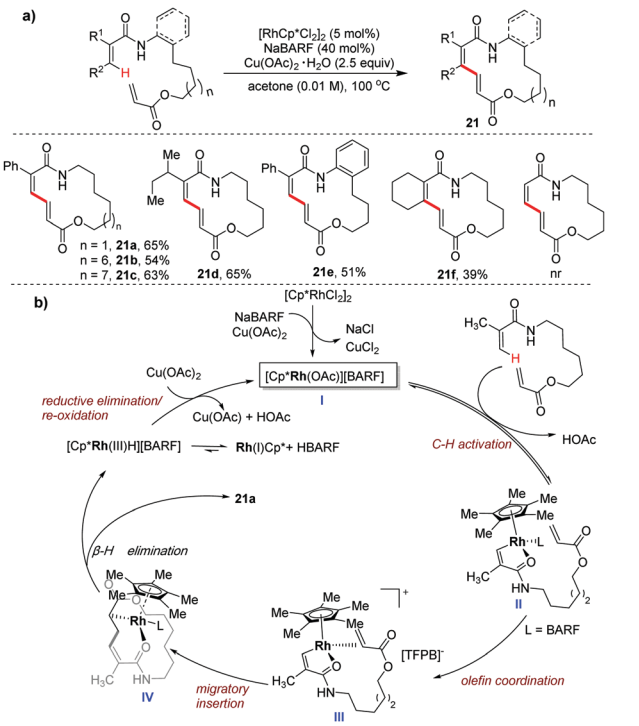
Scheme 15 Ru-Catalyzed olefinic C–H alkenylation of enol carbamates using alkynes (Zhang and Zhong, 2017).[44]

Bouillon, Poisson and co-workers disclosed a palladium-catalyzed C–H bond functionalization of acrylamides to prepare trifluoromethylated 1,3-butadienes **19** with excellent stereoselectivity. In this protocol, acrylamides were selectively C–H functionalized with 2-bromo-3,3,3-trifluoropropene, using a tertiary amide as the directing group. Notably, the methodology was also extended to the construction of pentafluoroethyl-substituted 1,3-dienes **20**. A redox neutral mechanism was proposed with the assistance of density functional theory calculations. The reaction proceeded by the formation of *O*-coordinated palladacycle intermediate **I**, and the subsequent carbopalladation led to the organopalladium intermediate **III**, which produced 1,3-diene by β-Br elimination (Scheme 16).[45]

Macrolides are an important class of organic molecules due to their wide occurrence in many natural products and pharmaceuticals. The Loh group disclosed an amide directed intramolecular oxidative C–H/C–H cross-coupling between two alkenyl C–H bonds for the synthesis of 12–20 membered macrolides **21** by using $[RhCp^*Cl_2]_2$ as the catalyst. This work provides a rapid and atom-economical synthetic pathway to prepare macrolide compounds with a *Z*,*E*-configured diene moiety in moderate to good yields and with excellent chemo- and stereoselectivity. Sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (NaBARF) was found to be crucial in the reaction. A plausible mechanism was proposed as follows. Anion exchange of $[RhCp^*Cl_2]_2$ with NaBARF and $Cu(OAc)_2{\cdot}H_2O$ afforded the reactive species **I**, which selectively activated the *Z*-olefinic C–H bond of the acrylamide derivative to form a vinylrhodium(III) species, **II**. Subsequent intramolecular olefin coordination and migratory insertion formed intermediates **IV**, which underwent β-hydride elimination to afford the macrolide compounds **21** (Scheme 17).[46]



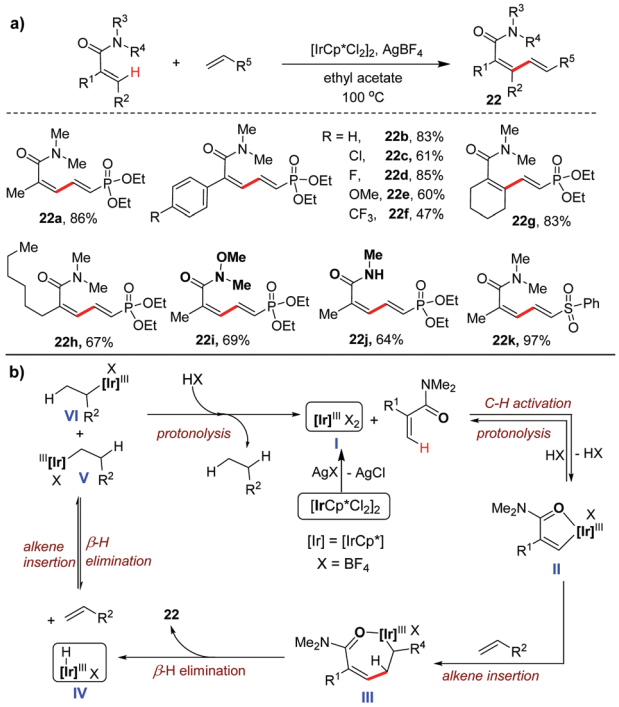
Scheme 16 Pd-Catalyzed olefinic C–H alkenylation using trifluoropropene (Bouillon and Poisson, 2017).[45]



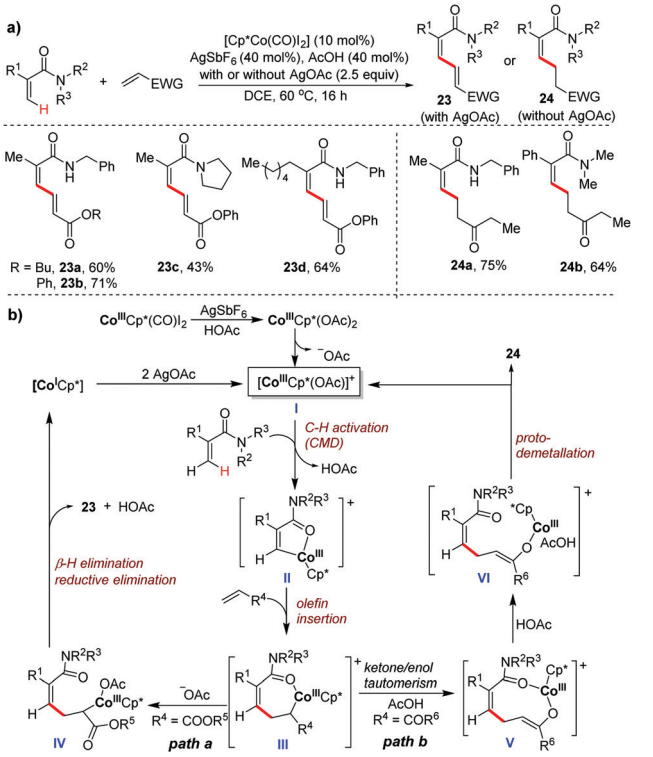
Scheme 17 Rh-Catalyzed intramolecular olefinic C–H alkenylation to afford macrolides (Xu and Loh, 2018).[46]

A wide variety of olefinic C–H/C–H cross-coupling reactions to produce 1,3-dienes have been realized under palladium-, rhodium- or ruthenium-catalysis, usually employing metal oxidants in quantitative amounts. Consequently, developing other transition-metal-catalysed cross-coupling reactions is appealing due to their complementary substrates and reaction types. Moreover, integration of hydrogenation transfer and C–H alkenylation in one cross-coupling reaction could obviate the use of metal oxidant; however, it remains a challenging goal due to the isomerization and reduction of olefins. Our group reported the first iridium-catalyzed amide-directed olefinic C–H alkenylation, using organic hydrogen acceptors such as benzaquinones or alkenes *via* hydrogenation transfer (Scheme 18a). A possible reaction mechanism is depicted in Scheme 18b. First, $[Cp^*IrCl_2]_2$ reacts with $AgSbF_6$ to afford Ir(III) species **I**, which inserts into the olefinic C–H bond of the acrylamide to provide **II**, and the subsequent migratory insertion of an olefin and β-H elimination lead to 1,3-diene **22** with the liberation of Ir(III) hydride species **IV**. **IV** inserts into the olefin to form alkyliridium species **V** and **VI**, which finally provides an alkane and regenerates the catalytic species **I** by protonolysis. An intermolecular competition experiment showed that the electron-rich one reacted preferentially, and a Hammett plot analysis indicated a linear fit with a negative slope of $\rho = -0.57$.[47]

After the advance in iridium-catalyzed cross-coupling of alkenes, our group also developed the first cobalt-catalyzed cross-couplings of olefins to provide 1,3-dienes **23** and tri-substituted alkenes **24**, using complex $[Cp^*Co(CO)I_2]$ as the catalyst. Notably, the reactions with acrylates and α,β-unsaturated ketones are



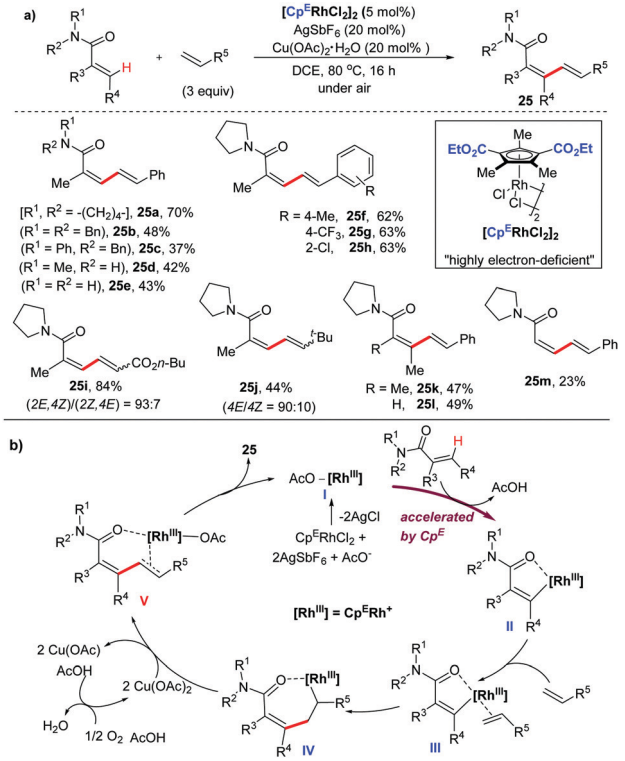
Scheme 18 Iridium-catalyzed alkenyl C–H alkenylation by hydrogen transfer (Zhang and Zhong, 2019).[47]



Scheme 19 Cobalt-catalyzed olefinic C–H alkenylation and alkylation (Zhang and Zhong, 2019).[48]

switchable, affording alkenylation and alkylation respectively (Scheme 19). A plausible catalytic mechanism is presented in Scheme 19b. Firstly, $AgSbF_6$ abstracted the halide from the $[CoCp^*(CO)I_2]$ complex to afford a mono-cationic species $[Cp^*Co(III)(OAc)]^+$ (**I**), which inserted into the vicinal olefinic C–H bond to form five-membered cobaltacycle **II**. Olefin migratory insertion followed by β-hydride elimination led to 1,3-diene **23**, and the active species **I** was regenerated *via* oxidation by AgOAc (path a). On the other hand, insertion of an α,β-unsaturated ketone into **II** provided intermediate **III** bound with an AcOH, which was then transformed into **VI** *via* a metallo-keto/enol isomerization followed by ''dechelation isomerisation''. The final protonation of **VI** furnished product **24** with the regeneration of active species **I** (path b).[34] While keto/enol isomerization led to the C–H alkylation process, the ester group promoted C–H alkenylation as it destabilized such isomerization.[48]

Shibata and Tanaka developed an aerobic oxidative cross-coupling reaction between acrylamides and both activated and unactivated olefins, using an electron-deficient $Cp^ERh(III)$ complex containing two ester groups on the Cp ring (Scheme 20a). The reaction is performed in air, using $[Cp^ERhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) in DCE at 80 °C, leading to (2*Z*,4*E*)-dienamides with the assistance of tertiary, secondary or primary amides as directing groups (**25a–e**). The turnover-limiting olefinic C–H bond activation is demonstrated by mechanistic studies to be facilitated by the electron-deficient properties of the $Cp^ERh(III)$ catalyst. A plausible mechanism is

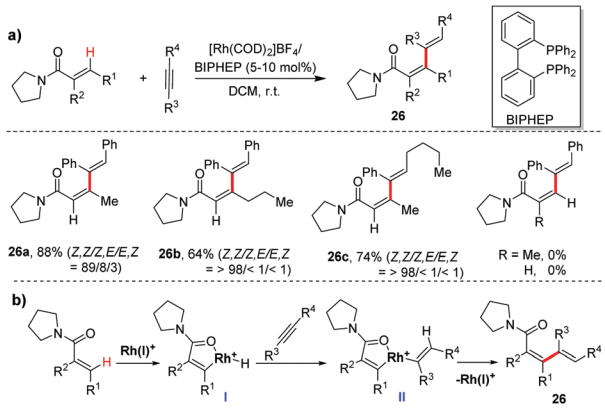


Scheme 20 Aerobic cross-coupling of alkenes catalyzed by an electron-deficient CpRh^{III} complex (Shibata and Tanaka, 2019).[49]

proposed to be initiated by the reaction of $[Cp^ERhCl_2]_2$ with $AgSbF_6$ and $Cu(OAc)_2$ to afford active species **I**. Then, olefinic C–H activation occurs to provide a five-membered rhodacycle, **II**, by an electrophilic CMD mechanism. Coordination and insertion of an alkene to **II** afford rhodacycle **IV**. The final β-hydride elimination produces diene **25** and generates rhodium(III) acetate **I** by oxidation with Cu(II) (Scheme 20b).[49]

Not only alkenes but also alkynes are good coupling partners in C–H alkenylations, and these reactions proceeded in the absence of any oxidant, representing greener chemistry. However, while directed cross-coupling between alkenes produces *Z*,*E*-configured 1,3-dienes, chelation-assisted cross-coupling between alkenes and alkynes led to *Z*,*Z*-configured 1,3-dienes due to *syn*-addition of alkynes to hydrido-metal species, which represents a complementary method. In 2009, the Tanaka group reported site-selective sp^2 C–H alkenylations of acrylamides and benzamides under rhodium(I)/BIPHEP catalysis, using 1-pyrrolidinecarbonyl as the directing group (Scheme 21a). A possible mechanism for the alkenylation of benzamides with alkynes is shown in Scheme 21b. Benzamide or acrylamide reacts with rhodium to give rhodium hydride **I** through 1-pyrrolidinecarbonyl-directed C–H bond activation. Insertion of an alkyne *via* *syn*-addition followed by reductive elimination furnishes alkenylation product **26** and regenerates the Rh(I) species.[50]

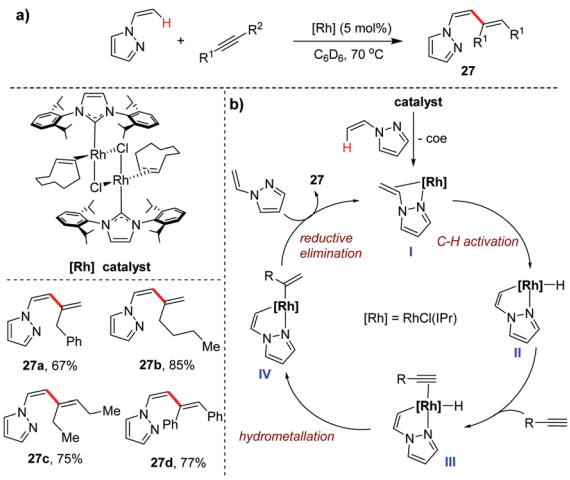
The Oro group also demonstrated an efficient cross-coupling of alkynes and *N*-vinylpyrazoles *via* directed olefinic C–H activation, leading to Markovnikov-selective butadienyl pyrazole derivatives **27** using a carbene and *cis*-cyclooctene liganded



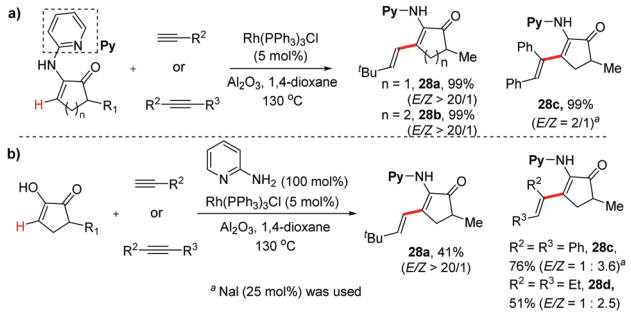
Scheme 21 Rh-Catalyzed olefinic C–H alkenylation of acrylamides using alkynes (Tanaka, 2009).[50]

rhodium catalyst (Scheme 22a). The carbene ligand is crucial for this C–H alkenylation of the electron-rich alkenes. This protocol also provides an efficient preparation of conjugated acyclic trienes by a tandem alkyne dimerization and hydrovinylation sequence in a one-pot fashion. The possible mechanism starts with pyrazole-directed olefinic C–H activation, followed by alkyne coordination/insertion and reductive elimination steps, leading to the coupling products **27** (Scheme 22b). Notably, aliphatic terminal alkynes are preferentially hydrovinylated without dimerization, cyclotrimerization, or polymerization of the alkyne.[51]

The Dong group developed an olefinic C–H alkenylation and alkylation of enamines to afford α-substituted ketones cocatalyzed by a Rh(I) complex and organic molecules such as 2-aminopyridine and 7-azaindoline.[52] In 2014, they demonstrated an olefinic C–H alkenylation of enamino-ketones by using $Rh(PPh_3)_3Cl$ as the catalyst. In this protocol, the slow addition of terminal alkyne substrates (through a syringe-pump) is crucial to prevent multiple alkyne insertions. Interestingly, employment of NaI significantly promotes the reaction, presumably due to the disfavored formation



Scheme 22 Rh-Catalyzed cross-coupling of alkynes and *N*-vinylpyrazoles (Oro, 2014).[51]



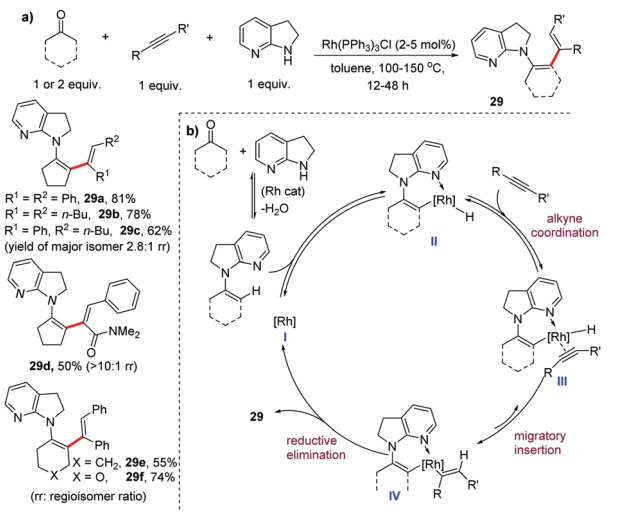
Scheme 23 Rhodium-catalyzed C–H alkenylation of enamino-ketones (Dong, 2014).[53]

of metal vinylidenes (Scheme 23a). Terminal alkynes also reacted well with cyclic enamino-ketones with excellent regioselectivity, and only *E*-alkenes by *anti*-Markovnikov addition were obtained (**28a** and **28b**). Notably, a significant amount of *Z*-alkene was observed with internal alkynes, presumably due to the thermodynamically controlled *E*/*Z* isomerization. Moreover, a tandem three component coupling was also successful which proceeded *via* condensation between 2-aminopyridine and 1,2-diketones, albeit with decreased product yields (Scheme 23b).[53]

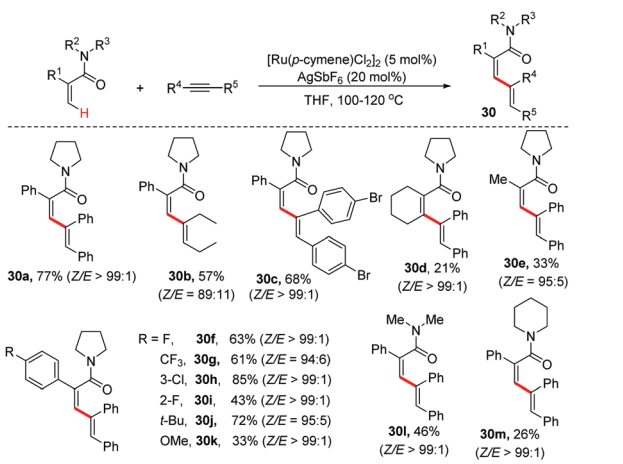
After that, the same group developed a rhodium(I)-catalyzed α-C–H alkenylation of ketones employing internal alkynes. This protocol provides conjugated enamines **29** using an active bifunctional 7-azaindoline as a ligand and $Rh(PPh_3)_3Cl$ as a catalyst. Aromatic and aliphatic alkynes were all suitable coupling partners (**29a** and **29b**). Unsymmetrical alkynes preferably afforded a C–C bond at the aryl site, and the major isomer was obtained in synthetically valuable yield (**29c**). Notably, electron-deficient phenylpropiolic dimethyl amide also reacted well, providing the "reverse conjugate addition" product **29d** with high selectivity. However, if a mono-substituted alkyne was used, hydroamination with 7-azaindoline was observed as the major side reaction. A plausible catalytic cycle is depicted in Scheme 24b. Firstly, condensation of 7-azaindoline with the ketone generates an enamine, **I**, and vinyl C–H bond activation occurs to give rhodium–hydride species **II**. Alkyne coordination, followed by Rh–H migratory insertion and reductive elimination, would produce the alkenylated products **29**.[54]

In 2017, our group also developed a ruthenium-catalyzed cross-coupling reaction between acrylamides and internal alkynes, using *N*,*N*-disubstituted aminocarbonyl as a directing group. The reaction provides an atom economic synthesis of (*Z*,*Z*)-butadiene skeletons **30** under mild and oxidant-free conditions with excellent stereo-selectivities (Scheme 25). Unfortunately, β-substituted acrylamides such as cinnamamide and plain acrylamide are totally inactive even at elevated temperatures. Competition experiments not only highlighted alkylalkynes to be more reactive than arylalkynes, but also revealed the more electron-deficient acrylamide to be converted preferentially. In addition, deuterium-labeling experiments indicated an irreversible cyclometalation event and a KIE value of 1.9 revealed the olefinic C–H activation to be probably involved in the rate-determining step.[55]

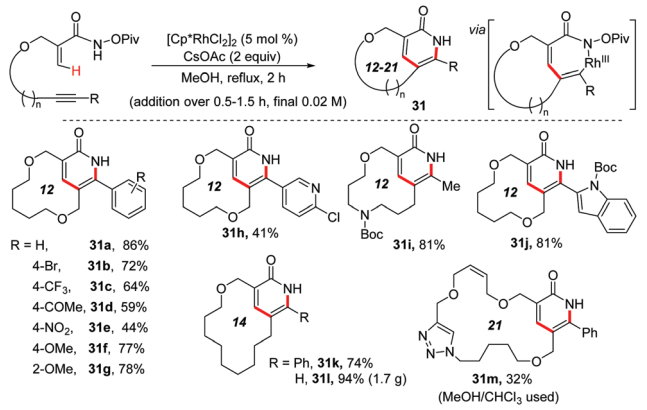
In the same year, Cossy and Meyer reported a synthesis of macrocyclic pyridines **31** from ω-alkynyl α-substituted acrylic hydroxamates, which proceeded by Rh(III)-catalyzed C–H activation to afford rhodacycles followed by heterocyclization. This redox-neutral protocol employs *O*-pivaloyl hydroxamate as the directing group. The reaction is performed in a solution of $[Cp^*RhCl_2]_2$ and CsOAc in a refluxing MeOH with a slow addition of the substrate *via* a syringe pump. Various phenyl-substituted alkynes underwent cyclization to afford pyridines in moderate to good yields, and the electron-deficiency of the arene led to decreased yields, which was consistent with the previous Rh(III)-catalyzed heterocyclization of benzamides with diarylalkynes. Heteroaryl-substituted alkynes bearing 6-chloropyridin-2-yl and N-Boc-indolyl groups also reacted well to afford 41% (**31h**) and 81% (**31j**) yields respectively. 14-Membered pyridones **31** were also isolated in good to excellent yields (**31k** and **31l**). However, 21-membered pyridine **31m** bearing a triazole was obtained in only 32% yield (Scheme 26).[56]



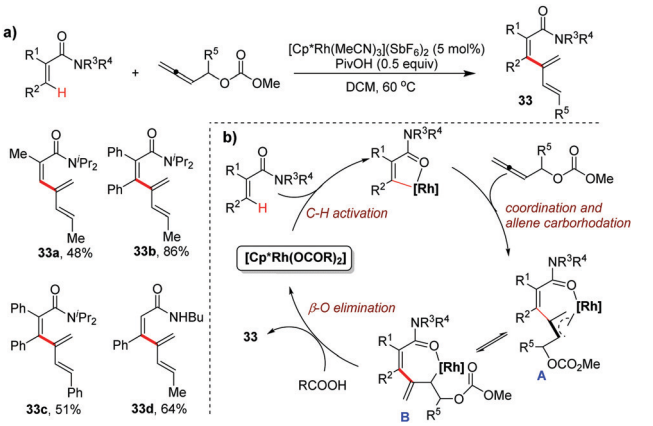
Scheme 24 Bifunctional ligand-assisted α-alkenylation of ketones using internal alkynes (Dong, 2015).[54]



Scheme 25 Ruthenium-catalyzed olefinic C–H alkenylation of acrylamides using alkynes (Zhang and Zhong, 2017).[55]

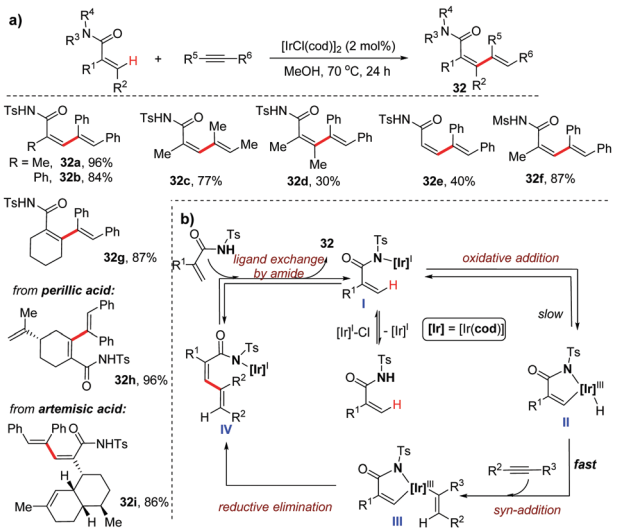


Scheme 26 Rh-Catalyzed synthesis of macrocyclic pyridines from ω-alkynyl α-substituted acrylic hydroxamates (Cossy and Meyer, 2017).[56]



Scheme 28 Rh-Catalyzed olefinic C–H alkenylation of acrylamides using allenyl carbinol carbonates (Glorius, 2013).[58]

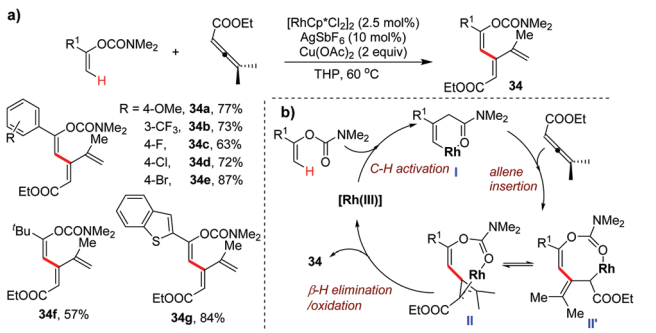
After the advances in ruthenium-catalyzed alkene–alkyne coupling reaction, an iridium-catalyzed protocol was realized under milder and simpler conditions by us recently (Scheme 27). Compared to the previous Ru-catalyzed protocol,[37] this reaction showed better reactivity and a much wider range of substrates reacted smoothly to provide (*Z*,*Z*)-configured 1,3-dienes with excellent site- and stereo-selectivities. Even plain acrylamide led to a moderate yield and excellent stereo-selectivity (**32e**). The robustness of this method is highlighted by successes in gram-scale preparation and vinylic C–H modification of artemisic- and perillic acid derived amides (**32h** and **32i**). A possible mechanism started with the formation of an amidoiridium species (**I**) by the reaction between [Ir]–Cl and *N*-sulfonyl acrylamide, and then olefinic C–H activation occurred to afford a hydridoiridium species, **II**, which underwent *syn*-addition of an alkyne and reductive elimination to form **IV**. Finally, **IV** underwent ligand exchange by an acrylamide substrate to produce 1,3-diene **32** with the regeneration of active species **I** (Scheme 27b).[57]



Scheme 27 Iridium-catalyzed olefinic C–H alkenylation of acrylamides using alkynes (Zhang and Zhong, 2019).[57]

Allenes are powerful organic synthons which are used in a variety of transformations, including alkenyl C–H alkenylation. The Glorius group disclosed a Rh(III)-catalyzed synthesis of trienes **33** by an amide-directed alkenyl C–H activation and coupling reaction using acrylamides and allenyl carbinol carbonates, in the absence of any oxidant. The atom-economic protocol was also applied to aromatic C–H activation to generate diene-substituted arenes with high efficiency. The robustness and practicality of the reaction are attributed to the excellent site- and stereoselectivities and tolerance of different directing groups and numerous functional groups. The reaction is induced by amide-directed olefinic C–H activation with the assistance of PivOH. The subsequent coordination of allenes followed by site-selective carborhodation affords allyl- and alkyl Rh(III) species **A** and **B** which are in equilibrium. A subsequent β-oxygen elimination delivers the final triene product **33** and regenerates the rhodium catalytic species (Scheme 28).[58]

The Fu group developed a carbamate-directed olefinic C–H alkenylation with allenes to produce highly unsaturated conjugated trienes **34** by Rh(III) catalysis, using copper acetate as the oxidant (Scheme 29a). Both olefinic and aromatic substrates are suitable for this protocol and a broad spectrum of functional groups are well tolerated. A possible mechanism was proposed to be initiated by olefinic C–H activation to form a rhodacycle, **I**, which underwent coordination/insertion of



Scheme 29 Rh-Catalyzed carbamate-directed olefinic C–H alkenylation with allenes to produce conjugated trienes (Fu, 2014).[59]

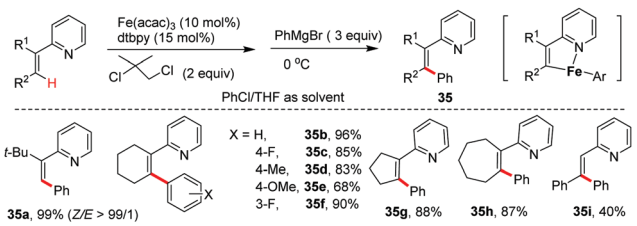
allenes into the C–Rh bond to form **II** or **II′**. The final β-H elimination led to product **34** and regenerated the active Rh(III) species by oxidation (Scheme 29b).[59]

2.2 Vicinal group-directed olefinic C–H arylation

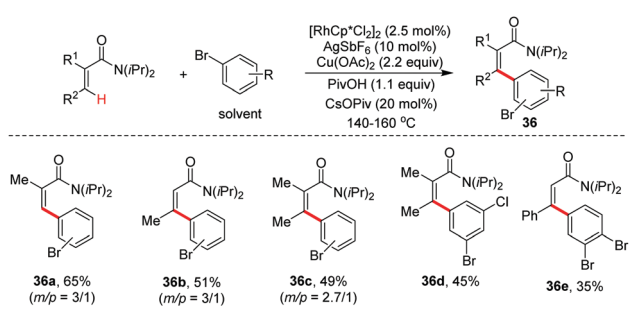
Olefinic C–H arylation represents a powerful method toward the selective synthesis of styrene derivatives. Nakamura and co-workers previously reported a pyridine- or imine-directed vinylic C–H arylation reaction using aryl Grignard reagent under iron catalysis. The reaction proceeded well in the presence of 1,2-dichloro-2-methylpropane as a mild oxidant, leading to stereospecific arylation of the alkenyl C–H bond *syn* to the directing group (**35a–35i**). The protocol is proposed to proceed *via* a five-membered metallacycle intermediate followed by reductive elimination (Scheme 30).[60]

Glorius and co-workers developed a Rh(III)-catalyzed oxidative C–H/C–H cross-coupling reaction between acrylamides and bromoarenes, which were also used as solvents. Due to the efficient directing effect of the amides, *Z*-configured styrenes **36** were successfully obtained under harsh conditions, with the bromo group remaining intact. However, non-directed aromatic C–H activation of the bromoarenes led to moderate yields as well as poor regio-selectivity in most of the cases which were controlled by both electronic and steric effects (Scheme 31).[61]

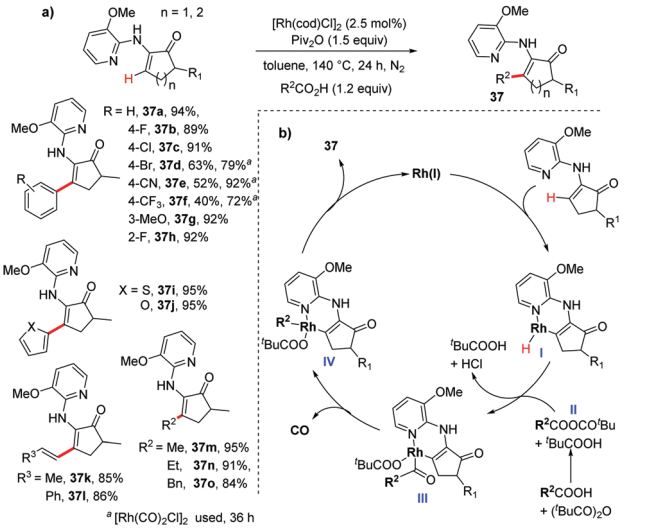
Enamines and enamides are important synthetic intermediates, and the Shi group demonstrated an aminopyridinyl directed β-C–H functionalization of five- and six-membered cyclic enamines, using carboxylic acids as arylation and alkylation partners (Scheme 32a). The 3-methoxypyridinyl amino DG of the products is easily removable under acid hydrolysis, and this protocol affords an efficient approach to *C*-alkylated and arylated cyclic diketones, employing $[Rh(CO)_2Cl]_2$ or $[Rh(cod)Cl]_2$ as the catalyst. A mechanism was proposed by



Scheme 30 Fe-Catalyzed olefinic C–H arylation (Nakamura, 2011).[60]



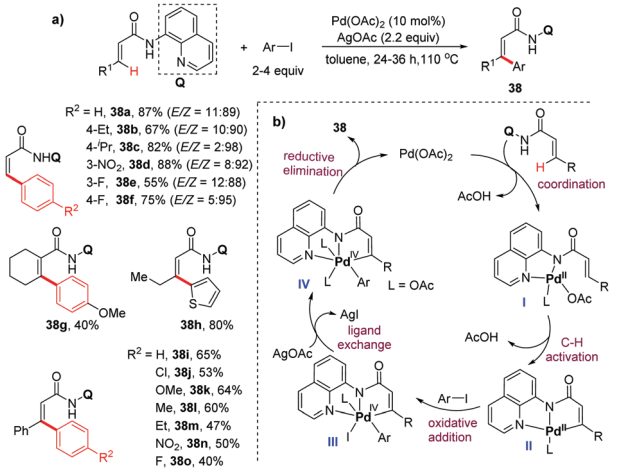
Scheme 31 Rh-Catalyzed olefinic C–H arylation of acrylamides (Glorius, 2012).[61]



Scheme 32 Rh-Catalyzed aminopyridinyl directed β-C–H functionalization of cyclic enamines (Sun and Shi, 2014).[62]

the authors (Scheme 32b). The reaction starts with olefinic C–H bond activation with the assistance of the DG to afford rhodacycle **I**, which reacts with anhydride **II** generated from carboxylic acid and $(^tBuCO)_2O$ to afford intermediate **III**. The subsequent decarbonylation and reductive elimination of **IV** provide the desired product **37** and regenerates the rhodium(I) catalyst.[62]

The Babu group reported a Pd-catalyzed olefinic C–H arylation reaction of *N*-(quinolin-8-yl)acrylamides using aryl- and heteroaryl iodides to prepare various *Z*-cinnamamides and β,β-diarylated acrylamides (**38a–o**). This bidentate 8-aminoquinoline-directed C–H activation proceeded in the presence of $Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 110 °C. *N*-(Quinolin-8-yl)acrylamides bearing *para*- or *meta*-NO_2, F, Cl, OMe and alkyl were all smoothly converted (Scheme 33a). A plausible reaction mechanism is proposed to be initiated by

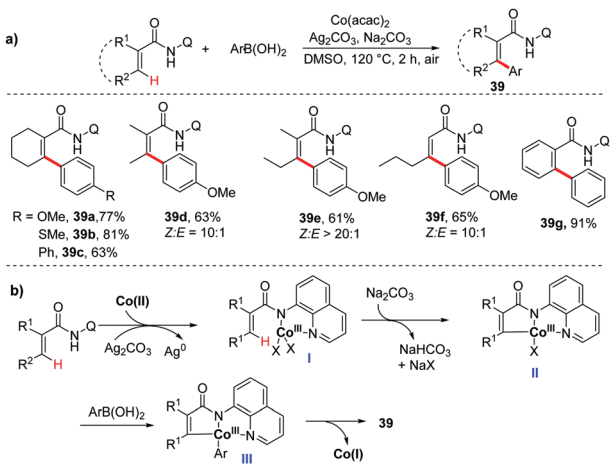


Scheme 33 Palladium-catalyzed olefinic C–H arylation reaction of *N*-(quinolin-8-yl)acrylamides (Babu, 2015).[63]

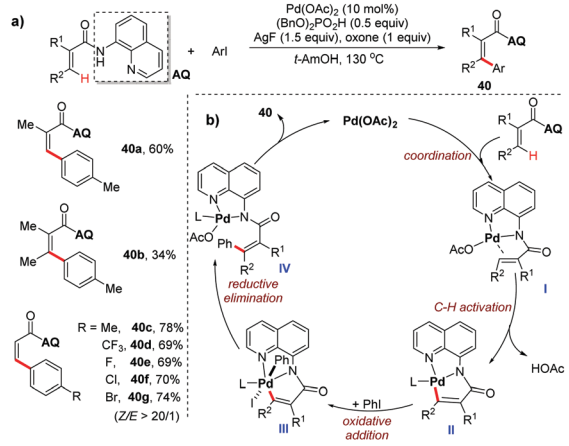
coordination of the *N*,*N*-bidentate directing group to the Pd(II) center, followed by olefinic C–H activation to afford the Pd(II) species **II**. The subsequent oxidative addition of the Pd(II) species with aryl iodide affords Pd(IV) species **III**. Next, ligand exchange occurs with the assistance of AgOAc and the reductive elimination of the Pd(IV) species **IV** yields the desired product **38** with the formation of the Pd(II) catalyst which re-enters the next cycle (Scheme 33b).[63]

In 2016, Zhu and co-workers reported a cobalt-promoted C–H arylation of acrylamides with arylboronic acids, also using 8-aminoquinoline as the directing group. The C–H arylation completed in 2 h and was performed employing quantitative amounts of $Co(acac)_2$, Ag_2CO_3 and Na_2CO_3 in DMSO at 120 °C in air, which were also applied to benzamide substrates (**39g**) (Scheme 34a). Both cyclic and acyclic acrylamides were smoothly converted to provide the corresponding styrenes **39a–f** in 61–81% yields with good stereoselectivities (*Z*/*E* up to 20/1). A possible mechanism is depicted in Scheme 34b. Firstly, Co(II) is oxidized by Ag_2CO_3 to afford Co(III) species **I** by base assisted ligand exchange, and then C–H activation occurs to provide the aryl Co(III) species **II**. Notably, the sequence of oxidation and ligand exchange may be reversed in order. Next, transmetallation between intermediate **II** and phenylboronic acid occurs to give complex **III**, and the final reductive elimination leads to the desired product **39**.[64]

Jiang and Xue also reported a method for Pd-catalyzed, aminoquinoline-directed arylation of vinylic C–H bonds with aryl iodides (Scheme 35a). This olefinic C–H functionalization of acrylamides provides a site- and stereoselective construction of *Z*-styrenes **40**. A wide variety of functional groups were well tolerated in this protocol. A plausible mechanism involving a Pd(II)/Pd(IV) catalytic cycle was proposed (Scheme 35b). The coordination of acrylamides with palladium acetate formed complex **I**, which further underwent a rapid C–H cyclometalation of the vinyl group, resulting in intermediate **II**. Then aryl iodide reacted with **II** by oxidative addition to generate a Pd(IV) species, **III**, which underwent reductive elimination and ligand exchange to produce styrene **40** with the regeneration of the active Pd(II) catalyst. Little electronic effect was observed in the reaction with differently substituted aryl iodides.[65]



Scheme 34 Cobalt-promoted C–H arylation of acrylamides with arylboronic acids (Zhu, 2016).[64]



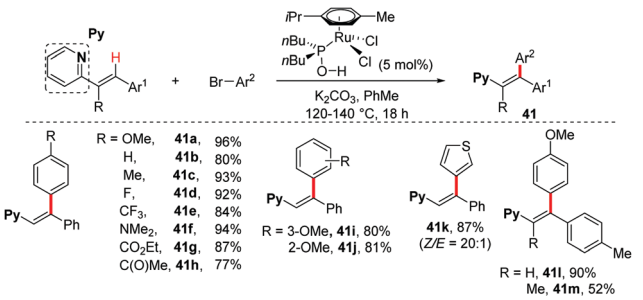
Scheme 35 Pd-Catalyzed aminoquinoline-directed arylation of vinylic C–H bonds with aryl iodides (Jiang and Xue, 2016).[65]

In the same year, the Ackermann group demonstrated an olefinic C–H arylation using a Ru(II) phosphinous acid (PA) complex as a catalyst. The reaction exhibited excellent site- and stereoselectivity to afford styrene derivatives **41** using 2-pyridyl as the directing group. A broad substrate scope was observed, as well as a wide range of functionality tolerance, and both tri- and tetra-substituted alkenes were prepared in a stereoselective manner (Scheme 36).[66]

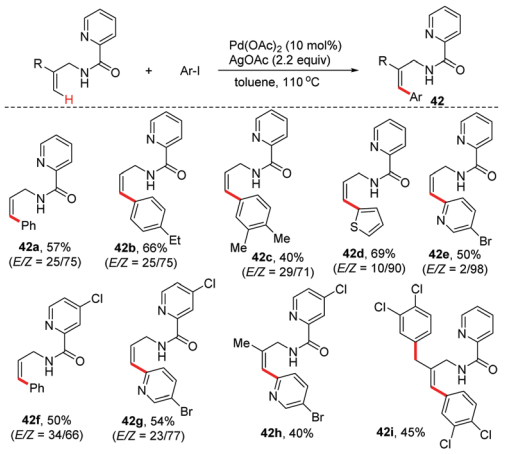
The Babu group reported a Pd(II)-catalyzed *N*,*N*-bidentate-chelation-assisted olefinic C–H arylation of allyl picolinamides, using $Pd(OAc)_2$ as the catalyst and AgOAc as an additive (Scheme 37). Various *Z*-cinnamylamines **42** were smoothly obtained from *N*-allyl picolinamides and aryl iodides with good to high stereo-selectivities. Interestingly, both γ-C(olefinic)–H and γ-C(alkyl)–H bonds in one allylamine molecule underwent olefinic C–H arylation to afford bisarylated product **42i** in moderate yield. In this work, a bidentate chelation-assisted alkenyl C–H activation mechanism was proposed due to *Z*-selective γ-C(olefinic)–H arylations.[67]

2.3 Vicinal group-directed olefinic C–H alkynylation

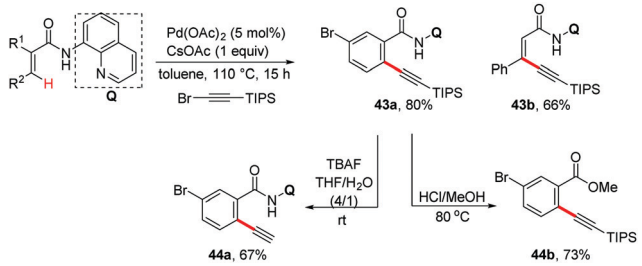
1,3-Enynes are widely occurring structural motifs in countless natural products and pharmaceutical molecules, and they are also versatile building blocks in synthetic chemistry.



Scheme 36 Ru-PA-catalyzed olefinic C–H arylation (Ackermann, 2017).[66]



Scheme 37 Pd-Catalyzed olefinic C–H arylation of allyl amides (Babu, 2017).[67]

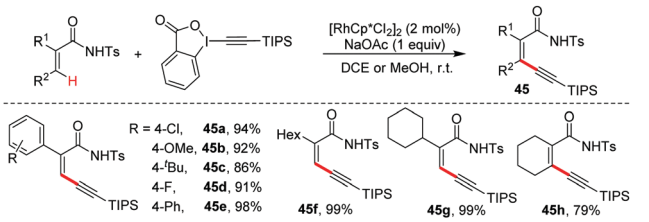


Scheme 38 Palladium-catalyzed C–H alkynylation of aromatic/olefinic amides (Tobisu and Chatani, 2014).[68]

Tobisu and Chatani reported a palladium-catalyzed *ortho* C–H alkynylation of aromatic amides with TIPS-protected bromoalkynes using 8-aminoquinoline amide as a directing group, which was performed in the presence of 5 mol% $Pd(OAc)_2$ and 1 equivalent of CsOAc in toluene at 110 °C (Scheme 38). Notably, the TIPS-substituent on product **43a** is easily removable by simple treatment with TBAF to afford terminal alkynes **44a**, and 8-aminoquinoline amide is also converted to ester **44b** through simple acidic hydrolysis with the TIPS-alkyne moiety intact. This protocol is also applicable to olefinic C–H alkynylation to prepare conjugated enynes from an acrylamide (**43b**, 66%).[68]

The Loh group reported a Rh-catalyzed vinylic C–H alkynylation of acrylamides using a hypervalent alkynyl iodine reagent. Using weakly coordinating Ts-imide as the directing group, this reaction displays broad functional group tolerance and high efficiency, leading to a wide range of functionalized 1,3-enynes **45** (Scheme 39). Notably, using methanol as reaction solvent in place of DCE was proved to prompt the C–H alkynylation of α,β-disubstituted acrylamide derivatives.[69]

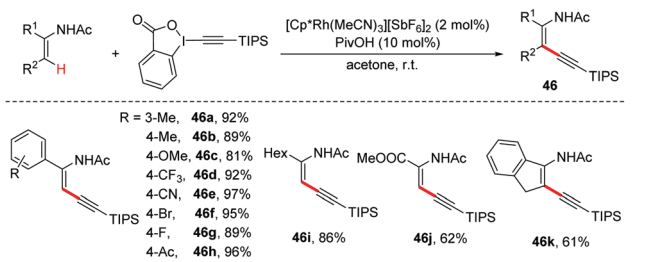
After that, the same group disclosed a Rh(III)-catalyzed olefinic C–H alkynylation of enamides for the stereospecific construction of synthetically useful *Z*-type enynamides **46**. By taking advantage of the *ortho*-directing effect of the amide group, this reaction proceeded by stereospecific activation of olefinic C–H bonds, thus providing a straightforward and



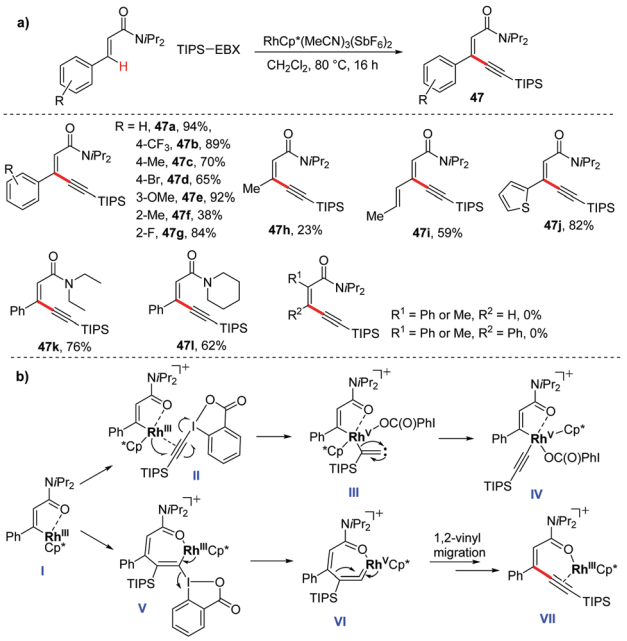
Scheme 39 Rh-Catalyzed olefinic C–H alkynylation of acrylamides (Loh, 2014).[69]

efficient method for the construction of *cis*-enynamide frameworks. The reaction was performed using 2 mol% $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as a catalyst, 10 mol% PivOH as an additive, and acetone as solvent at room temperature. A wide variety of sensitive functionalities such as CF_3, CN, Br and F were well tolerated under such mild reaction conditions. Moreover, the obtained enynamide products highlighted their utilization by cycloaddition and Sonogashira reactions (Scheme 40).[70]

The Glorius group also developed a directed C–H alkynylation of acrylamides using the cationic $RhCp^*(MeCN)_3(SbF_6)_2$ complex as the catalyst without any additive. This protocol employs hypervalent 1-[(triisopropylsilyl)ethynyl]1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) as the alkyne source, providing valuable conjugated enynes **47** bearing a removable silyl-group (Scheme 41a). Notably, the reaction proceeded in air and was insensitive to moisture. Exploration of the scope of the transformation showed that (hetero)aromatic, alkyl and alkenyl substituents were all well tolerated. Notably, diethyl and piperidine tertiary amides were also suitable directing groups. Unfortunately, a substrate bearing a geminal substituent on α-carbon failed to afford the product. Two feasible mechanisms were proposed (Scheme 41b). One included alkyne coordination, rhodium addition and 2-iodobenzoic acid liberation to give carbene intermediate **III**. The subsequent carbene rearrangement and reductive elimination provided the desired product. The possibility of direct oxidative-addition of TIPS-EBX to give **IV** could not be excluded. In the other possible mechanism, regio-selective carborhodation of **I** would generate alkenyl-rhodacycle **V** due to the steric clashes between the Cp* ligand and the TIPS as well as the electronic polarisation of TIPS-EBX, and the subsequent α-elimination of 2-iodobenzoic acid would produce rhodium vinylidene **VI**. After that, a stepwise or concerted vinyl-migration and subsequent elimination would produce **47** and regenerate active Rh(III) species.[71]

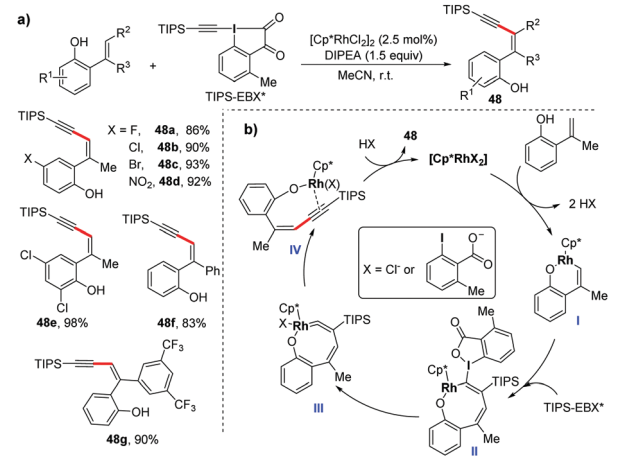


Scheme 40 Rh-Catalyzed olefinic C–H alkynylation of enamides (Loh, 2014).[70]



Scheme 41 Rh-Catalyzed additive-free C–H alkynylation of acrylamides (Glorius, 2014).[71]

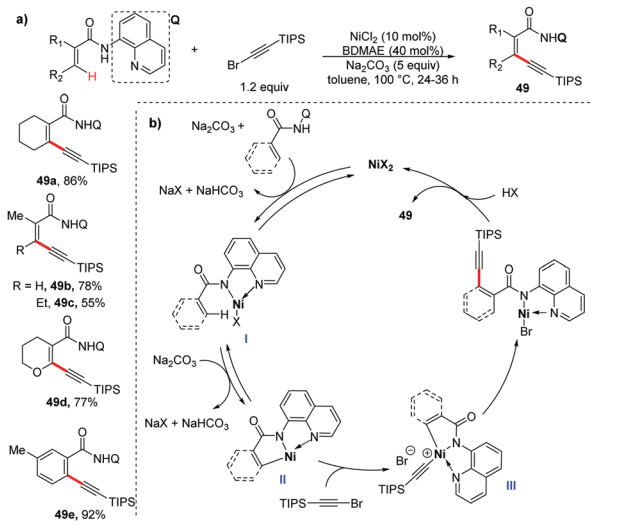
Nachtsheim and co-workers reported the first hydroxyl directed olefinic C–H alkynylation of 2-vinylphenols using a hypervalent iodine reagent, TIPS-EBX*. This mild protocol used $[(Cp^*RhCl_2)_2]$ as a transition metal catalyst and DIPEA as base, enabling the construction of a variety of highly substituted and exclusively (*Z*)-configured 1,3-enynes **48** in high yields and with excellent stereoselectivities at room temperature (Scheme 42a). A possible reaction mechanism is shown. Base-assisted ligand exchange with styrene followed by C–H bond activation through an addition/elimination cascade leads to the formation of rhodacycle intermediate **I**. Insertion of the triple bond adjacent to the hypervalent iodine of TIPS-EBX* gives rhodacycle **II**, which undergoes elimination of 2-iodo-6-methylbenzoate to give the rhodium vinylidene intermediate **III**. 1,2-Migration of the vinylic moiety followed by a ligand exchange finally releases the desired 1,3-enyne **48** and regenerates the active rhodium(III) species (Scheme 42b).[72]



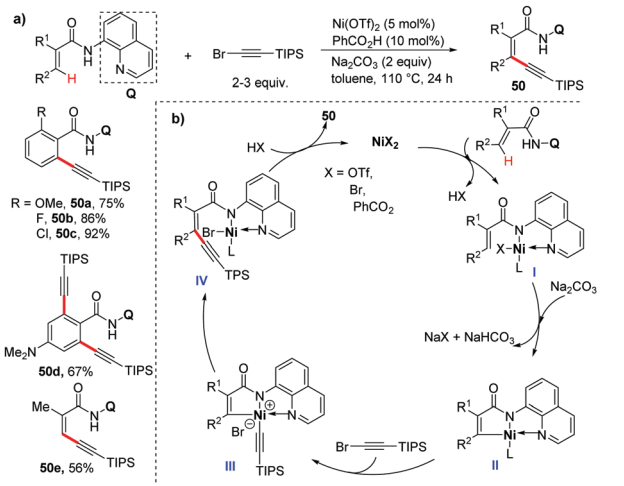
Scheme 42 Rh-Catalyzed olefinic C–H alkynylation of 2-vinylphenols (Nachtsheim, 2015).[72]

Li and co-workers developed a nickel-catalyzed C–H alkynylation of acrylamides with the assistance of 8-aminoquinoline as the directing group. The reaction was performed using an appropriate combination of $NiCl_2$ and the bis(2-dimethylaminoethyl) ether (BDMAE) ligand to give 1,3-enynes employing TIPS-protected bromoalkyne as an alkynylation reagent. This Ni/BDMAE catalytic system was suitable for both cyclic and acyclic acrylamide substrates, giving the corresponding 1,3-enynes **49** in good yields (Scheme 43a). However, the substituent at the α-carbon was critical for the reactivity. A plausible mechanism was proposed as shown in Scheme 43b. Initially, coordination of the amide to nickel catalyst was followed by ligand exchange to form complex **I**, which could go through cyclometalation to give intermediate **II**; oxidative addition of the bromoalkyne afforded the Ni(IV) complex **III**, which underwent reductive elimination and protonation to yield the alkynylation product **49** with regeneration of the Ni(II) catalyst.[73]

Balaraman and co-workers developed a nickel-catalyzed $C(sp^2)$–H alkynylation of amides using (triisopropylsilyl)ethynyl bromide with the assistance of 8-aminoquinoline as a bidentate directing group (Scheme 44a). The reaction was performed with Na_2CO_3 as a base, $Ni(OTf)_2$ as a catalyst and benzoic acid as an additive. Various benzamides were efficiently converted, leading to mono- and bis-alkynylated products **50a–d**. This protocol was also applied to the reaction of acrylamide, giving the corresponding alkynylated product **50e** in 56% yield. A possible mechanism is shown in Scheme 44b. The coordination of the amide to Ni(II) followed by a ligand exchange provides **I** with the aid of base due to the acidic N–H bond of 8-aminoquinoline. Then C–H cyclometallation occurs to afford **II** *via* a concerted metalation–deprotonation mechanism. After that, oxidative addition of TIPS-alkynyl bromide provides intermediate **III**, which is converted to intermediate **IV** by reductive elimination.



Scheme 43 Ni-Catalyzed C–H alkynylation of acrylamides (Li, 2015).[73]



Scheme 44 Nickel-catalyzed C–H alkynylation of acrylamides (Balaraman, 2016).[74]

The final protonation leads to alkynylated product **50** and regenerates the active Ni(ii) species which enters the next catalytic cycle.[74]

In 2018, the Echavarren group demonstrated a vinylic and aromatic C–H alkynylation using bromoalkynes (inverse-Sonogashira reaction) directed by synthetically useful ester and ketone groups under rhodium catalysis (**51a–e**). Other less common directing groups such as amine, thioether, sulfoxide, sulfone, phenol ester, and carbamate groups are also suitable directing groups in olefinic or aromatic C(sp^2)–H alkynylation (**51f–j**). The mechanistic experiments of aromatic substrates show that sequential electrophilic C–H activation, bromoalkyne insertion and AgOAc-assisted bromide elimination are involved in this transformation of aromatic substrates (Scheme 45).[75]

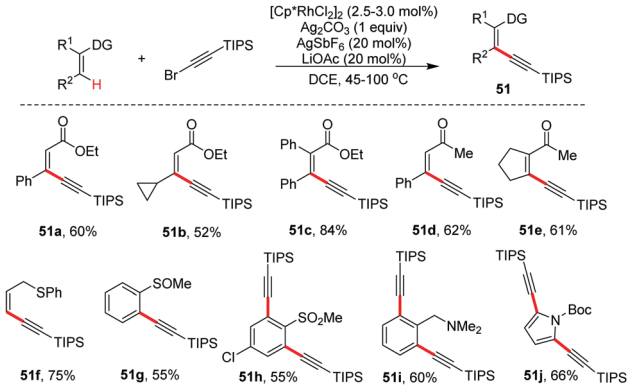
2.4 Vicinal group-directed olefinic C–H alkylation

Directed C–H alkylation represents an important organic reaction to construct C–C bonds. In the past two decades, a series of alkylation methods have been demonstrated by chelation-assisted olefin C–H bond activation. Compared to traditional methods using alkylating agents such as sulfonates or alkyl halides, addition of C–H bonds across electronically biased alkenes, carbonyls or imines for alkylations is more appealing from the viewpoint of atom efficiency, redox economy, and streamlined synthesis.[76]

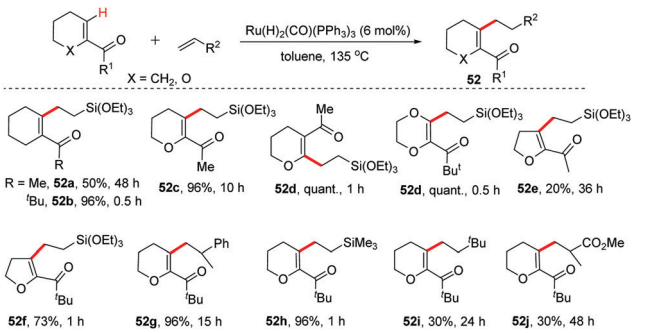
The first report on olefinic C–H alkylation was demonstrated by the Murai group in 1995, using $RuH_2(CO)(PPh_3)_3$ as the catalyst (Scheme 46). In this protocol, α,β-enones reacted well with alkenes such as triethoxyvinylsilane, styrenes, trimethylvinylsilane and vinylcyclohexane to give the corresponding alkylation products **52a–j** in 20% to quantitative yields. However, the substrate scope of this protocol was only restricted to five- and six-membered cyclic enones.[77]

(−)-Incarvillateine, a monoterpene alkaloid, has attracted attention due to its potent analgesic properties. In 2008, the Bergman and Ellman group reported an asymmetric synthesis of (−)-incarvillateine employing an intramolecular alkenyl C–H alkylation to stereoselectively construct an exocyclic and tetra-substituted olefin moiety with the simultaneous formation of two stereocenters. The formation of cyclopentane **53** bearing an exocyclic double bond is proposed to proceed by imine-directed olefinic C–H activation, *syn*-type olefin insertion and reductive elimination, exclusively leading to an *anti*-configuration of ester and methyl groups. Ferrocenyl (Fc) dialkyl phosphines and 4-(dimethylamino)phenyl (DMAPh) based phosphines were examined, and many of the ligands were active, leading to quantitative cyclization of **53-S**. (DMAPh)-PEt_2 was the optimal ligand to provide diastereomers **53** and **53′** in an ∼5 : 1 ratio using only 2.5 mol% catalyst loading (Scheme 47).[78]

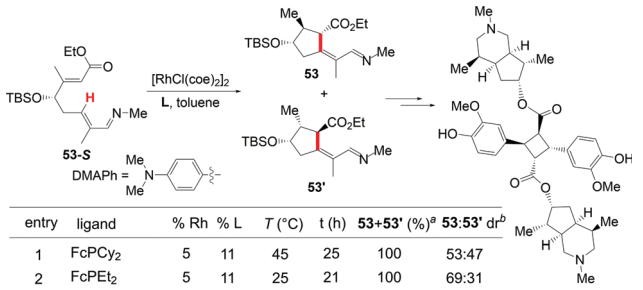
The Kuninobu and Takai group reported a C–H alkylation of olefins bearing an imine directing group with unsaturated carbonyl compounds, alkynes, or aldehydes in the presence of a rhenium catalyst $[ReBr(CO)_3(thf)]_2$, giving γ,δ-unsaturated carbonyl compounds **54**, dienes **55**, and allyl silyl ethers **56**, respectively (Scheme 48a). A possible mechanism including insertion of unsaturated molecules into an olefinic C–H bond is proposed (represented by the reaction of aldehydes). Firstly, oxidative addition of an olefinic C–H bond to the rhenium center provides a metallocycle intermediate. Secondly, insertion of an unsaturated molecule into the rhenium–carbon bond produces a seven-membered metallocycle intermediate. In the final step, silyl protection by dehydrogenation produces the desired silyl ethers **56** (Scheme 48b).[79]



Scheme 45 Rh-Catalyzed olefinic C–H alkynylation of acrylates and vinyl ketones (Echavarren, 2018).[75]



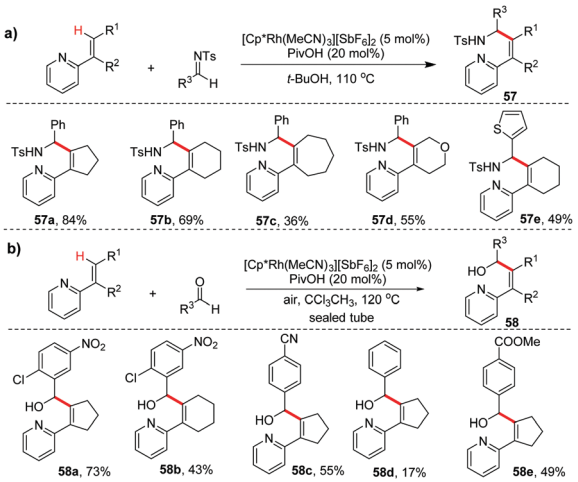
Scheme 46 Ruthenium-catalyzed C–H alkylation of α,β-enones (Murai, 1995).[77]



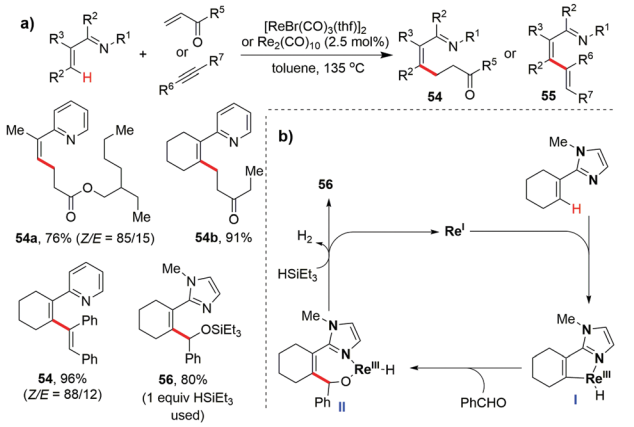
entry	ligand	% Rh	% L	T (°C)	t (h)	53+53' (%)[a]	53:53' dr[b]
1	$FcPCy_2$	5	11	45	25	100	53:47
2	$FcPEt_2$	5	11	25	21	100	69:31
3	$(DMAPh)_2PMe$	10	22	25	8	100	75:25
4	$(DMAPh)PMe_2$	10	22	45	19	100	75:24
5	$(DMAPh)PCy_2$	5	11	45	21	34	62:38
6	$(DMAPh)PEt_2$	5	11	22	54	100	86:14
7	$(DMAPh)PEt_2$	5	11	45	6	100	83:17
8	**$(DMAPh)PEt_2$**	**2.5**	**5.5**	**45**	**6**	**100**	**83:17**

[a,b] Yields and diastereomeric ratios were determined by ^1H NMR.
Fc: ferrocenyl. DMAPh: 4-(dimethylamino)phenyl.

Scheme 47 Rh-Catalyzed intramolecular alkenyl C–H alkylation (Bergman and Ellman, 2008).[78]



Scheme 49 Rh-Catalyzed olefinic C–H addition to *N*-sulfonylaldimines and aryl aldehydes (Shi, 2012).[80]

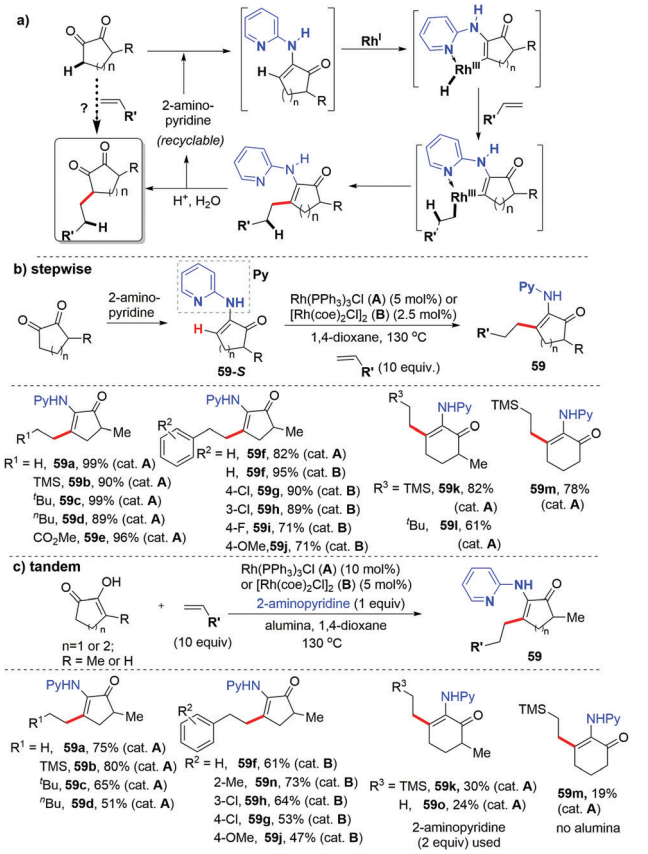


Scheme 48 Rhenium-catalyzed olefinic C–H alkylation/alkenylation (Kuninobu and Takai, 2009).[79]

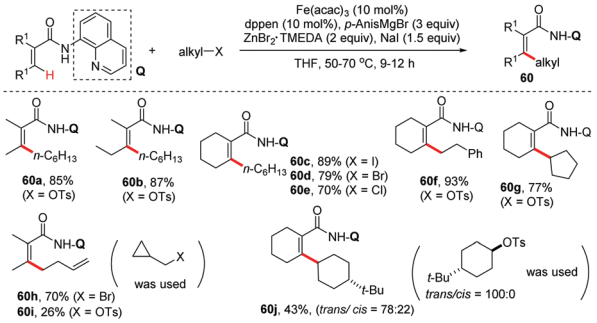
The Shi group reported the first example of olefinic C–H addition to *N*-sulfonylaldimines and aryl aldehydes using rhodium catalyst $[Cp^*Rh(MeCN)_3][SbF_6]_2$. This strategy offered a concise and highly atom-economic approach to vinyl amines **57** and vinyl alcohols **58.** However, this protocol was restricted to cyclic vinylic substrates, and the ring size of vinyl substrates was investigated with *N*-tosyl benzaldimines. The five-, six- and seven-membered substrates gave 84%, 69% and 36% isolated yields, respectively, presumably reflected by torsional effects (**57a–c**). Notably, heterocyclic substrates were smoothly converted and acceptable yields were obtained (**57d** and **57e**; Scheme 49a). The alkenyl C–H addition to aldehydes was also realized with a decreased amount of PivOH using 1,1,1-trichloroethane as solvent instead (**58a–e**). Similarly, the five-membered substrate showed the best results, while the seven-membered ring led to no desired product (Scheme 49b).[80]

The α-C–H alkylation of ketones is fundamental and widely utilized in organic synthesis, although it requires stoichiometric amounts of strong base and toxic halides. The Dong group developed a more atom-economical and "greener" addition of α-C–H bonds of cyclic 1,2-diketones across alkenes to prepare enolate-alkylation products. Their strategy is shown in Scheme 50a, using 2-aminopyridine as a directing group to activate the α-C–H bond of cyclic 1,2-diketones at a less hindered site. The reaction was proposed to proceed by condensation to generate an enamine and then olefinic C–H activation to afford a six-membered rhodacycle. The subsequent alkene insertion and reductive elimination would lead to a C–H alkylation product, and the 2-aminopyridine was released by acidic hydrolysis. After optimization of conditions, enamines, generated from ketones and 2-aminopyridine, coupled with a wide range of terminal olefins to afford the corresponding alkylation products **59** (Scheme 50b). Among them, while catalyst $Rh(PPh_3)_3Cl$ (5 mol%) was the most effective in the reaction with aliphatic alkenes, $[Rh(coe)_2Cl]_2$ (2.5 mol%) (coe = cyclooctene) was proved to be the best catalyst for aromatic olefins. A series of functionalities such as F, Cl and TMS were well tolerated. A tandem sequence including enamine formation and C–H alkylation was also successful, and neutral alumina was crucial to promote the enamine formation (Scheme 50c). Both aliphatic and aromatic alkenes converted well with five-membered diketones; however, six-membered cyclic substrates are still challenging for this tandem transformation presumably due to the decomposition to arenes in the enamine-generation step.[81]

In 2014, Ilies and Nakamura reported an iron-catalyzed olefinic C–H alkylation of acrylamides, using an 8-quinolylamide as the directing group (Scheme 51). This C–H alkylation proceeded stereospecifically in the presence of primary and secondary alkyl tosylates, mesylates, and halides using $Fe(acac)_3$ as a catalyst with the assistance of diphosphine dppen possessing a π bridge and ArZnBr as a base. Interestingly, complete ring opening of the cyclopropyl ring was observed in the reaction of cyclopropylmethyl bromide and tosylate, suggesting a radical-like character of the alkyliron intermediate (**60h** and **60i**). However, the starting secondary



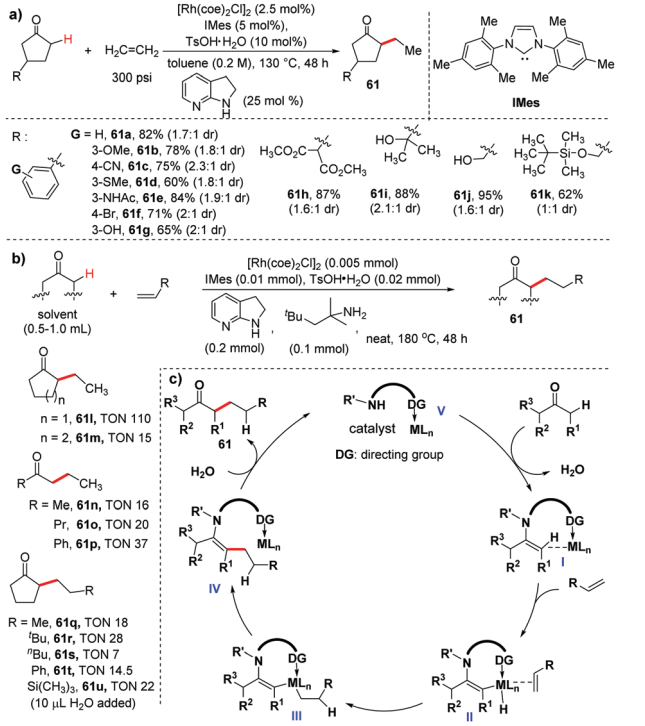
Scheme 50 Rhodium-catalyzed addition of α-C–H bonds of cyclic 1,2-diketones across alkenes (Dong, 2012).[81]



Scheme 51 Iron-catalyzed olefinic C–H alkylation of acrylamides (Ilies and Nakamura, 2014).[82]

tosylate reacted without loss of regioselective integrity but with erosion of the stereoselectivity of the chirality (**60j**).[82]

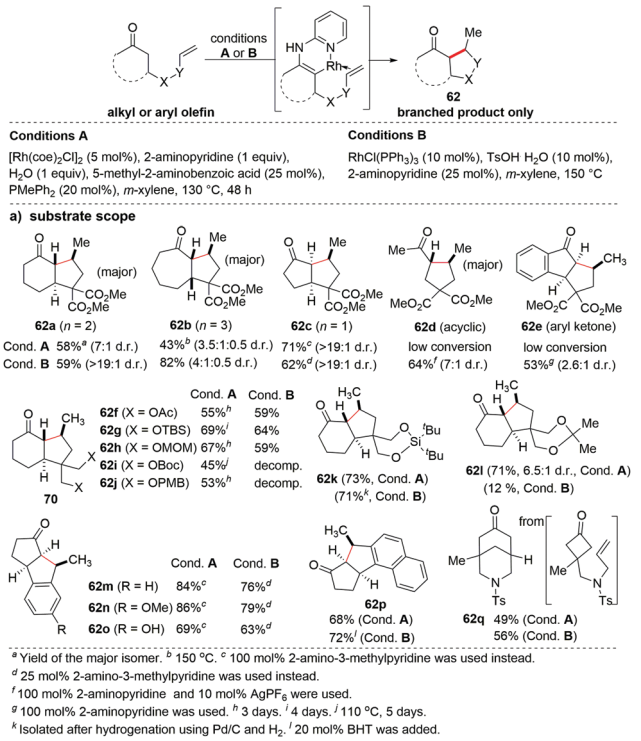
In 2014, the Dong group developed a α-C–H alkylation of ketones using simple olefins as the alkylating agents. This reaction was performed using $[Rh(coe)_2Cl]_2$ and 7-azaindoline as a bifunctional catalyst to activate ketones and olefins. A wide variety of functionalities were well tolerated under the C–H alkylation conditions, including ether, aryl bromide, ester, nitrile, thioether, amide, phenol, and even tertiary and primary alcohols (**61a–k**, Scheme 52a). Both cyclic and acyclic ketones were successfully reacted with simple terminal olefins to afford



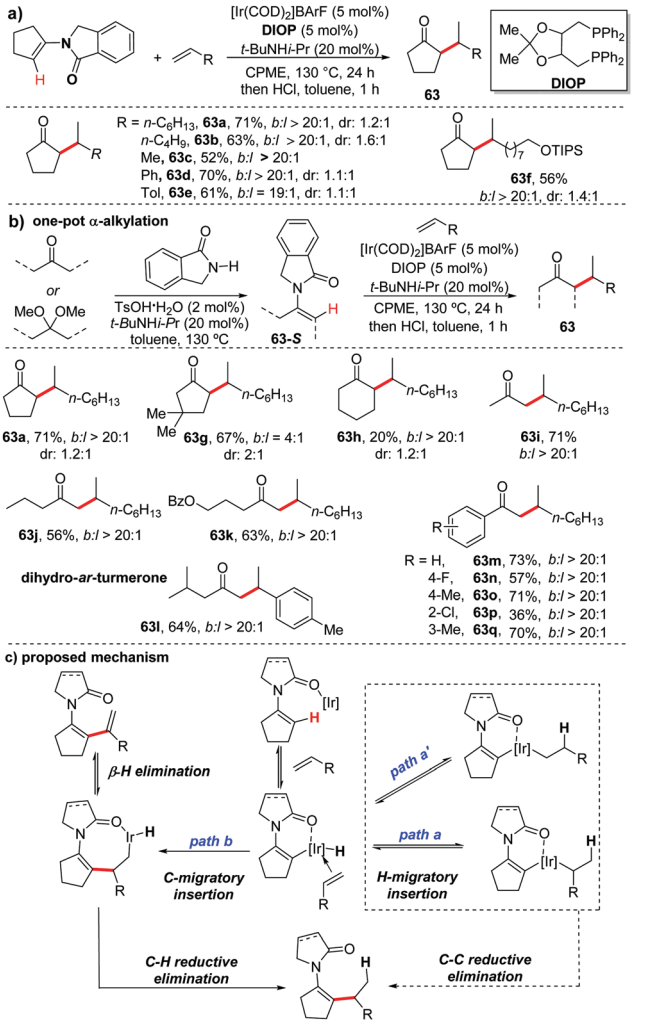
Scheme 52 Rhodium-catalyzed α-C–H alkylation of simple ketones using olefins (Dong, 2014).[83]

alkyl-substituted ketones; however, the ketones were employed as the solvents and the turnover numbers (TONs) based on the Rh catalyst were used to determine the reaction efficiency (**61l–u**, Scheme 52b). Notably, addition of a catalytic amount of 2,4,4-trimethylpentan-2-amine efficiently promoted the α-alkylation of ketones, although the reason remains elusive. Meanwhile, additional water facilitated the selectivity for monoalkylation of ketones. Control experiments were also conducted to support the proposed mechanism: the amine reacted with the ketone to generate an enamine, and then insertion of Rh(i) species into the enamine C–H bonds occurred to give rhodium hydride species **II**, which was facilitated by the directing group. The subsequent olefin insertion and reductive elimination produced the desired alkylated enamine **IV**, which led to α-alkylation product **61** by hydrolysis and regenerated the catalyst.[83]

After their advance in intermolecular ketone α-alkylation using the bifunctional ligand 7-azaindoline, the same group reported two complementary protocols for Conia-ene-type reactions which proceeded by Rh(i)-catalyzed intramolecular C–H alkylation of ketones with unactivated alkenes. The protocols are atom-economical and obviate the use of any oxidants or reductants using 2-aminopyridine as a cocatalyst, and 5-methyl-2-aminobenzoic acid was used to promote condensation of 2-aminopyridine with the ketone (Cond. A). Five- to eight-membered cyclic ketones were all smoothly converted to provide the corresponding products (**62a–62c** and **62f–62p**) under (modified) Cond. A and/or Cond. B. Although acyclic and aryl ketones led to low reactivity under Cond. A, they afforded the desired cyclization products **62d** and **62e** in



Scheme 53 Rhodium-catalyzed α-alkylation using 7-azaindoline as a bifunctional ligand (Dong, 2015).[84]

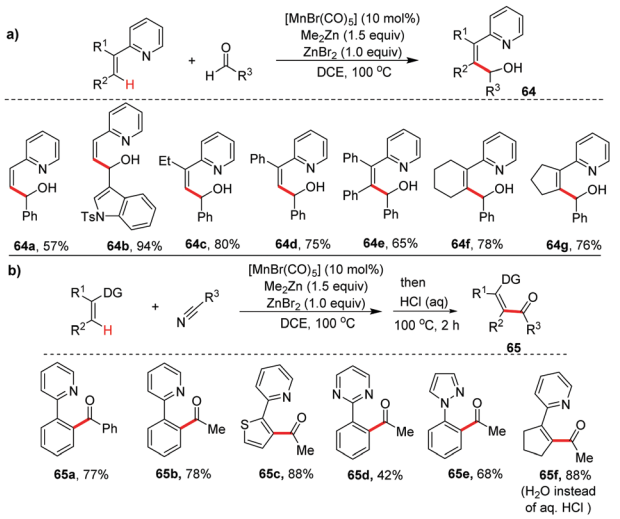


Scheme 54 Enamide-directed branched-selective ketone α-alkylation using olefins by iridium catalysis (Dong, 2017).[85]

synthetically useful yields under modified Cond. B. A wide variety of functionalities were well tolerated in the reaction with cyclohexanone substrates, showing the robustness of the protocols. Although aryl alkenes were known to be unstable under strongly acidic conditions, they were also successful in this dual activation reaction. Surprisingly, in the reaction of cyclobutanone, C–C bond activation occurred to provide bridged bicycle **62q** in 56%yield (Scheme 53).[84]

After their advances in Rh-catalyzed linear-selective α-C–H alkylation,[83] the Dong group demonstrated a branched-selective α-alkylation of ketones using a cationic iridium catalyst, employing isoindolin-1-one derived enamides as directing templates (Scheme 54). The cationic iridium system previously exhibited a broad range of applications in branched-selective hydroarylation of olefins assisted by suitable directing groups. In this protocol, a catalytic amount of ^{t}BuNH^{i}Pr was used as an additive to improve both reactivity and regioselectivity, and the bidentate phosphine ligand DIOP gave optimal results, using cyclopentyl methyl ether (CPME) as a solvent. α-Alkylation of enamides followed by a one-pot hydrolysis successfully afforded the corresponding branched alkylated ketones with good regioselectivity and high yields, using both aliphatic and aromatic alkenes (Scheme 54a, **63a–f**). Notably, small quantities of alkenylation products were formed with substrates such as *para*-Me styrenes (**63e**). One-pot α-alkylation of enamides, which was successfully applied to the synthesis of bioactive dihydro-ar-turmerone (**63l**) (Scheme 54b), was also successful with cyclic or acyclic ketones/dimethyl ketal substrates. Deuterium/control experiments show that both reversible 1,2- and 2,1-migratory insertions of Ir–H species into the olefin are possible (Scheme 54c, path a/a′) and a small amount of alkenylation product is formed by Ir−C migratory insertion into the olefin (Scheme 54c, path b). Using *cis*-β-methylstyrene as a ''probe reagent'', further mechanistic experiments demonstrate that the Ir−C migratory insertion/C–H reductive elimination leads to the product (Scheme 54c, path b).[85]

The Wang group developed a manganese-catalyzed direct nucleophilic addition of olefinic and aromatic C–H bonds to aldehydes to provide the corresponding alcohols **64a–g** by a dual activation strategy. The reaction required mild reaction conditions, and exhibited excellent regio- and stereoselectivity and a wide substrate scope. Due to the directing effect of the pyridine group, 2-vinylpyridines were well converted to their *Z*- stereoisomers by a C–H cyclomanganation event using $MnBr(CO)_5$ as the catalyst, and dimethylzinc (Me_2Zn) and zinc bromide ($ZnBr_2$) were essential to obtain high efficiency. Using pyridine, pyrimidine or pyrazole as the directing group, this manganese-catalyzed protocol was also applied to C–H nucleophilic addition to nitriles bearing the more challenging C–N

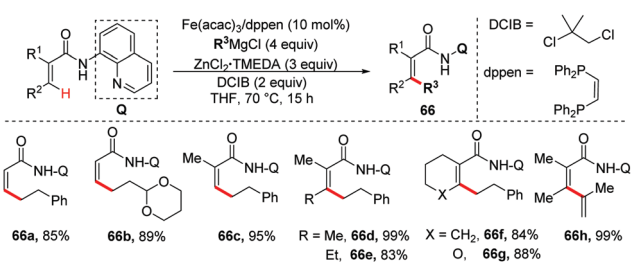


Scheme 55 Mn-Catalyzed nucleophilic addition of olefinic C–H bonds to aldehydes (Wang, 2015).[86]

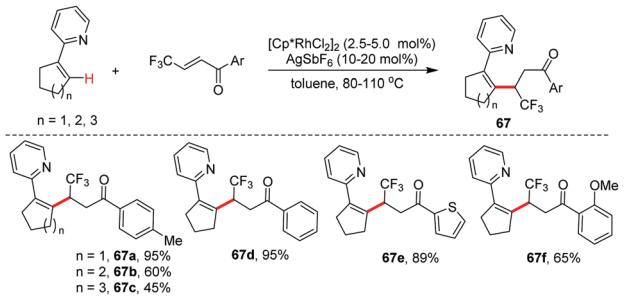
triple bonds, affording ketones **65a–f** after acidic hydrolysis. Deuterium-labeling experiments indicated the C–H activation step to be irreversible, which also implied that the C–H bond cleavage was not involved in the rate-determining step (Scheme 55).[86]

Ilies and Nakamura reported *N*,*N*-bidentate-chelation-assisted olefinic C–H alkylation of acrylamides with primary or secondary alkylzinc halides, using iron/diphosphine as a catalyst and dichloroalkane as an oxidant (Scheme 56). Various acyclic and cyclic acrylamides converted stereoselectively with $Fe(acac)_3$ (10 mol%), dppen (10 mol%), $ZnCl_2$·TMEDA (3 equiv.), alkylmagnesium chloride (4 equiv.), and DCIB (2 equiv.) in THF at 70 °C. Notably, 4 equiv. of Grignard reagent were used to deprotonate the amide and generate an organozinc halide. The formed organozinc halide acts not only as the alkylating reagent but also as a base to remove the β-hydrogen of the acrylamide and to generate an organoiron species. This protocol was suitable for a variety of acyclic and cyclic *N*-(quinolin-8-yl)acrylamides (**66a–h**).[87]

Trifluoromethylated compounds have recently received great attention due to their wide application in pharmaceutical, agricultural, and materials sciences. The Yu group reported a rhodium(III)-catalyzed conjugate addition of aromatic and olefinic C–H bonds to trifluoromethyl-substituted unsaturated ketones. A variety of CF_3 substituted unsaturated ketones coupled with cyclopentenes containing a pyridine group efficiently to



Scheme 56 Iron-catalyzed olefinic C–H alkylation with primary or secondary alkylzinc halides (Ilies and Nakamura, 2015).[87]

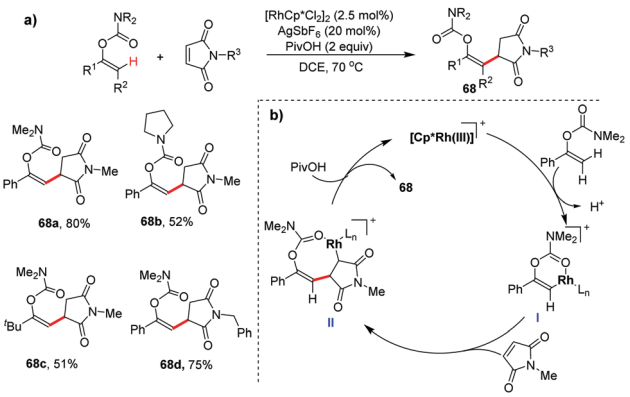


Scheme 57 Rh(III)-Catalyzed conjugate addition of olefinic C–H bonds to CF_3-substituted unsaturated ketones (Yu, 2016).[88]

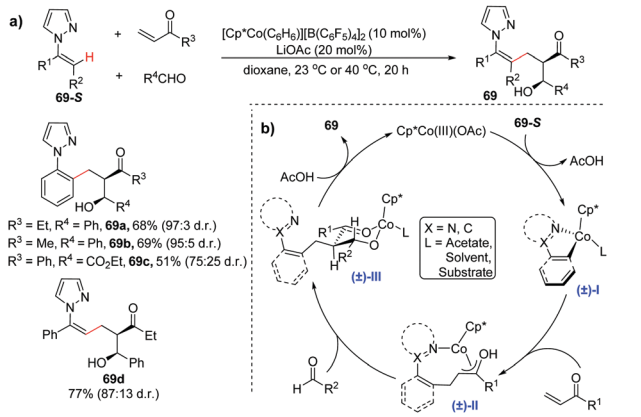
afford alkylation products **67a–f** in good to excellent yields. However, the corresponding six- and seven-membered cyclic olefin analogues exhibited much lower reactivities even at a higher temperature and/or catalyst loading (Scheme 57).[88]

The Kim group reported a rhodium(III)-catalyzed direct C–H alkylation reaction of enol carbamates with maleimides to afford enol carbamates **68** bearing succinimide (Scheme 58a). This transformation has been applied to a wide range of substrates, and typically proceeds with excellent chemoselectivity as well as with high functional group tolerance. The enol carbamate group of the products can readily be converted into other useful functionalities. A plausible reaction mechanism is outlined in Scheme 58b. The coordination of a cationic Rh(III) catalyst and subsequent vinylic C–H bond cleavage of enol carbamate afford six-membered rhodacycle intermediate **I**, which undergoes coordination and migratory insertion of maleimide to afford eight-membered rhodacycle species **II**. Finally, protonation by PivOH takes place to generate alkylated product **68** and recycle the active Rh(III) species which enters the next catalytic cycle. However, the corresponding Heck-type product by β-H elimination was not observed due to the absence of a *syn*-planar β-H atom relative to the transition metal.[89]

The Ellman group previously reported an aromatic or alkenyl C–H bond addition across enones and aldehydes in a highly stereoselective manner under cobalt catalysis (Scheme 59a). Various aromatic and alkyl aldehydes and enones were suitable for this three-component cascade reaction, leading to $C(sp^2)$–H



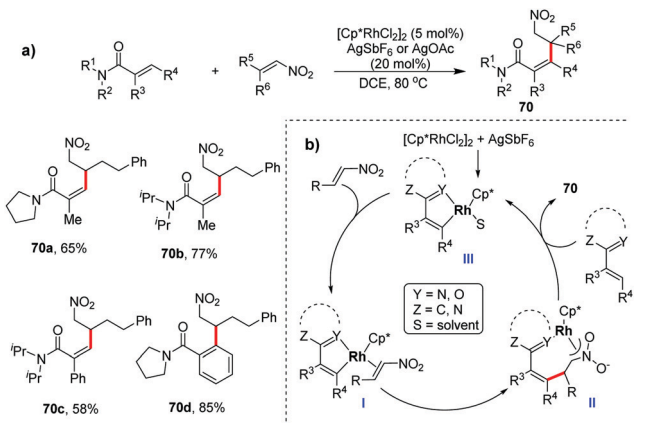
Scheme 58 Rh(III)-Catalyzed olefinic C–H alkylation reaction of enol carbamates using maleimides (Kim, 2016).[89]



Scheme 59 Stereoselective three-component C(sp^2)–H bond addition across alkenes and aldehydes (Ellman, 2016).[90]

alkylation using directing groups such as pyrazole. Alkenyl pyrazole reacted with benzaldehyde and ethyl vinyl ketone to produce **69d** in 77% yield and with 87 : 13 diastereoselectivity. A tentative mechanism is shown in Scheme 59b. Directed C–H bond activation occurred to afford cobaltacycle **I**, which underwent conjugate addition into an enone to form racemic cobalt enolate **II**. Next, cobalt enolate **II** added diastereoselectively to the aldehyde *via* a chair transition state to afford cobalt alkoxide **III**, and the subsequent proto-demetalation yielded alcohol **69** and regenerated the active Co(III) species. Reaction of Z–Co(III) enolate with the aldehyde *via* a boat transition state could alternatively give an explanation for the high diastereoselectivity of the transformation.[90]

The Ellman group reported a rhodium-catalyzed C–H bond addition to nitro-alkenes, which are suitable for a broad range of nitroalkenes, including aliphatic, aromatic, and β,β-disubstituted derivatives (Scheme 60a). Additionally, various directing groups were effective in both aromatic and alkenyl C–H alkylation reactions. Representative nitroalkane products were converted to dihydroisoquinolones and dihydropyridones in a single step and in high yield by iron-mediated reduction and *in situ* cyclization. Moreover, preliminary success in enantioselective Rh(III)-catalyzed

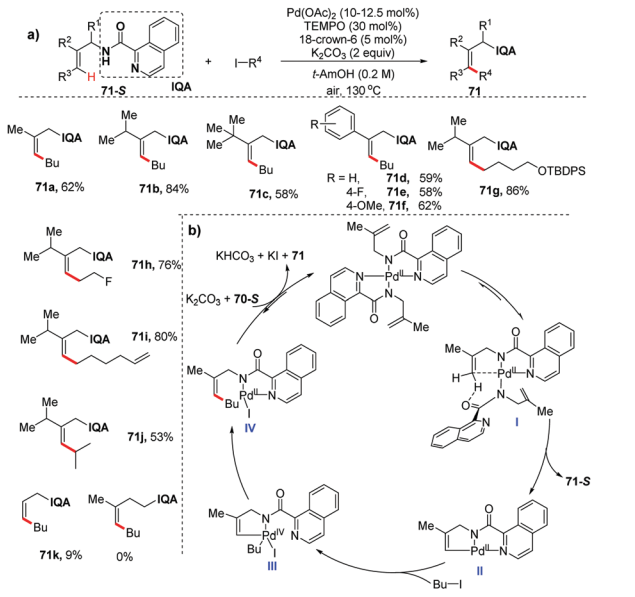


Scheme 60 Rh-Catalyzed olefinic C–H bond addition to nitro-alkenes (Ellman, 2017).[91]

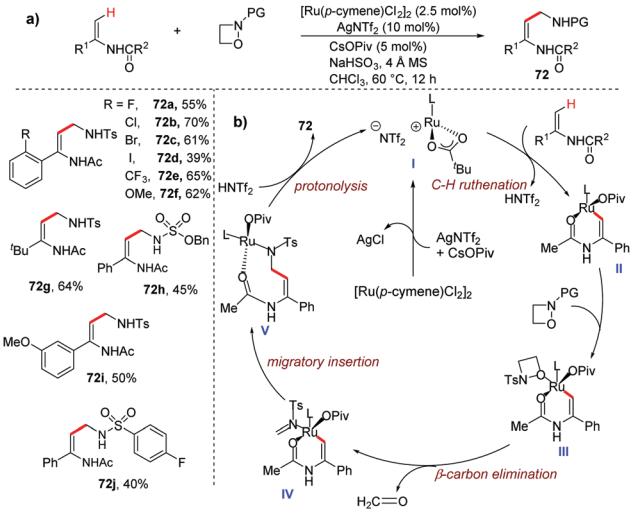
C–H bond addition to nitroalkenes was achieved. A plausible mechanism for the Rh(III)-catalyzed C–H bond addition to nitroalkenes is shown in Scheme 60b. Concerted metalation/deprotonation of acrylamides generates rhodacycle **III**. Coordination of the nitroalkene provides complex **I**, which upon insertion into the nitroalkene provides the Rh(III) nitronate **II**. Then, coordination of acrylamide followed by concerted metalation/deprotonation releases product **70** and regenerates rhodacycle **III**.[91]

Very recently, Loh and Xu also demonstrated a palladium-catalyzed stereospecific C–H alkylation of allylamines with primary and secondary alkyl iodides to generate *cis*-configured multi-substituted alkenes **71**, with the assistance of isoquinoline-1-carboxamide (IQA) as the directing group (Scheme 61a). Various 1,1-disubstituted aliphatic and aromatic alkenes bearing different functionalities reacted well, affording the C–H alkylation products **71a–i** in moderate to high yields. Unfortunately, the monosubstituted alkene and homoallylamine substrate led to unsuccessful results. Secondary alkyl iodides were less reactive than primary alkyl iodides to give moderate yields using increased catalyst loading and iodoalkanes (**71j**). Mechanistic studies suggest that alkenyl C–H bond activation is the rate-determining step. A plausible catalytic cycle is proposed in Scheme 61b. First, the palladium complex **I** generated from $Pd(OAc)_2$ and allylamine underwent alkenyl C–H activation by concerted base-assisted metalation–deprotonation to afford intermediate **II**. The subsequent oxidative addition of iodoalkane and reductive elimination led to the desired alkylation product **71** and catalytic species were generated with base and another allyl isoquinoline-1-carboxamide substrate.[92]

Hu and co-workers developed an amide-directed olefinic C–H aminomethylation of enamides by ruthenium catalysis, using 1,2-oxazetidines as nontrivial but effective aminomethyl reagents (Scheme 62a). This protocol provides a novel synthesis of *Z*-aminomethyl substituted enamides **72a–j** by integrating



Scheme 61 Pd-Catalyzed alkenyl C–H alkylation of allylamines (Xu and Loh, 2019).[92]



Scheme 62 Ru-Catalyzed amide-directed olefinic C–H aminomethylation of enamides (Hu, 2020).[93]

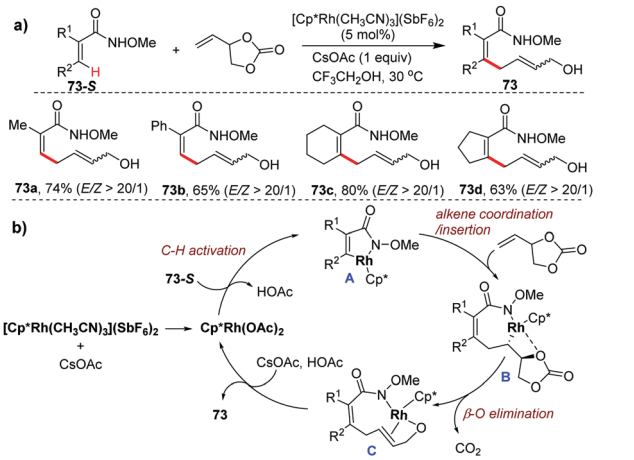
alkenyl C–H activation and ring-opening of 1,2-oxazetidines. A plausible catalytic cycle for this Ru-catalyzed aminomethylation is depicted in Scheme 62b. The alkenyl C–H bond cleavage of the enamide delivered a six-membered ruthenacycle intermediate, **II**. Then coordination of 1,2-oxazetidine to intermediate **II** and β-carbon elimination occurred to release a molecule of formaldehyde. Finally, migratory insertion of formaldimine and protonolysis led to the formation of aminomethyl substituted enamides **72**, along with the regeneration of Ru(II) species **I**. However, an alternative pathway involving the Ru(IV) species by oxidative addition of the Ru(II) complex cannot be fully ruled out.[93]

2.5 Vicinal group-directed olefinic C–H allylation

1,4-Dienes represent ubiquitous components in many biologically active molecules, and they are also versatile building blocks in synthetic organic chemistry. Directed alkenyl C–H allylation provides powerful access to selective preparation of 1,4-dienes.

In 2014, the Wang group reported a rhodium(III)-catalyzed direct C–H allylation reaction of N–OMe acrylamides with 4-vinyl-1,3-dioxolan-2-ones (Scheme 63a). The reaction provides facile and stereoselective access to multi-functionalized skipped dienes **73** in good yields. A tentative mechanism for this transformation is depicted in Scheme 63b. Firstly, complex $[Cp^*Rh(MeCN)_3](SbF_6)_2$ reacted with CsOAc to give active $Cp^*Rh(OAc)_2$ by ligand exchange, which inserted into the olefinic C–H bond to afford rhodacycle **A** and liberated an acetic acid. Coordination and migratory insertion of the 4-vinyl-1,3-dioxolan-2-one generated intermediate **B**. The *E*/*Z* ratio of the product might be determined by π-facial-selectivity of this step influenced by the substituent. Subsequently, intermediate **B** underwent β-oxygen elimination and protonation to produce allyl alcohol **73** and one molecule of CO_2, as well as rhodium catalyst.[94]

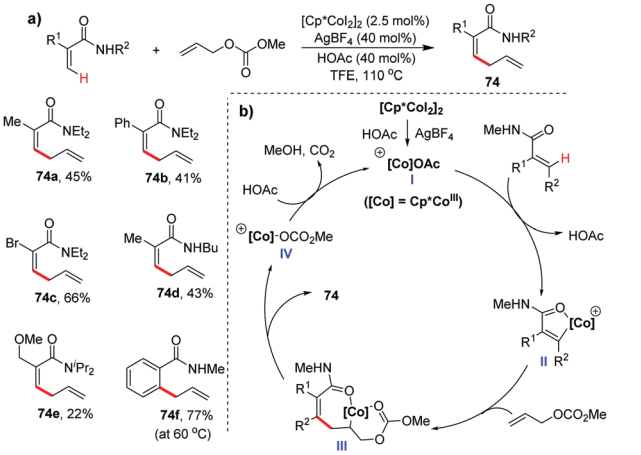
The Glorius group demonstrated a cobalt(III)-catalyzed amide-directed C–H activation/allylation of arenes, heteroarenes, and olefins, using Cp*Co(III) catalyst with the assistance of $AgBF_4$ and HOAc (Scheme 64a). A variety of differently substituted allyl



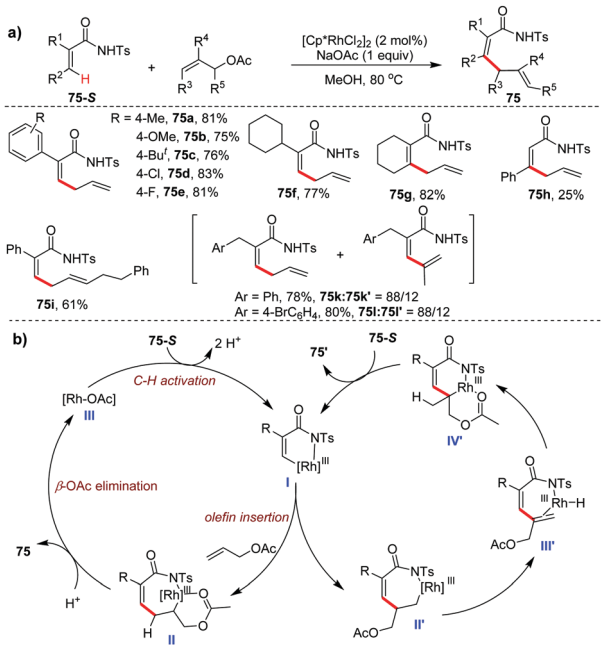
Scheme 63 Rh(III)-Catalyzed alkenyl C–H allylation reaction using 4-vinyl-1,3-dioxolan-2-ones (Wang, 2014).[94]

carbonates can be employed. The C–H allylation proceeded well with 2-substituted secondary and tertiary acrylamides, and alkyl and phenyl substituents and bromo- and methoxy groups were tolerated, leading to moderate yields (**74a–e**). The kinetic isotope effect was determined to be 2.0 and 6.4 in parallel and competition experiments, respectively, indicating that C–H activation likely occurred in the rate-limiting step. Also, H/D scrambling was observed and showed a reversible C–H activation. A proposed mechanism is shown in Scheme 64b. The formation of a catalytically active cobalt species (**I**) from the precursors is followed by C–H activation to produce cobaltacycle **II**. Olefin insertion leads to intermediate **III** that is stabilized by intramolecular coordination. In this geometry, β-hydride elimination is disfavored, and β-oxygen elimination occurs and leads to the allylated product **74**. However, some other pathways such as the formation of π-allyl species from the allyl precursors cannot be excluded at this stage.[95]

In the same year, the Loh group reported a rhodium-catalyzed C–H allylation of acrylamides with allyl acetates using $[RhCp^*Cl_2]_2$ as the catalyst (Scheme 65a). The use of weakly



Scheme 64 Co(III)-Catalyzed amide-directed C–H allylation using allyl carbonates (Glorius, 2015).[95]

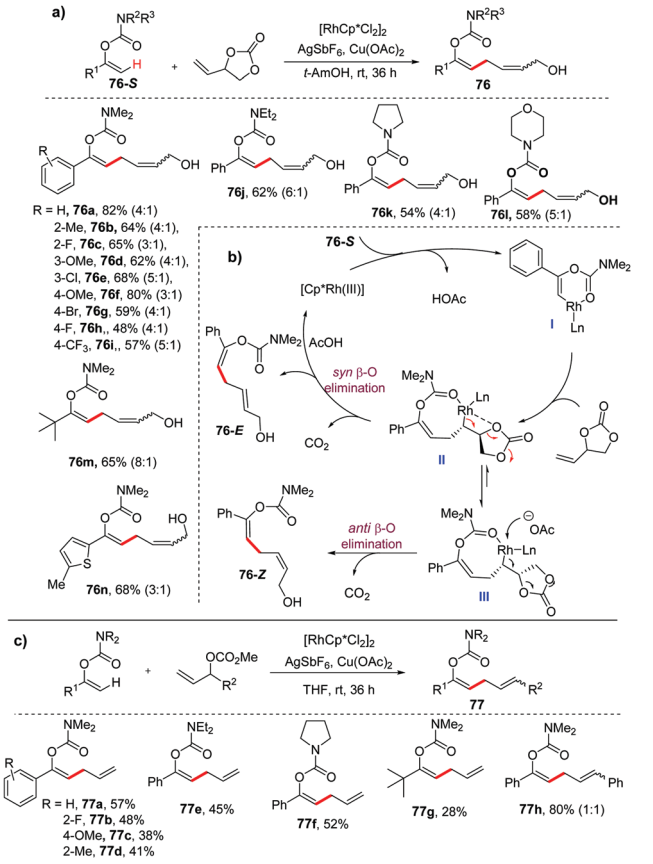


Scheme 65 Rh-Catalyzed C–H allylation of acrylamides with allyl acetates (Loh, 2015).[96]

coordinating NH-Ts amide as the directing group resulted in broad functionality tolerance and excellent site- and stereo-selectivity, leading to efficient access to skipped dienes **75**. When benzyl substituted acrylamide was used, the formation of a small amount of diene isomers was noticed as well (**75k′** and **75l′**). The catalytic cycle is initiated by the NHTs amide directed C–H activation by rhodium catalyst [Rh^{III}–OAc] to deliver intermediate **I** *via* a CMD pathway. The subsequent migratory insertion of the allyl C–C double bond allows the formation of the seven-membered rhodacycle **II**, where the carbonyl coordination to the rhodium center facilitates β-acetate elimination to afford allylation product **75** and regenerates the active rhodium catalyst. As for the formation of dienes **75′**, intermediate **I** undergoes migratory insertion of allyl acetate with reversed regioselectivity followed by hydride elimination/re-insertion through **III′** and affords **IV′**, which finally undergoes β-OAc elimination to deliver the isomer (Scheme 65b).[96]

The Kim group developed a Rh(III)-catalyzed olefinic C–H allylation of (hetero)aryl or alkyl enol carbamates with the assistance of carbamoyl groups such as pyrrolidinyl, diethyl, and morpholinyl amides (Scheme 66). While 4-vinyl-1,3-dioxolan-2-one led to allylic alcohols **76** with the *cis*-isomer as the major product, allylic carbonates produced terminal allylated products **77**. A possible reaction mechanism is depicted in Scheme 66b. Coordination of a carbamoyl group to active Rh(III) catalyst followed by C–H activation affords rhodacycle species **I**, which undergoes migratory insertion of 4-vinyl-1,3-dioxolan-2-one to produce an eight-membered rhodacycle (**II**) and a more favorable **III**. While intermediate **III** undergoes *anti*-β-oxygen elimination to afford **76-*Z***, *syn*-β-oxygen elimination of **II** produces **76-*E*** and liberates 1 mol of CO_2.[97]

The Zhang group reported a Cp*Co(III)-catalyzed olefinic C–H allylation of enamides to prepare allylated Z-enamides **78**.

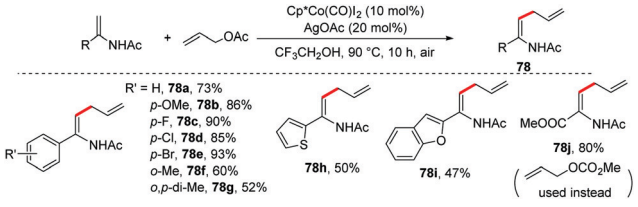


Scheme 66 Allylation of enol carbamates with allylic carbonates under rhodium catalysis (Kim, 2016).[97]

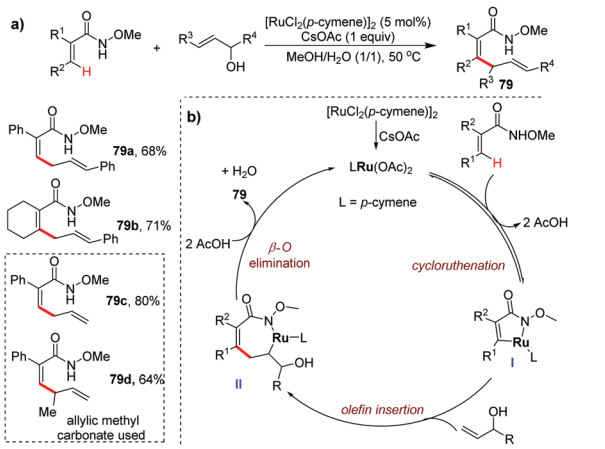
The reaction was performed using 10 mol% Cp*Co(CO)I_2 and 20 mol% AgOAc in CF_3CH_2OH at 90 °C. The protocol tolerated a wide range of functionalities such as OMe, F, Cl and Br, regardless of their electron-donating or electron-withdrawing properties (Scheme 67).[98]

Recently, the Ji group also disclosed an interesting Ru(II)-catalyzed C–H allylation of NH–OMe acrylamides with allyl alcohols in aqueous solution (Scheme 68a). With the assistance of the *N*-methoxycarbamoyl as the directing group, this C–H allylation reaction provided straightforward and efficient access to 1,4-diene skeletons **79**, featuring a broad substrate scope with good functional group tolerance, and excellent regio- and stereoselectivity. The mechanistic studies indicated that the process of the reversible C–H bond ruthenation was assisted by acetate, and the rate-determining step was unlikely to be the C–H bond cleavage step. The mechanism was initiated by *N*-methoxycarbamoyl group directed C–H activation of acrylamide by the active catalyst from [$RuCl_2$(*p*-cymene)]$_2$ catalyst and cesium acetate, giving five-membered ruthenacycle **I** *via* acetate assistance. Subsequently, coordination and insertion of an olefin afforded intermediate **II**, which underwent β-hydroxide elimination to generate product **79** (Scheme 68b).[99]

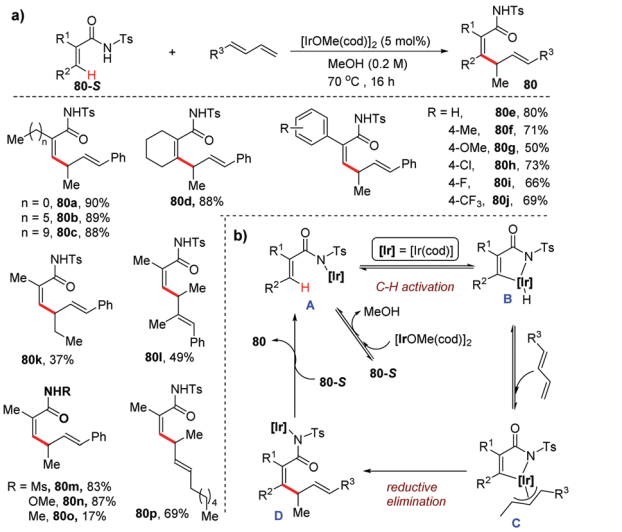
In 2019, our group developed atom-economic cross-coupling reactions between arylamides and 1,3-dienes, leading to site- and stereo-selective preparation of 1,4-dienes **80** by directed alkenyl



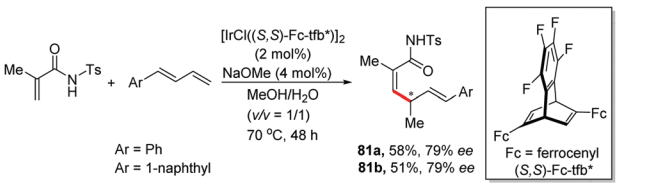
Scheme 67 Allylation of enamides by Co-catalysis (Zhang, 2017).[98]



Scheme 68 Ru(II)-Catalyzed C–H allylation of NH–OMe acrylamides with allyl alcohols (Ji, 2018).[99]



Scheme 69 Iridium-catalyzed C–H allylation of acrylamides with conjugated dienes (Zhang and Zhong, 2019).[100]



Scheme 70 Iridium-catalyzed asymmetric C–H allylation of acrylamides with conjugated dienes (Zhang and Zhong, 2020).[101]

C–H allylation. This additive-free and mild protocol simply employs $[IrOMe(cod)]_2$ as the catalyst and is performed in MeOH at 70 °C, and a series of valuable functional groups are well tolerated, including CF_3, F, Cl and Br (Scheme 69a). The method is also highlighted by successful conversion of artemisic amide and preparative scale synthesis, as well as easy removal of NH-Ts amide by methylation/hydrolysis. A deuterium-labeling study suggested a fast and reversible C(alkenyl)–H activation step as well as hydro-metalation. The catalytic cycle possibly starts with the generation of amidoiridium(I) **A** from the catalyst and acrylamide. Then, reversible olefinic C–H activation occurs to provide iridacycle **B**, and the subsequent insertion of 1,3-diene to **B** affords π-allyliridium(III) **C**. The final reductive elimination and ligand exchange by NHTs amide produces **80** with the liberation of **A**. The regioselectivity is governed by a combination of electronic and steric effects in the migratory insertion of the diene into the Ir–C(alkenyl) bond (Scheme 69b).[100]

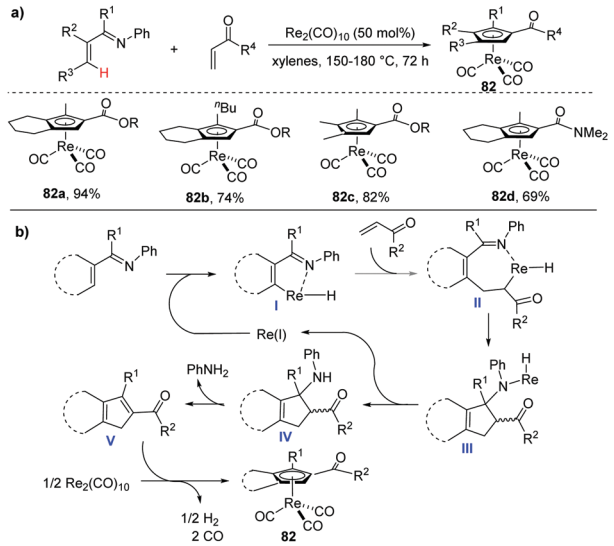
With our ongoing interest in this research field, we recently developed an asymmetric variant of this alkenyl C–H allylation. Neither chiral bisphosphine such as binap nor bisoxazole ligands exhibited enantioselectivity under iridium catalysis. Fortunately, the reaction between acrylamide and 1,3-diene (Ar = Ph) afforded chiral 1,4-diene **81a** in 58% with 79% ee, using $[IrCl((S,S)\text{-Fc-tfb}^*)]_2$ as a chiral catalyst and NaOMe as a base in a mixed solvent of MeOH/H_2O (v/v = 1/1). 1,3-Diene bearing a bulky naphthyl group was also tested, leading to **81b** in 51% yield with 79% ee. This is the first example of Ir-catalyzed asymmetric olefinic C–H allylation. These results showed that the enantioselectivity of the reaction could be further improved and chiral dienes are promising ligands (Scheme 70).[101]

2.6 Annulation by vicinal group-directed olefinic C–H activation

Chelation-assisted C–H activation induced tandem C–H activation/coupling/cyclization represents one powerful method toward the synthesis of (hetero)cycle molecules in a step- and atom-economic fashion, using unsaturated molecules such as alkenes, alkynes, allenes, sulfoxonium ylides, 1-alkynyl triazenes, isocyanates, diazo compounds, and even CO.

In 2008, Kuninobu and Takai reported a domino synthesis of Cp–Re complexes **82** by using α,β-unsaturated ketimines and carbonyl compounds, in the presence of 50 mol% $Re_2(CO)_{10}$ complex, which acts as both the catalyst and substrate. The reaction mechanism is proposed in Scheme 71b. The ketimine undergoes an olefinic C–H bond activation with the rhenium center to afford 5-membered rhenacycle **I**, and alkene insertion followed by intramolecular nucleophilic annulation leads to intermediate **III**. The subsequent reductive elimination and aniline liberation give a cyclopentadiene, **V**, which coordinates with the rhenium complex to produce Cp–Re complexes **82**.[102]

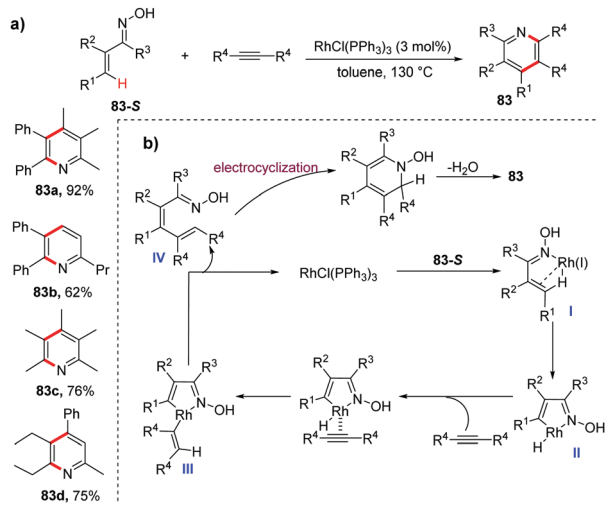
In the same year, the Cheng group developed a Rh-catalyzed annulation between α,β-unsaturated ketoximes and alkynes to afford highly substituted pyridines **83**. The reaction was



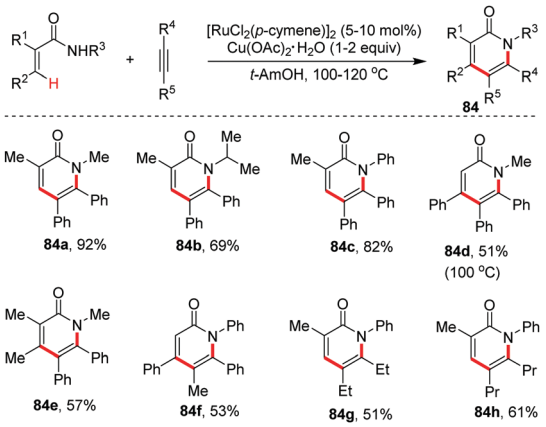
Scheme 71 Synthesis of Cp–Re complexes *via* olefinic C–H activation (Kuninobu and Takai, 2008).[102]

performed simply with complex $RhCl(PPh_3)_3$ (3 mol%) in toluene by heating at 130 °C. Various cyclic and acyclic unsaturated ketoximes reacted well with aromatic and alkyl alkynes, exhibiting a broad substrate scope. The reaction mechanism initially involved N–Rh coordination followed by alkenyl C–H activation to generate hydrometallacycle **II**, and *syn*-addition of the Rh–H bond to the coordinated alkyne to form **III**. Intermediate **III** underwent reductive elimination to afford **IV**, which was converted to final pyridine **83** by electrocyclization and then water elimination (Scheme 72).[103]

Ackermann *et al.* previously reported ruthenium-catalyzed oxidative C–H activation/annulations using acrylamides and alkynes, leading to efficient preparation of valuable 2-pyridones **84**. Various electron-rich and electron-deficient acrylamides as well as aryl- and alkyl-substituted internal alkynes can be used as



Scheme 72 Rh-Catalyzed synthesis of pyridines from unsaturated ketoximes and alkynes (Cheng, 2008).[103]

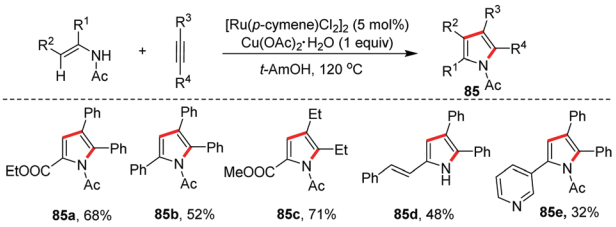


Scheme 73 Ru-Catalyzed oxidative C–H activation/annulations of acrylamides to prepare 2-pyridones (Ackermann, 2011).[104]

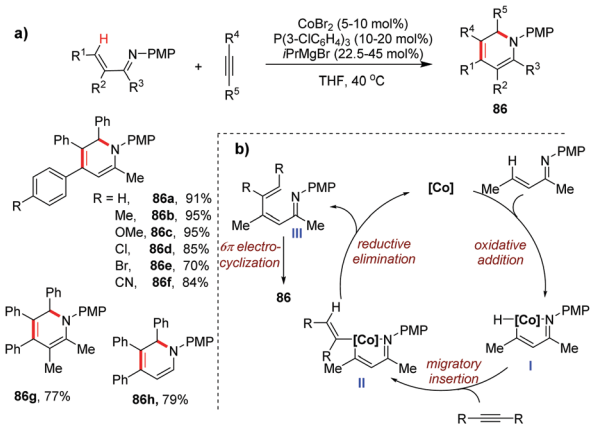
suitable substrates. The protocol is simple and without the use of silver salt. Notably, unsymmetrically substituted alkynes proved to be converted with remarkably high regioselectivity (**84f**). A possible mechanism includes the initial intermolecular carboruthenation of alkynes, along with a subsequent intramolecular C–N bond formation by reductive elimination (Scheme 73).[104]

After their advance in the synthesis of 2-pyridones, the same group disclosed an efficient pyrrole (**85**) synthesis from electron-rich enamines and alkynes, under an aerobic atmosphere using the same ruthenium complex $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst (Scheme 74). Intermolecular competition experiments with alkynes revealed the more electron-rich alkyne to react preferentially. Meanwhile, competition experiments with differently substituted enamines highlighted electron-donating substituents on the aryl moiety to be beneficial. Isotopically labelled experiments demonstrated the C–H bond activation on enamines to be reversible.[105]

The Yoshikai group reported a cobalt-catalyzed annulation reaction of α,β-unsaturated imines with internal alkynes to synthesise multi-substituted dihydropyridine derivatives **86**, using triarylphosphine as the ligand and Grignard reagent i-PrMgBr as the effective reducing agent (Scheme 75a). A possible mechanism is proposed in Scheme 75b. In the presence of a low-valent cobalt species, imine-directed C(alkenyl)–H activation occurred to generate a five-membered cobaltacycle, **I**, which underwent alkyne insertion and reductive elimination to provide an azatriene intermediate, **II**. Finally, 6π electrocyclization of azatriene **II** furnishes the formation of dihydropyridine product **86**.[106]

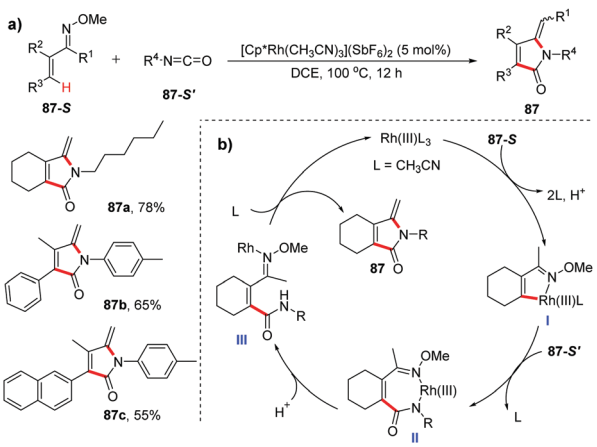


Scheme 74 Ruthenium-catalyzed pyrrole synthesis from electron-rich enamines and alkynes (Ackermann, 2013).[105]

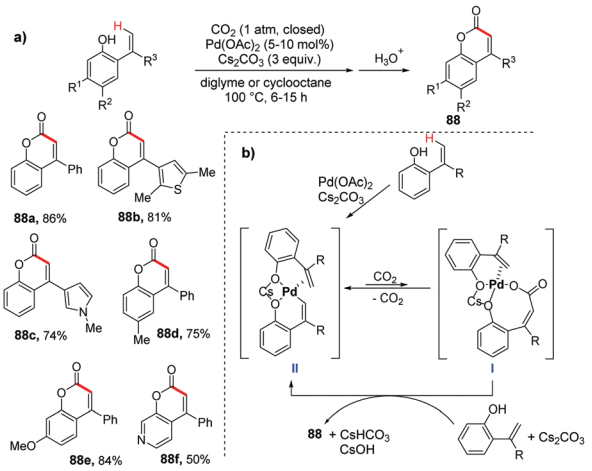


Scheme 75 Co-Catalyzed annulation of α,β-unsaturated imines and internal alkynes to access dihydropyridines (Yoshikai, 2013).[106]

In the same year, Li and Zhou reported a rhodium-catalyzed addition of an alkenyl C–H bond to isocyanates followed by an intramolecular cyclization, leading to biologically active 5-ylidene pyrrol-2(5*H*) ones **87**. This atom-economic transformation proceeded under mild and neutral conditions in the absence of any additives and no hazardous waste was produced. Phenyl isocyanates, and primary and secondary alkyl isocyanates were all suitable substrates in this reaction, as well as a range of α,β-unsaturated cyclic and acyclic oximes (Scheme 76a). The annulation reaction was initiated by the oxime-directed alkenyl C–H bond activation to form a five-membered rhodacycle, **I**, with the liberation of a proton. Selective insertion of an isocyanate into the Rh–C bond of intermediate **I** gave the seven membered rhodacycle **II**, which was converted to intermediate **III** by protonation, and intermediate **III** was observed during the reaction performed at 85 °C for 5 h. Finally, intramolecular nucleophilic addition followed by elimination of one molecule of methoxyamine provided 5-ylidene pyrrol-2(5*H*)ones **87** and regenerated the catalyst (Scheme 76b).[107]



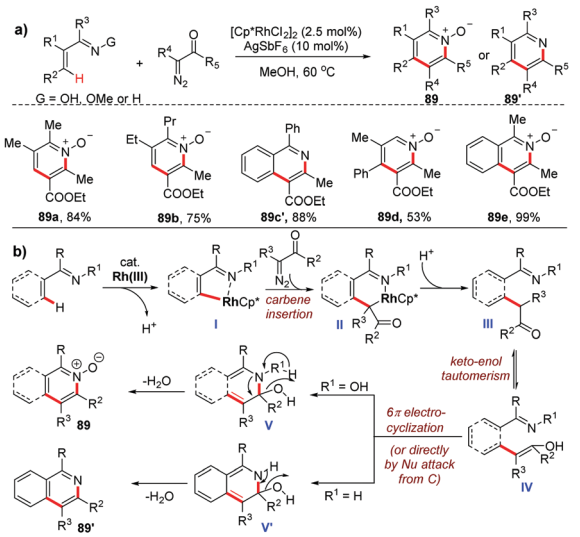
Scheme 76 Rh(III)-Catalyzed addition of an alkenyl C–H bond to isocyanates and intramolecular cyclization (Zhou and Li, 2013).[107]



Scheme 77 Pd-Catalyzed direct carboxylation of alkenyl C–H bonds with carbon dioxide (Iwasawa, 2013).[108]

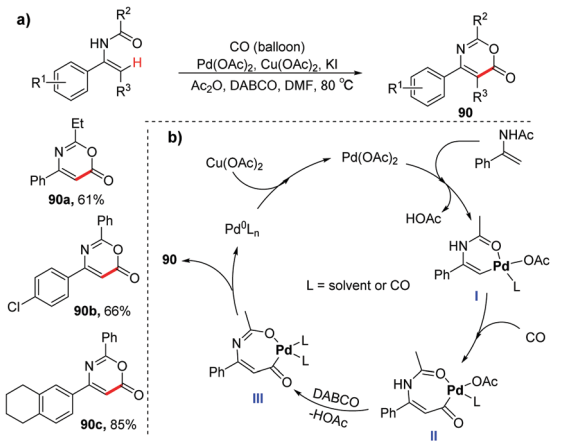
The Iwasawa group reported a Pd-catalyzed direct carboxylation of alkenyl C–H bonds of 2-hydroxystyrenes with carbon dioxide to afford valuable coumarins **88** (Scheme 77a). The reaction was performed using a catalytic amount of $Pd(OAc)_2$ with Cs_2CO_3 under atmospheric pressure of CO_2. The reaction was proposed to start with the formation of six-membered alkenyl palladium intermediate **II** by chelation-assisted alkenyl C–H bond activation and coordination of the second 2-hydroxystyrene with $Pd(OAc)_2$ and the cesium salt. Subsequently, alkenyl palladium(II) species **II** underwent reversible nucleophilic carboxylation to afford palladium carboxylate intermediate **I**, which reacted with another molecule of 2-hydroxystyrene and base to give coumarin **88** with regeneration of intermediate **II** (Scheme 77b). Notably, the key alkenylpalladium intermediate was isolated and characterized. Moreover, treatment of cesium carboxylate from coumarin hydrolysis with $Pd(OAc)_2$ led to easy decarboxylation, exhibiting the reversibility of the carboxylation, with the equilibrium favoring the decarboxylation.[108]

The Glorius group reported a synthesis of multi-substituted pyridine *N*-oxides **89** and isoquinolines **89′** by Rh(III)-catalyzed cyclization of oximes and diazo compounds by aryl and vinylic C–H activation and carbene insertion (Scheme 78a). This tandem C–H activation/coupling/annulation sequence proceeded under mild conditions in the absence of any oxidant with the liberation of nitrogen and water as the byproducts, and exhibited a broad substrate scope. The reaction was proposed to proceed by the coordination of the substrate to a $[Rh^{III}Cp^*]$ species as the key step for the regioselective C–H bond cleavage to afford rhodacycle **I**. This rhodacycle could coordinate with the diazo compound to give rhodium species **II** by carbene insertion. Subsequently, protonolysis of **II** delivered alkylated intermediate **III**, and the subsequent tautomerization provided enol intermediate **IV** *in situ*. With oxime and imine substrates, the formed enol species **IV** could selectively undergo 6π electrocyclization and water elimination to give products **89** and **89′**. However, an alternative cyclization pathway by the nucleophilic attack of the N atom on the carbonyl group in **III** to afford **V** and **V′** was also possible (Scheme 78b).[109]



Scheme 78 Rh(III)-Catalyzed cyclization of oximes and diazo compounds (Glorius, 2013).[109]

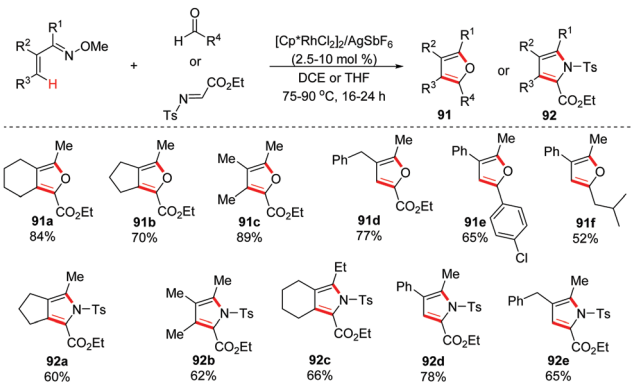
The Guan group developed a palladium-catalyzed carbonylation of alkenyl C–H bonds of enamides with CO to prepare 1,3-oxazin-6-ones **90** (Scheme 79a). The reaction proceeds under mildly basic conditions and employs KI and Ac_2O as simple additives, DABCO (1,4-diazabicyclo[2.2.2]octane) as the base, $Cu(OAc)_2$ as the oxidant and $Pd(OAc)_2$ as the catalyst. A wide range of functional groups can be well tolerated and this carbonylation reaction provides rapid elaboration of enamides into a variety of substituted 1,3-oxazin-6 ones under atmospheric pressure of CO. A tentative mechanism for this carbonylation was proposed by the authors. Alkenyl C–H activation by $Pd(OAc)_2$ formed the vinylpalladium species **I**, which provided the acylpalladium species **II** by CO coordination/insertion and then intermediate **III** with DABCO. Finally, intermediate **III** underwent reductive elimination to produce 1,3-oxazin-6 one **90** with the formation of Pd(0), which was converted to an active Pd(II) species *via* oxidation by Cu(II) (Scheme 79b).[110]



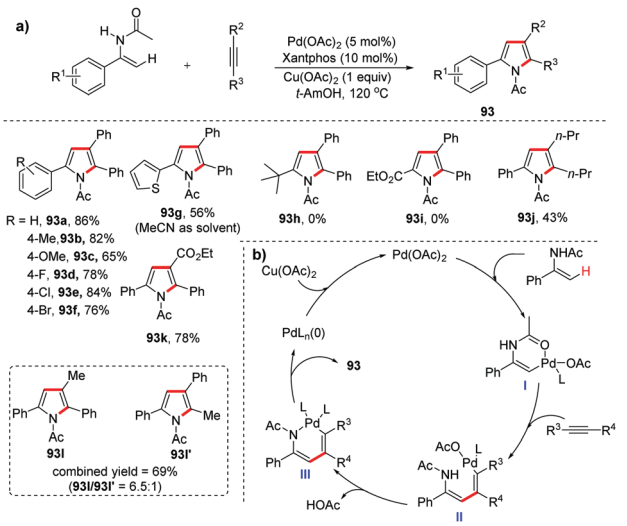
Scheme 79 Palladium-catalyzed alkenyl C–H carbonylation of enamides to afford 1,3-oxazin-6-ones (Guan, 2013).[110]

The Ellman group developed a type of annulation for the synthesis of substituted furans **91** and pyrroles **92**, using α,β-unsaturated oximes and aldehydes or imines as substrates. The transformation proceeded by Rh(III)-catalyzed and imine-directed olefinic C–H bond activation/addition across C=O or C=N double bonds, followed by annulation and the final aromatization. A number of α,β-unsaturated oximes bearing different substituents were suitable in this operationally simple reaction. However, the R^2 substituent was crucial because no product was obtained when R^2 was H. The terminal substituent R^3 was not essential for the success of the reaction, and variations at R^1 with different alkyl groups also worked well in this transformation. A broad range of aromatic and aliphatic aldehydes smoothly worked in the reaction to provide excellent functionality tolerance (Scheme 80).[111]

After their advances in alkenyl C–H carbonylation of enamides, the Guan group demonstrated another palladium(II)-catalyzed oxidative annulation of enamides with alkynes by alkenyl C–H activation, providing valuable substituted pyrroles **93** (Scheme 81a). A wide range of functional groups are well



Scheme 80 Rh(III)-Catalyzed annulation using unsaturated oximes for the synthesis of furans and pyrroles (Ellman, 2013).[111]



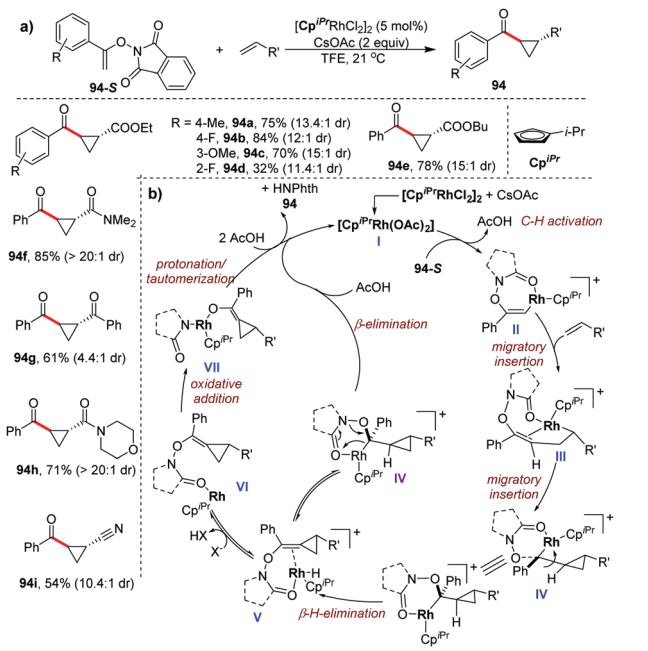
Scheme 81 Pd-Catalyzed oxidative annulation of enamides with alkynes (Guan, 2014).[112]

tolerated, leading to a reliable approach toward triaryl-substituted pyrroles. A tentative mechanism is initiated by alkenyl C–H activation of the enamide to form a palladacycle intermediate, **I**. Coordinative insertion of an alkyne into the Pd–C bond leads to intermediate **II**. Intramolecular deprotonated cyclization of intermediate **II** generates a six-membered palladacycle, **III**, and the final reductive elimination affords the *N*-acetyl-substituted pyrroles **93** and Pd(0) species, which were reoxidized by $Cu(OAc)_2$ to regenerate the active Pd(II) species. Reductive elimination of Pd(II) from the vinylamido complex **III** is supposed to be the rate-determining step as the C–H activation of the enamide is fast. The Xantphos ligand likely promotes reductive elimination of Pd(II) from intermediate **III** due to the wide bite-angle of bisphosphine (Scheme 81b).[112]

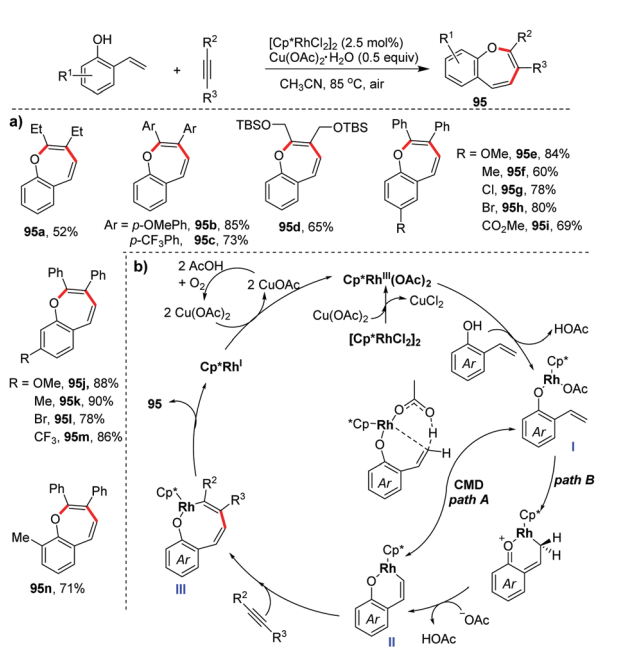
Cyclopropane represents one challenging target to prepare due to its high ring strain. The Rovis group reported a cyclopropanation of electron deficient alkenes initiated by Rh(III)-catalyzed olefinic C–H activation of *N*-enoxyphthalimides, using a newly designed isopropyl cyclopentadienyl ligand (Scheme 82a). Deuterium experiments showed the olefinic C–H functionalization to be irreversible and chemoselective for the double bond at the expense of the neighboring phenyl ring. If the reaction is performed in the absence of cesium acetate or using triethylamine as a base instead, no cyclopropane product is obtained, supporting a C–H activation event by a concerted metalation–deprotonation (CMD) mechanism. The reaction mechanism proposed is shown in Scheme 82b. After the formation of the active Rh(III) catalyst **I**, irreversible alkenyl C–H activation occurred to afford rhodacycle intermediate **II**, which underwent migratory insertion of an olefin to afford σ-alkyl Rh(III) species **III**. Then, a 3-*exo*-trig intramolecular carborhodation occurred to generate intermediate **IV**. β-Hydride elimination could give the Rh–H complex **V** after C–C bond rotation. After that, two different pathways are possible. One mechanism involved collapse of **V** to afford Rh(I) species **VI**, insertion of Rh(I) into the N–O bond and protonation/tautomerization of **VII**. Alternatively, reversible re-insertion of **V** into a double bond to afford **IV** followed by β-elimination could produce **94**, with the N–O bond cleaved.[113]

The Gulías group developed a practical and atom-economical synthesis of benzoxepine derivatives **95** by a formal (5+2) cycloaddition from readily available *O*-vinylphenols and alkynes using a catalytic amount of $[Cp^*RhCl_2]_2$ and a quantitative amount of $Cu(OAc)_2$. By using unsubstituted *O*-vinylphenols instead of α-substituted 2-alkenylphenols, appealing seven-membered benzoxepine derivatives were smoothly obtained (Scheme 83a). A tentative reaction mechanism is outlined which starts with the phenolic substrate replacing one of the acetates of the catalyst to give intermediate **I**. This complex **I** then evolves into rhodacycle **II** by a concerted-metalation–deprotonation (CMD) mechanism. Alternatively, rhodacycle **II** is presumably generated from **I** by intramolecular addition of electrophilic Rh(I) to the conjugated olefin and a subsequent deprotonation assisted by base. After that, intermediate **II** involves alkyne coordination followed by migratory insertion to give intermediate **III**, which undergoes reductive elimination to the final product **95** and a Rh(I) species which is then reoxidized to re-enter the next catalytic cycle (Scheme 83b).[114]

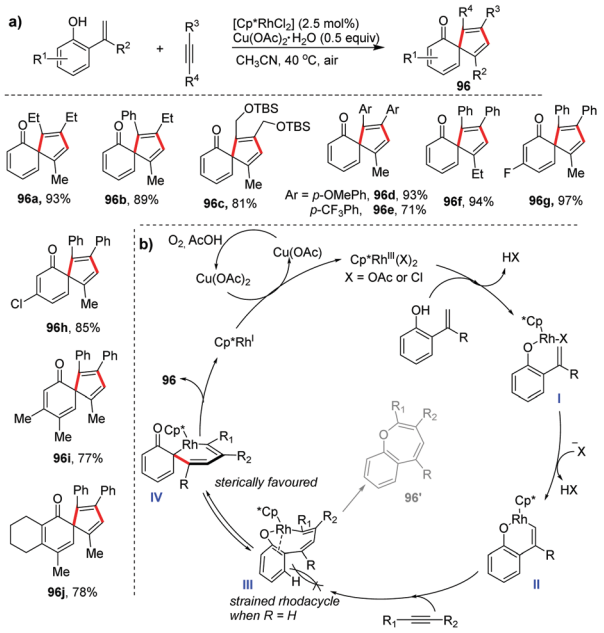
In the same year, Gulías and co-workers reported another Rh(III)-catalyzed formal [3C+2C] cycloaddition of α-substituted 2-alkenylphenols and alkynes using copper(II) acetate as the oxidant to afford highly appealing spirocyclic skeletons **96** (Scheme 84a). Intermolecular competition KIE experiments suggest that the C–H bond cleavage is involved in a rate



Scheme 82 Rh(III)-Catalyzed C–H activation initiated cyclopropanation of *N*-enoxyphthalimides (Rovis, 2014).[113]



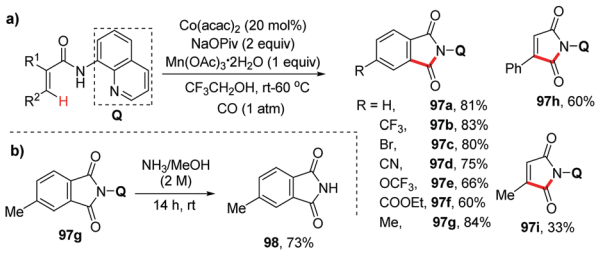
Scheme 83 Synthesis of benzoxepine derivatives by a formal (5+2) cycloaddition using *O*-vinylphenols and alkynes (Gulías, 2014).[114]



Scheme 84 Synthesis of spirocyclic skeletons from [3C+2C] cycloaddition of 2-alkenylphenols and alkynes (Gulías, 2014).[115]

determining step, and the deuterium labelled experiments support the alkyne carbometalation to be irreversible. The catalytic cycle is likely initiated by the ligand exchange of the catalyst by the phenolic substrate to afford intermediate **I**. The subsequent C–H activation leads to rhodacycle **II**. The subsequent alkyne coordination and migratory insertion give the eight-membered rhodacycle **III** that is in equilibrium with its keto form **IV**. In the case of alkenylphenol substrates equipped with a nonsubstituted vinyl group, the reductive elimination yields oxepine products **96′**, but the presence of the R substituent in the alkenyl moiety generates a steric push that favors a reductive elimination from the less strained rhodacyclohexane **IV** to afford **96**. After the reductive elimination, the Rh(I) species is reoxidized by $Cu(OAc)_2$ to enter the next catalytic cycle (Scheme 84b).[115]

The Daugulis group reported a cobalt-catalyzed carbonylation of aminoquinoline acrylamides and benzamides to afford cyclic imide derivatives (**97a–i**, Scheme 85). The reaction proceeds in trifluoroethanol using $Co(acac)_2$ as a catalyst, NaOPiv as a base, and $Mn(OAc)_3{\cdot}2H_2O$ as a cocatalyst under 1 atm of CO. Functional groups such as Br, CF_3, CN, OCF_3, and

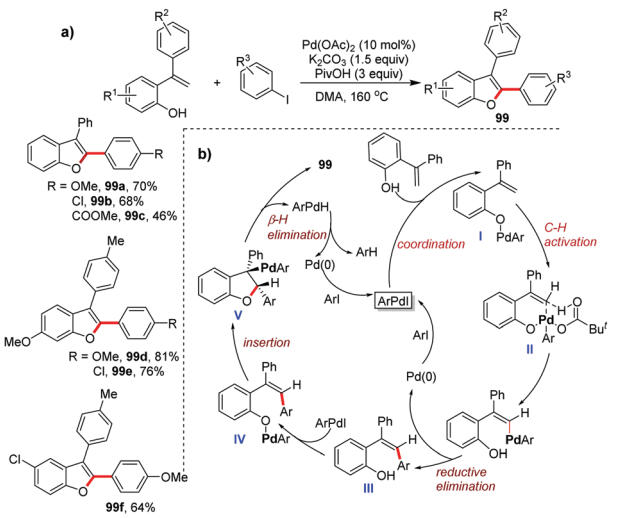


Scheme 85 Cobalt-catalyzed imide synthesis by C–H carbonylation (Daugulis, 2014).[116]

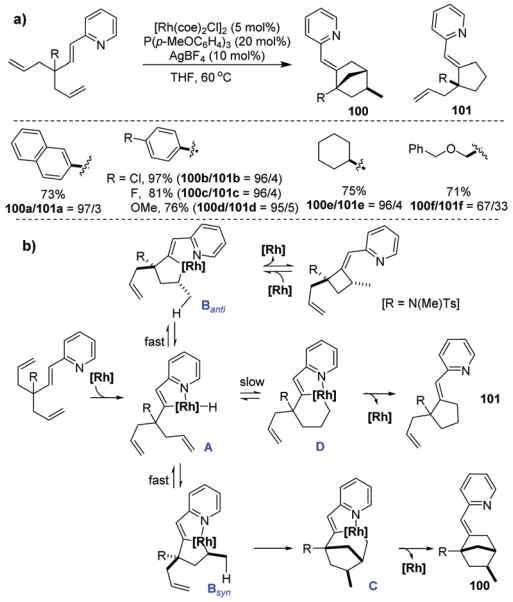
esters are all well tolerated. Moreover, the directing group can be easily removed by treatment with NH_3/MeOH to obtain phthalimide derivative **98** in 73% yield.[116]

The Jia group disclosed a Pd-catalyzed preparation of benzofurans **99** which proceeded by a tandem C–H activation/oxidation process, using 2-hydroxystyrenes and iodobenzenes as the substrates (Scheme 86a). A control experiment showed a phenol directed olefinic C–H activation, which was further confirmed by a KIE experiment (k_H/k_D = 1.9) to be the rate determining step in the reaction. Mechanistic studies prompted the authors to propose the possible mechanisms (Scheme 86b). The reaction starts with the generation of aryl-Pd(II) species by oxidative addition of ArI by Pd(0), and the subsequent ligand exchange with phenol leads to intermediate **I**. Next, **I** undergoes vinylic C–H cleavage to form six-membered palladacycle **II**, which delivers the cross-coupling *Z*-isomer **III** and palladium(0) upon reductive elimination. The isomer **III** coordinates with the Ar–Pd(II)–**I** species to afford the palladium aryl phenoxide species **IV**. Intramolecular *syn*-insertion of the alkene into the Pd–O bond gives intermediate **V**, which subsequently undergoes *syn*-β-hydride elimination to provide the desired benzofuran **99** and H–Pd–Ar species, which again leads to Pd(0) and an arene by reductive elimination.[117]

The use of 1,6-dienes as directed olefinic C–H functionalization substrates has been rarely demonstrated. In 2014, the Aïssa group disclosed a Rh(I)-catalyzed synthesis of [2,2,1]-cycloheptanes **100** containing three stereogenic centers, using prochiral 1,6-heptadienes by rearrangement reaction (Scheme 87a). Based on deuterium-labeling studies and the key intermediate characterization, the reaction mechanism is proposed as follows (Scheme 87b). Firstly, pyridine-directed C(alkenyl)–H bond activation occurred to afford rhodacycle **A**, and then the insertion of a double bond into the [Rh]–H bond of **A** gave intermediates B-*syn* and B-*anti* rapidly and reversibly. In the case of B-*anti*, the second olefin insertion is disfavored, leading to a four-membered ring *via* reductive elimination. Notably, the formation of this strained



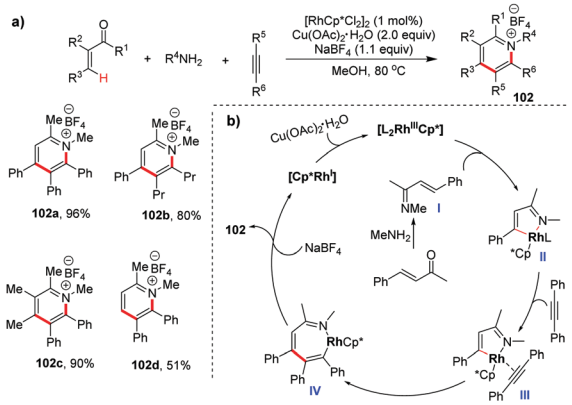
Scheme 86 Pd-Catalyzed synthesis of benzofurans from 2-hydroxystyrenes and iodobenzenes (Jia, 2014).[117]



Scheme 87 Rh(I)-Catalyzed rearrangement of prochiral 1,6-heptadienes into [2,2,1]-cycloheptane derivatives (Aïssa, 2014).[118]

molecule is reversible and it can be converted back to B-*anti* by directed C–C bond activation. In contrast, intramolecular alkene insertion in B-*syn* is more favorable, leading to species **C** and finally **100** by reductive elimination. Moreover, if the second olefin is also substituted or if the substrate bears a sterically undemanding R group, the formation of **D** from **A** is more competitive than the generation of **C**, thus providing **101**.[118]

Pyridinium salts are important structural motifs occurring in many natural and bioactive compounds. The Cheng group demonstrated a rhodium-catalyzed preparation of highly substituted pyridinium salts **102** from simple vinyl ketones/aldehydes, amines, and alkynes, which was performed in the presence of $[RhCl_2Cp^*]_2$, $Cu(OAc)_2{\cdot}H_2O$, and $NaBF_4$ in MeOH (Scheme 88a). Not only symmetrical alkynes but also unsymmetrical alkynes underwent [4+2] cyclization smoothly to form pyridinium salts in high yield with good regioselectivity.

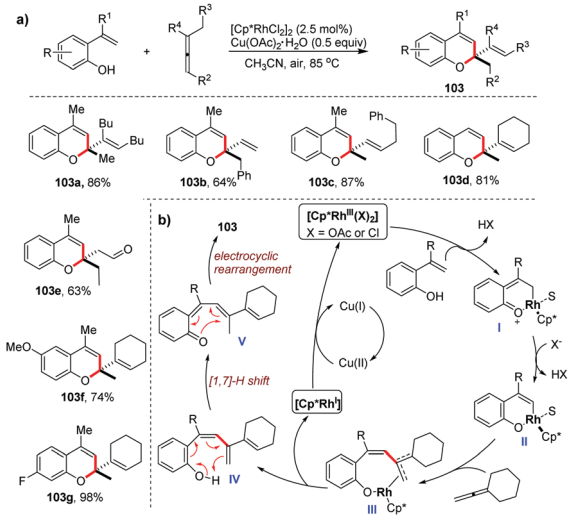


Scheme 88 Rh-Catalyzed preparation of pyridinium salts from vinyl ketones/aldehydes, amines, and alkynes (Cheng, 2015).[119]

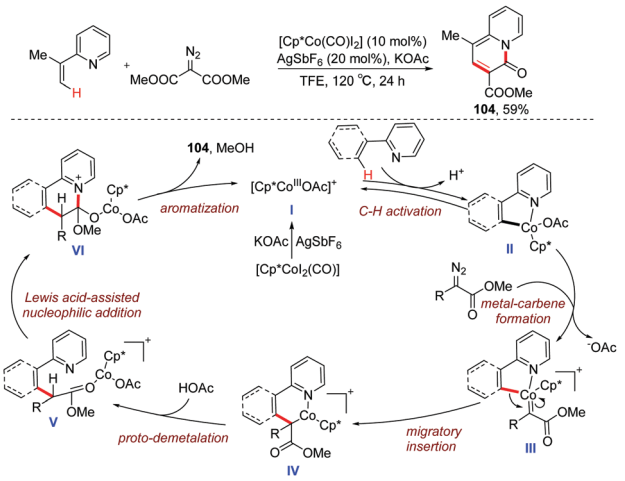
The *N*-methylpyridinium salts obtained can be easily transformed into corresponding neutral pyridine products by heating in a pyridine solvent. The catalytic reaction is proposed to be initiated by the coordination of α,β-unsaturated imine **I** *in situ* formed from the ketone and amine to Rh(III)-species, followed by vinylic C–H cleavage to give a five-membered rhodacycle, **II**. Coordination of the internal alkyne to intermediate **II** and regioselective insertion into the carbon–rhodium bond affords a seven-membered rhodacycle, **IV**. Facile C–N bond forming reductive elimination of intermediate **IV** affords pyridinium salt **102** and a Rh(I) species. The latter is oxidized by Cu(II) salt to generate the active Rh(III) species for the next catalytic cycle (Scheme 88b).[119]

The Mascareñas and Gulías group demonstrated a synthesis of valuable 2,2-disubstituted 2*H*-chromenes **103** employing alkenylphenols and allenes under rhodium catalysis. The cyclization was demonstrated to be a simple, versatile, and atom-economical (5+1) heteroannulation under the catalysis of Cp*Rh(III), using Cu(II) as the oxidant under aerobic conditions (Scheme 89a). The reaction tolerates a broad range of substituents both in the alkenylphenol and in the allene. The catalytic cycle is initiated by the formation of intermediate **I** by intramolecular attack of the conjugated alkene on the *O*-coordinated metal, followed by a fast subsequent rearomatization to generate rhodacycle **II**. Deuterium-labeled experiments exhibited that this rhodacycle intermediate is generated from a dearomatization/rearomatization process instead of a CMD process. Next, allene coordination followed by migratory insertion gives the π-allylic rhodacycle **III**. Then species **III** undergoes β-hydride elimination to give the conjugated diene **IV**, and this intermediate undergoes a [1,7]-proton transfer to generate the dearomatized enone **V**. Finally, **V** evolves and leads to chromenes **103** by means of an electrocyclic annulation. Again, the Rh(I) species generated in the catalytic cycle is reoxidized by Cu(II) to be re-activated (Scheme 89b).[120]

The Glorius group successfully developed a cobalt(III)-catalyzed coupling of diazo compounds with aromatic compounds *via* C–H



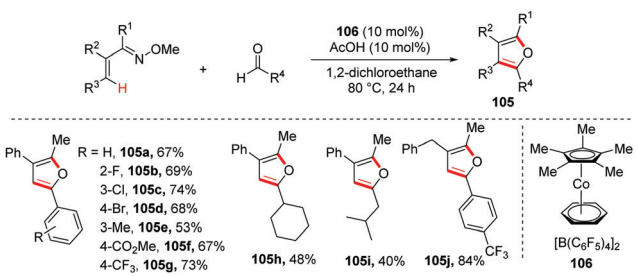
Scheme 89 Synthesis of 2,2-disubstituted 2*H*-chromenes using alkenylphenols and allenes (Mascareñas and Gulías, 2015).[120]



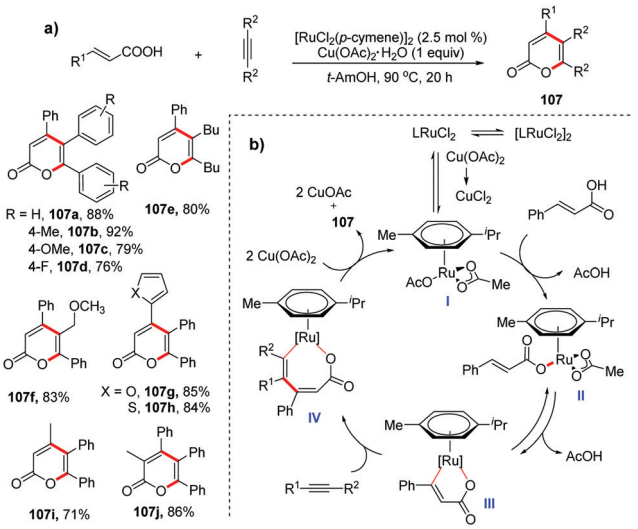
Scheme 90 Cobalt(III)-catalyzed coupling of diazo compounds with 2-(propenyl)pyridine (Glorius, 2015).[121]

activation towards extended π-systems. This efficient protocol is also suitable for the C–H coupling of olefins such as 2-(propenyl)pyridine *via* alkenyl C–H activation, leading to pharmaceutically valuable 4*H*-quinolizin-4-one **104**. The authors proposed a directed reversible C–H bond activation to form cobaltacycle **II** as the first step after generation of the Cp*Co(III) species **I**. Further reaction with the diazo compound forms the metal–carbene intermediate **III** by dediazonization. Subsequently, cobalt–carbene migratory insertion in intermediate **III** affords the cobaltacycle **IV**, which undergoes proto-demetalation and Lewis acid promoted nucleophilic addition to form intermediate **VI**. Finally, aromatization gives the desired product **104** and regenerates the active species **I**. The dual role of the Cp*Co(III) complex as both a transition metal and a Lewis acid catalyst might be vital to C–H activation and sequential annulation (Scheme 90).[121]

The Ellman group developed a synthesis of highly functionalized furans **105** from α,β-unsaturated oximes and aldehydes which proceeded by alkenyl C–H bond activation, aldehyde insertion, annulation and aromatization, using an air stable cationic Co(III) catalyst, **106** (Scheme 91). A wide range of α,β-unsaturated oximes and aldehydes were suitable, leading to tri- and tetra-substituted furans. Valuable functional groups such as F, Cl, Br and CF_3 were all compatible. Notably, this Co(III)-catalyzed protocol afforded comparable yields to the previous preparation using Rh(III) catalysis.[122]



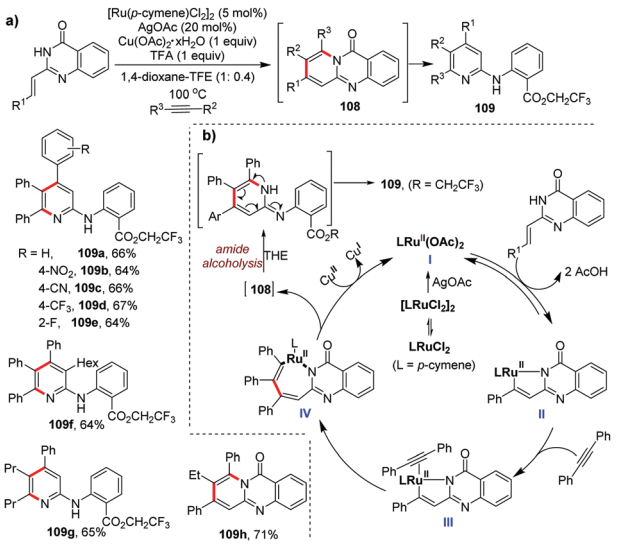
Scheme 91 Synthesis of furans from α,β-unsaturated oximes and aldehydes by Co(III)-catalysis (Ellman, 2015).[122]



Scheme 92 Synthesis of α-pyrones from cinnamic acids and alkynes (Gogoi, 2015).[123]

Gogoi and co-workers reported a Ru-catalyzed oxidative annulation between cinnamic acid and alkynes to produce multi-substituted α-pyrones **107**. Both diaryl- and dialkyl-substituted alkynes reacted smoothly with various cinnamic acids, exhibiting a broad substrate scope (Scheme 92). A tentative mechanism was proposed by the authors. Reversible C–H cycloruthenation of cinnamic acid with **I** occurred to afford ruthenacycle **III**, which underwent subsequent alkyne insertion and reductive elimination to produce compound **107**.[123]

Cook *et al.* demonstrated a novel cascade integrating ruthenium-catalyzed olefinic C–H functionalization/cyclization and amide alcoholysis for the synthesis of 2-aminopyridines **109** (Scheme 93a). The reaction worked well by the use of $[Ru(p\text{-cymene})Cl_2]_2$, $AgOAc/Cu(OAc)_2$ and TFA in a mixed solvent (dioxane/TFE), and other alcohols such as MeOH, EtOH and

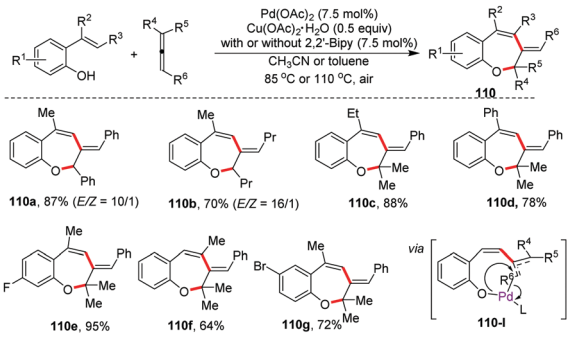


Scheme 93 Synthesis of 2-aminopyridines by integrating olefinic C–H functionalization/cyclization and amide alcoholysis (Cook, 2016).[124]

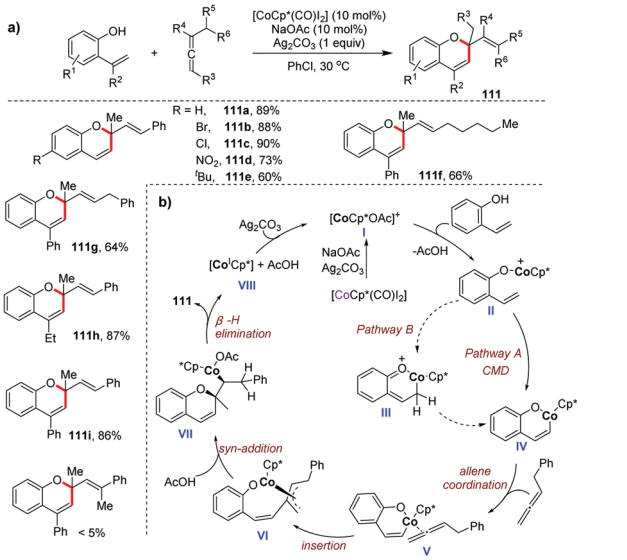
*i*PrOH are inferior for alcoholysis. Deuterium-labelled experiments demonstrated a reversible C–H activation to form a ruthenacycle intermediate. Parallel and competitive KIE experiments suggest the C–H activation to be the rate-determining step, which is in good agreement with a concerted acetate-assisted metalation transition state. The reaction started with the removal of the chloride ligand from the Ru-complex by AgOAc, providing the cationic ruthenium acetate species **I**. Then, concerted acetate-assisted C–H activation occurred to afford five-membered ruthenacycle **II**. Alkyne coordination and migratory insertion generated the seven-membered ruthenacycle **IV**. Subsequently, reductive elimination led to pyrido[2,1-b]quinazolin-11-ones **108**, which were converted to products **109** by amide alcoholysis (Scheme 93b). Unsymmetric alkylarylacetylene led to regioselective annulation (**109h**), supporting that C–C bond formation occurred prior to C–N bond formation.[124]

The Mascareñas and Gulías group also disclosed a regio- and diastereoselective synthesis of benzoxepines **110** from 2-alkenylphenols and allenes by Pd(II)-catalysis using Cu(II) as the oxidant under aerobic conditions. The transformation represents versatile and atom economical access to a wide variety of benzoxepine skeletons. Notably, as the geometry of the palladium is square planar, the reductive elimination is favorable for producing oxepines, which is supported by computational studies. A plausible catalytic cycle was proposed to proceed by a concerted metalation–deprotonation C–H activation, or a base-induced rearomatization to form a six-membered palladacycle, followed by coordination and regioselective migratory insertion of allenes to give a π-allylic palladacycle, **110-I**, which underwent a reductive elimination step to afford the benzoxepine products **110**. The selectivity of the ring closing depends on the allene structure and electronic characteristics of the substituents (Scheme 94).[125]

In the same year, the Cheng group reported a cobalt-catalyzed phenolic OH-directed C–H functionalization of 2-vinylphenols using allenes to give various 2*H*-chromene derivatives **111** *via* oxidative [5+1] annulation (Scheme 95a). Substrate scope analysis revealed that *meta*- and *ortho*-substituted 2-vinylphenols gave lower yields of the expected products than the corresponding *para* ones. Notably, the presence of an alkyl and aryl group at the internal carbon of the vinyl group of 2-vinylphenols



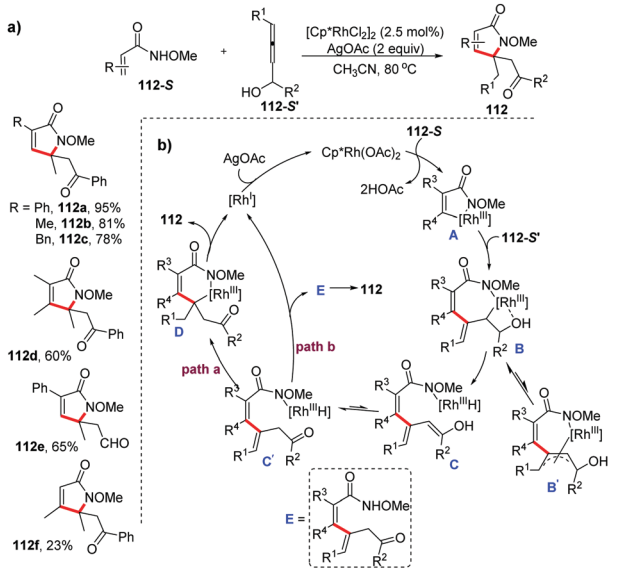
Scheme 94 Synthesis of benzoxepines from 2-alkenylphenols and allenes (Mascareñas and Gulías, 2016).[125]



Scheme 95 OH-Directed C–H functionalization of 2-vinylphenols using allenes to give 2*H*-chromenes (Cheng, 2016).[126]

did not significantly affect the reaction and gave excellent product yields, but the substituent at terminal carbon totally retarded the reaction. Intermolecular competition experiments suggest that the electron-deficient vinylic arene and allene reacted preferentially. Experimental KIE values suggest that the C–H bond cleavage is probably involved in the rate-determining step. The catalytic reaction is proposed to proceed *via* the C–H activation of the vinyl group to afford **IV**. Then, allene coordination and regioselective insertion give π-allylic cobaltacycle **VI**, which undergoes cyclization *via* intra-molecular addition of the Co–O bond to the π-allylic moiety to afford **VII** by protonation with AcOH, and the final β-H elimination produces **111** (Scheme 95b). Although there are two possible pathways for the formation of intermediate **IV** from **II**, KIE experimental results suggest that the C–H metalation occurs *via* a CMD pathway (path A).[126]

In 2016, Lu and Liu reported a selective [4+1] annulation of vinylic amides with α-allenols to prepare pyrrol-2-ones **112** containing a *tetra*-substituted carbon center (Scheme 96). The excellent chemo- and site-selectivities of the reaction are controlled by the hydroxyl group in allenes, presumably due to its coordination to the rhodium center. Both mono- and di-substituted *N*-methoxyacrylamides reacted well with representative α-allenols to afford the corresponding lactams in moderate to excellent yields. However, the absence of an α-substituent in acrylamides significantly decreases the reaction efficiency (**112f**). The reaction mechanism may be initiated by olefinic C–H activation to generate rhodacycle **A**, and the subsequent site-selective allene insertion affords a seven-membered rhodacycle, **B**, where the site-selectivity is governed by the binding affinity of hydroxyl to the Rh center. Thus, the formation of π-allyl rhodium species **B′** is disfavored. After that, β-H elimination and then the enol–keto tautomerism lead to species **C′**, which undergoes insertion of an olefin into the

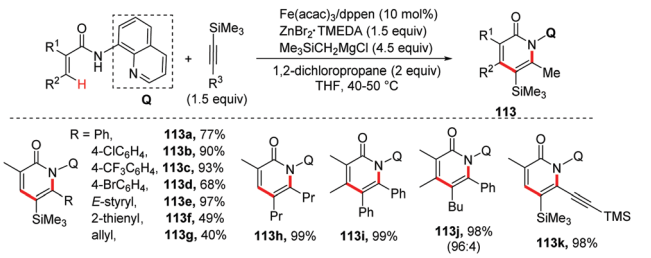


Scheme 96 Annulation of vinylic amides with α-allenols to prepare pyrrol-2-ones (Liu and Lu, 2016).[127]

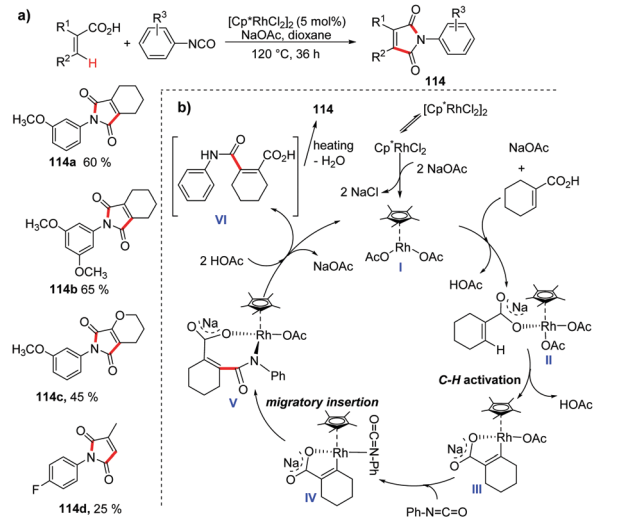
Rh–H bond to afford intermediate **D**, which finally gives rise to product **112** by reductive elimination (path a). However, reductive elimination of intermediate **C′** to form **E** followed by intramolecular hydro-amination provides an alternative pathway toward **112** (path b).[127]

Nakamura and Ilies reported an iron-catalyzed synthesis of 2-pyridones **113** from acrylamides and internal alkynes. The reaction was mild and was performed using $Fe(acac)_3$/dppen (catalyst), bis(trimethylsilylmethyl)zinc (base) and 1,2-dichloropropane (oxidant) in THF at 40–50 °C. Both acyclic and cyclic olefins bearing an *N*-8-quinoline group reacted well with internal alkynes without isomerization of the acrylamide substrate. Alkynes containing alkenyl, allyl, alkynyl, thienyl and silyl groups were all smoothly converted, showing the robustness of the protocol. Notably, even unsymmetrical alkynes provided pyridines with excellent site-selectivity presumably due to the compact size of iron (Scheme 97).[128]

The Li group demonstrated a Rh(III)-catalyzed synthesis of cyclic imides **114** from acrylic acids and aryl isocyanates which proceeded by COOH-directed alkenyl C–H bond activation followed by intramolecular cyclization (Scheme 98). This protocol was applied to cyclic and acyclic alkenyl carboxylic



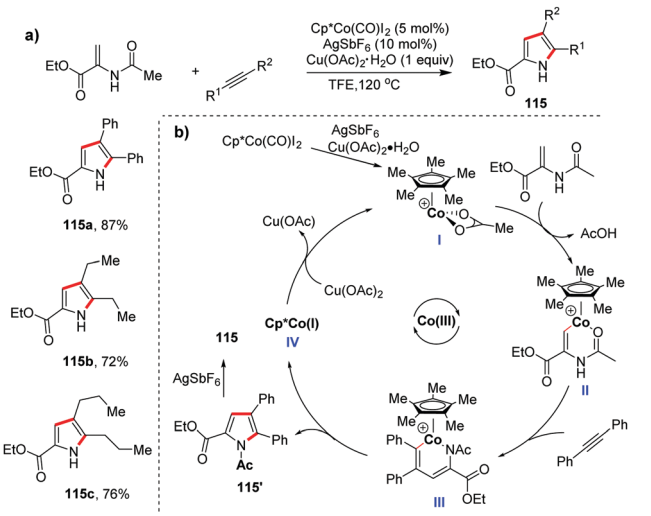
Scheme 97 Iron-catalyzed synthesis of 2-pyridones from acrylamides and internal alkynes (Nakamura and Ilies, 2016).[128]



Scheme 98 Rh(III)-Catalyzed synthesis of cyclic imides from acrylic acids and aryl isocyanates (Li, 2016).[129]

acids such as 1-cyclohexene-1-carboxylic acid and 2-methylpropenoic acid, albeit leading to moderate yields in most of the cases. A plausible mechanism involves Cp*Rh(III)-catalyzed olefinic C–H activation and isocyanate insertion to afford a rhodium alkoxide, **V**, which underwent protonation and water elimination to produce the desired cyclic imides **114**.[129]

A cobalt(III)-catalyzed (3+2) oxidative annulation of enamides and alkynes was reported by the Pawar group, for the synthesis of pyrroles **115** under Cp*Co(III) catalysis (Scheme 99a). The reaction was generally performed at room temperature using various internal alkynes, affording *N*-acetyl pyrroles with broad substrate scopes and functionality tolerance. However, valuable N–H pyrroles were successfully prepared by simply heating the reaction mixture to 120 °C. The reaction was likely to be initiated by the reaction of $Cp^*Co(CO)I_2$ and $AgSbF_6$ with $Cu(OAc)_2$ to generate the catalytically active species **I**, which

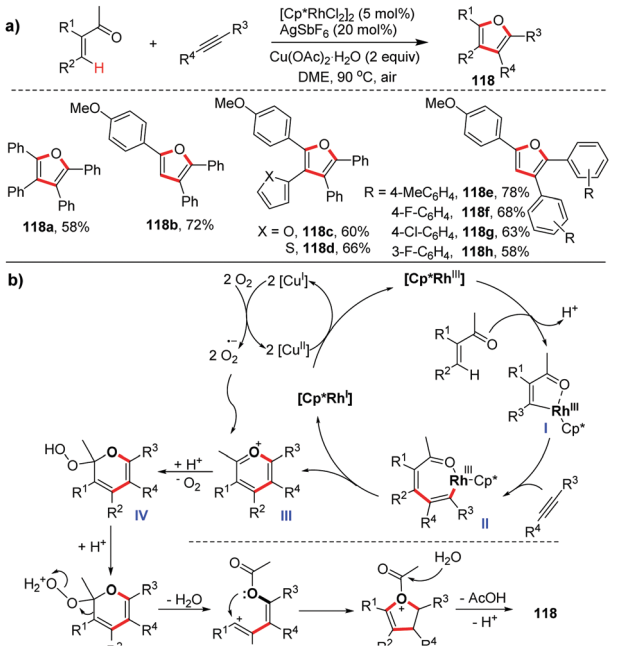


Scheme 99 Co(III)-Catalyzed (3+2) oxidative annulation of enamides and alkynes for the synthesis of pyrroles (Pawar, 2016).[130]

underwent vinylic C–H bond activation to form cobaltacycle **II**. Then species **II** underwent migratory insertion of an alkyne to form the six-membered cobaltacycle **III**, which produced pyrrole and cobalt(I) species **IV** by reductive elimination. The *N*-acetyl group was deprotected in the presence of $AgSbF_6$ at elevated temperature to produce N–H pyrroles **115** (Scheme 99b).[130]

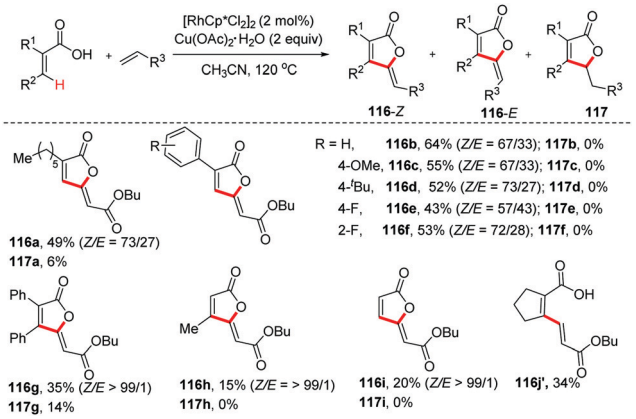
γ-Alkylidenebutenolides are an important class of organic compounds with biological significance and structural diversity. Our group developed a tandem cross-coupling/oxa-Michael addition/dehydrogenation process by rhodium catalysis, providing a straightforward and atom-economical protocol for the synthesis of a wide range of valuable γ-alkylidenebutenolides **116**, with disfavored the formation of butenolides **117**. This method is of particular interest employing widely available and inexpensive vinyl carboxylic acids and electron-deficient alkenes such as acrylates as building blocks. Notably, vinyl carboxylic acid bearing a cyclopentenyl unit produced only dienoic acid **116j′** presumably due to the disfavored ring strain. Moreover, the methodology can be applied to a gram scale synthesis with 1 mol% catalyst loading. Deuterium labelled experiments revealed a reversible C–H cyclometalation mode, and a KIE value of 4.0 was determined, which suggested the C–H bond cleavage to be involved in the rate-limiting step (Scheme 100).[131]

Recently, You's group disclosed a preparation of multiaryl-substituted furans **118** using α-aryl enones and internal alkynes under rhodium catalysis, which proceeded by tandem ketone-directed C(alkenyl)–H cleavage, [4+2] cyclization and aerobic ring contraction by copper catalysis (Scheme 101a). Addition of 2 equivalents of TEMPO to the reaction led to no reaction, indicating that radical intermediates were probably involved. A tentative mechanism is proposed in Scheme 101b. The reaction starts with an irreversible vinylic C–H activation of vinyl ketone to give a five-membered rhodacycle, **I**. The alkyne insertion forms the seven-membered intermediate **II**. The direct reductive elimination generates the pyrylium salt **III** and releases the Rh(I) species, which is oxidized to regenerate the Rh(III) complex. Then **III** undergoes nucleophilic attack at the α-position by the superoxide radical generated from the single electron transfer (SET) from Cu(I) to oxygen, forming α-hydroperoxide **IV** after protonation. Further protonation promotes heterolysis of the O–O bond, generating a 4-acetoxy-1,3-diene cation, **VI**, which is stabilized by an aryl substituent (R^1 = aryl). The intramolecular cyclization gives O-acylated furanium **VII**, which is hydrolyzed to release furan **118**. Pyrylium salt **III** was obtained and treated with optimal conditions to yield a furan in good yield, identifying its formation as the key intermediate.[132]

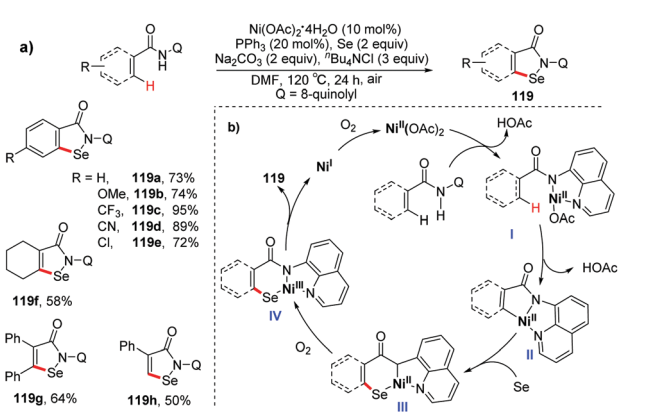


Scheme 101 Rh-Catalyzed ketone-directed vinylic C–H activation/[4+2] O-annulation of aryl enones and internal alkynes (You, 2017).[132]

The isoselenazolone skeleton is attracting increasing interest as a biologically active molecule. The Nishihara group developed a nickel-catalyzed and chelate-assisted direct selenation of aryl and alkenyl C–H bonds with elemental selenium, which provides a new synthetic route to isoselenazolone derivatives **119** *via* C–Se and N–Se bond formation (Scheme 102a). The reaction



Scheme 100 γ-Alkylidenebutenolide synthesis from vinyl carboxylic acids and electron-deficient alkenes (Zhang and Zhong, 2017).[131]



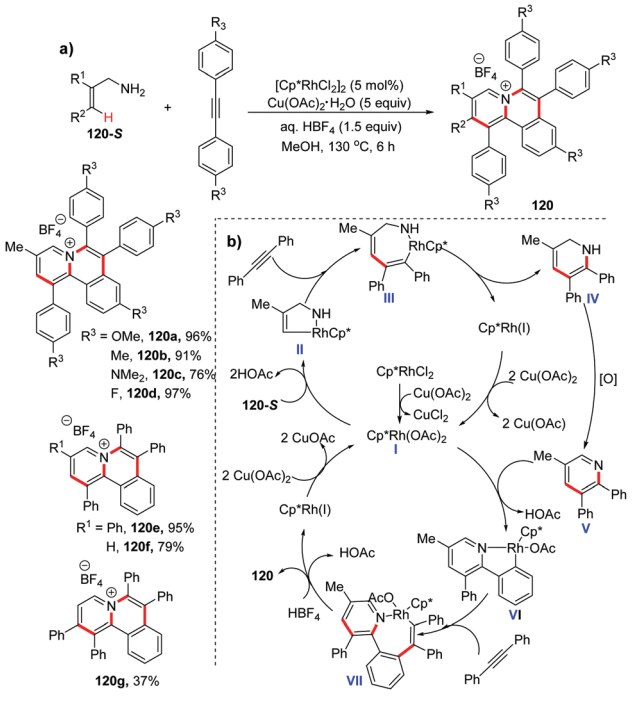
Scheme 102 Ni-Catalyzed C–H selenation toward isoselenazolone derivatives *via* C–Se and N–Se bond formation (Nishihara, 2017).[133]

was conducted under mild conditions and showed excellent functionality tolerance, under the chelation-assistance of an 8-quinolyl auxiliary. Mechanistic analysis shows that the reaction proceeds through a rate-determining C–H bond cleavage. As the oxygen atmosphere remarkably promotes the reductive elimination step, a possible mechanism based on high-valent nickel species is as follows. *N*,*N*-Bidentate chelation-assisted C–H activation gives an aza nickelacycle intermediate, **II**. Insertion of elemental selenium into the C–Ni bond generates a 6-membered nickelacycle, **III**. Aerobic oxidation of nickel(II) prompts the subsequent reductive elimination to provide **119** with the liberation of a nickel(I) species, which is converted to the initial nickel(II) species by oxidation. An alternative mechanism involving reductive elimination from **C** and generation of a nickel(0) species was less likely to occur (Scheme 102b).[133]

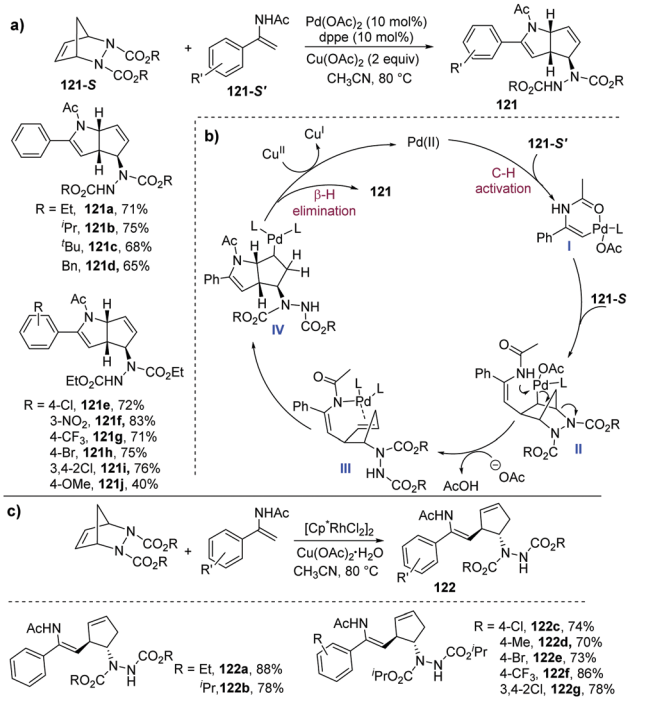
In 2017, Jun and co-workers reported a synthesis of benzoquinolizinium salts **120** from allylamines and internal alkynes, which was performed with $[Cp^*RhCl_2]_2/Cu(OAc)_2$ complexes and HBF_4 in MeOH. A wide variety of primary allylamines and aromatic internal alkynes were suitable. Unsubstituted allylamine also led to 79% yield, and diphenylacetylenes bearing *para*-OMe, NMe_2, and F groups underwent efficient double N-annulations. Notably, 3-phenylprop-2-en-1-amine exhibited much lower reactivity due to steric hindrance between phenyl groups which disfavored the formation of a seven-membered rhodacycle. A plausible mechanism is depicted in Scheme 103b. The initial Rh(III)-catalyzed olefinic C–H bond activation occurs to afford five-membered rhodacycle **II**, which undergoes carbometallation with acetylene to form seven-membered rhodacycle **III**. Reductive elimination of **III** leads to dihydropyridine **IV**, which is converted to diphenylpyridine **V** by oxidation with $Cu(OAc)_2$. Then, aromatic C–H activation occurs to **V** to form five-membered rhodacycle **VI**, and the subsequent alkyne insertion provides rhodacycle **VII**. Finally, reaction of rhodacycle **VII** with HBF_4 produces benzoquinolizinium salt **120**, and the liberated Rh(I) species is oxidized by copper(II) to regenerate the Rh(III) species.[134]

In the same year, Radhakrishnan and John reported a Pd-catalyzed synthesis of cyclopentene fused 2-pyrrolines **121** using simple aryl enamides with diazabicyclic olefins as the substrates. The reaction is simply performed with a combination of $Pd(OAc)_2$/dppe and $Cu(OAc)_2$ in MeCN by heating to 80 °C. A two-stage mechanism was proposed based on control experiments (Scheme 104b). In the first stage, amide-directed alkenyl C–H bond activation occurs to enamide with $Pd(OAc)_2$ to afford six-membered palladacycle **I**, and *endo*-coordination of an alkene to **I** followed by carbopalladation leads to the generation of **II**, which undergoes aminopalladation and *exo*-ring opening to produce species **III**. In the second stage, intramolecular olefin insertion into aminopalladated species affords **IV**, and subsequent β-hydride elimination leads to product **121**. The authors also developed a rhodium-catalyzed preparation of 3,4-bisfunctionalized cyclopentenes **122** which proceeded by olefinic C–H activation followed by the ring opening of diazabicyclic alkenes. The reaction was performed using a simple combination of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ in MeCN, and the generality of the protocol was featured by the smooth conversion of various diazabicyclic olefins and aromatic enamides (Scheme 104c).[135]

The Sahoo group reported a Ru-catalyzed double cyclization between acrylamides and alkynes, promoted by the methylphenyl



Scheme 103 Synthesis of benzoquinolizinium salts from allylamines and internal alkynes (Jun, 2017).[134]

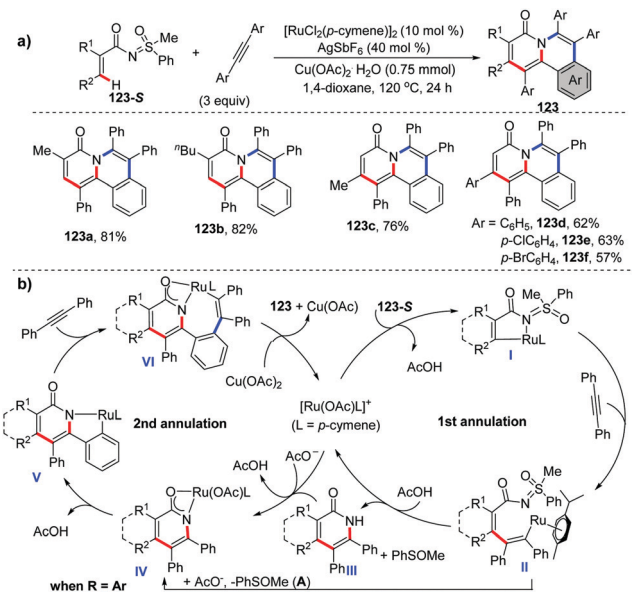


Scheme 104 Directed olefinic C–H functionalization of enamides using diazabicyclic olefins (Radhakrishnan and John, 2017).[135]

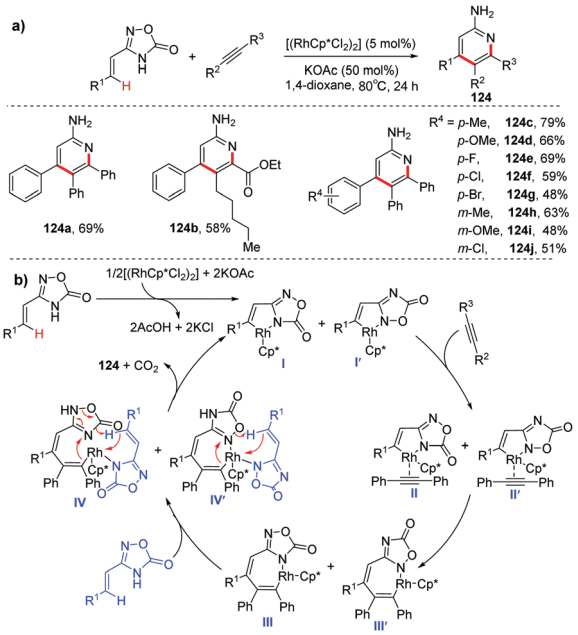
sulfoximine (MPS) group. A wide range of pyrido-fused-isoquinolinones **123** were efficiently obtained by the formation of two C–C and C–N bonds in a one-pot fashion. The reaction was performed using a combination of $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ in a solvent of 1,4-dioxane at 120 °C. Such double annulation could involve MPS-N-chelation-assisted olefinic C–H activation to form a five-membered ruthenacycle, **I**, and the subsequent migratory insertion of an alkyne formed a seven-membered ruthenacycle, **II**. Subsequent reductive elimination led to monoannulation product **III** and released methyl phenylsulfoxide. The formation of five-membered ruthenacycle **V** *via* Ru species **IV** and annulation with alkynes would eventually give the cyclization product **123**. Copper acetate not only behaves as an oxidant but also helps in activating the catalyst (Scheme 105b).[136]

Primary pyridinylamines are versatile intermediates for diverse synthetically and pharmaceutically important compounds. Zhu and co-workers developed an oxadiazolone-directed alkenyl C–H coupling with alkynes under rhodium(III) catalysis to prepare primary pyridinylamines **124**, representing an intriguing associative covalent relay mode. Based on deuterium-labelled and control experiments, the authors proposed that a possible mechanism proceeds by deprotonation of oxadiazolone by KOAc, coordination of Rh(III), C–H activation assisted by acetate, migratory insertion of the alkyne, proton exchange between oxadiazolone and an alkenylated Rh(III) intermediate and coordination of deprotonated oxadiazolone, simultaneous C–H activation of oxadiazolone, and the final liberation of primary pyridinylamine product **124** (Scheme 106).[137]

In 2018, Gao and co-workers reported a synthesis of 1*H*-benzo[*f*]chromene derivatives **125** by a Rh-catalyzed vinylic C–H activation/annulation reaction between *exo*-cyclic α,β-enones and alkynes by the formation of active pyrylium intermediates

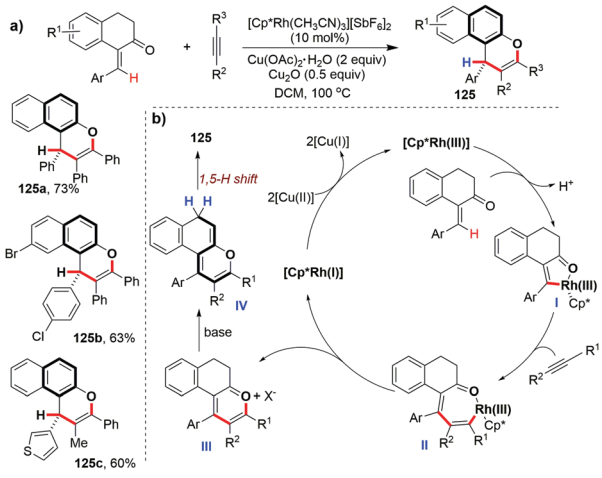


Scheme 105 Sulfoximine directed double annulation of olefinic C–H bonds with alkynes (Sahoo, 2017).[136]



Scheme 106 Oxadiazolone-directed alkenyl C–H coupling with alkynes by rhodium catalysis (Zhu, 2017).[137]

(Scheme 107a). The H/D exchange experiment showed that the initial vinylic C–H bond cleavage was irreversible, and the KIE value was determined to be 1.5, suggesting that the vinylic C–H bond cleavage was not involved in the turnover-limiting step. A plausible mechanism is depicted in Scheme 107b. The reaction started with an irreversible vinylic C–H bond activation to give the five-membered rhodacycle **I**, followed by the alkyne insertion to generate the seven-membered rhodacycle **II**. Direct reductive elimination delivered the key pyrylium intermediate **III** and released the Rh(I) species, which was oxidized by Cu(II) to regenerate the Rh(III) catalyst. Then intermediate **III** evolved into a conjugated triene (**IV**) by deprotonation at the benzylic position of the pyrylium ring with base, and **IV** was further aromatized into

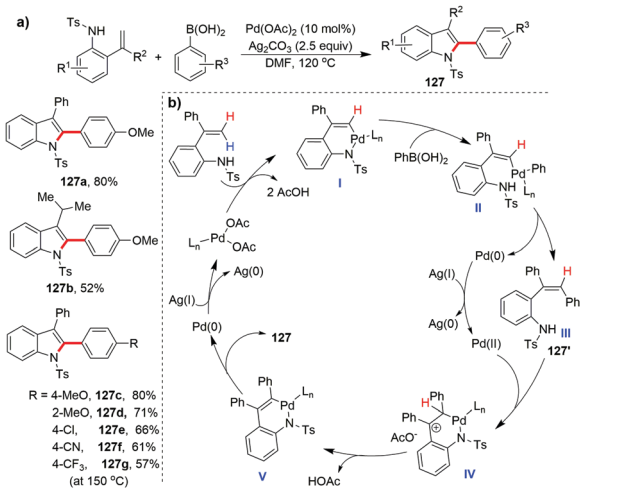


Scheme 107 Rh-Catalyzed vinylic C–H annulation reaction between exocyclic α,β-enones and alkynes (Gao, 2018).[138]

the more stable 1*H*-benzo[*f*]chromene **125** through [1,5]-*H* shift, which has been confirmed by control experiments.[138]

Next, Gulías and co-workers reported an unusual cyclization between alkynes and 2-alkenyl anilides to form appealing 2-substituted indolines **126** using a Rh(III) catalyst with an electron-deficient cyclopentadienyl ligand under aerobic conditions (Scheme 108a). Herein, the use of an electron-deficient Cp^E ligand in the Rh(III) catalysis and the nitrogen substituents are both important in terms of selectivity and efficiency of the transformation. Mechanistic experiments suggest that the transformation starts with the acetate exchange by the amide of the anilide on rhodium complexes, and the resulting intermediate **I** then undergoes alkenyl C–H bond activation to afford rhodocycle **IIa**, and the subsequent migratory insertion of the alkyne and rhodium C–C migration with a simultaneous [1,5]-*H*-shift lead to the formation of intermediate **IV**. The final reductive elimination occurs to produce **126** (Scheme 108b). Another mechanism including π-allyl **IIb** by allylic C–H activation, alkyne carbometalation and 1,3-rhodium migration is less likely to occur based on deuterium-labeling experiments.[139]

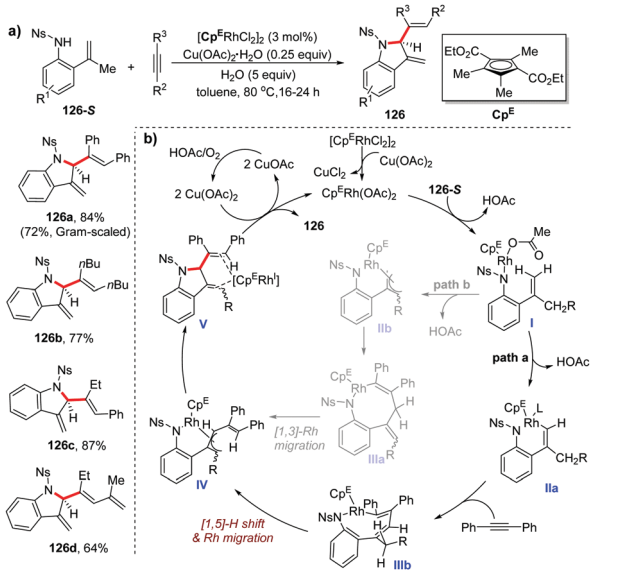
Recently, Zeng and co-workers also reported a synthesis of multifunctionalized indoles **127** by a palladium-catalyzed vinylic C–H arylation/amination sequence from 2-vinylanilines and aryl boronic acids (Scheme 109a). This protocol tolerates a wide range of typical functional groups and represents a selective and successive 1,1-difunctionalization of the terminal vinyl on 2-vinylanlines to construct indoles. A possible mechanism starts with the formation of palladacycle **I** *via* vinylic C–H bond activation with the liberation of AcOH. Then, the Pd(II) species transmetalates with boronic acid and the reductive elimination affords the intermediate product **127′** and generates a palladium(0) species, which is reoxidized to the active Pd(II) species by Ag_2CO_3. After that, an intramolecular nucleophilic attack of the conjugated alkene on the Pd(II) center,



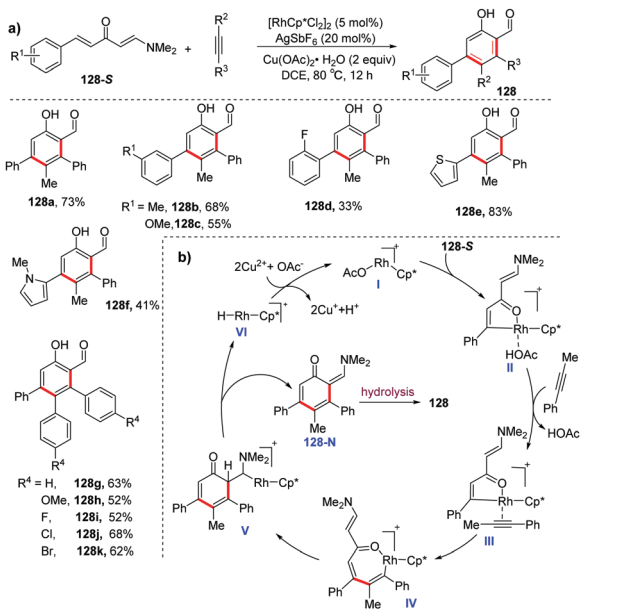
Scheme 109 Synthesis of multifunctionalized indoles by a Pd-catalyzed vinylic C–H arylation/amination sequence (Zeng, 2018).[140]

followed by a base-assisted deprotonation, results in product **127** after reductive elimination. However, there is another possible pathway by a benzylic carbon cation and radical mechanism which cannot be excluded (Scheme 109b).[140]

Zhu and co-workers reported a Rh(III)-catalyzed enaminone-directed alkenyl C–H activation/coupling with alkynes for the synthesis of salicylaldehydes **128** bearing two reactive aldehyde and hydroxy groups. Notably, a wide range of (1*E*,4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-one derivatives and alkynes are compatible with the protocol (Scheme 110a). Deuterium labelled experiments showed that the reversible C–H activation step is the rate-determining step. A plausible reaction mechanism is proposed to be initiated by coordination of the ketone group and olefinic C–H activation to afford



Scheme 108 Rh(III)-Catalyzed cyclization between alkynes and 2-alkenyl anilides to form 2-substituted indolines (Gulías, 2018).[139]

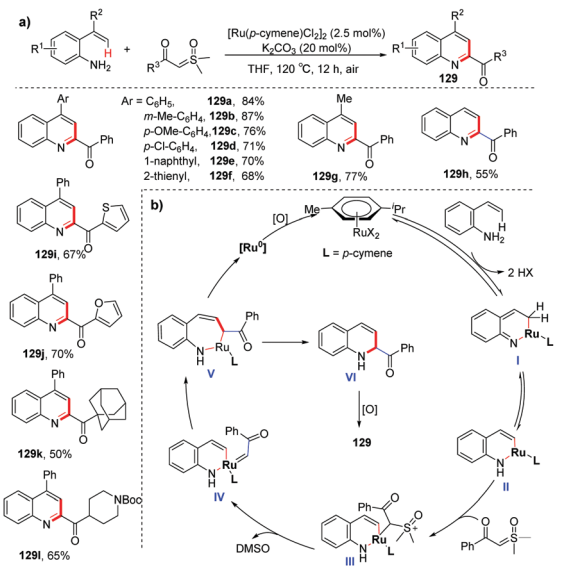


Scheme 110 Rh(III)-Catalyzed enaminone-directed alkenyl C–H activation/coupling with alkynes for the synthesis of salicylaldehydes (Zhu, 2018).[141]

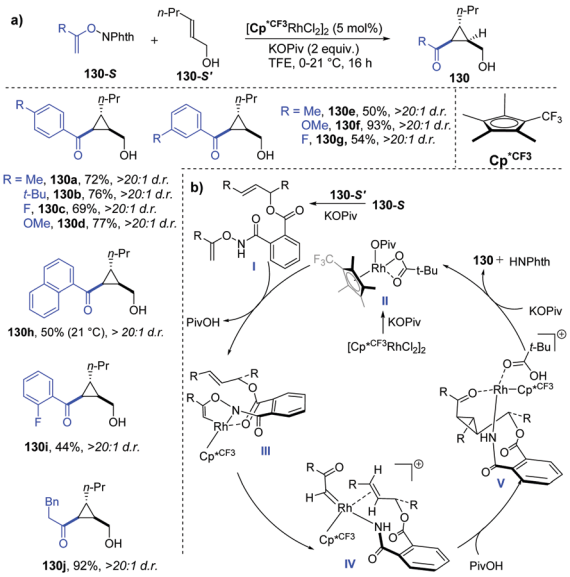
rhodacycle complex **II**, and further coordination and migratory insertion of the alkyne yield **IV**. After that, migratory insertion of the C–C double bond of the enaminone moiety and β-H elimination provide intermediate **V** and then **VI** along with the formation of **128-N**, which leads to **128** by hydrolysis. The selectivity for 6-*exo* (insertion of the alkene) rather than 5-*exo* (insertion of the ketone) cyclization likely reflects the dominance of the steric effect in this process (Scheme 110b).[141]

In 2019, Ma and Nan reported a ruthenium-catalyzed [5+1] annulation of 2-alkenylanilines with sulfoxonium ylides for the preparation of quinolines **129** (Scheme 111a). In this catalytic process, the free amino functionality was used to achieve alkenyl C–H activation and sulfoxonium ylides were used as one-carbon coupling partners. Intermolecular competition reactions revealed the electron-rich 2-alkenylaniline to be more reactive. Next, related H/D scrambling experiments disclosed a reversible C–H cycloruthenation process. The KIE experiment suggested that the ruthenium-mediated C–H cleavage might not be involved in the turnover-determining step. A tentative catalyzed process is proposed in Scheme 111b. The reaction is induced by olefinic C–H activation to afford cycloruthenium **II**, generated from intermediate **I** by rearomatization. The coordination of the sulfoxonium ylide occurs to afford alkyl-Ru(II) species **III**, followed by extrusion of DMSO to deliver ruthenium carbene **IV**. Subsequently, carbene migratory insertion leads to the formation of seven-membered ruthenacycle **V**. Notably, this key intermediate undergoes reductive elimination to produce **VI** instead of protonation. The final oxidation of **VI** affords product **129**.[142]

In the same year, with their ongoing interest in cyclopropanation using *N*-enoxyphthalimide as a unique one-carbon component, the Rovis group demonstrated a Rh(III)-catalyzed directed diastereoselective [2+1] annulation employing allyl alcohols initiated by alkenyl C–H activation for the synthesis of



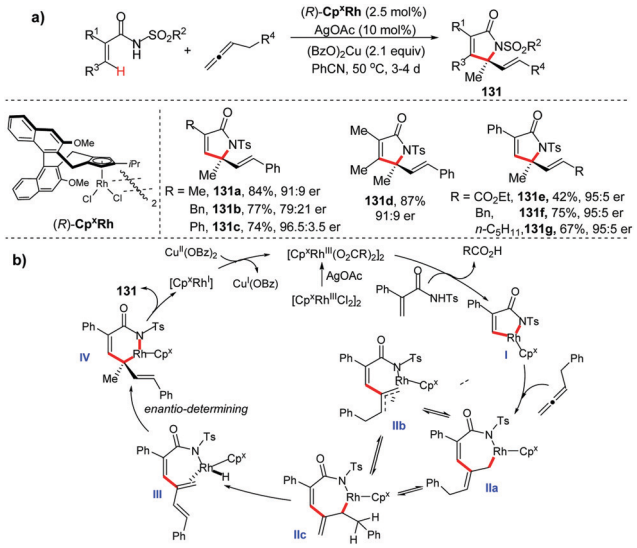
Scheme 111 Ru-Catalyzed [5+1] annulation of 2-alkenylanilines with sulfoxonium ylides toward quinolines (Ma and Nan, 2019).[142]



Scheme 112 Rh(III)-Catalyzed diastereoselective cyclopropanation of *N*-enoxyphthalimides (Rovis, 2019).[143]

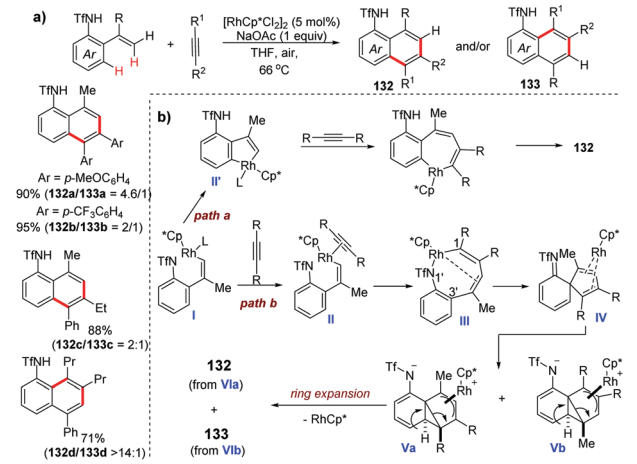
substituted cyclopropyl-ketones **130** (Scheme 112a). This intriguing protocol employed traceless oxyphthalimide functionality exhibiting three functions: directing group, oxidation of Rh(III), and directing cyclopropanation with allylic alcohol. The proposed mechanism involves acylation of allyl alcohol with ring-opening of the phthalimide to provide intermediate **I**, which undergoes irreversible C–H activation to give rhodacycle **III**. At this stage, the authors hypothesized the formation of Rh-carbene **IV** by N–O bond cleavage. Due to the prior acylation of the allylic alcohol, intermediate **V** is formed *via* the intramolecular cyclopropanation in a stereoselective fashion. Proto-demetalation and subsequent phthalimide ring closure release cyclopropyl-ketones **130** and the rhodium species **II** (Scheme 112b).[143]

Chiral 2*H*-pyrrol-2-ones and their derivatives represent the cores of numerous natural products and biologically active compounds. Cramer and co-workers reported a $Cp^xRh(III)$-catalyzed enantioselective alkenyl C–H functionalization/[4+1] annulation of acryl amides and allenes, producing quaternary stereocenter containing lactams **131** (Scheme 113a). This mild protocol exhibits a broad substrate scope and functionality tolerance, leading to excellent enantio-selectivity by using a chiral cyclopentadienyl ligand. A possible mechanism is proposed based on previous reports. The catalytic cycle begins with a carboxylate-assisted and amide directed CMD-type C–H activation to afford rhodacycle intermediate **I**. Herein, the chiral Cp^xRh^{III} complex binds to the nitrogen atom due to the increased acidity of the TsN-H groups of the acrylamide. Then, migratory insertion of the allene affords seven-membered rhodacycle intermediate **IIa**, which was interconverted to allyl-rhodium species **IIb** and **IIc**. The subsequent β-H elimination affords diene **III**, in which rhodium hydride adds across the double bond in the enantio determining step to provide six-membered rhodacycle **IV**. The final reductive elimination produced chiral lactam **131** (Scheme 113b).[144]



Scheme 113 Enantioselective alkenyl C–H functionalization/[4+1] annulation of acryl amides and allenes (Cramer, 2019).[144]

After their advances in the synthesis of oxepines and spirocyclic products from 2-alkenyl phenols and alkynes, Mascareñas and Gulías extended this chemistry to the annulation using *o*-alkenyl *N*-triflylanilide and alkynes to produce various naphthylamides **132** and **133** involving double C–H bond activation (Scheme 114a). Symmetrical diarylacetylenes provided the expected naphthylamides **132** in good site-selectivity and isomeric ratios of up to **132**/**133** = 4.6 : 1. Unsymmetrical alkyl arylalkynes also led to only one regioisomer. However, the employment of aliphatic alkynes led to a total change in selectivity to afford mainly the rearranged products **133**. The catalytic process might start with the alkenyl C–H activation to give rhodacycle **I**. The second C–H activation step occurred by rhodium rolling over to afford intermediate **II′**, and the subsequent alkyne migratory insertion and reductive elimination provided product **132** (Scheme 114b, path a). In the reaction of aliphatic alkynes, intermediate **I** might alternatively evolve to afford intermediate **III** after migratory insertion of the alkyne, which underwent a [1,3′] reductive elimination to provide spirocycles **IV** (path b). The Rh(I) spirocyclic complexes could readily convert to the cyclopropyl tricyclic intermediates **Va** or **Vb**, but with a kinetic preference for the formation of **Vb** when using aliphatic alkynes, which are supported by DFT calculations. It is supposed that the presence of the alkyl substituents generates a more sterically congested transition-state to afford **Va**. The lower activation barrier to **Vb** is consistent with the preferred experimental formation of the rearranged adducts **132**. Aromatization through ring expansion generates the naphthylamides **132** and **133**.[145]

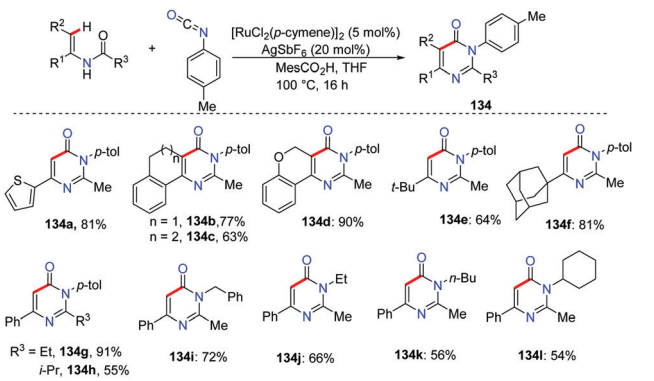


Scheme 114 Rhodium-catalyzed annulation of *o*-alkenyl anilides with alkynes (Mascareñas and Gulías, 2019).[145]

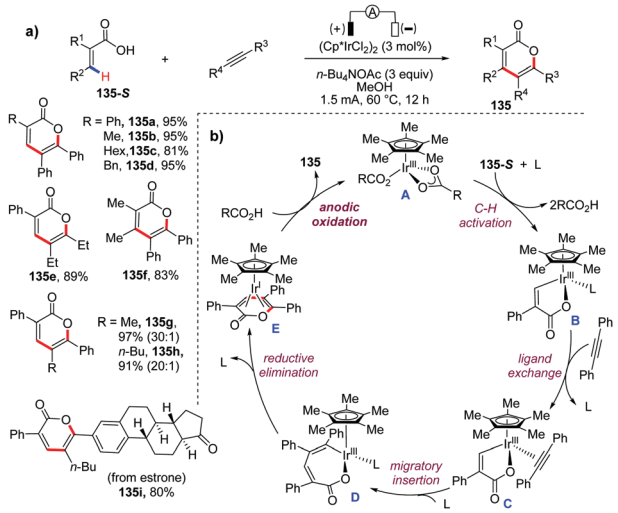
Recently, Loh and Hu reported a Ru-catalyzed synthesis of multi-substituted pyrimidin-4-ones **134** from enamides and isocyanates. The protocol is supposed to proceed by a tandem alkenyl C–H aminocarbonylation and hetero-cyclization with the liberation of water as the sole by-product. A broad range of enamides and isocyanates were well converted, and many valuable functional groups were nicely tolerated (Scheme 115).[146]

Electrochemical olefinic C–H functionalization is rare due to the easier electrochemical oxidation of the π-bond than olefinic C–H activation. However, in 2019, the Mei group developed an electrochemical olefinic C–H functionalization/annulation of acrylic acids and alkynes, leading to α-pyrones **135** in an undivided cell. This protocol employs an iridium catalyst, $[Cp^*IrCl_2]_2$, and anodic oxidation is found to be crucial for Ir(III) regeneration from the diene-Ir(I) species and the product liberation. A plausible catalytic cycle is depicted in Scheme 116b. An initial olefinic C–H activation occurs to provide five-membered iridacycle **B**, and the subsequent ligand exchange and migratory insertion of an alkyne lead to seven-membered iridium species **D**. The final reductive elimination affords Ir(I) complex **E**, which is converted to α-pyrone **135** and releases species **A** upon anodic oxidation.[147]

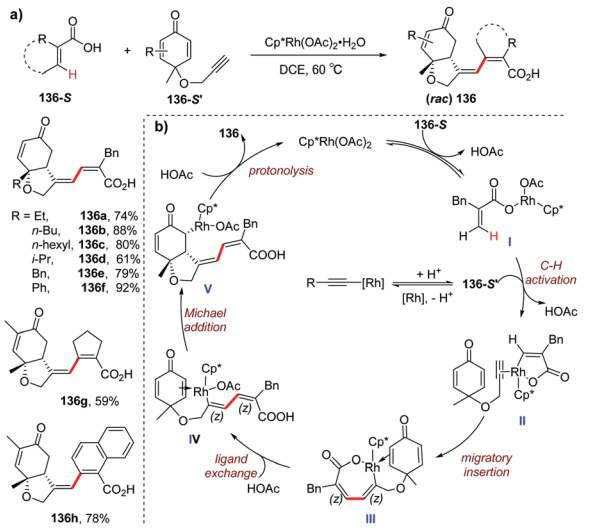
Carboxylate groups are widely occurring functional groups that are relatively convenient to install and to remove, but COOH-directed olefinic C–H functionalization remains underexplored. The Li group developed a cascade reaction of acrylic acids with yndienones to obtain *cis*-hydrobenzofuranones **136**



Scheme 115 Ru-Catalyzed annulation of enamides with isocyanates to afford pyrimidin-4-ones (Loh and Hu, 2019).[146]



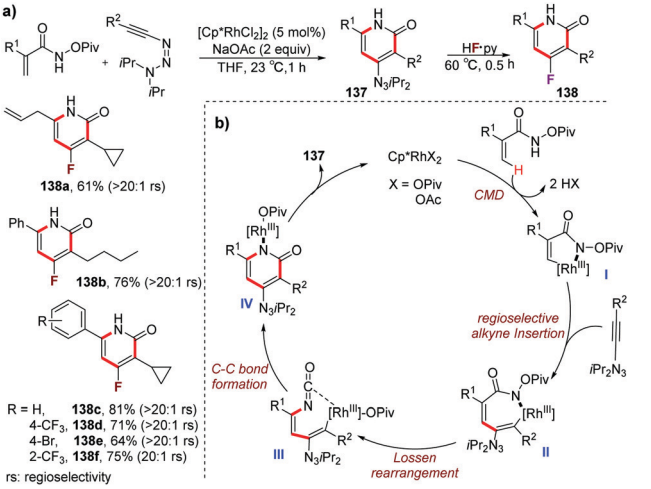
Scheme 116 Electrochemistry-enabled Ir-catalyzed vinylic C–H functionalization (Mei, 2019).[147]



Scheme 117 Rh(III)-Catalyzed cascade reaction between acrylic acids and yndienones toward *cis*-hydrobenzofuranones (Li, 2020).[148]

under rhodium catalysis (Scheme 117a). The mild and redox-neutral protocol exhibits excellent site- and stereoselectivity, using $Cp^*Rh(OAc)_2{\cdot}H_2O$ as the catalyst in the absence of any base. Deuterium labeling experiments indicate the reversibility of the olefinic C–H activation, and KIE experiments support the C(alkenyl)–H bond activation to be involved in the turnover-limiting step. The reaction is supposed to proceed *via* a sequence of carboxylic acid-directed olefinic C–H activation, alkyne insertion, and Michael addition (Scheme 117b).[148]

Fluorinated pyridones are an important class of scaffolds showing relevant biological activities, but the regioselective construction of fluorinated pyridones is a formidable challenge. Cramer and co-workers reported a regioselective synthesis of 4-fluoro-2-pyridones **138** using 1-alkynyl triazenes as fluoroalkyne surrogates (Scheme 118a). The protocol comprises an alkenyl C–H



Scheme 118 Synthesis of 4-fluoro-2-pyridones using 1-alkynyl triazenes (Cramer, 2020).[149]

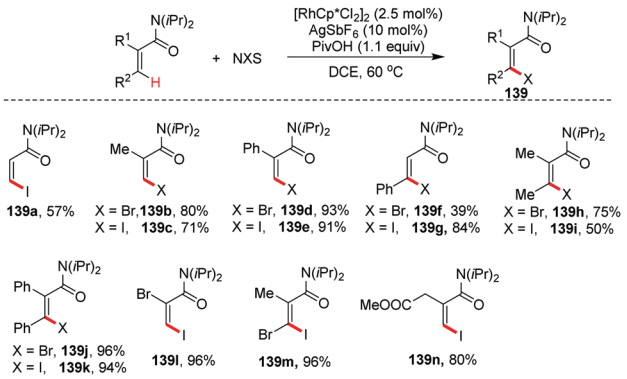
annulation with 1-alkynyl triazenes followed by a treatment with HF·pyridine, smoothly delivering a broad range of 4-fluoro-2-pyridones in a one-pot fashion. Notably, the triazenyl pyridones was also converted to fluorinated alkoxy pyridines and trifluoromethyl pyridones. Interestingly, benzoyl hydroxamate resulted in the formation of triazenyl-isoquinolone without the formation of an isocyanate by Lossen rearrangement. The authors proposed a plausible catalytic cycle for the formation of **137**. C–H activation occurs by the CMD-pathway with the Cp*Rh(III) catalyst, delivering rhodacyclopentene **I**. Migratory insertion of a triazenyl alkyne provides 7-membered rhodacycle **II**. The high regioselectivity of the carborhodation step can be attributed to the strong polarization of the alkyne, which favors metalation at the β-carbon atom. Reductive C–N bond formation is slower than a competing Lossen rearrangement forming presumed isocyanate **III**. Subsequent intramolecular addition of the vinyl rhodium across the C–N forms **IV**. The final protolysis affords rearranged product **137** (Scheme 118b).[149]

2.7 Vicinal group-directed olefinic C–H halogenation

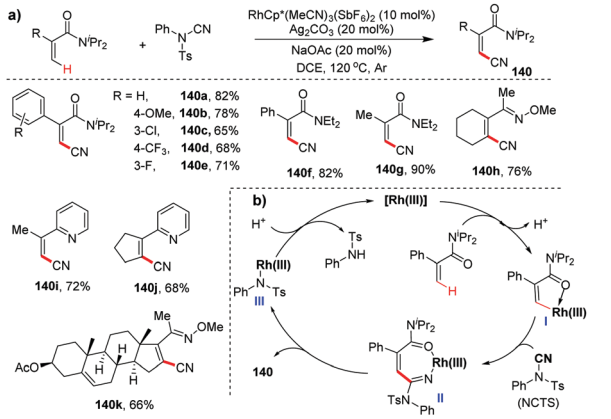
Z-Haloacrylic acid derivatives represent attractive building blocks for the selective construction of the ubiquitous *Z*-configured olefin motif. The Glorius group disclosed a site- and stereoselective iodination and bromination of acrylamides to produce a variety of *Z*-halo acrylamide derivatives **139**. The mild protocol allowed the tolerance of broad functional groups and moieties. Interestingly, the α- and β-brominated acrylamides smoothly reacted under standard reaction conditions, providing the corresponding dihalogenated products **139l** and **139m** in excellent yields (Scheme 119).[150]

2.8 Vicinal group-directed olefinic C–H cyanation

Alkenylnitriles are highly versatile and widely occurring in countless dyes, herbicides and natural products. Direct cyanation through C–H bond functionalization is an attractive strategy without pre-functionalization. In 2015, the Fu group reported a Rh(III)-catalyzed direct vinylic C–H cyanation



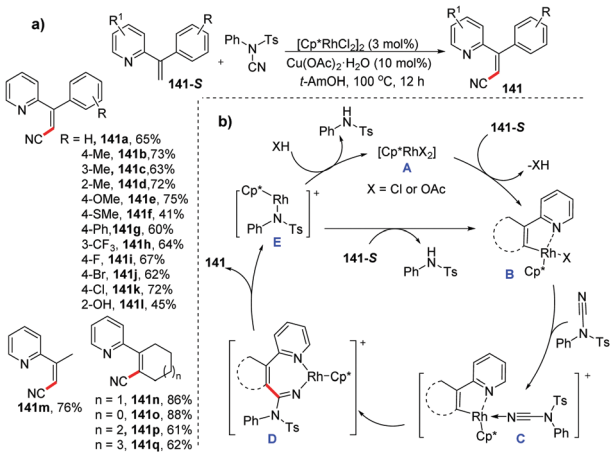
Scheme 119 Synthesis of *Z*-halo acrylamide derivatives by directed C–H iodination and bromination of acrylamides (Glorius, 2013).[150]



Scheme 120 Rh(iii)-Catalyzed vinylic C–H cyanation reaction for the synthesis of alkenyl nitriles (Fu, 2015).[151]

reaction for the synthesis of alkenyl nitriles **140**, using *N*-cyano-*N*-phenyl-*p*-methyl benzenesulfonamide (NCTS) as a cyanation reagent (Scheme 120a). Both acrylamides and ketoximes can be employed in this C–H cyanation process. When dehydropregnenolone derivatives were treated with the Rh-catalyzed C–H cyanation process, cyanated products **140k** were successfully obtained in 66% isolated yield. A possible mechanism was proposed based on previous reports. Firstly, the Rh(III) catalyst reacted with acrylamide through the alkenyl C–H activation step to generate a rhodacycle(III) intermediate, **I**. Secondly, intermediate **I** was coordinated with NCTS followed by insertion of the C–N triple bond into the C–Rh(iii) bond to produce **II**. Finally, elimination of a tosyl aniline-coordinated Rh(iii) complex from **II** took place to generate the target product **140** and the active Rh(iii) species which re-entered the catalytic cycle (Scheme 120b).[151]

In the same year, Anbarasan and co-workers also developed an alkenyl C–H cyanation using the same cyanating reagent NCTS under rhodium catalysis. The reaction was simply performed with $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ in *t*-AmOH at 100 °C, leading to a wide variety of substituted acrylonitriles **141** in good to excellent yields. The C–H cyanation was proposed to proceed by the formation of rhodacycle **B** by



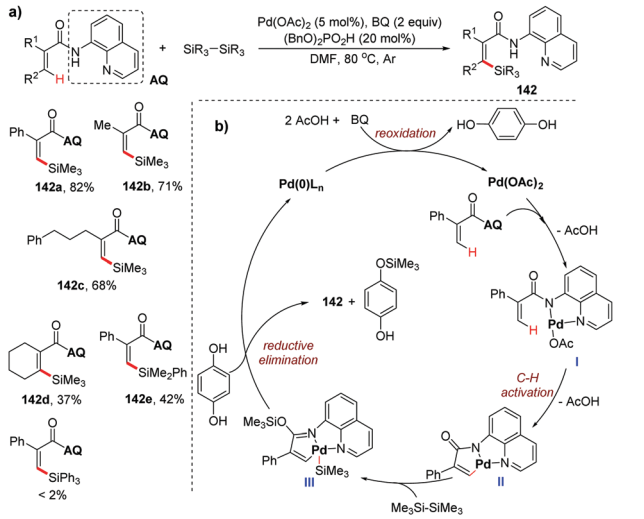
Scheme 121 Rh(III)-Catalyzed olefinic C–H cyanation toward alkenyl nitriles (Anbarasan, 2015).[152]

olefinic C–H bond activation, and the subsequent coordination and migratory insertion of NCTS afforded intermediate **D**, which was converted to product **141** and released rhodium species **A**. Active rhodium species **A** could be regenerated by ligand exchange in **E** with XH. Alternatively, the reaction of **E** with the alkene substrate to form rhodacycle **B** provided another possible pathway (Scheme 121).[152]

2.9 Vicinal group-directed olefinic C–H silylation

Vinylsilanes represent an important class of valuable building blocks widely utilized in organic synthesis, polymer chemistry, and medicinal chemistry. Numerous transformations have been developed for the preparation of vinylsilane compounds, such as hydrosilylation, silylmetalation, metathesis, silyl–Heck coupling, silylative coupling and dehydrogenative silylation. In particular, transition-metal-catalyzed olefinic C–H silylation is one of the most attractive synthetic approaches due to its high efficiency and atom economy.

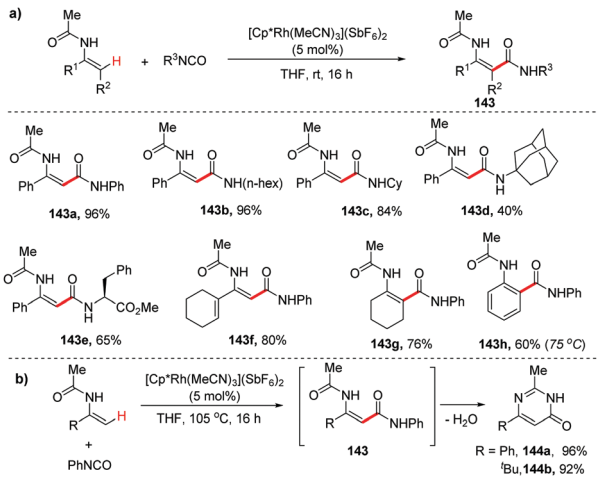
The Zhang group developed a palladium-catalyzed olefinic C–H silylation of acrylamides using a bidentate directing group. In this protocol, disilanes were used as the silicon sources to provide a regio- and stereoselective method for the preparation of *Z*-vinylsilanes **142** with broad functional group compatibility (Scheme 122a). A primary kinetic isotope effect (~1.0) was determined, indicating that the C–H palladation was not the rate-limiting step. The effects of other directing groups were carefully investigated, demonstrating that the *N*,*N*-bidentate directing group plays a critical role. A plausible reaction mechanistic pathway is shown in Scheme 122b. First, Pd(II) species **I** was afforded by the initial chelation of the acrylamide with Pd(II) catalyst followed by ligand exchange. The key palladacycle intermediate **II** was produced *via* a CMD process. Subsequently, intermediate **III** was formed by insertion of the Si–Si bond and simultaneous transfer of the trimethylsilyl group. Finally, a reductive elimination and a final protonation of the amide gave the desired silylation product **142** with the generation of a Pd(0) species, which will be reoxidized to Pd(II) with the assistance of 1,4-benzoquinone to continue the catalytic cycle.[153]



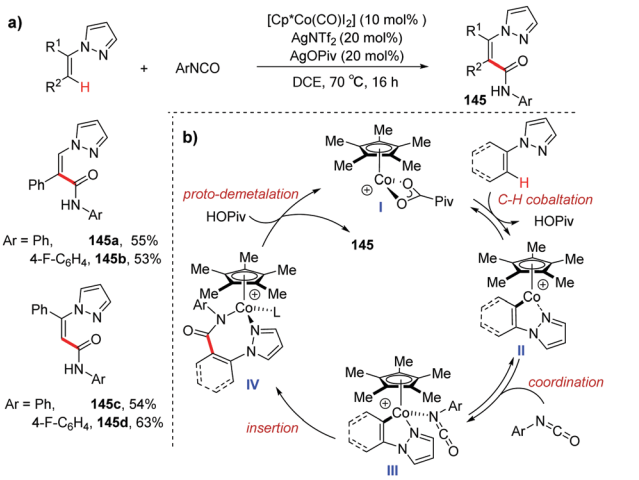
Scheme 122 Palladium-catalyzed olefinic C–H silylation of acrylamides (Zhang, 2017).[153]

2.10 Vicinal group-directed olefinic C–H aminocarbonylation

Bergman and Ellman reported a Rh(III)-catalyzed C–H amidation of enamides using isocyanates to provide direct and efficient preparation of enamine amides **143**, using $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst and THF as the solvent at room temperature (Scheme 123a). All phenyl isocyanates and primary and secondary alkyl isocyanate substrates reacted well with enamines to afford excellent yields. However, tertiary 1-adamantyl isocyanate led to a moderate yield (**143d**). Interestingly, an isocyanate generated from phenylalanine was also a good amidation reagent (**143e**). Some other suitable substrates include enamides generated from 1-acetyl-cyclohexene and cyclohexanone, as well as anilides to generate anthranilamides **143f–h**. Moreover, enamides bearing the phenyl or *tert*-butyl group reacted with phenylisocyanate at 105 °C, affording pyrimidin-4-ones **144a** and **144b** in excellent yields, using the same catalyst. This transformation proceeded by isocyanate coupling and then cyclodehydration (Scheme 123b).[154]



Scheme 123 Rh(III)-Catalyzed C–H amidation of enamides using isocyanates (Bergman and Ellman, 2011).[154]



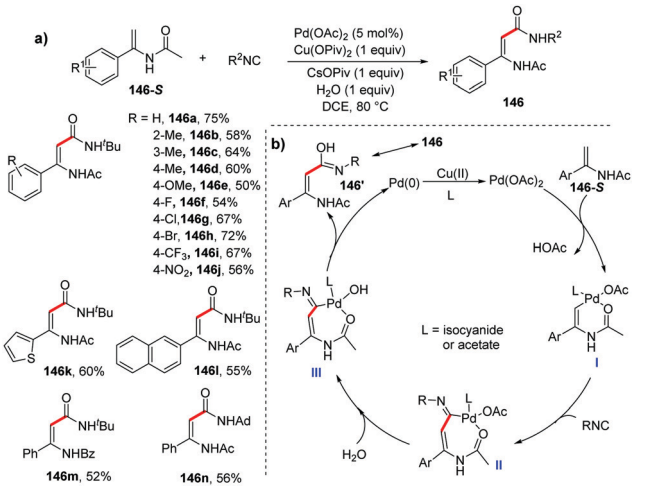
Scheme 124 Alkenyl C–H aminocarbonylations using isocyanates (Ackermann, 2015).[155]

Ackermann and co-workers reported expedient C–H aminocarbonylations of unactivated (hetero)arenes and alkenes using isocyanates for stereo-selective synthesis of multi-substituted benzamides and acrylamides **145** (Scheme 124a). Complex $[Cp^*CoI_2(CO)]$ was highly effective with the assistance of AgOPiv with $AgNTf_2$, showing high functional group tolerance. It is proposed that the catalytic cycle starts with a reversible carboxylate assisted C–H activation to afford **II**, which is followed by coordination of the isocyanate and a rate-determining insertion to generate intermediate **IV**. The final protodemetalation gives the desired acrylamides **145** and regenerates the catalytically active complex **I** (Scheme 124b).[155]

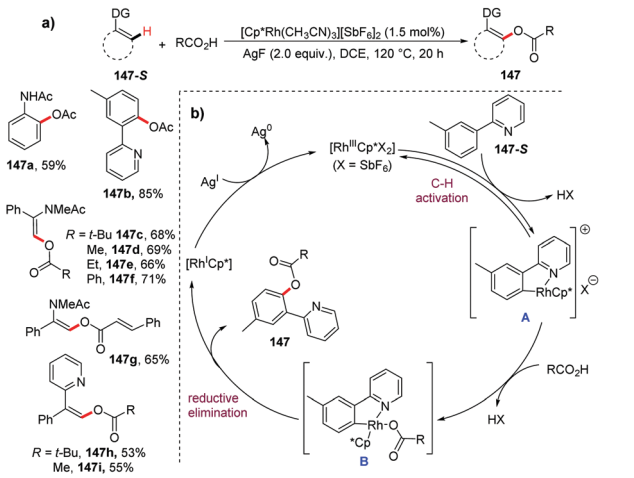
In 2017, Luo and Liang reported a palladium-catalyzed preparation of *N*-acyl enamine amides **146** which proceeded by amide-directed olefinic C–H activation followed by isocyanide insertion. This mild C–H carboxamidation tolerated a wide range of functionalities such as F, Cl, Br, CF_3 and even NO_2. The reaction starts with the amide directed vinylic C–H activation to afford 6-membered palladacycle **I**, which then undergoes isocyanide insertion to form **II**. Ligand exchange and reductive elimination give rise to **146a′** which converts to **146** *via* isomerization, and the generated Pd(0) is oxidized to active Pd(II) which enters the next catalytic cycle (Scheme 125).[156]

2.11 Vicinal group-directed olefinic C–H acyloxylation

Li and Xu developed Rh(III)-catalyzed $C(sp^2)$–H acyloxylation of alkenes and arenes bearing amides or *N*-heterocycles as directing groups. A broad range of alkyl, alkenyl and aryl carboxylic acids were converted smoothly to afford various acyloxylated products **147**. A plausible reaction mechanism proposed is shown in Scheme 126b. A 5-membered rhodacycle (**A**) was generated *via* a reversible chelation-assisted C–H carbometallation, and the subsequent reaction of **A** with carboxylic acid resulted in the generation of intermediate **B**. Subsequently, reductive elimination led to the acyloxylated product **147** with the liberation of a Rh(I) species, which was re-oxidized by AgF to regenerate the active Rh(III) species.[157]



Scheme 125 Pd-Catalyzed C–H amidation of enamides using isocyanides (Luo and Liang, 2017).[156]

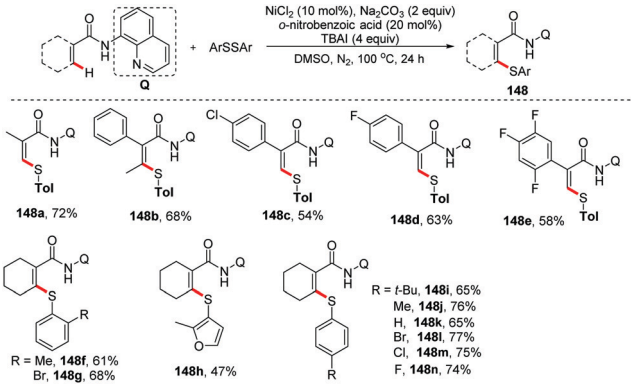


Scheme 126 Rh(III)-Catalyzed C(sp^2)–H acyloxylation of alkenes and arenes (Li and Xu, 2018).[157]

2.12 Vicinal group-directed olefinic C–H thiolation

Directed C–H thiolation represents one step- and atom-economic approach to prepare sulfur-containing compounds, which play key roles in organic synthesis. The Zhang group developed an alkenyl C–H thiolation using diaryl disulfides by nickel catalysis, with the assistance of an 8-aminoquinolyl auxiliary. The transformation displayed a wide range of functional tolerance and both mono- and disubstituted alkenes reacted well to afford various multi-substituted *Z*-alkenyl sulfides **148**. As addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) did not influence the reaction under the standard conditions, a possible radical involved Ni(I)/Ni(III) mechanism could be excluded. A tentative mechanism involves the formation of a five-membered nickelacycle by proton abstraction, oxidative addition of a disulfide to metal and the final reductive elimination to form the C–S bond (Scheme 127).[158]

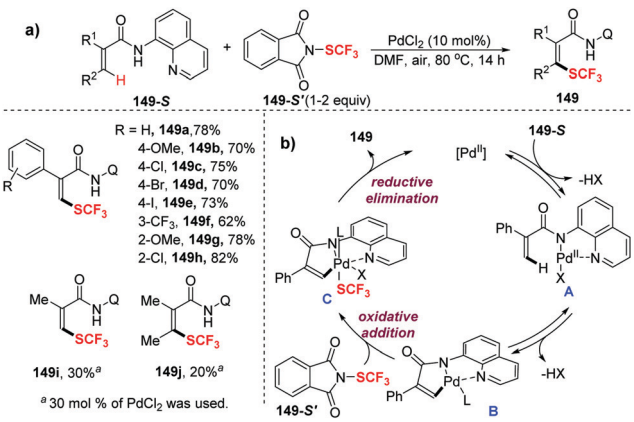
Molecules bearing the SCF_3 group exhibited specific biological activities due to its unique Hansch hydrophobic



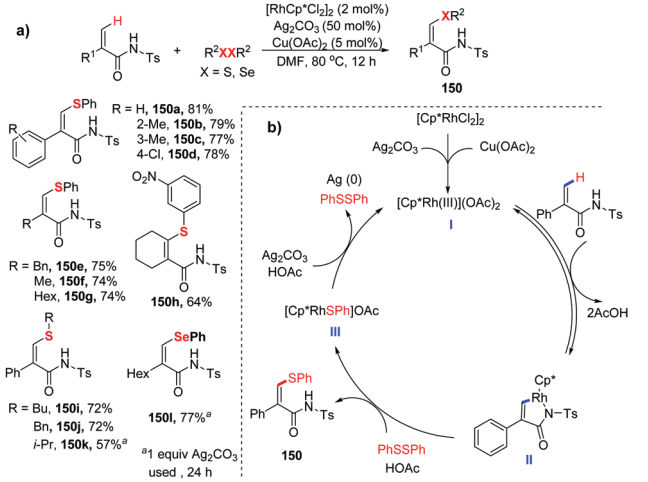
Scheme 127 Alkenyl C–H thiolation of alkenes by nickel catalysis (Zhang, 2015).[158]

parameter as well as high electron-withdrawing character. Bouillon and Besset reported an olefinic C–H trifluoromethylthiolation of acrylamides with Munavalli reagent **149-*S*′** under palladium catalysis. This operationally simple protocol was performed with 10 mol% $PdCl_2$ in DMF at 80 °C in air, leading to *Z*-configured trifluoromethylthiolated alkenes **149**, using 8-aminoquinoline as a directing group. A broad range of mono- and disubstituted acrylamides were smoothly converted, also exhibiting good tolerance of sensitive functionalities such as Cl, Br, I and CF_3. Deuterium labelled experiments showed the C–H activation step to be reversible and the rate-determining step. The reaction is proposed to start with the bidentate-chelation of the directing group to the metal to form intermediate **A**, and the subsequent olefinic C–H activation occurs to afford palladacycle **B**. Subsequently, the electrophilic SCF_3-source reacts with **B** to generate a putative Pd(IV) species (**C**) by oxidative addition, and the final reductive elimination produces **149** and regenerates the active Pd(II) species (Scheme 128).[159]

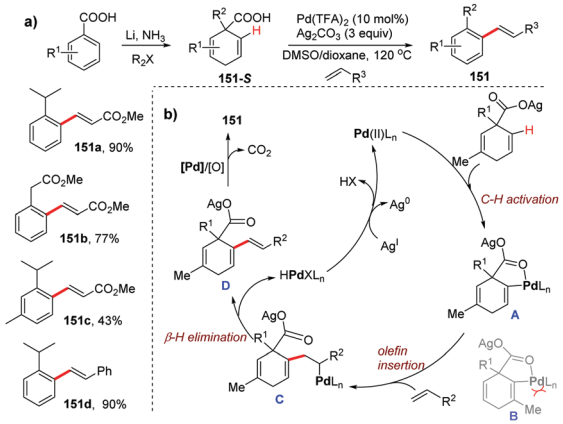
In 2018, Ji and Wang reported a Rh-catalyzed alkenyl C–H thiolation of *N*-tosyl acrylamides using disulfides, leading to (*Z*)-alkenyl sulfides. Also, (*Z*)-β-alkenyl selenides were also successfully obtained with diphenyl diselenide under identical



Scheme 128 Pd-Catalyzed alkenyl C–H trifluoromethylthiolation of acrylamides (Bouillon and Besset, 2017).[159]



Scheme 129 Rh-Catalyzed alkenyl C–H thiolation of *N*-tosyl acrylamides (Ji and Wang, 2018).[160]



Scheme 130 Synthesis of *ortho*-alkyl substituted styrene derivatives using benzoic acids (Chou, 2018).[165]

conditions. Notably, utilization of only 0.01 mol% Rh(III) catalyst still led to 71% product yield, exhibiting a high turnover number (TON) of 7100. A plausible reaction mechanism was proposed to be initiated by the reaction between $[Cp^*RhCl_2]_2$, Ag_2CO_3 and $Cu(OAc)_2$ to afford active Rh(III) species **I**, which reacted with the acrylamide to give the five-membered rhodacycle **II** by olefinic C–H activation. Subsequent nucleophilic substitution of **II** with disulfide afforded product **150** and intermediate **III**, and the latter one was converted to active species **I** by oxidation with Ag_2CO_3 (Scheme 129).[160]

3. Geminal-group-directed olefinic C–H functionalization

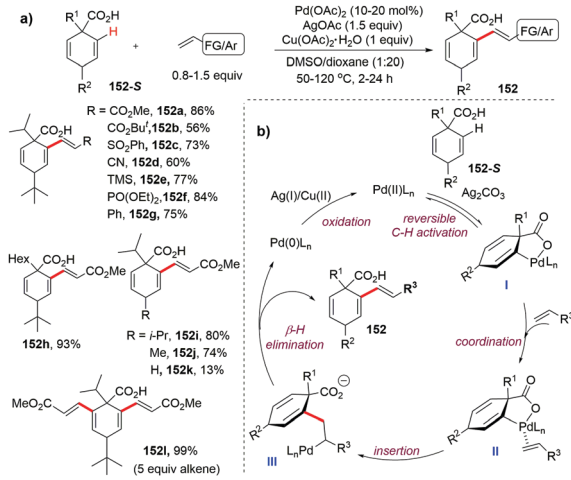
According to previous reports, examples of the formation of *exo*-metallocycle intermediates are rare, presumably due to their disfavored formation under transition-metal-catalysis.[161–164] The Dong group demonstrated aliphatic C–H functionalizations using an *exo*-directing-group, leading to β-acetoxylation, tosyloxylation, and γ/δ-arylation.[161,162] The Yu group developed a Pd-catalyzed α-olefinic C–H activation of simple α,β-unsaturated olefins to produce 4-imino-β-lactams by the formation of a proposed *exo*-palladacycle intermediate, generated by 1,1-insertion of *t*-BuNC into the Pd–N bond, acyl migration and the subsequent C–H activation.[163] Herein, we will introduce recent progress in geminal-group-directed olefinic C–H functionalization by the formation of *exo*-metallocycle intermediates, including alkenylation, allylation, iodination and alkynylation reactions.[165–172] In particular, distal C(alkenyl)–H functionalization under Pd/NBE cooperative catalysis initiated by geminal-group-directed olefinic C–H functionalization is also covered.[174]

3.1 Geminal-group-directed olefinic C–H alkenylation

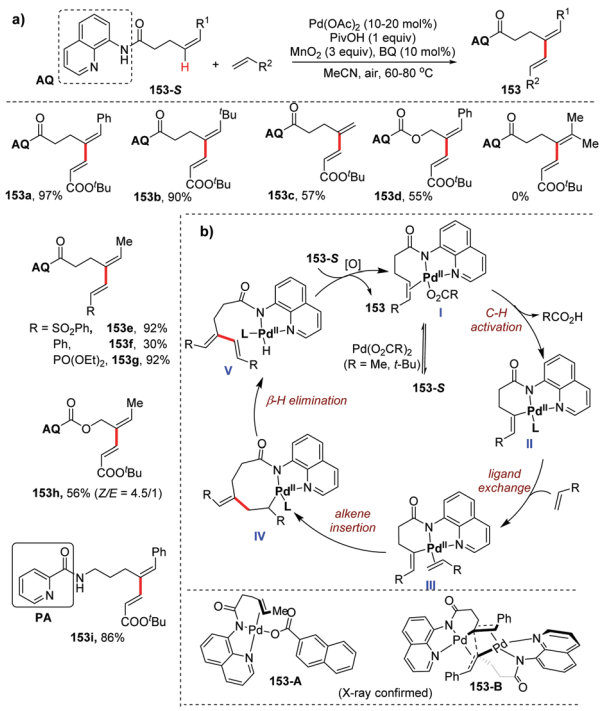
In 2018, the Chou group disclosed a straightforward method for the synthesis of *ortho*-alkyl substituted styrene derivatives **151** using benzoic acids as the starting materials. This two-step synthetic transformation involves the dearomatization of benzoic acids by Birch reduction to provide alkylated cyclohexa-2,5-dienyl-1-carboxylic acids **151-*S*** and subsequent tandem decarboxylative C–H olefination/rearomatization to deliver *ortho*-alkyl substituted styrenes **151** (Scheme 130a). It has been demonstrated that the Pd/Ag bimetallic system is critical for decarboxylative C–H olefination under optimal conditions. A plausible mechanism is proposed in Scheme 130b. Carboxylate-directed olefinic C–H activation of the Ag–carboxylate substrate generated a five-membered and less sterically hindered cyclopalladated intermediate, **A**. Olefin migratory insertion followed by β-H elimination and reductive elimination occurred to deliver the olefinated Ag-carboxylate adduct **D**, which finally underwent decarboxylation and rearomatization to produce *ortho*-alkylated styrenes **151**.[165]

Very recently, the Chou group developed a Pd-catalyzed proaromatic alkenyl C–H alkenylation using carboxylic acid as a directing group. This transformation employs 1,4-cyclohexadienes and various alkenes as the substrates to construct densely functionalized 1,3-dienes **152**. This reaction also proceeds by a reversible olefinic C–H bond activation to generate a proaromatic *exo*-palladacycle, **I**, which undergoes alkene insertion and β-H elimination to afford olefinated product **152** (Scheme 131).[166]

In 2018, Engle and co-workers reported a *N*,*N*-bidentate chelation-assisted alkenyl C–H alkenylation of nonconjugated alkenes by palladium(ii) catalysis, leading to highly substituted 1,3-dienes **153** (Scheme 132a). The transformation exhibits a broad scope across three synthetically useful substrate classes including 4-pentenoic acids, allylic alcohols, and bishomoallylic amines bearing suitable bidentate auxiliaries such as Daugulis's 8-aminoquinolinamide and picolinamide. The catalytic reaction is enabled by either MnO_2 as the stoichiometric oxidant or co-catalytic $Co(OAc)_2$ and O_2 (1 atm). The transformation allows gram-scale preparation and a broad substrate scope, and the amide auxiliary can be removed under nickel-catalyzed methanolysis conditions with slight erosion of *Z*/*E* stereochemistry. Notably, treatment of alkenes and carboxylic



Scheme 131 Pd-Catalyzed proaromatic C(alkenyl)–H olefination to synthesise densely functionalized 1,3-dienes (Chou, 2020).[166]



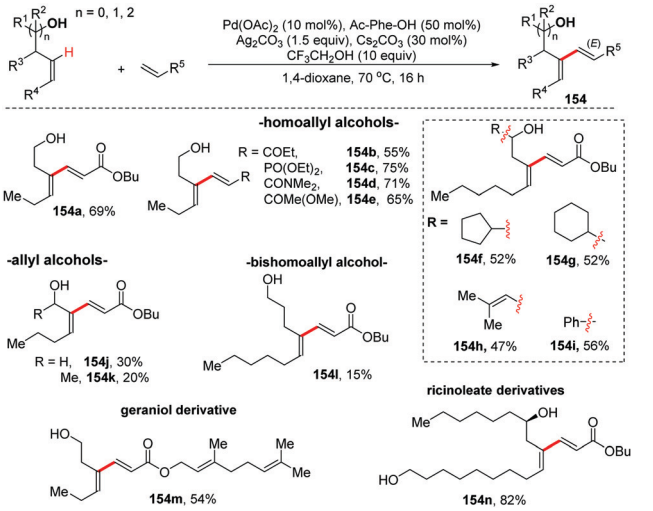
Scheme 132 Geminal C–H alkenylation of alkenyl amides using alkenes (Engle, 2018).[167]

acid additives with stoichiometric quantities of $Pd(OAc)_2$ leads to π-alkene complex **153-A** and alkenylpalladium(II) dimer **153-B** bearing a six-membered *exo*-palladacycle, and both of them were found to be catalytically competent in the reaction. A plausible catalytic cycle is initiated by *N'N*-bidentate chelation-assisted alkenyl C–H activation to afford six-membered *exo*-palladacycle **II** from a π-alkene palladium complex, **I**. Coordination and migratory insertion of the electron-deficient alkene deliver eight-membered *exo*-palladacycle **IV**. The subsequent β-H elimination and ligand exchange provide product **153** (Scheme 132b).

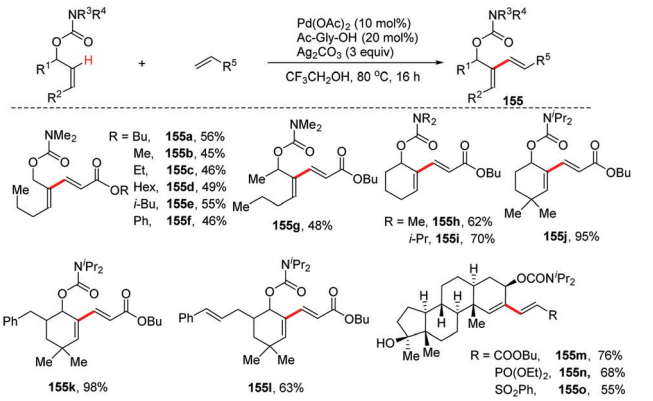
Unfortunately, the formation of only a six-membered *exo*-palladacycle leads to the activation of specific olefinic C–H bonds, representing a major limitation of this protocol. Furthermore, practical application of the protocol could be remarkably impeded due to the tedious installation of a directing group as well as its removal procedure.[167]

Our group reported on hydroxyl-, carbamate- or amide-directed C(alkenyl)–H functionalization by the formation of small- to medium-sized *exo*-palladacycles, leading to C–H alkenylation of a variety of allyl-, homoallyl- and bishomoallyl-alcohols and carbamates, as well as amides (Schemes 133–135).[168]

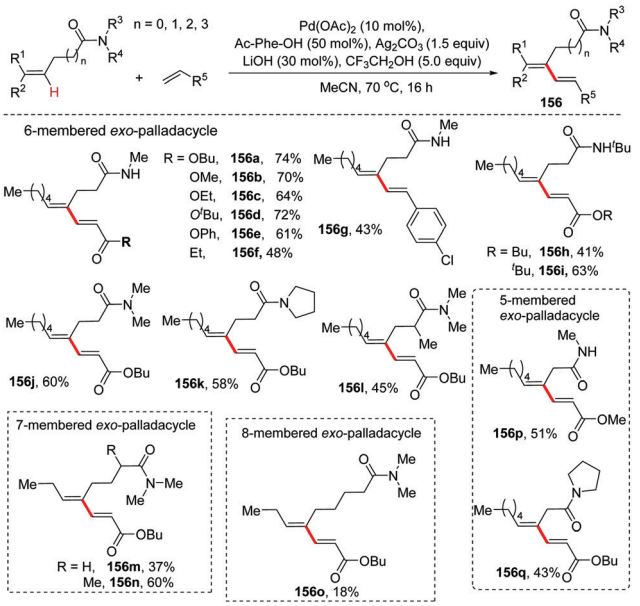
As shown in Scheme 133, a wide range of primary and secondary homoallyl alcohols smoothly reacted with electron-deficient alkenes to afford branched 1,3-dienes **154**. Notably, simple allyl alcohols, widely used as allylation reagents, also led to C–H alkenylation in moderate yields, which proceeded *via* a four-membered metallocycle which is very rare in catalytic C–H activation reactions (**154j** and **154k**). Moreover, *cis*-4-decen-1-ol was proved to be reactive by a six-membered



Scheme 133 Geminal C–H alkenylation of alkenyl alcohols (Zhang and Zhong, 2019).[168]



Scheme 134 Geminal C–H alkenylation of alkenyl carbamates (Zhang and Zhong, 2019).[168]



Scheme 135 Geminal C–H alkenylation of alkenyl amides (Zhang and Zhong, 2019).[168]

metallocycle, albeit with reduced efficiency (**154l**). The synthetic flexibility afforded by homoallyl-, allyl- and bishomoallyl alcohols greatly expands the range of substrates of our protocol. Gratifyingly, these protocols were successful in C–H modifications of sensitive geraniol and ricinoleate derivatives (**154m** and **154n**).

Although allyl alcohols showed moderate reactivity, allyl alcohol derived allyl carbamate could be well C–H functionalized with the help of the Ac-Gly-OH ligand instead. Installation of a bulky isopropyl group was found to promote the reaction significantly. 3-Hydroxyl cyclohexene is a widely occurring skeleton in bioactive molecules, and carbamate masked 3-hydroxyl cyclohexene provided good yields (**155h** and **155i**). Notably, cyclohexenes bearing quaternary carbon and sensitive benzyl and even cinnamyl moieties led to 95% yield (**155j–155l**). Methyl-1-testosterone is an anabolic steroid derivative to treat male testosterone deficiency. Herein, three different C–H alkenylation analogs from steroid-derived carbamates were readily accessed (**155m–o**, 55–76% yields) (Scheme 134).

The substrate scope of alkyl amide directed geminal C(alkenyl)–H functionalization showed that unsaturated carbonyl coupling partners and differently *N*-substituted secondary/tertiary amides led to good to moderate yields. Notably, this protocol allowed the alkenylation of the C(alkenyl)–H bond by five-, six-, seven- and eight-membered *exo*-cyclopalladation (**156a–q**). Previously, C–H activation by the formation of seven- and eight-membered metallocycles is challenging due to the increased entropic barrier by free rotation (Scheme 135).

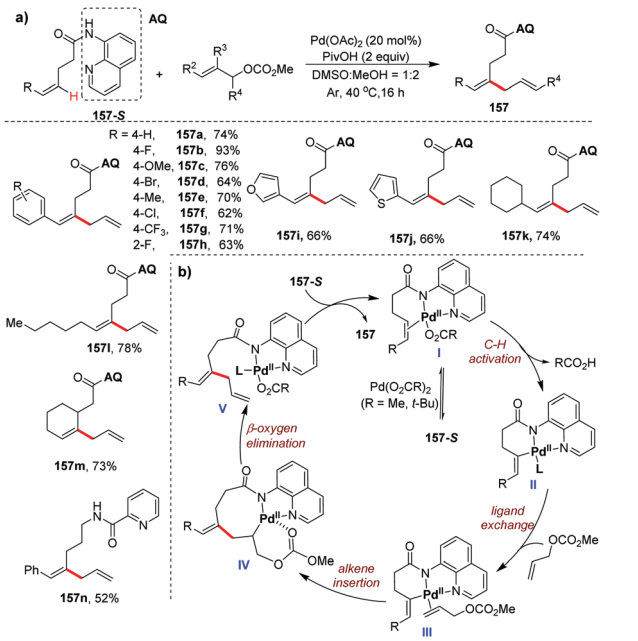
Furthermore, competition experiments were performed for alkenyl alcohols or alkenyl amides under optimal conditions to rank the relative reactivities, showing the formation of either *exo*- or *endo*-palladacycles in the C–H cleavage to be controlled by both conformation and chelation properties. Mechanistic experiments suggested that the irreversible C–H activation step originated the regio-selectivity of the reaction.

3.2 Geminal-group-directed olefinic C–H allylation

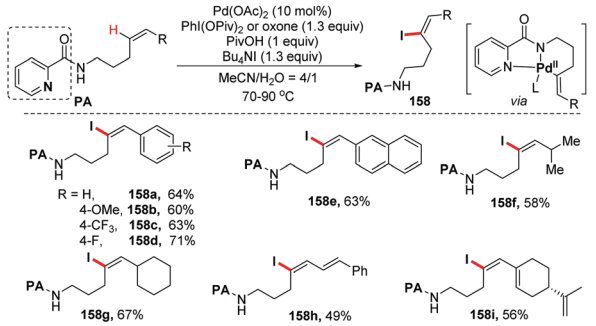
Recently, our group developed a cross-coupling reaction between (*Z*)-alkenyl amides and allyl carbonates which proceeded by C–H allylation *via exo*-cyclopalladation, with the assistance of 8-aminoquinoline (AQ) amide as a directing group (Scheme 136a). This operationally simple protocol was performed under mild conditions, using $Pd(OAc)_2$ as the catalyst and PivOH as the additive. Daugulis's picolinamide (PA) directing group also assisted C(alkenyl)–H allylation of a bishomoallylic amine substrate (**157n**, 52% yield). However, the *E*-substituted alkene showed no reactivity, only leading to *Z*/*E*-isomerization of the substrate. Mechanistic experiments exhibited a reversible and rate-determining C(alkenyl)–H bond cleavage, which is much slower than the subsequent allylation step. Interestingly, if an inseparable *Z*/*E*-isomeric alkene was used under optimal conditions, only the *Z*-isomer was converted smoothly, with nearly the total recovery of the *E*-isomer. A plausible catalytic cycle for this reaction is shown in Scheme 136. Following substrate and metal coordination to give a π-alkene palladium complex, **I**, a reversible γ-C(alkenyl)–H activation took place to generate the six-membered palladacycle **II**. Coordination of the allyl carbonate, followed by alkene insertion and β-oxygen elimination, produced 1,4-diene **157** (Scheme 136b).[169]

3.3 Geminal-group-directed olefinic C–H iodination

In 2019, the Carreira group reported a palladium-catalyzed geminal olefinic C–H iodination of (*Z*)-alkenes, using picolinamide as the directing group. By using a quantitative amount of



Scheme 136 Alkenyl C–H allylation by *exo*-palladacycles (Zhang and Zhong, 2019).[169]

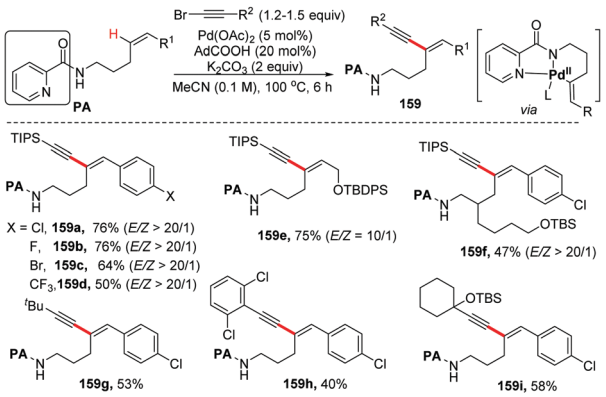


Scheme 137 Palladium-catalyzed olefinic C–H iodination of (*Z*)-alkenes (Carreira, 2019).[170]

di(pivaloyloxy)-iodobenzene and TBAI as C–H iodination reagent, $Pd(OAc)_2$ as catalyst and PivOH as an additive in aqueous acetonitrile, this protocol enables selective C–H iodination of a wide range of olefins to produce alkenyl iodides (**158a–i**). The synthetic versatility of the alkenyl iodides was demonstrated by easy removal of the picolinamide auxiliary and intramolecular Ullmann amidation, as well as palladium catalyzed alkylation and alkynylation. A deuterium-labelled experiment with β-substituted styrenes led to selective deuterium incorporation at the β-carbon, exhibiting a reversible formation of *exo*-palladacycles. Measurement of the initial rate constant by parallel reactions shows that C–H cleavage is the turnover-limiting step and the magnitude of the KIE suggests a CMD mechanism induced C–H bond activation (Scheme 137).[170]

3.4 Geminal-group-directed olefinic C–H alkynylation

After their advance in olefinic C–H iodination, the Carreira group extended the *N*,*N*-bidentate-chelation-assisted geminal C–H activation toward the C–H alkynylation of electronically unbiased olefins using bromoalkynes, under palladium catalysis. The protocol also employed picolinamide as the directing group to enable the formation of 5-/6-*exo*-metallacycles to provide conjugated 1,3-enynes **159** in a stereospecific fashion. Notably, facile removal of the picolinamide auxiliary and the TIPS acetylene is successful, thus greatly extending its synthetic utility (Scheme 138).[171]



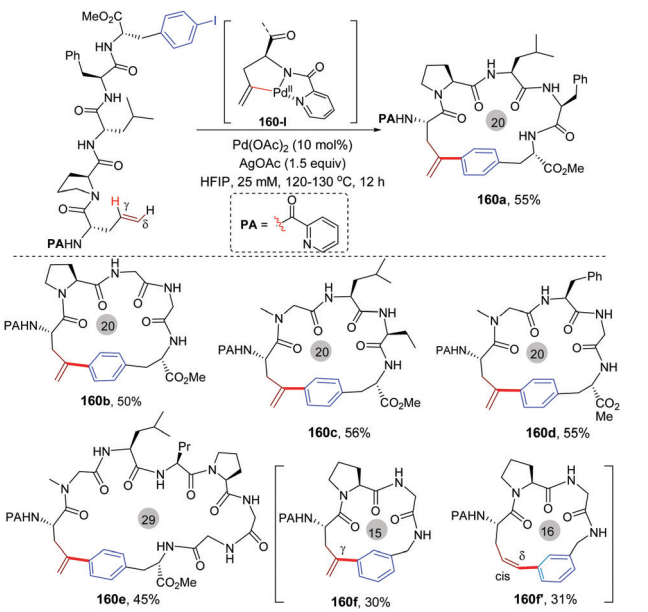
Scheme 138 Palladium-catalyzed olefinic C–H alkynylation of (*Z*)-alkenes (Carreira, 2020).[171]

3.5 Geminal-group-directed olefinic C–H arylation

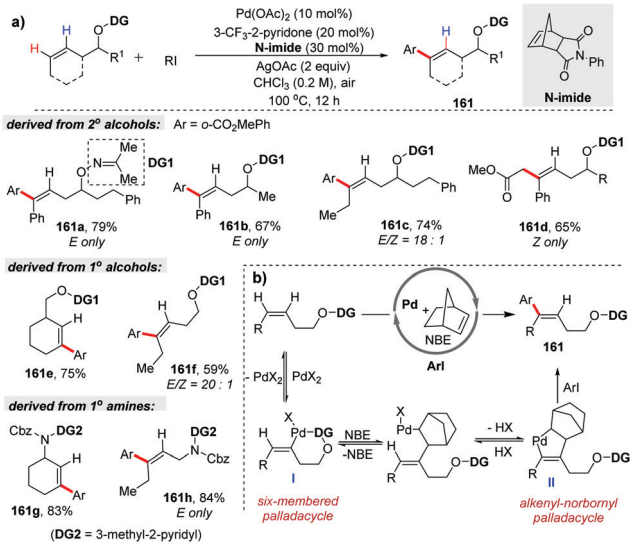
Peptide macrocycles are widely utilized in drug discovery and occurring in many natural products. The Chen group reported a Pd-catalyzed intramolecular C(alkenyl)–H arylation reaction to construct aryl−alkene-braced peptide macrocycles from easily accessible linear *N*-terminal allylglycines, using picolinamide as a directing group. The reaction was simply performed with catalyst $Pd(OAc)_2$ and additive AgOAc in HFIP solvent, providing γ-arylated peptide macrocycles **160** in moderate to good yields (Scheme 139). The reaction was proposed to proceed by the formation of five-membered *exo*-palladacycle intermediate **160-I**. Peptide macrocycles **160a–e** were obtained in 45–56% yields followed by the generation of their δ-regioisomers in less than 10% yield; however, a smaller-sized macrocyclization increased δ-arylation significantly and afforded a 1 : 1 mixture of γ- and δ-regioisomers (**160f** and **160f′**) (Scheme 139).[172]

3.6 Geminal-group-directed olefinic C–H alkenylation under Pd/NBE cooperative catalysis

Recently, palladium/norbornene (Pd/NBE) catalysis, originally discovered by Catellani, has emerged as a powerful tool for arene functionalization.[173] An intriguing question is whether such a distal C–H functionalization strategy could be extended to alkenes; however, there exist several challenges such as the easier decomposition and higher reactivity of alkenes, as well as the easy cyclopropanation *via* alkene insertion. Recently, the Dong group developed a distal-selective alkenyl C–H arylation through a directed Pd/NBE cooperative catalysis, which was performed with catalytic conditions comprising $Pd(OAc)_2$, imide-based NBE, 3-CF_3-2-pyridone, and AgOAc in $CHCl_3$ at 100 °C, using oxime-ether as the "*exo*"-type directing group (Scheme 140a). Protected allylic and homoallylic amines



Scheme 139 Synthesis of peptide macrocycles by intramolecular olefinic C–H arylation (Chen, 2020).[172]



Scheme 140 Alkenyl C–H functionalization under Pd/NBE cooperative catalysis (Dong, 2020).[174]

worked well with a different DG2. The reaction was initiated by a geminal-group directed C(alkenyl)–H palladation to form **I**, which underwent NBE insertion and a distal C(vinylic)–H activation to generate palladacycle **II**. The subsequent reaction of intermediate **II** with electrophiles, followed by NBE extrusion and then protonation, led to distal C(vinylic)–H functionalization products **161** (Scheme 140b). Deuterium labeling experiments indicated the reversible formation of C–H cyclopalladation intermediates **I** and **II** as the alkene substrate was recovered with 20% and 22% deuterium incorporation at both the distal and proximal vinyl positions with CD_3CO_2D, showing the reversible formations of **I** and **II**. A four-membered-ring side product was isolated in 10% yield, which also implied the formation of alkenyl–norbornyl palladacycle **II**. An (*E*)-alkene substrate gave no arylation product, and *Z*/*E* isomerization was not observed under optimal conditions, which excluded an alkene isomerization-then-Heck or a Heck-then-alkene isomerization mechanism.[174]

4. Conclusions

The chelation-assisted alkenyl C–H functionalization by cyclometallation has been rapidly growing over the past few decades. This review highlights the well-defined vicinal-group-directed C(alkenyl)–H functionalization by *endo*-cyclometallation, as well as the very recent successes in geminal C(alkenyl)–H activation by an *exo*-cyclometallation process. These methods represent versatile and powerful synthetic tools that complement traditional metal-catalyzed vinylic C–H functionalization by addition/elimination mechanisms. Despite the remarkable progress, there is still a high demand for indepth investigations in this exciting and developing area, and these will no doubt be applied in the late stage functionalisation of biologically relevant molecules, in drug development, and in the creation of novel building blocks.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (No. 21672048), the Natural Science Foundation of Zhejiang Province (ZJNSF) (No. LY19B020006), and Hangzhou Normal University for the financial support.

Notes and references

1 J. Wang, *Stereoselective alkene synthesis*, Springer Verlag, Heidelberg, New York, 2012.
2 M. S. Sigman and E. W. Werner, *Acc. Chem. Res.*, 2012, **45**, 874–884.
3 A. Deb and D. Maiti, *Eur. J. Org. Chem.*, 2017, 1239–1252.
4 X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.*, 2013, **42**, 3253–3260.
5 S. Tang, K. Liu, C. Liu and A. Lei, *Chem. Soc. Rev.*, 2015, **44**, 1070–1082.
6 K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802.
7 C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743.
8 D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655.
9 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.
10 P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918.
11 J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786.
12 G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450–2494.
13 F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906–6919.
14 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295.
15 M. R. Yadav, R. K. Rit, M. Shankar and A. K. Sahoo, *Asian J. Org. Chem.*, 2015, **4**, 846–864.
16 O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064.
17 J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145–7153.
18 F. F. Khan, S. K. Sinha, G. K. Lahiri and D. Maiti, *Chem. – Asian J.*, 2018, **13**, 2243–2256.
19 M. T. Mihai, G. R. Genov and R. J. Phipps, *Chem. Soc. Rev.*, 2018, **47**, 149–171.
20 S. Rej and N. Chatani, *Angew. Chem., Int. Ed.*, 2019, **58**, 8304–8329.
21 H.-G. Cheng, S. Chen, R. Chen and Q. Zhou, *Angew. Chem., Int. Ed.*, 2019, **58**, 5832–5844.

22 P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192–2452.
23 A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 10820–10843.
24 S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887.
25 D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518–522.
26 J. Xu, J. Chen, F. Gao, S. Xie, X. Xu, Z. Jin and J.-Q. Yu, *J. Am. Chem. Soc.*, 2019, **141**(5), 1903–1907.
27 S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc.*, 2015, **137**, 11888–11891.
28 J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2016, **55**, 217–257.
29 J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145–7153.
30 M. T. Mihai, G. R. Genov and R. J. Phipps, *Chem. Soc. Rev.*, 2018, **47**, 149–171.
31 F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906–6919.
32 K. Wang, F. Hu, Y. Zhang and J. Wang, *Sci. China: Chem.*, 2015, **58**, 1252–1265.
33 T. Besset, N. Kuhl, F. W. Patureau and F. Glorius, *Chem. – Eur. J.*, 2011, **17**, 7167–7171.
34 J. Zhang and T.-P. Loh, *Chem. Commun.*, 2012, **48**, 11232–11234.
35 S. Hu, D. Wang, J. Liu and X. Li, *Org. Biomol. Chem.*, 2013, **11**, 2761–2765.
36 M. Boultadakis-Arapinis, M. N. Hopkinson and F. Glorius, *Org. Lett.*, 2014, **16**, 1630–1633.
37 R. Feng, W. Yu, K. Wang, Z. Liu and Y. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 1501–1508.
38 X.-H. Hu, J. Zhang, X.-F. Yang, Y.-H. Xu and T.-P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 3169–3172.
39 X.-H. Hu, X.-F. Yang and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2015, **54**, 15535–15539.
40 F. Li, C. Yu, J. Zhang and G. Zhong, *Org. Lett.*, 2016, **18**, 4582–4585.
41 F. Li, C. Yu, J. Zhang and G. Zhong, *Org. Biomol. Chem.*, 2017, **15**, 1236–1244.
42 C. Yu, F. Li, J. Zhang and G. Zhong, *Chem. Commun.*, 2017, **53**, 533–536.
43 Q.-J. Liang, C. Yang, F.-F. Meng, B. Jiang, Y.-H. Xu and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2017, **56**, 5091–5095.
44 T. Li, J. Zhang, C. Yu, X. Lu, L. Xu and G. Zhong, *Chem. Commun.*, 2017, **53**, 12926–12929.
45 Q. Zhao, V. Tognetti, L. Joubert, T. Besset, X. Pannecoucke, J.-P. Bouillon and T. Poisson, *Org. Lett.*, 2017, **19**, 2106–2109.
46 B. Jiang, M. Zhao, S.-S. Li, Y.-H. Xu and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2018, **57**, 555–559.
47 K. Meng, Y. Sun, J. Zhang, K. Zhang, X. Ji, L. Ding and G. Zhong, *Org. Lett.*, 2019, **21**, 8219–8224.
48 T. Li, C. Shen, Y. Sun, J. Zhang, P. Xiang, X. Lu and G. Zhong, *Org. Lett.*, 2019, **21**, 7772–7777.
49 R. Yoshimura, Y. Shibata and K. Tanaka, *J. Org. Chem.*, 2019, **84**, 13164–13171.
50 Y. Shibata, Y. Otake, M. Hirano and K. Tanaka, *Org. Lett.*, 2009, **11**, 689–692.
51 R. Azpíroz, L. Rubio-Pérez, A. Di Giuseppe, V. Passarelli, F. J. Lahoz, R. Castarlenas, J. J. Pérez-Torrente and L. A. Oro, *ACS Catal.*, 2014, **4**, 4244–4253.
52 H. N. Lim, D. Xing and G. Dong, *Synlett*, 2019, 674–685.
53 Z. Wang, B. J. Reinus and G. Dong, *Chem. Commun.*, 2014, **50**, 5230–5232.
54 F. Mo, H. N. Lim and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 15518–15527.
55 K. Meng, J. Zhang, F. Li, Z. Lin, K. Zhang and G. Zhong, *Org. Lett.*, 2017, **19**, 2498–2501.
56 J.-P. Krieger, D. Lesuisse, G. Ricci, M.-A. Perrin, C. Meyer and J. Cossy, *Org. Lett.*, 2017, **19**, 2706–2709.
57 Y. Sun, K. Meng, J. Zhang, M. Jin, N. Huang and G. Zhong, *Org. Lett.*, 2019, **21**, 4868–4872.
58 H. Wang, B. Beiring, D.-G. Yu, K. D. Collins and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12430–12434.
59 T.-J. Gong, W. Su, Z.-J. Liu, W.-M. Cheng, B. Xiao and Y. Fu, *Org. Lett.*, 2014, **16**, 330–333.
60 L. Ilies, S. Asako and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 7672–7675.
61 J. Wencel-Delord, C. Nimphius, F. W. Patureau and F. Glorius, *Chem. – Asian J.*, 2012, **7**, 1208–1212.
62 Z.-Q. Lei, J.-H. Ye, J. Sun and Z.-J. Shi, *Org. Chem. Front.*, 2014, **1**, 634–638.
63 R. Parella and S. A. Babu, *J. Org. Chem.*, 2015, **80**, 12379–12396.
64 L. Hu, Q. Gui, X. Chen, Z. Tan and G. Zhu, *Org. Biomol. Chem.*, 2016, **14**, 11070–11075.
65 X. Cheng, Z. Chen, Y. Gao, F. Xue and C. Jiang, *Org. Biomol. Chem.*, 2016, **14**, 3298–3306.
66 D. Zell, S. Warratz, D. Gelman, S. J. Garden and L. Ackermann, *Chem. – Eur. J.*, 2016, **22**, 1248–1252.
67 R. Parella and S. A. Babu, *J. Org. Chem.*, 2017, **82**, 6550–6567.
68 Y. Ano, M. Tobisu and N. Chatani, *Org. Lett.*, 2012, **14**, 354–357.
69 C. Feng, D. Feng, Y. Luo and T.-P. Loh, *Org. Lett.*, 2014, **16**, 5956–5959.
70 C. Feng, D. Feng and T.-P. Loh, *Chem. Commun.*, 2014, **50**, 9865–9868.
71 K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459–4461.
72 P. Finkbeiner, U. Kloeckner and B. J. Nachtsheim, *Angew. Chem., Int. Ed.*, 2015, **54**, 4949–4952.
73 J. Yi, L. Yang, C. Xia and F. Li, *J. Org. Chem.*, 2015, **80**, 6213–6221.
74 V. G. Landge, C. H. Shewale, G. Jaiswal, M. K. Sahoo, S. P. Midya and E. Balaraman, *Catal. Sci. Technol.*, 2016, **6**, 1946–1951.
75 E. Tan, O. Quinonero, M. E. de Orbe and A. M. Echavarren, *ACS Catal.*, 2018, **8**, 2166–2172.
76 Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333–9403.

77 F. Kakiuchi, Y. Tanaka, T. Sato, N. Chatani and S. Murai, *Chem. Lett.*, 1995, 679–680.
78 A. S. Tsai, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 6316–6317.
79 Y. Kuninobu, Y. Fujii, T. Matsuki, Y. Nishina and K. Takai, *Org. Lett.*, 2009, **11**, 2711–2714.
80 Y. Li, X.-S. Zhang, Q.-L. Zhu and Z.-J. Shi, *Org. Lett.*, 2012, **14**, 4498–4501.
81 Z. Wang, B. J. Reinus and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 13954–13957.
82 L. Ilies, T. Matsubara, S. Ichikawa, S. Asako and E. Nakamura, *J. Am. Chem. Soc.*, 2014, **136**, 13126–13129.
83 F. Mo and G. Dong, *Science*, 2014, **345**, 68–72.
84 H. N. Lim and G. Dong, *Angew. Chem., Int. Ed.*, 2015, **54**, 15294–15298.
85 D. Xing and G. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 13664–13667.
86 B. Zhou, Y. Hu and C. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13659–13663.
87 L. Ilies, S. Ichikawa, S. Asako, T. Matsubara and E. Nakamura, *Adv. Synth. Catal.*, 2015, **357**, 2175–2179.
88 Q. Jiang, T. Guo, K. Wu and Z. Yu, *Chem. Commun.*, 2016, **52**, 2913–2915.
89 S. Sharma, S. H. Han, H. Jo, S. Han, N. Kumar Mishra, M. Choi, T. Jeong, J. Park and I. Su Kim, *Eur. J. Org. Chem.*, 2016, 3611–3618.
90 J. A. Boerth, J. R. Hummel and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2016, **55**, 12650–12654.
91 T. J. Potter, D. N. Kamber, B. Q. Mercado and J. A. Ellman, *ACS Catal.*, 2017, **7**, 150–153.
92 Y.-C. Luo, C. Yang, S.-Q. Qiu, Q.-J. Liang, Y.-H. Xu and T.-P. Loh, *ACS Catal.*, 2019, **9**, 4271–4276.
93 S. Li, Q.-C. Shan, L.-M. Hu, X.-Q. Ma and X.-H. Hu, *Chem. Commun.*, 2020, **56**, 7969–7972.
94 S.-S. Zhang, J.-Q. Wu, Y.-X. Lao, X.-G. Liu, Y. Liu, W.-X. Lv, D.-H. Tan, Y.-F. Zeng and H. Wang, *Org. Lett.*, 2014, **16**, 6412–6415.
95 T. Gensch, S. Vásquez-Céspedes, D.-G. Yu and F. Glorius, *Org. Lett.*, 2015, **17**, 3714–3717.
96 C. Feng, D. Feng and T.-P. Loh, *Chem. Commun.*, 2015, **51**, 342–345.
97 S. Sharma, S. H. Han, Y. Oh, N. K. Mishra, S. Han, J. H. Kwak, S.-Y. Lee, Y. H. Jung and I. S. Kim, *J. Org. Chem.*, 2016, **81**, 2243–2251.
98 W. Yu, W. Zhang, Y. Liu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2017, **4**, 77–80.
99 X. Wu and H. Ji, *J. Org. Chem.*, 2018, **83**, 12094–12102.
100 L. Xu, K. Meng, J. Zhang, Y. Sun, X. Lu, T. Li, Y. Jiang and G. Zhong, *Chem. Commun.*, 2019, **55**, 9757–9760.
101 Y. Huang, L. Xu, F. Yu, W. Shen, X. Lu, L. Ding, L. Zhong, G. Zhong and J. Zhang, *J. Org. Chem.*, 2020, **85**, 7225–7237.
102 Y. Kuninobu, Y. Nishina, T. Matsuki and K. Takai, *J. Am. Chem. Soc.*, 2008, **130**, 14062–14063.
103 K. Parthasarathy, M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, 2008, **10**, 325–328.
104 L. Ackermann, A. V. Lygin and N. Hofmann, *Org. Lett.*, 2011, **13**, 3278–3281.
105 L. Wang and L. Ackermann, *Org. Lett.*, 2013, **15**, 176–179.
106 T. Yamakawa and N. Yoshikai, *Org. Lett.*, 2013, **15**, 196–199.
107 W. Hou, B. Zhou, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, 2013, **15**, 1814–1817.
108 K. Sasano, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2013, **135**, 10954–10957.
109 Z. Shi, D. C. Koester, M. Boultadakis-Arapinis and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 12204–12207.
110 M. Chen, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Angew. Chem., Int. Ed.*, 2013, **52**, 14196–14199.
111 Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2013, **52**, 629–633.
112 M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2014, **16**, 608–611.
113 T. Piou and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 11292–11295.
114 A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas and M. Gulías, *J. Am. Chem. Soc.*, 2014, **136**, 834–837.
115 A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas and M. Gulías, *J. Am. Chem. Soc.*, 2014, **136**, 7607–7610.
116 L. Grigorjeva and O. Daugulis, *Org. Lett.*, 2014, **16**, 4688–4690.
117 L. Guo, F. Zhang, W. Hu, L. Li and Y. Jia, *Chem. Commun.*, 2014, **50**, 3299–3302.
118 C. Aïssa, K. Y. T. Ho, D. J. Tetlow and M. Pin-Nó, *Angew. Chem., Int. Ed.*, 2014, **53**, 4209–4212.
119 C.-Z. Luo, J. Jayakumar, P. Gandeepan, Y.-C. Wu and C.-H. Cheng, *Org. Lett.*, 2015, **17**, 924–927.
120 N. Casanova, A. Seoane, J. L. Mascareñas and M. Gulías, *Angew. Chem., Int. Ed.*, 2015, **54**, 2374–2377.
121 D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, **54**, 4508–4511.
122 J. R. Hummel and J. A. Ellman, *J. Am. Chem. Soc.*, 2015, **137**, 490–498.
123 R. Prakash, K. Shekarrao and S. Gogoi, *Org. Lett.*, 2015, **17**, 5264–5267.
124 D. Kumar, S. R. Vemula and G. R. Cook, *ACS Catal.*, 2016, **6**, 3531–3536.
125 N. Casanova, K. P. Del Rio, R. García-Fandiño, J. L. Mascareñas and M. Gulías, *ACS Catal.*, 2016, **6**, 3349–3353.
126 R. Kuppusamy, K. Muralirajan and C.-H. Cheng, *ACS Catal.*, 2016, **6**, 3909–3913.
127 Z. Zhou, G. Liu and X. Lu, *Org. Lett.*, 2016, **18**, 5668–5671.
128 T. Matsubara, L. Ilies and E. Nakamura, *Chem. – Asian J.*, 2016, **11**, 380–384.
129 Y.-Q. Zhu, Y. Liu, H. Wang, W. Liu and C.-J. Li, *Org. Chem. Front.*, 2016, **3**, 971–974.
130 D. M. Lade and A. B. Pawar, *Org. Chem. Front.*, 2016, **3**, 836–840.
131 C. Yu, J. Zhang and G. Zhong, *Chem. Commun.*, 2017, **53**, 9902–9905.
132 Y. Zhao, S. Li, X. Zheng, J. Tang, Z. She, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 4286–4289.
133 M. Iwasaki, N. Miki, Y. Tsuchiya, K. Nakajima and Y. Nishihara, *Org. Lett.*, 2017, **19**, 1092–1095.

134 Y. R. Han, S.-H. Shim, D.-S. Kim and C.-H. Jun, *Org. Lett.*, 2017, **19**, 2941–2944.
135 P. V. Santhini, G. Nimisha, J. John, E. Suresh, R. L. Varmaab and K. V. Radhakrishnan, *Chem. Commun.*, 2017, **53**, 1848–1851.
136 M. Shankar, T. Guntreddi, E. Ramesh and A. K. Sahoo, *Org. Lett.*, 2017, **19**, 5665–5668.
137 X. Yu, K. Chen, Q. Wang, S. Guo, S. Zha and J. Zhu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5222–5226.
138 Y. Zhao, C. Yu, T. Wang, Z. She, X. Zheng, J. You and G. Gao, *Org. Lett.*, 2018, **20**, 1074–1077.
139 M. Font, B. Cendón, A. Seoane, J. L. Mascareñas and M. Gulías, *Angew. Chem., Int. Ed.*, 2018, **57**, 8255–8259.
140 R. Yu, D. Li and F. Zeng, *J. Org. Chem.*, 2018, **83**, 323–329.
141 B. Qi, S. Guo, W. Zhang, X. Yu, C. Song and J. Zhu, *Org. Lett.*, 2018, **20**, 3996–3999.
142 P. Chen, J. Nan, Y. Hu, Q. Ma and Y. Ma, *Org. Lett.*, 2019, **21**, 4812–4815.
143 E. J. T. Phipps and T. Rovis, *J. Am. Chem. Soc.*, 2019, **141**, 6807–6811.
144 S.-G. ang, Y. Liu and N. Cramer, *Angew. Chem., Int. Ed.*, 2019, **58**, 18136–18140.
145 A. Seoane, C. Comanescu, N. Casanova, R. García-Fandiño, X. Diz, J. L. Mascareñas and M. Gulías, *Angew. Chem., Int. Ed.*, 2019, **58**, 1700–1704.
146 P. Shi, S. Li, L.-M. Hu, C. Wang, T.-P. Loh and X.-H. Hu, *Chem. Commun.*, 2019, **55**, 11115–11118.
147 Q.-L. Yang, Y.-K. Xing, X.-Y. Wang, H.-X. Ma, X.-J. Weng, X. Yang, H.-M. Guo and T.-S. Mei, *J. Am. Chem. Soc.*, 2019, **141**, 18970–18976.
148 Y. Jiang, P. Li, J. Wang, J. Zhao, Y. Li, Y. Zhang, J. Chang, B. Liu and X. Li, *Org. Lett.*, 2020, **22**, 438–442.
149 J.-F. Tan, C. T. Bormann, K. Severin and N. Cramer, *ACS Catal.*, 2020, **10**, 3790–3796.
150 N. Kuhl, N. Schröder and F. Glorius, *Org. Lett.*, 2013, **15**, 3860–3863.
151 W. Su, T.-J. Gong, B. Xiao and Y. Fu, *Chem. Commun.*, 2015, **51**, 11848–11851.
152 M. Chaitanya and P. Anbarasan, *Org. Lett.*, 2015, **17**, 3766–3769.
153 J.-L. Pan, C. Chen, Z.-G. Ma, J. Zhou, L.-R. Wang and S.-Y. Zhang, *Org. Lett.*, 2017, **19**, 5216–5219.
154 K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430–11433.
155 J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 8551–8554.
156 Z. Xiong, D. Liang and S. Luo, *Org. Chem. Front.*, 2017, **4**, 1103–1106.
157 C. Chen, Y. Pan, H. Zhao, X. Xu, J. Xu, Z. Zhang, S. Xi, L. Xu and H. Li, *Org. Chem. Front.*, 2018, **5**, 415–422.
158 C. Lin, D. Li, B. Wang, J. Yao and Y. Zhang, *Org. Lett.*, 2015, **17**, 1328–1331.
159 Q. Zhao, T. Poisson, X. Pannecoucke, J.-P. Bouillon and T. Besset, *Org. Lett.*, 2017, **19**, 5106–5109.
160 C. Liu, Y. Fang, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2018, **20**, 6112–6116.
161 Z. Ren, F. Mo and G. Dong, *J. Am. Chem. Soc.*, 2012, **134**, 16991–16994.
162 Z. Huang, C. Wang and G. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 5299–5303.
163 W.-J. Kong, Y.-J. Liu, H. Xu, Y.-Q. Chen, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**(7), 2146–2149.
164 R. Y. Mawo, S. Mustakim, V. G. Young, M. R. Hoffmann and I. P. Smoliakova, *Organometallics*, 2007, **26**, 1801–1810.
165 H.-C. Tsai, Y.-H. Huang and C.-M. Chou, *Org. Lett.*, 2018, **20**, 1328–1332.
166 Y.-C. Wang, Y.-H. Huang, H.-C. Tsai, R. S. Basha and C.-M. Chou, *Org. Lett.*, 2020, **22**, 6765–6770.
167 M. Liu, P. Yang, M. K. Karunananda, Y. Wang, P. Liu and K. M. Engle, *J. Am. Chem. Soc.*, 2018, **140**, 5805–5813.
168 K. Meng, T. Li, C. Yu, C. Shen, J. Zhang and G. Zhong, *Nat. Commun.*, 2019, **10**, 5109.
169 C. Shen, X. Lu, J. Zhang, L. Ding, Y. Sun and G. Zhong, *Chem. Commun.*, 2019, **55**, 13582–13585.
170 B. S. Schreib and E. M. Carreira, *J. Am. Chem. Soc.*, 2019, **141**, 8758–8763.
171 B. S. Schreib, M. Fadel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2020, **59**, 7818–7822.
172 B. Han, B. Li, L. Qi, P. Yang, G. He and G. Chen, *Org. Lett.*, 2020, **22**, 6879–6883.
173 J. Wang and G. Dong, *Chem. Rev.*, 2019, **119**, 7478–7528.
174 Z. Wu, N. Fatuzzo and G. Dong, *J. Am. Chem. Soc.*, 2020, **142**, 2715–2720.

