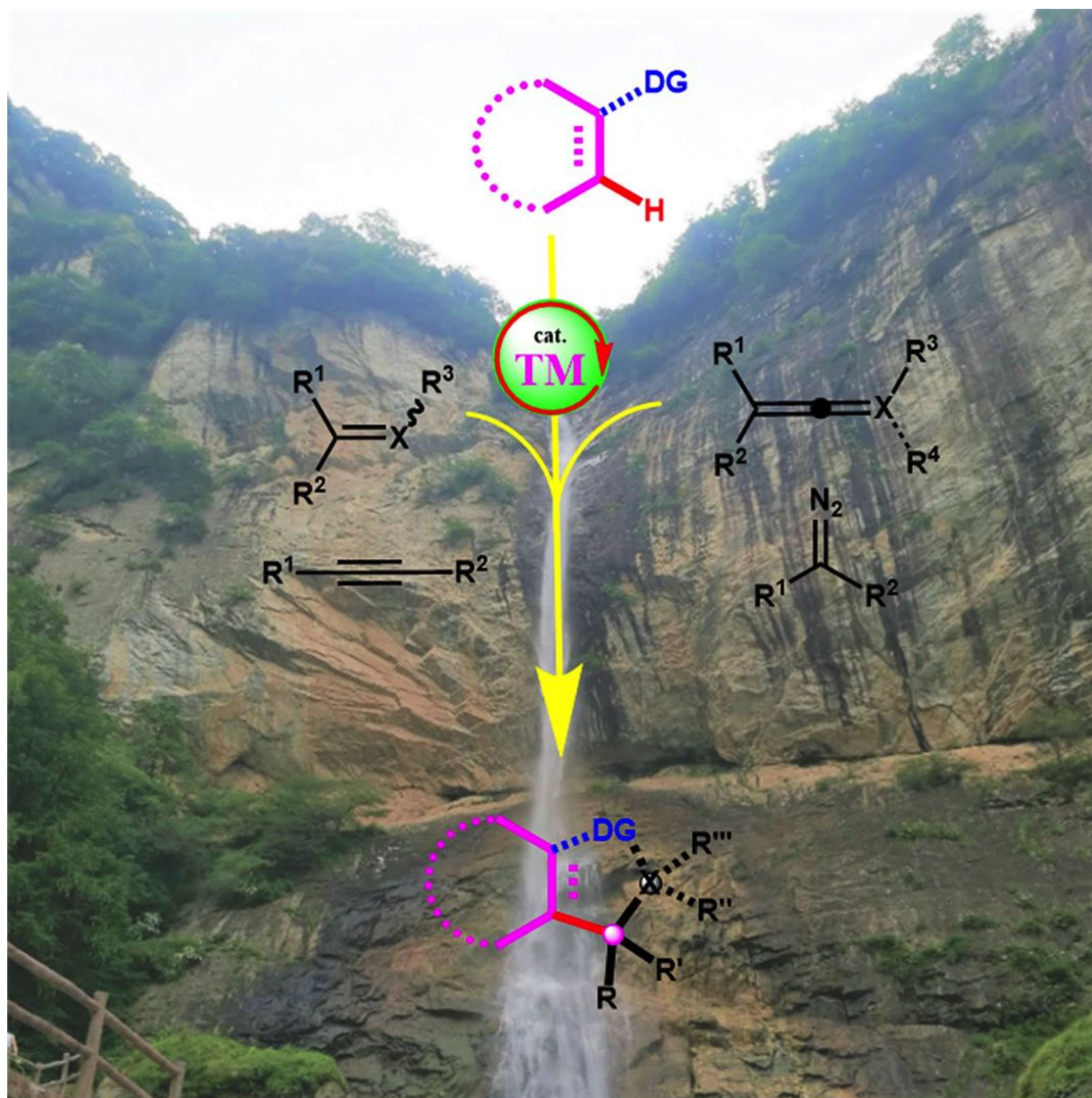ChemPubSoc
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Synthetic Methods

Transition-Metal-Catalyzed C—H Functionalization for Construction of Quaternary Carbon Centers

Yang Li* and Silong Xu*[a]

Abstract: Efficient construction of quaternary carbon centers represents one of the most challenging goals in organic synthesis, and it has drawn tremendous research interest from organic chemist community. The past decade has witnessed a significant advancement of direct C—H functionalization, which delivers various synthetic tools for assembling struc-turally diversified architectures with the advantage of step- and atom-economy, operational simplicity, and readily available substrates. In this Minireview, synthetic methods based on transition-metal-catalyzed C—H functionalization as efficient tools for the construction of quaternary carbon centers are summarized.

1. Introduction

Quaternary carbon centers are ubiquitous structural units found in natural products and biological significant molecules.[1] However, highly efficient construction of quaternary centers is synthetically challenging, partially due to the significant steric encumbrance often encountered in the bond formation. Therefore, it has been a long-term interest from synthetic community in developing new and effective methods for the assembly of quaternary centers.[2] The direct functionalization of unactivated C—H bonds offers a conceptually new strategy to organic synthesis.[3] In contrast with traditional bond-forming processes, which often require prefunctionalization of substrates, direct C—H functionalization allows for straightforward and rapid generation of molecular complexity by taking advantage of the ubiquity of C—H bonds in chemical feedstocks. Since Murai's pioneering discovery[4] in 1993 of ruthenium-catalyzed C—H bond functionalization of aromatic ketones with olefins, this area has advanced in a drastic rate in the past decades. Particularly since the turn of the millennium, various new modes of activation and new catalytic systems have been discovered. In recent years this dynamic research field has been extensively reviewed.[3]

The great strides in transition-metal-catalyzed C—H functionalization fueled a surge to developing new methods for the construction of quaternary carbon centers. The inherent advantage of direct C—H functionalization provides a new and unique approach to this synthetically challenge. In this Minireview, we highlight recent examples on the construction of quaternary carbon centers by using transition-metal-catalyzed C—H functionalization. This review aims to offer a "critical catalogue" of reactions to synthetic chemists for grasping new ideas for constructing quaternary carbon centers. For simplicity, the reactions described herein are classified by the type of quaternary centers formed, namely, all-carbon quaternary centers, O-substituted quaternary centers, and N-substituted quaternary centers. When appropriate, mechanistic pathways are discussed. To the best of our knowledge, this is the first review addressing the construction of quaternary centers by using C—H functionalization strategy. Of note is that the C—H functionalization only refers to the intrinsically unactivated C—H bonds with pK_a values larger than 25, so acidic C—H bonds at the alpha position of esters, ketones, nitriles and related compounds will not be discussed. In addition, the reactions proceeded in electrophilic aromatic substitution or radical process will not be reviewed.

Catalytic functionalization of C—H bonds typically starts with the cleavage of the C—H bonds with transition metals to form in situ a reactive C—M intermediate **1** (Scheme 1), which is
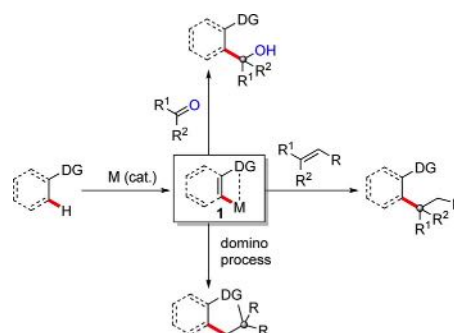
Scheme 1. General reaction patterns for the construction of quaternary centers via C—H functionalization.

widely referred to as C—H activation. To ensure the reactivity and selectivity of the C—H cleavage, a strategy of chelation-assistance with proximal directing groups (DGs) is often employed to facilitate *ortho* C—H activation by enhancing the effective concentration of the catalyst.[5] The resulting C—M complex **1** then undergoes functionalization with appropriate coupling partners proceeding in different pathways to afford various structural motifs (Scheme 1). In the reactions employing 1,1-disubstituted alkenes as coupling partners, the C—H functionalization leads to the formation of all-carbon quaternary centers. Ketones are also employed as coupling partners to generate O-substituted quaternary centers; however, ketimines are rarely involved in such addition processes. Additionally, transition-metal-catalyzed C—H functionalization often occurs within domino sequences to yield a wide array of carbo- and heterocyclic products containing quaternary centers. These key reaction patterns are summarized in Scheme 1 which will be discussed in detail in the sections below.

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2. All-Carbon Quaternary Centers

Efficient construction of all-carbon quaternary centers represent a particularly challenging synthetic topic in organic synthesis.[6] As a burgeoning methodology, C−H functionalization can be engaged in this context via many catalytic systems. The related transformations are usually intercepted within domino process to generate various carbo- or heterocycles bearing all-carbon quaternary centers.

### 2.1. Addition of C−H bonds to alkenes

2.1.1. Intramolecular C−H addition to alkenes

The most basic method one can imagine for the construction of all-carbon quaternary centers via C−H functionalization may be the addition of C−H bonds to 1,1-disubstituted alkenes. Indeed, this strategy is viable for a range of substrate combinations via C−H functionalization, especially intramolecular reactions. Addition of C−H bonds to unsymmetrical alkenes always gives rise to a question of which end of the double bond is involved in the C−C bond formation. Studies in this context reveal that the regioselectivity depends on both substrates and catalysts. Bergman and Ellman[7] in 2001 demonstrated that imine-directed C−H addition to trisubstituted olefins with Wilkinson's catalyst gave anti-Markovnikov products; however, recent findings showed that using amide directing groups under rhodium catalysis favored the Markovnikov products generating all-carbon quaternary centers. For example, in 2013 Rovis and co-workers[8] by using benzamides tethered with tri-substituted olefins realized rhodium-catalyzed intramolecular C−H addition to afford divergent alkylation products bearing all-carbon quaternary centers (Scheme 2). Intriguingly, different amide directing groups lead to distinct reaction pathways under similar conditions. While a normal amide group led to hydroarylation products **3**, oxidizing amides with *N*-OMe and *N*-OPiv substituents resulted in dehydrogenative Heck-type products **5** and amidoarylation products **7**, respectively (Scheme 2).

Sahoo and co-workers[9] subsequently in 2016 extended the hydroarylation by using less-expensive ruthenium catalyst with normal amide[10] or sulfoximide directing groups. Interestingly,
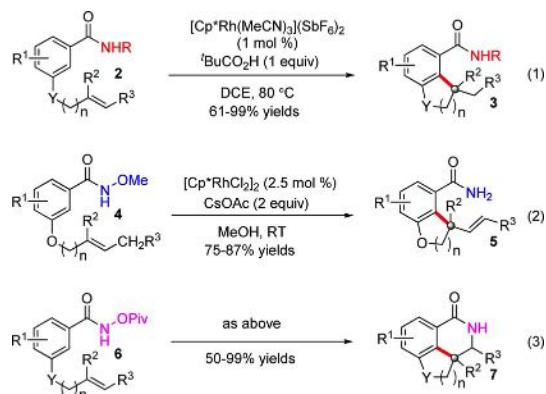
Scheme 2. Amide-dependent alkylations via C−H functionalization.
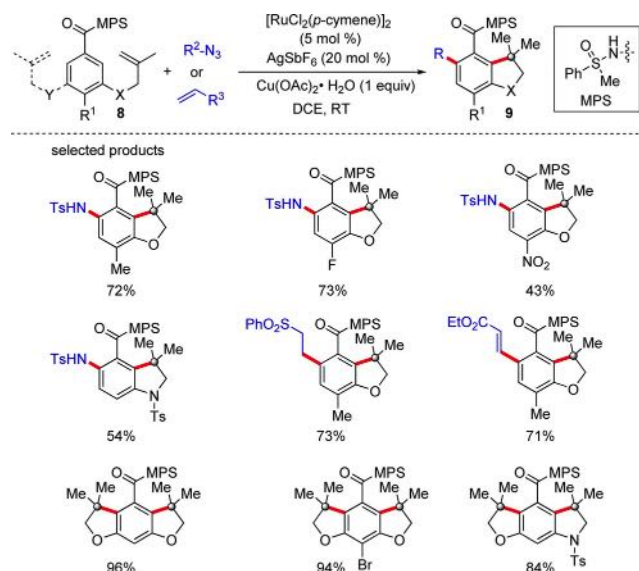
**Scheme 3.** Sulfoximide-directed double C−H functionalization.

the sulfoximide is able to direct a second *ortho* C−H activation leading to either twofold hydroarylations or one-pot sequential hydroarylation/amidation, alkylation, or annulation reactions to give various polysubstituted heterocycles (Scheme 3).

The asymmetric version of the intramolecular hydroarylation was realized by the group of Cramer[11] by using a rhodium catalyst bearing a chiral BINOL-derived Cp ligand **11** (Scheme 4). The corresponding hydroarylation products were obtained in

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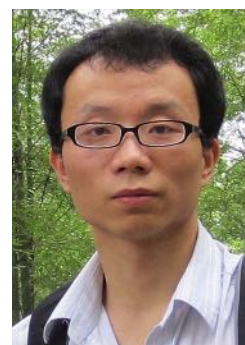
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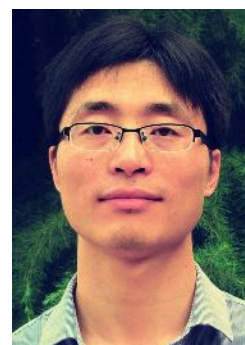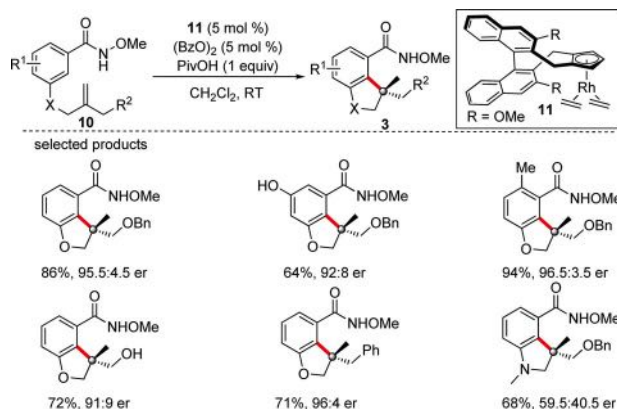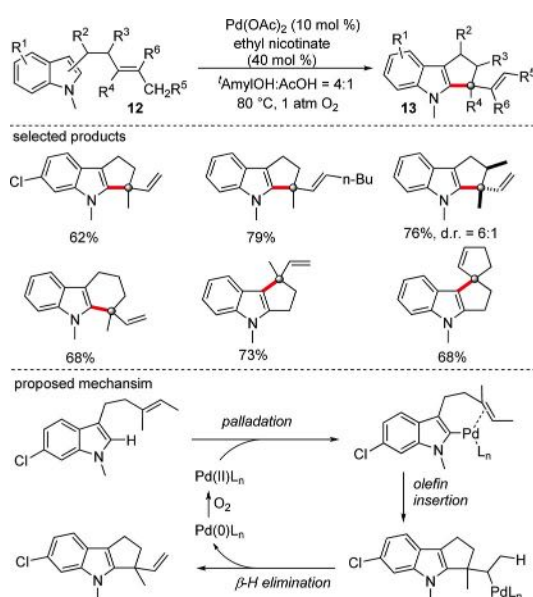
**Scheme 4.** Asymmetric intramolecular hydroarylation.

good yields with generally high enantioselectivity that contains an all-carbon quaternary center. In contrast to the racemic reaction [Scheme 2, Eq. (2)],[8] the asymmetric reaction predominantly proceed in hydroarylation pathway instead of giving dehydrogenative Heck-type products.

An efficient palladium-catalyzed intramolecular Fjiwara–Moritani annulation of indoles with alkenes was developed by Ferreira and Stoltz[12] (Scheme 5). The reaction produced polysubstituted indoles **13** fused by a five- or six-membered rings that bearing an all-carbon quaternary center in good yields. Mechanistically, the reaction proceeds through initial indole palladation, a follow-up migratory insertion, and final β-H elimination to deliver the products **13** and Pd⁰ complex. Mild oxidative conditions by using molecular oxygen converts Pd⁰ to Pdᴵᴵ to complete the catalytic cycle (Scheme 5). By using chiral oxazoline ligands, for example, **14**, the Oestreich group[13] have attempted the asymmetric variants of the cyclization; however, only moderate enantioselectivity has been achieved

(Scheme 6). It was found that the *Z/E* configuration of double bond of starting alkenes is relevant to the enantioinduction of the reaction giving different *ee* values. As a reliable protocol for building all-carbon quaternary centers, the utility of Fujiwara–Moritani cyclization have been demonstrated in the synthesis of several natural products, such as (+)-hydratoaustamide,[14] (+)-austamide,[14] (+)-deoxyisoaustamide,[14] (±)-rhazinicine,[15] and (±)-rhazinal[16] (Scheme 7).
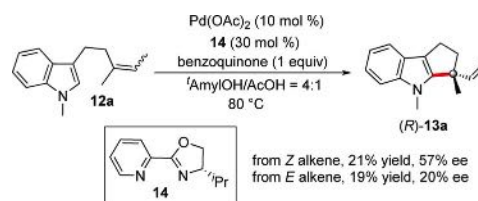
**Scheme 6.** Pd-catalyzed asymmetric Fujiwara–Moritani annulation using an oxazoline ligand.
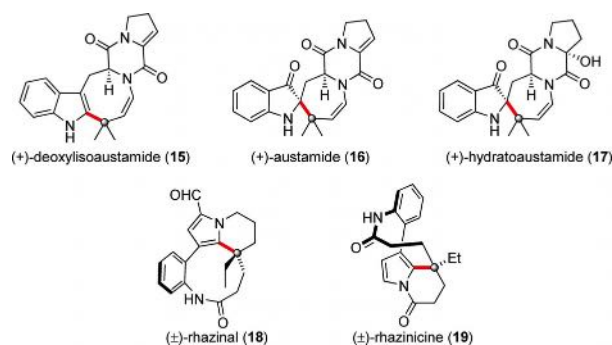
Scheme 7. Pd-catalyzed Fujiwara–Moritani annulations for natural product synthesis.

Stoltz et al.[17] also extended the oxidative palladium-catalyzed cyclization to electron-rich arenes **20** by using benzoquinone as an optimal oxidant. With pendant trisubstituted alkenes, highly substituted dihydrobenzofurans **21** bearing all-carbon quaternary centers were generated in good to excellent yields (Scheme 8).

In addition to arene C–H addition reactions, Yu and co-workers[18] in 2010 disclosed a rhodium-catalyzed allylic C–H addition to tethered conjugated dienes. By using a chiral phosphoramidite ligand **24**, they subsequently realized the asym-
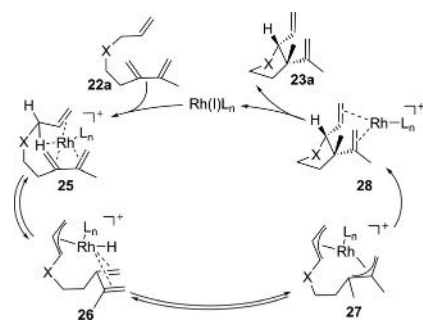

Scheme 5. Pd-catalyzed intramolecular Fujiwara–Moritani annulation of indoles and mechanistic rationale.
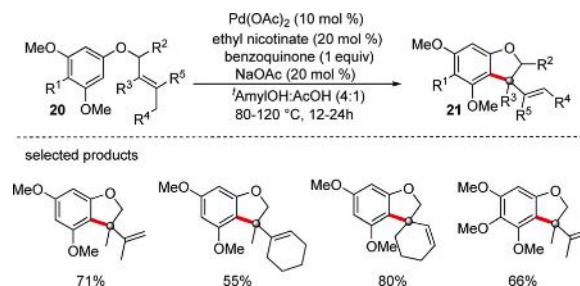
Scheme 8. Pd-catalyzed oxidative cyclization of electron-rich arenes with alkenes.

metric cyclization reactions leading to the formation of tetrahy-dropyrroles, tetrahydrofurans, and cyclopentanes **23** contain-ing all-carbon quaternary centers in high yields and good to excellent enantioselectivities (Scheme 9).[19] Interestingly, the obtained chiral diene products can be used as excellent chiral ligands for rhodium-catalyzed asymmetric 1,4-addition of orga-noboronic acids to α,β-unsaturated compounds.[20]
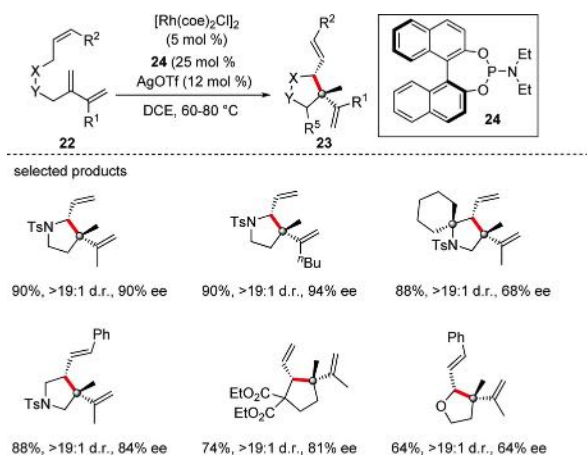
Scheme 9. Rh-catalyzed enantioselective intramolecular allylic C−H addition to conjugated dienes.

It is proposed that the diene moiety in **22** behaves as a di-recting group to facilitate allylic C−H bond cleavage with a rhodium catalyst (Scheme 10). The thus-formed Rh-H species **26** then inserts into the diene to furnish a bis-allylic Rh com-plex **27**, which undergoes reductive elimination to give the products **23** bearing adjacent *cis*-divinyl groups. A DFT study[21] supports the mechanism and unveils that the final reductive elimination is irreversible and rate-determining.


Scheme 10. Proposed mechanism for the Rh-catalyzed intramolecular allylic C−H addition to conjugated dienes.

2.1.2. Intermolecular C−H addition to alkenes

In contrast with intramolecular C−H additions to alkenes for building quaternary centers, the intermolecular variants mainly rely on highly reactive coupling partners, and in many cases are driven by domino processes. Methylenecyclopropanes (MCPs, **29**), a class of highly strained molecules,[22] was em-

ployed as coupling partners by Cui and co-workers[23] in rhodi-um-catalyzed C−H activation/annulation with *N*-pivaloyloxy-benzamides **30a**, which delivered spiro dihydroisoquinolinone products **31** in good yields containing an all-carbon quaternary center [Scheme 11, Eq. (1)]. Interestingly, when furan-2-carbox-
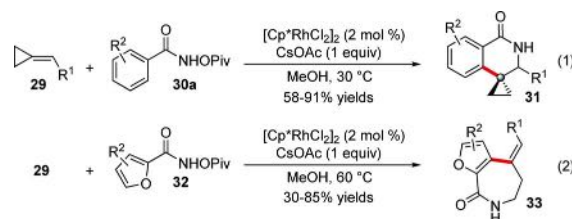
Scheme 11. Rh-catalyzed C−H activation/annualtion of benzamides with methylenecyclopropanes.

amides **32** was employed, the reaction chemoselectively pro-duced azepinone products **33** with the cleavage of the cyclo-propane ring [Scheme 11, Eq. (2)]. The fused electron-rich furan moiety was believed to slow down the departure of rhodium catalyst and thus facilitate the ring opening of the three-mem-bered ring.

Alkenes, when bearing proper directing groups, can still be applied in transition-metal-catalyzed C(sp²)−H functionaliza-tion. Rovis's group[24] demonstrated that α,β-unsaturated oxime pivalates **34**, in the presence of cationic rhodium com-plexes **37**, readily coupled with 1,1-disubstituted olefins to pro-duce 2,3-dihydropyridine products **36** containing an all-carbon quaternary center (Scheme 12). The resulting semi-saturated heterocycles could be hydrogenated in one-pot to generate polysubstituted piperidines.
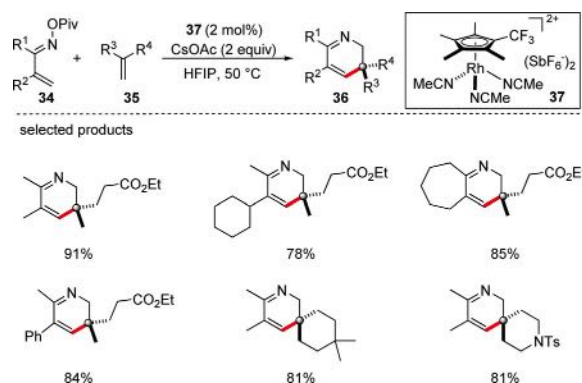

Scheme 12. Rh-catalyzed annulation of α,β-unsaturated oxime pivalates with alkenes.

By the use of a redox relay strategy,[25] Sigman and co-work-ers[26] in 2015 developed a palladium-catalyzed asymmetric C−H addition of indoles to trisubstituted alkenes **38** tethered with a remote hydroxyl group (Scheme 13). With PyrOx **41** as a ligand, the C−H addition occurs selectively at C3-postion of in-doles, which produces indoles **40** with a pendent ketone con-taining an all-carbon quaternary center in high yields and good to excellent enantioselectivities.
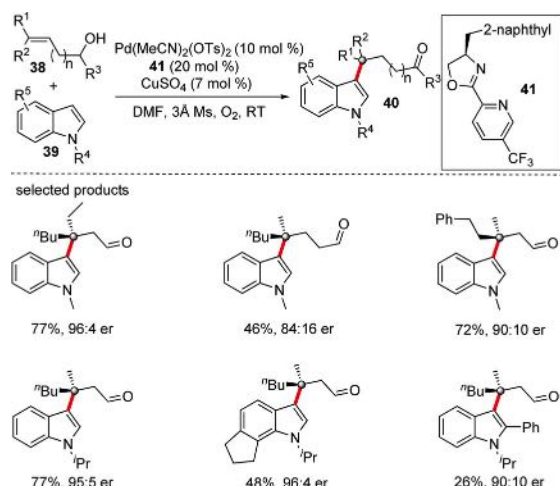
Scheme 13. Pd-catalyzed asymmetric C−H addition of indoles to trisubstituted alkenes with a redox relay process.

In addition to alkenes, allenes and ketenimines are also viable coupling partners for transition-metal-catalyzed C−H functionalization. A palladium-catalyzed cycloaddition of alkynyl aryl ethers **42** with allenes triggered by C−H activation has been reported by Minami, Hiyama, and co-workers.[27] When 1,1-dimethylallene **43** was employed, the reaction was able to furnish benzopyran products **44** with an all-carbon quaternary center albeit with the formation of regioisomeric product **45** (Scheme 14).
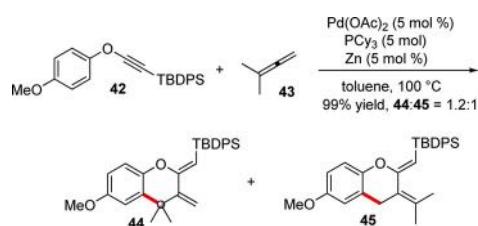
Scheme 14. Pd-catalyzed annulation of alkynyl aryl ether with 1,1-dimethylallene.

Ketenimines were successfully employed as coupling partners in a rhodium-catalyzed C−H activation/annulation with N-methoxybenzamides by Lu, Wang, and co-workers[28] to offer divergent cyclic products (Scheme 15). While β,β-alkyl,aryl-disubstituted ketenimines **46** favor a formal [4+2] annulation
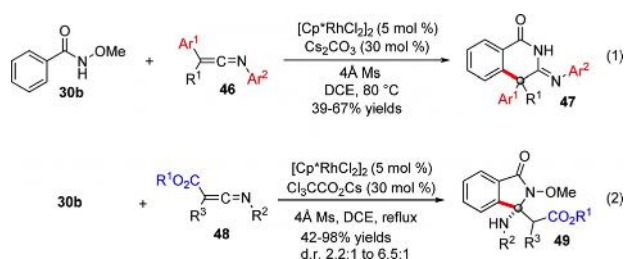

Scheme 15. Substrate-dependent annulations between ketenimines and N-methoxybenzamides.

with N-methoxybenzamides to deliver 3-iminoisoquinolin-1(2H)-ones **47**, β-ester functionalized ketenimines **48** undergo formal [4+1] annulation to produce 3-aminoisoindolin-1-ones **49**, with both products containing quaternary carbon centers. The observed substrate-dependent annulation modes were investigated by DFT calculations. A β-ester group on the ketenimines was believed to direct the coordination of Rh species to the nitrogen atom other than the C=C bond of the ketenimines, thus leading to different annulation products.

2.2. Addition of C−H bonds to alkynes

Unlike alkenes, C−H addition to alkynes often proceeds in domino cyclization reactions after the initial migratory insertion event. In 2012, an efficient ruthenium-catalyzed oxidative [3+2] annulation of 2-aryl-1,3-dicarbonyl compounds **51** with alkynes via C−H functionalization was developed by Lam and co-workers[29] for accessing indenes with a spirocyclic all-carbon quaternary center (Scheme 16). Various 2-aryl-1,3-dicar-
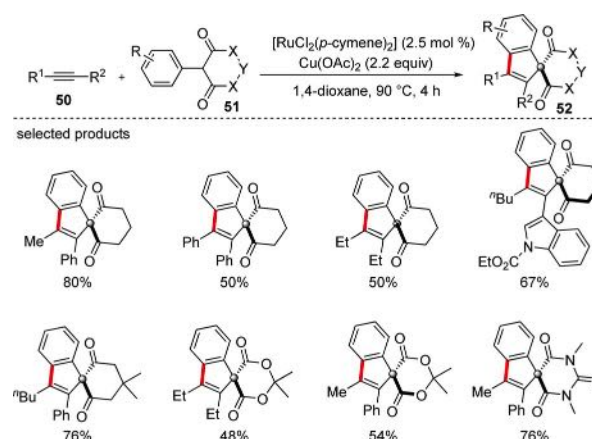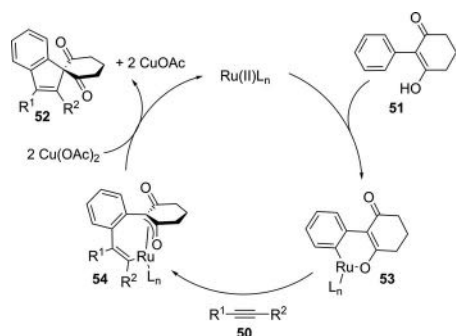

Scheme 16. Ru-catalyzed [3+2] spiroannulation of 2-aryl-1,3-dicarbonyl compounds with alkynes.

bonyl compounds readily coupled with symmetrical or unsymmetrical alkynes to generate spiroindene products **52** in good to excellent yields. The annulation is proposed to proceed through initial enolate-assisted cycloruthenation to form **53**. Migratory insertion of **53** into the alkyne then gives **54**, which undergoes C-C reductive elimination to afford spiroindene products **52** and Ru⁰ species that can be oxidized by Cu(OAc)₂ to regenerate the active catalyst (Scheme 17).

With different transition-metal catalysts, the Lam group[30] achieved a site-selective C−H activation of substrates **55** to chemoselectively produce spiroindenes **56** with all-carbon quaternary center and fused benzopyrans **58** under palladium catalysis and ruthenium catalysis, respectively (Scheme 18).

By using a chiral rhodium catalyst **59**, Lam and co-workers[31] in 2015 realized the asymmetric version of the [3+2] annulation of 2-aryl-1,3-dicarbonyl compounds with alkynes to obtain high levels of enantioselectivity [Scheme 19, Eq. (1)]. Very recently, with 4-aryl-5-pyrazolones **60** as the C−H precursor, You and co-workers[32] developed the corresponding asymmetric

Scheme 17. Proposed mechanism for the Ru-catalyzed [3+2] annulation.

[3+2] annulation to provide 4-spiro-5-pyrazolones **61** in good yields and high enantioselectivity by using a chiral rhodium catalyst **62** [Scheme 19, Eq. (2)].

In 2015, Lam et al.[33] subsequently extended the above [3+2] annulations with alkynes to a [3+3] annulations of 2-aryl-1,3-dicarbonyl compounds with 1,3-enynes for the prepa-
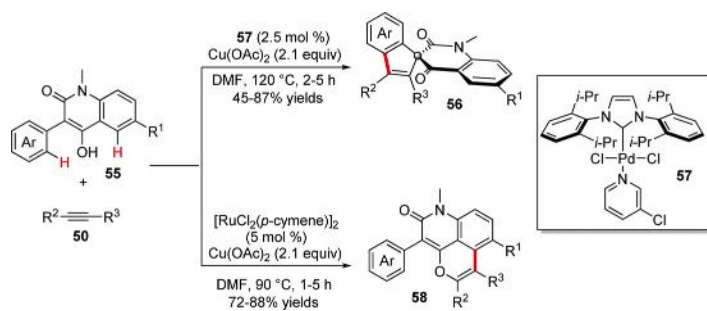

Scheme 18. Catalyst-controlled site-selective C−H activation/annulation.
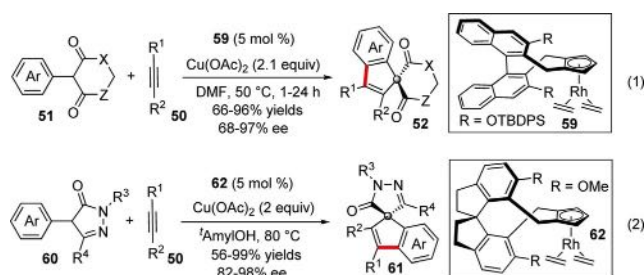
Scheme 19. Asymmetric [3+2] annulation of 2-aryl-1,3-dicarbonyl compounds or 4-aryl-5-pyrazolones with alkynes.

ration of six-membered spirodialin products **64** containing an all-carbon quaternary center (Scheme 20). Allylic hydrogens *cis* to the alkyne in the enynes are required to facilitate the [3+3] annulation, otherwise the [3+2] annulation would take place to provide aforementioned spiroindenes **52**. Trisubstituted alkene unit of the enynes could be tolerated, leading to the formation of products containing vicinal all-carbon quaternary centers in good yields. For the mechanism of the [3+3] annulation (Scheme 21), initial enolate-assisted cyclorhodation and migratory insertion into the alkyne to produce rhodacycle **66**,
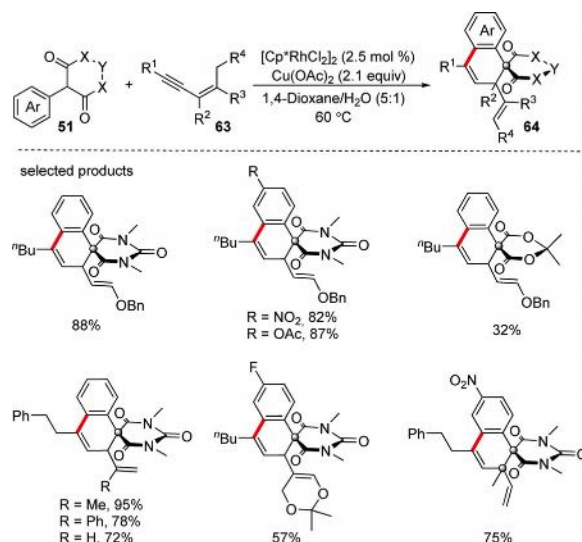
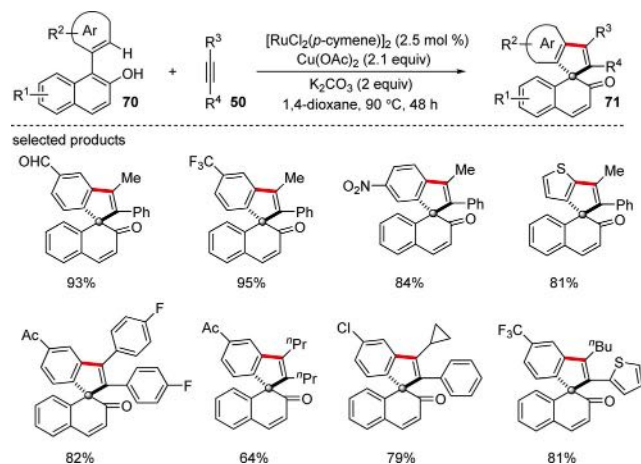**Scheme 20.** Rh-catalyzed [3+3] annulation of 1,3-enynes with 2-aryl-1,3-dicarbonyl compounds.

which, instead of reductive elimination leading to [3+2] annulation, undergoes reversible protonolysis to form alkenyrhodium species **67**. A 1,4-Rh migration[34] then occurs to give π-allylrhodium species **68**. Enolization of **68** leads to the formation of intermediate **69**, which is attacked by the nucleophilic C5 of the barbituric acid to give the [3+3] annulation products and rhodium(I) species. The active rhodium(III) catalyst can be regenerated by Cu(OAc)$_2$ oxidation.

As formal analogues of enolates, phenolic hydroxyl group also proved as effective directing groups for
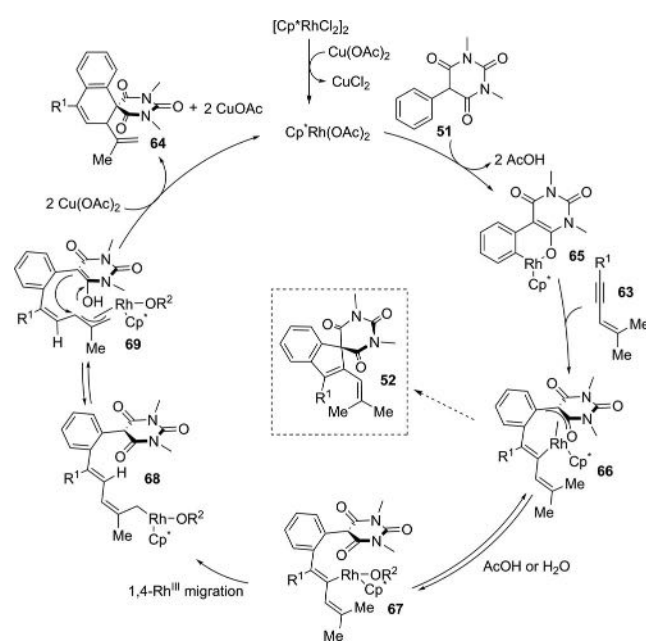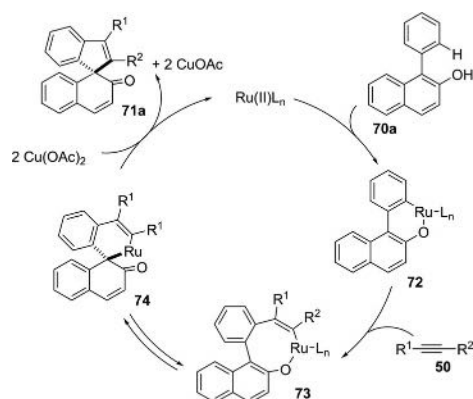

Scheme 21. Mechanism for the Rh-catalyzed [3+3] annulation of 1,3-enynes with 2-aryl-1,3-dicarbonyl compounds.

C—H functionalization under transition metal catalysis. Luan et al.[35] in 2013 reported a ruthenium-catalyzed dearomatizing [3+2] annulation of 1-aryl-2-naphthols **70** with alkynes to generate spiro indene-1,1′-naphthalen products **71** containing an all-carbon quaternary center in high yields (Scheme 22). Mech-

Scheme 24. Asymmetric dearomatization/annulation of naphthols with alkynes.

Scheme 22. Ru-catalyzed dearomatization/annulation of naphthols with alkynes.

Scheme 25. Dearomatization/annulation of 2-arylphenols with alkynes.
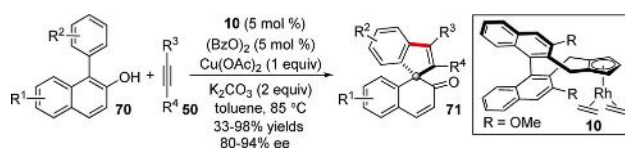
anistically, an eight-membered ruthenacycle **73** is generated from the initial C—H activation and follow-up migratory insertion to the alkyne. After enol-keto tautomerization, the resulting Ru-C intermediate **74** undergoes C—C reductive elimination to furnish the products and regenerate the Ru^{II} catalyst in the presence of Cu(OAc)$_2$(Scheme 23). This dearomatizing annula-
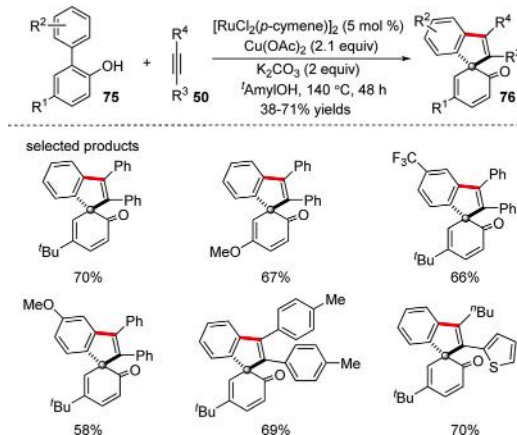

Scheme 23. Mechanism for the Ru-catalyzed dearomatization/annulation of naphthols with alkynes.

tion has been rendered enantioselective by You and co-workers[36] in 2015 by employing the chiral rhodium catalyst **10**, which provides the spirocyclic products **71** in high yields and excellent enantioselectivities (Scheme 24).

The Luan group[37] also extended the dearomatizing [3+2] annulation to include more challenging 2-arylphenols **75** (Scheme 25). A relatively higher temperature is required to promote the annulation probably due to the energy barrier for

dearomatizing phenols is higher than that of naphthols. Noteworthy is that tAmylOH as the solvent is crucial to the success of the reaction. A broad range of 2-arylphenols has been shown to couple with internal alkynes to deliver functionalized spirocyclic products **76** containing all-carbon quaternary centers in moderate yields with high regioselectivities.

Similar to 2-arylphenols, 2-alkenylphenols **77** also participate in the dearomatizing [3+2] spiroannualtions with alkynes and 1,3-enynes under rhodium catalysis through C(sp^2)—H activation, as reported by Mascareñas, Gulías, and co-workers[38] and Lam group,[39] respectively [Scheme 26, Eq. (1) and (2)]. The annulation generates the spirocyclic enone products with all-carbon quaternary centers in good to excellent yields. It was found that a substituent on the internal position of the olefin is crucial to the [3+2] annulation, otherwise it would lead to a [5+2] annulation to generate benzoxepines **79** [Scheme 26, Eq. (3)].[40] For the [3+2] annulation, the authors proposed that the strained eight-membered rhodacycle **81**, generated from
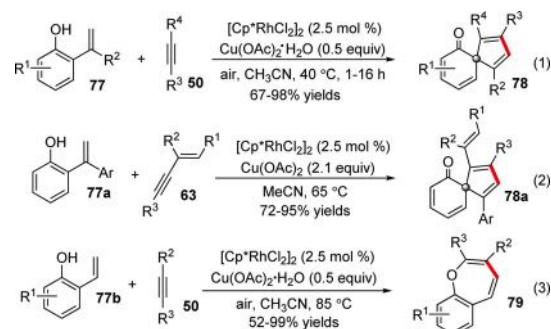

Scheme 26. Rh-catalyzed annualtions of 2-alkenylphenols with alkynes.

initial C–H activation and subsequent alkyne insertion, tends to isomerize to a more stable six-membered spirometalacycle **82** due to steric repulsion, which then undergoes reductive elimination to deliver the spirocyclic products **78**. While in the case of 2-vinylphenols without an internal substituent, the less steric clash in the eight-membered rhodacycle **81** favors a direct C–O reductive elimination to yield benzoxepines **79** as the [5+2] annulation products (Scheme 27).
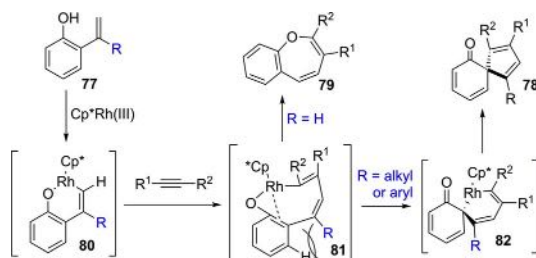

Scheme 27. Mechanistic rational for the divergent [3+2] and [5+2] annualtions of 2-alkenylphenols with alkynes.

Since 2-vinylphenols can be regarded as *ortho* C–H functionalization products of phenols with alkynes, it is possible to achieve a spiroannulation with phenols and two molecules of alkynes through a joint arene C–H activaton/dearomatization process. The Luan group[41] in 2014 demonstrated that simple 2-naphthols participated in a palladium-catalyzed [2+2+1] spiroannulation with two molecules of alkynes to provide spirocyclic compounds **84** in good yields that contains an all-carbon quaternary center (Scheme 28).
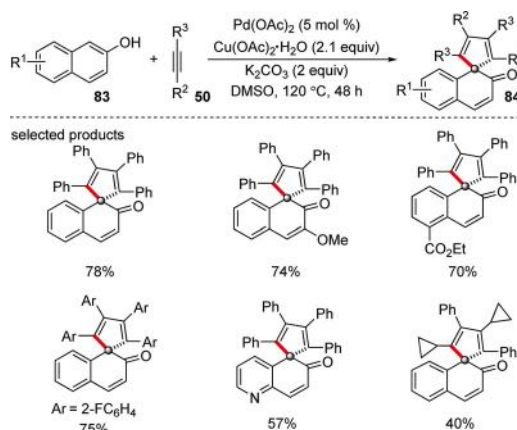

Scheme 28. Pd-catalyzed [2+2+1] spiroannulation of 2-naphthols with alkynes.

By employing α-arylidene pyrazolones **85** as the C–H precursor, Lin, Yao and co-workers[42] very recently developed a rhodium-catalyzed oxidative [3+2] C–H activation/annulation with alkynes for the synthesis of spiropentadiene pyrazolones **86** in good to excellent yields and high regioselectivity (Scheme 29). Under the conditions, tautomerization of α-arylidene pyrazolones **85** generates an intermediate **87** resembling the structure of 2-vinyphenols. Hence, a similar mechanism to that of
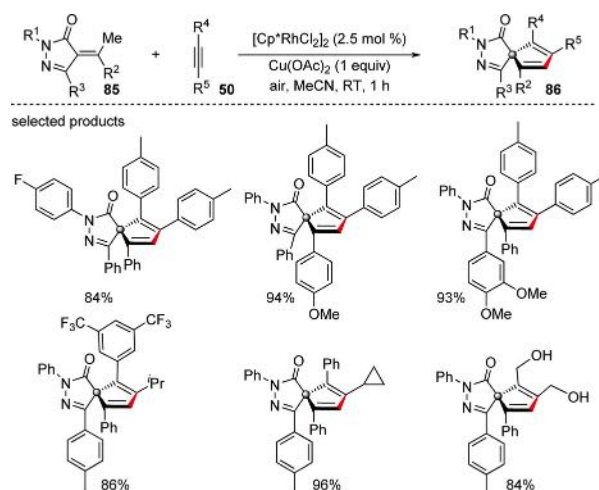
Scheme 29. Rh-catalyzed [3+2] annulation of α-arylidene pyrazolones with alkynes.

the [3+2] spiroannulation of vinylphenols with alkynes follows delivering the corresponding spirocyclic compounds **86**, as shown in Scheme 30.
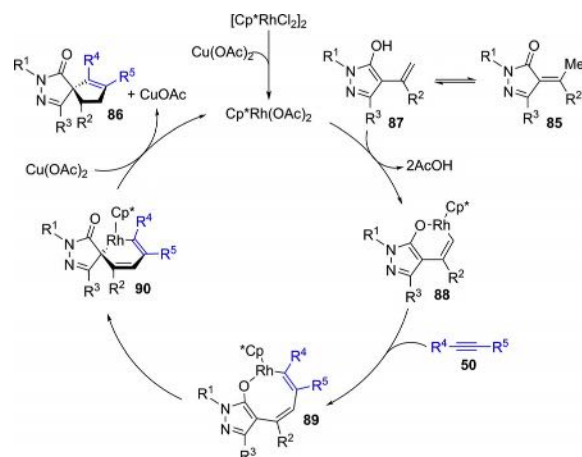
Scheme 30. Mechanism for the Rh-catalyzed [3+2] annulation of α-arylidene pyrazolones with alkynes.

Chang and co-workers[43] in 2015 disclosed a rhodium-catalyzed C–H activation/annulation of arylnitrones with alkynes under external oxidant-free conditions, which provides indolines **92** bearing an all-carbon quaternary center in good yields with moderate to high diastereoselectivities (Scheme 31). An intriguing intramolecular O-atom transfer process[44] was observed in the reaction, with a proposed mechanism shown in Scheme 31.

2.3. Reactions with diazo compounds

Diazo compounds has been extensively explored and widely used in modern organic synthesis.[45] In particular, transition-metal-catalyzed reactions of diazo compounds for the generation of metal cabenoids have found wide use in a range of
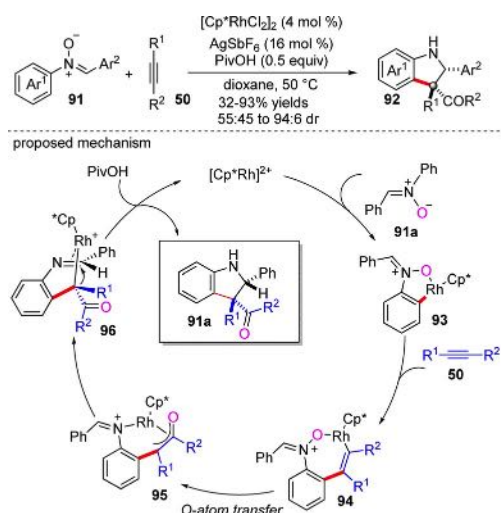
Scheme 31. Rh-catalyzed C–H activation/annulation of arylnitrones with alkynes and a proposed mechanism.

Scheme 32. Rh-catalyzed [4+1] annulation of arylnitrones with diazo compounds.
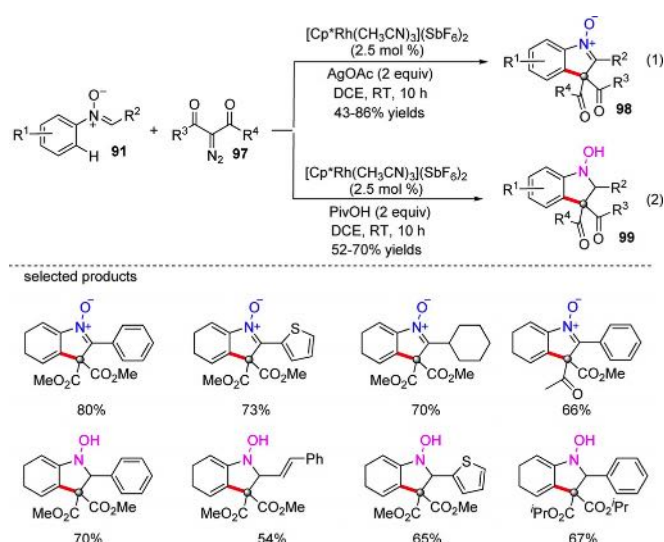
transformations, such as X–H (X = C, Si, N, O, S etc.) insertions, cyclopropanations, 1,2-migrations, etc.[46] Since the pioneering report by Yu and co-workers,[47] C–H functionalizaton using diazo compounds as coupling partners have also been extensively studied, especially for building of quaternary carbon centers.

A rhodium-catalyzed [4+1] annulation of arylnitrones with diazo compounds through C–H activation/cyclization was reported by Zhou and co-workers[48] in 2015, which furnishes 3H-indole-N-oxides **98** bearing an all-carbon quaternary center in good yields with a broad substrate scope [Scheme 32, Eq. (1)]. Without external oxidants and using PivOH as an additive, the reaction was found to be able to produce N-hydroxyindolines **99** in good yields. Around the same time, Dateer and Chang[49] also reported the same reaction for the synthesis of N-hydroxy-indolines **99** under similar conditions (Scheme 32, Eq (2)). As shown in Scheme 33, the mechanism for the [4+1] annulation was proposed to start with nitrone-directed *ortho* C–H cleavage to form a five-membered rhodacycle **93**. Coordination of a diazo compound to the rhodium, followed by aryl migration and the extrusion of N₂, affords a six-membered rhodacycle **101**. A Grignard-type addition of Rh–C to the C=N double bond and protonation then provide the desired N-hydroxyindolines **99** and releases the rhodium catalyst. In the presence of AgOAc, oxidation of N-hydroxyindolines occurs to give 3H-indole-N-oxides **98**.

A dual C–H activation of C(sp³)–H and C(sp²)–H bonds was achieved in a rhodium-catalyzed formal [4+1] annulation of 1-naphthylamine N-oxides **103** with diazo compounds, reported by Zhou, Yang, Zhu and co-workers[50] (Scheme 34). The reaction generates biologically important 1H-benzo[g]indolines **104** bearing all-carbon quaternary centers in good to excellent yields with a broad substrate scope. Mechanistic investigations including DFT calculations
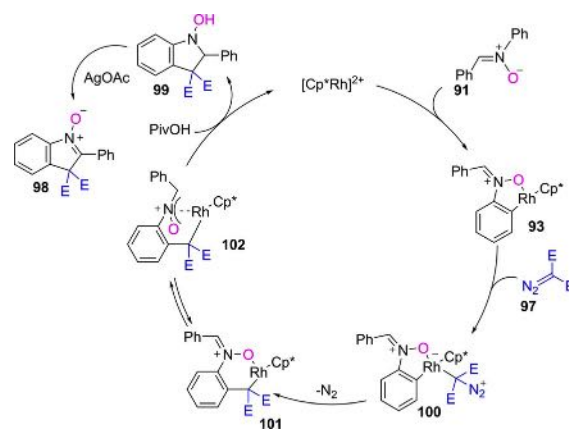
Scheme 33. Mechanism for the Rh-catalyzed [4+1] annulation of arylnitrones with diazo compounds.
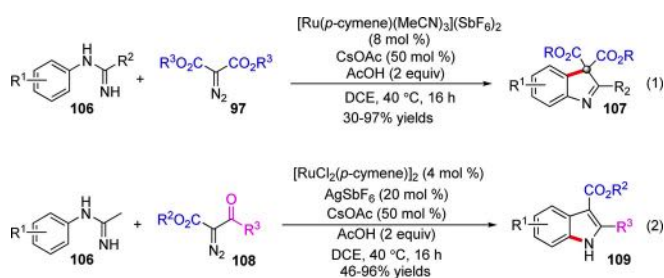
support an iminium intermediate **105** involved most likely in the catalytic cycle.
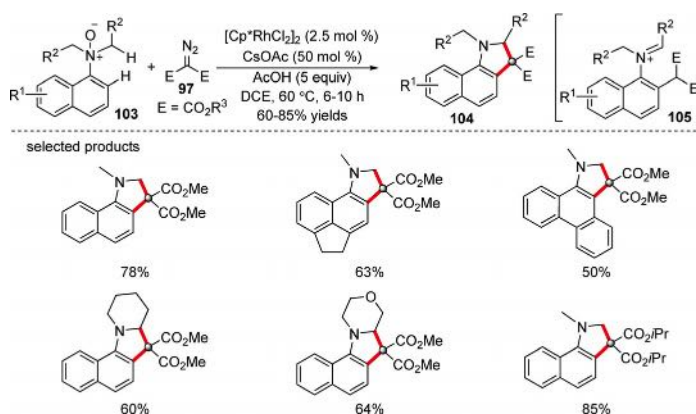
Scheme 34. Rh-catalyzed [4+1] annulation of 1-naphthylamine N-oxides with diazo compounds.

Aryl imidamides as C−H functionalization precursor have been employed by Li and co-workers[51] in the coupling with α-diazomalonates under ruthenium catalysis, which generates 3H-indoles **107** containing an all-carbon quaternary center in good to excellent yields [Scheme 35, Eq. (1)]. One of the C−N bonds is cleaved during the annulation to release a molecule of ammonia. Interestingly, when α-diazoketoesters were used as the coupling partner, 2,3-disubstituted N−H indoles **109** were generated selectively with an amide as a side product [Scheme 35, Eq. (2)].[51,52]
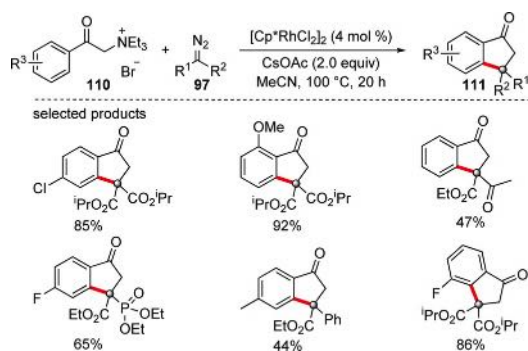
By employing acyl ammonium as an oxidizing directing group through the cleavage of the C−N bond, Li, Lan, and co-workers[53] in 2015 reported a

Scheme 37. Enantioselective trapping of zwitterionic Rh-intermediate **113**.

imines via 1,2-addition reaction using a chiral Brønsted acid **116** as co-catalyst. The reaction generates 3,3-disubstituted oxindoles **115** bearing an all-carbon quaternary center in good yields with excellent diastereoselectivity and enantioselectivity [Scheme 37, Eq. (1)]. Other than trapping by imines, Lautens group[56] reported that the intermediate **113** could be trapped via palladium-catalyzed asymmetric allylic alkylation. This dual-metal-catalyzed one-pot process, with **119** as an optimal ligand, enables the synthesis of chiral 3-allyl-3-aryl oxindoles **118** with an all-carbon quaternary center in high yields and good *ee* values [Scheme 37, Eq. (2)].

The dual catalysis was also extended by Hu and co-workers[55] to intermolecular carbenoid insertion into indole C−H bond (Scheme 38). The resulting intermediate **121** was trapped by an imine in one-pot, which provides indole derivatives **120** in high yields and excellent stereoselectivity that bearing two continuous stereogenic centers including an all-carbon quaternary one.
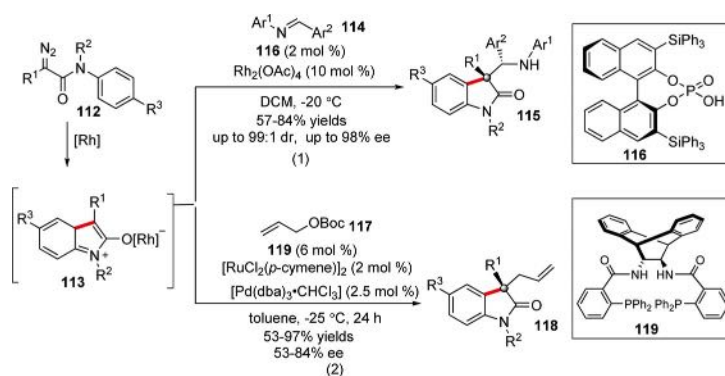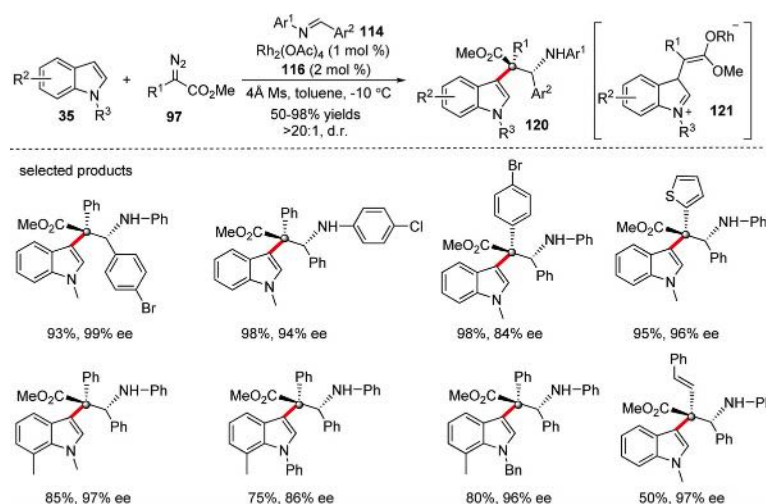

Scheme 35. Rh-catalyzed annulation of aryl imidamides with diazo compounds.

rhodium-catalyzed C−H activation/annulation of phenacyl ammonium salts with α-diazomalonates, which affords benzocyclopentanone products **111** bearing an all-carbon quaternary center in good to excellent yields (Scheme 36). Triethyl ammonium salt was identified as the best ammonium to promote the transformation. As also shown by the authors, this acyl ammonium-assisted redox-neutral C−H activation could be utilized in the synthesis of *ortho*-olefinated acetophenones.

Under the mediation of rhodium(II) complex, *N*-aryl diazoamides are known to undergo intramolecular insertion of carbenoid into *ortho* C−H bond to generate a cyclic zwitterionic intermediate **113** (Scheme 37).[54] Hu and co-workers[55] in 2012 demonstrated the successful trapping of this intermediate with

2.4. Miscellaneous reactions

A palladium-catalyzed annulation of *sec*-alkyl aryl ketones and aryl iodides via dual C−H activation was reported by Cheng and co-workers[57] for the synthesis of phenanthrone derivatives (Scheme 39). Five- to seven-membered cyclic alkyl aryl ketones readily coupled with electron-deficient aryl iodides to provide phenanthrones **124** with an all-carbon quaternary center in generally high yields. For the mechanism (Scheme 40), ketone-directed Pd-catalyzed *ortho* arylation via C−H activation occurs first, which is followed by a second C−H activation to form a seven-membered palladacycle **126**. Enolization and subsequent rearrangement likely via a π-oxallyl intermediate takes place to afford **128**, which undergoes final reductive elimination to afford the phenanthrone products. The resulting Pd⁰ species is oxidized by silver ion to regenerate the active catalyst.

Cyclobutanols are known to undergo transition-metal-catalyzed ring opening through β-carbon elimination. In 2009, Cramer[58] and Murakami[59] independently reported rhodium-catalyzed asymmetric intramolecular transannulations of *tert*-cyclobutanols for the synthesis of highly substituted indanols bearing two quaternary stereogenic centers (Scheme 41,

Scheme 36. Rh-catalyzed annulation of phenacyl ammonium salts with α-diazomalonates.

Scheme 38. Rh-catalyzed enantioselective coupling of α-aryl-α-diazoacetates, indoles, and imines.
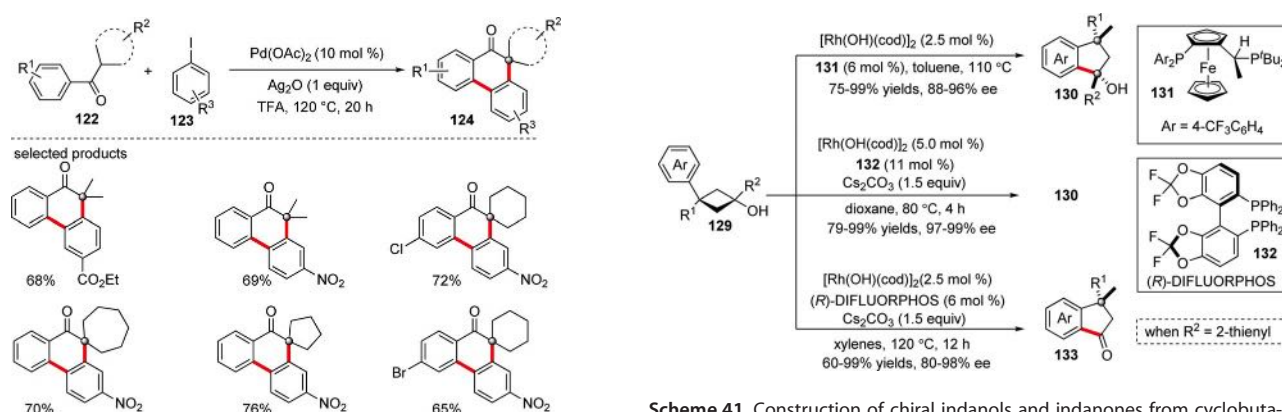
Scheme 39. Pd-catalyzed annulation of sec-alkyl aryl ketones and aryl iodides.
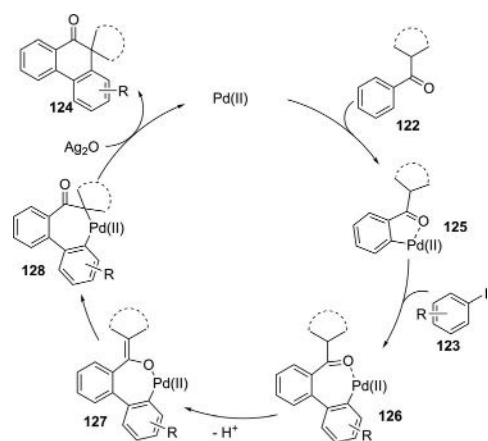
Scheme 40. Proposed mechanism for Pd-catalyzed annulation of sec-alkyl aryl ketones and aryl iodides.

Eqs (1) and (2)). A Josiphos-type ligand **131** and (R)-DIFLUORO-PHOS ligand **132** were employed by the two groups, respectively, both of which delivered the products in high enantio- and diastereoselectivities with a broad scope. The reaction can

Scheme 41. Construction of chiral indanols and indanones from cyclobutanols using rhodium catalysis.

be regarded as a formal insertion of arene C−H bond into a C−C bond with simultaneous C−H and C−C bond activation. For the mechanism (Scheme 42), it is believed that the reaction starts with the Rh-mediated ring cleavage via β-carbon elimination to give a Rh-alkyl species **135**. A 1,4-rhodium shift then follows to give **136**, which undergoes intramolecular addition
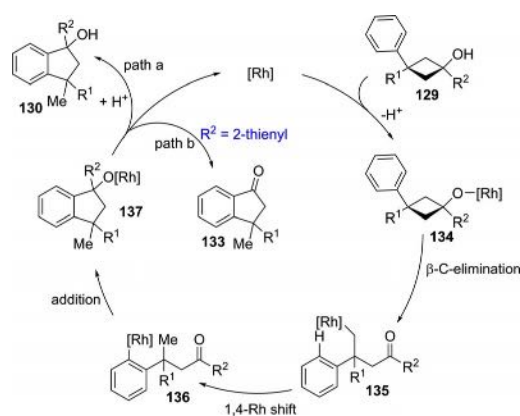
Scheme 42. Mechanism for the Rh-catalyzed construction of indanols and indanones from cyclobutanols.

of the Rh−C bond to the carbonyl providing the rhodium alkoxide **137**. Final protonolysis of **137** generates the tertiary alcohol products and releases the catalyst. Shortly after, Cramer et al.[60] demonstrated that 2-thienyl-substituted cyclobutanols preferentially converted to functionalized indanones under the same conditions [Scheme 41, Eq. (3)]. It is proposed that the final rhodium alkoxide **137** in the catalytic cycle prone to undergo β-carbon elimination to spill the thienyl ring rather than the protonolysis (Scheme 42).

A rhodium-catalyzed coupling of methylenecyclobutanes and sodium tetraarylborates with C−H bond activation was disclosed by Matsuda and co-workers[61] in 2012 (Scheme 43). The
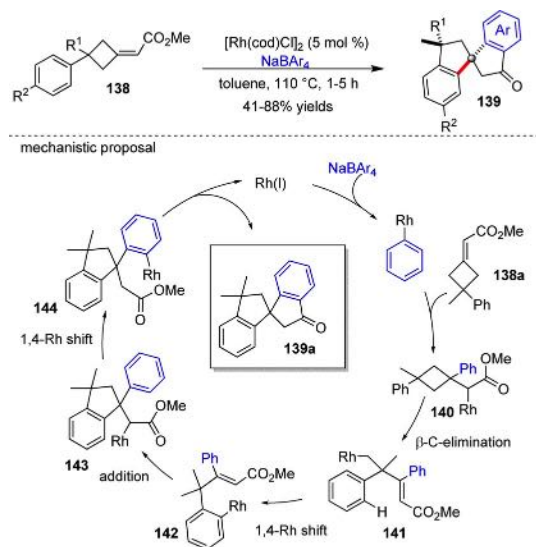
Scheme 43. Rh-catalyzed coupling of methylenecyclobutanes with arylborons and mechanism rationale.

reaction produced 1,1′-spirobiindanes **139** bearing a new all-carbon quaternary center in moderate to good yields. Mechanistically (Scheme 43), the annulation is proposed to start with transmetalation, and the reactive Rh-aryl intermediate attacks the olefin of methylenecyclobutanes to generate Rh-alkyl species **140**. Ring scission then occurs via β-carbon elimination to provides Rh-alkyl species **141**, which undergoes 1,4-rhodium shift to cleave the arene C−H bond giving the other Rh-aryl intermediate **142**. Intramolecular migratory insertion, followed by a second 1,4-rhodium shift, generates another Rh-aryl species **144**. Final insertion of the Rh−C bond into the ester carbonyl leads to the formation of 1,1′-spirobiindane products **139** with the departure of rhodium catalyst.

Matsuda group[62] in 2015 described an asymmetric annulation of 1,4-enynes with arylboronic acids under rhodium catalysis using (R)-MeO-BIPHEP as the chiral ligand (Scheme 44). The reaction delivered enantioenriched indanes bearing an all carbon quaternary center in good yields and high ee values. It is proposed that the initial generated arylrhodium via transmetalation undertakes a regioselective insertion to the alkyne to form **149**, which, upon a 1,4-Rh shift, yields an arylrhodium intermediate **150**. Intramolecular migratory insertion of **150** to the pendant 1,1-disubstituted alkene then generates **151** with
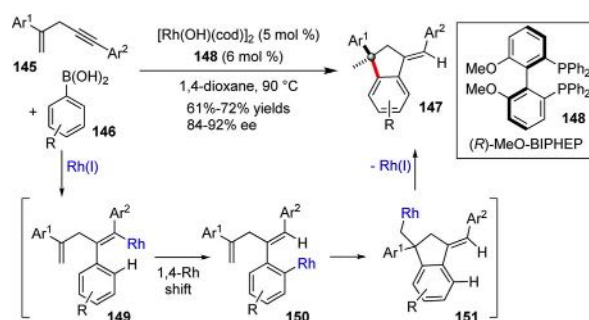
Scheme 44. Rh-catalyzed symmetric annulation of 1,4-enynes with arylboronic acids.

an all-carbon quaternary center. Final protonolysis produces the desired products **147** and release the catalyst.

An enantioselective cycloisomerization of 1,6-enynes via C(sp³)−H functionalization was reported by Tanaka group[63] in 2014 (Scheme 45). By using rhodium(I)/(S)-SEGPHOS as catalyst, the reaction afforded chiral bicyclo[3.1.0]hexane products **153** with an all-carbon quaternary center in good yields and ee values. It was observed that the carbonyl on the enyne linkage is crucial to the reaction which may serve as a chelating group to assist the C(sp³)−H activation.
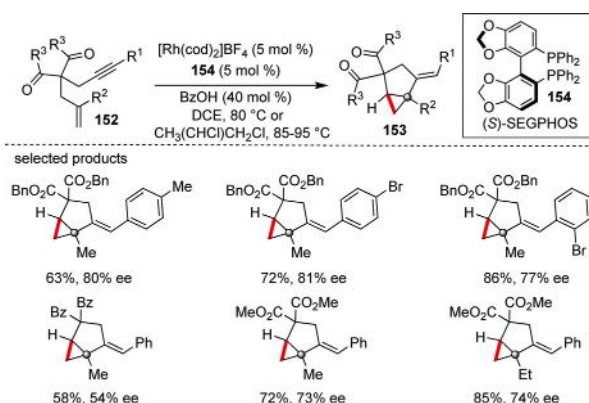
Scheme 45. Rh-catalyzed asymmetric cycloisomerization of 1,6-enynes.

The combination of C−H functionalization with intramolecular Heck reaction offers an efficient approach for the construction of polycyclic structures. In 2004, the Larock group[64] disclosed a palladium-catalyzed cyclization of substrate **155** to give fused polycycles **156** bearing all-carbon quaternary centers (Scheme 46). The cyclization is proposed to start with initial Heck-type reaction followed by 1,4-Pd shift to generate an arylpalladium intermediate **158**. Subsequent Pd-mediated C−H activation and final reductive elimination delivers the polycyclic products **156**. The proposed arylpalladium intermediate **158** can be also trapped intermolecularly through Heck, Suzuki, cyanation, and tandem reactions to generate the corresponding fused cyclic structures containing all-carbon quaternary centers.[65,66]

Interestingly, very recently Schoenebeck, Lautens, and co-workers[67] demonstrated that substrates **160**, with one-atom
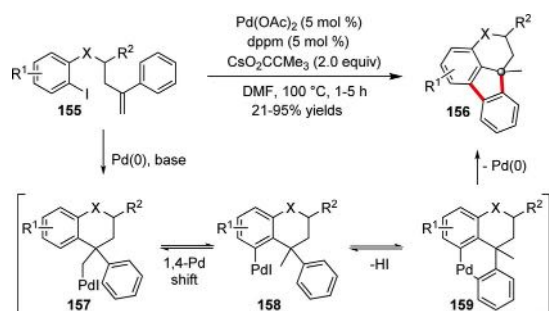
Scheme 46. Pd-catalyzed cyclization via Heck/C−H activation approach.

shorter linker than that of **155**, exhibited distinct reactivity under palladium catalysis via a common intermediate **161** (Scheme 47). Without external coupling partners, cyclization of **160** delivers spiro benzocyclobutene derivatives **162** in good yields under the catalysis of Pd(PtBu$_3$)$_2$ [Eq. (1)]. In the presence of alkyl halides, the reaction with a NHC-ligated palladium cat-
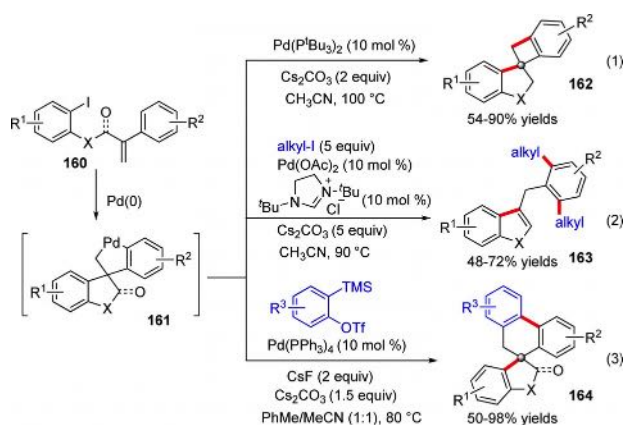
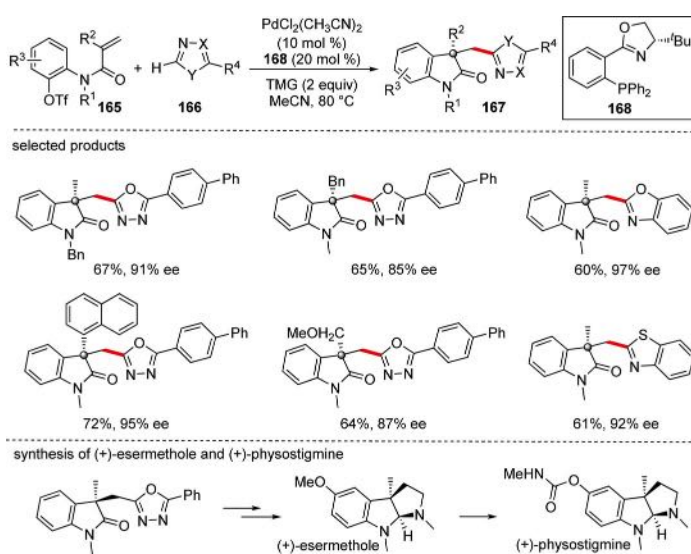**Scheme 47.** Pd-catalyzed divergent cyclizations via intermediate **161**.

Scheme 48. Pd-catalyzed asymmetric Heck/C−H functionalization between *N*-aryl acryl-amides and heteroarenes.

alyst proceeds in a pathway resembling the Catellani reaction[68] to generate *ortho* alkylated 3-benzylbenzofurans **163** [Eq. (2)]. In a subsequent report, Lautens and co-workers[69] employed benzyne as the coupling partner for the annulation, which leads to the formation of spirocycles **164** such as spirooxindoles and spirodihydrobenzofurans bearing all-carbon quaternary centers in good to excellent yields [Eq. (3)].

A intermolecular palladium-catalyzed enantioselective Heck/ C−H functionalization between *N*-aryl acrylamides and heteroarenes was reported by Zhu and co-workers[70] in 2015 for the formation of oxindoles with an all-carbon quaternary center (Scheme 48). By using PdCl$_2$(CH$_3$CN)$_2$ with a PHOX-type ligand **168** and TMG as a base, the products **167** could be obtained in 55–94% yields and 82–99% *ee* with good functional group compatibility. This domino process has been demonstrated in the synthesis of natural products such as (+)-esermethole and (+)-physostigmine (Scheme 48).

3. O-Substituted Quaternary Centers
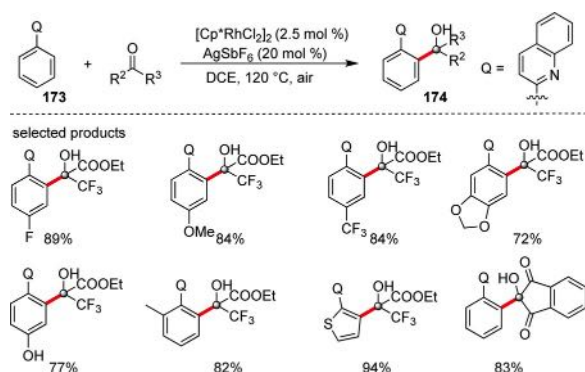
3.1. Addition of C−H bonds to ketones

Nucleophilic addition to ketones is one the most important reactions in organic synthesis for the construction of tertiary alcohols. Among various nucleophiles, unactivated C−H bonds, when properly activated by transition metals, have been recently established as a unique class of carbon sources for this purpose. Shibata and co-workers[71] in 2009 report a single case of intramolecular hydroarylation of *N*-aryl pyruvamide **169a**, by using iridium catalyst with (*S*)-H$_8$-BINAP as a ligand, to yield oxindole **170a** bearing a tertiary alcohol in 69% yield and 72% *ee* [Scheme 49, Eq. (1)]. Subsequently, Yamamoto and co-workers[72] expanded the scope of this reaction with *N*,*N*-dimethyl carbamoyl as a directing group by using iridium catalyst and a bidentate phosphoramidite ligand **172**. A variety of aromatic and aliphatic α-ketoamides were investigated to afford the desired 3-hydroxy-2-oxindoles **170b** in 69–99% yield and 80–99% *ee* [Scheme 49, Eq. (2)]. Based on a set of mechanistic investigations, it was demonstrated that the migratory insertion of the Ir−C bond to the carbonyl is both the rate-limiting and enantio-determining step.

Compared with intramolecular C−H addition to ketones, intermolecular counterparts require highly activated ketones because of high energy barrier of the addition step. Shi and co-workers[73] in 2013 reported a rhodium-catalyzed addition of arene C−H bond to activated ketones such as trifluoropyruvates and ninhydrin using quinoline as the directing group, which provides tertiary alcohols **174** in good to excellent yields (Scheme 50). It was found that a neighboring carbonyl to the ketone ensured a high yield, which may be used as a coordinating group to stabilize rhodium center and serve as a hydrogen bond acceptor to stabilize the alcohol products.

By using a pyrimidine as an directing group, the Kim laboratory[74] has recently demonstrated that
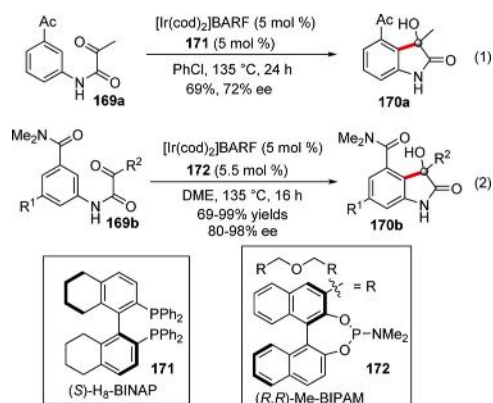
Scheme 49. Ir-catalyzed asymmetric intramolecular hydroarylation of ketones.

**Scheme 50.** Rh-catalyzed quinoline-directed addition of arene C—H bond to ketones.

heterocycles of indolines, indoles, pyrroles, and carbazoles underwent site-selective C—H bond addition to trifluoropyruvates under rhodium catalysis to provide the corresponding tertiary alcohols **177** in good yields (Scheme 51). It is noteworthy that indolines favor the C—H functionalization at C7 position, while indoles are selectively functionalized at C2 position. It was also found that pyrrole undertakes double C—H additions at sym-
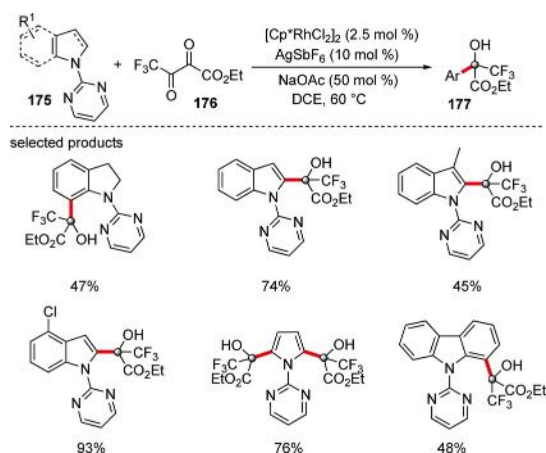
Scheme 51. Rh-catalyzed pyrimidine-directed addition of heterocyclic C—H bond to trifluoropyruvates.

metric C2 and C5 positions, but carbozole gives only single addition product.

A palladium-catalyzed addition of azole C—H bonds to isatins for the generation of 3-substituted-3-hydroxy-2-oxindoles was reported by Yang and co-workers[75] [Scheme 52, Eq. (1)]. Under
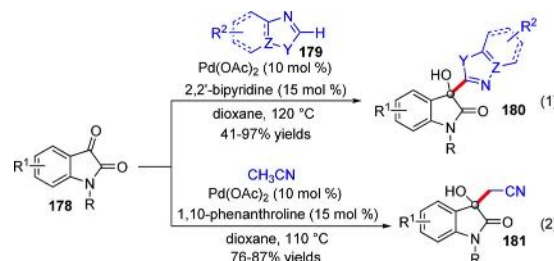

Scheme 52. Pd-catalyzed C—H additions to isatins.

the catalysis of Pd(OAc)$_2$ with 2,2′-bipyridine as the ligand, a series of azole derivatives including benzoxazoles, N-methylimidazole, benzimidazoles, thiazoles, benzothiazoles, and 1,3,4-oxadiazoles are all effective C—H sources for the addition reaction, generating the tertiary alcohol products **180** in good to excellent yields. In the same report, the author also demonstrated that acetonitrile could be used as a sp^3 C—H source to participate in palladium-catalyzed C—H addition to isatins, delivering the corresponding tertiary alcohols **181** in good yields [Scheme 52, Eq. (2)].

3.2. Additions to alkynes or allenes

Nucleophilic addition to ketones can be used as both directing and functionalizable groups in transition-metal-catalyzed C—H activation process to generate oxygen-containing functionalities. Woodgate and co-workers[76] in 1999, using a ruthenium catalyst, developed the first coupling of aryl ketones with alkynes to generate indenols, albeit with low yields and selectivity. This reaction was improved in 2011 by the Glorius group[77] by employing rhodium catalysis [Scheme 53, Eq. (1)]. Under optimized conditions, a range of aryl ketones readily annulated with alkynes to give tertiary indenols **182** in good to excellent yields. The reaction displayed high regioselectivity for unsym-
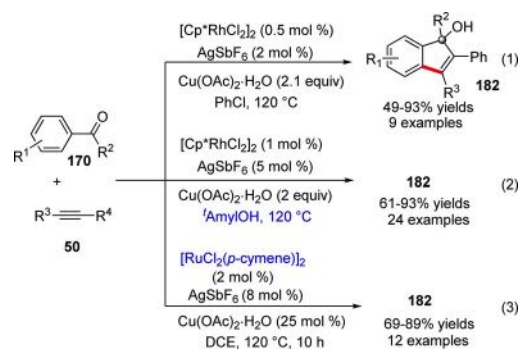
Scheme 53. Transition-metal-catalyzed annulation of aryl ketones with alkynes to generate indenols.

metrical alkyl aryl alkynes, but could not differentiate unsymmetrical aryl groups of the ketones, for example, 4-bromobenzophenone. In the same year, Cheng and co-workers[78] demonstrated that ^{t}AmylOH as the solvent was beneficial to ensure a high yield and a broader scope of the annulation [Scheme 53, Eq. (2)]. Jeganmohan and co-workers[79] in 2012 reinvestigated the ruthenium-catalyzed annulation by employing [RuCl$_2$(p-cymene)]$_2$ as the catalyst, which also delivered indenols **182** in high yields with a broad scope [Scheme 53, Eq. (3)].

Base on a previous vinylation protocol,[80] the group of Chen and Wang[81] developed a one-pot cascade sequence of rhodium-catalyzed vinylation/Ag$_2$CO$_3$-mediated dioxygenative cyclization between N-aryloxyacetamides and alkynes for the construction of dihydrobenzofuro[2,3-d]oxazoles **184** bearing two adjacent quaternary stereogenic centers (Scheme 54). Under the optimal conditions by using
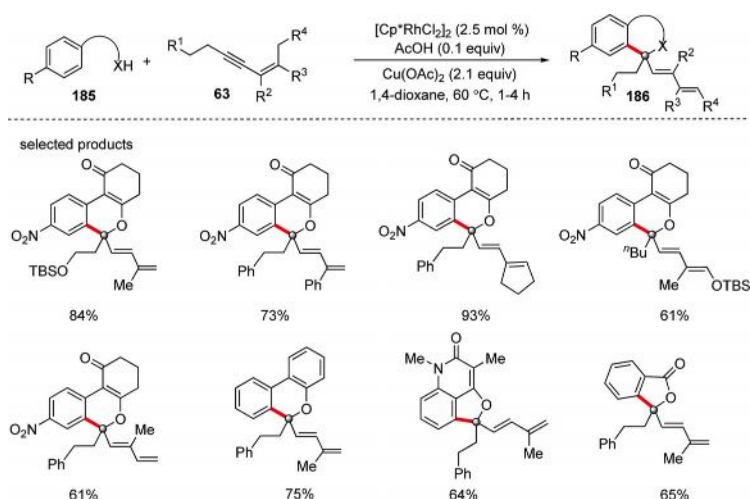

Scheme 55. Rh-catalyzed C—H activation/annulation with 1,3-enynes as one carbon component.

Scheme 54. Cyclization between N-aryloxyacetamides and alkynes.

5 mol % of [Cp*RhCl$_2$]$_2$ and 1.2 equivalent of Ag$_2$CO$_3$ in methanol at room temperature, a number of aryloxyacetamides readily coupled with symmetrical or unsymmetrical internal alkynes to form the desired heterocycles in high yields and regioselectivities.

Lam and co-workers[34] in 2014 reported a Rh-catalyzed oxidative annulation of 2-aryl-1,3-dicarbonyl compounds with 1,3-enynes to provide benzopyran or benzofuran derivatives **186** containing a quaternary center, in which the enynes served as one carbon partner for the annulation (Scheme 55). In addition to 2-aryl-1,3-dicarbonyl compounds, a range of arenes with enol, phenol, carboxylic acid, or imide directing groups are efficient C—H precursors, whose annulation with the 1,3-enynes produces a diverse range of heterocycles in good yields containing a quaternary center. It is noteworthy that the enynes containing allylic hydrogens cis to the alkyne was crucial to the annulation, which probably facilitates a 1,4-Rh shift process in the mechanism.

An interesting rhodium-catalyzed [3+2]/[5+2] annulation of 4-aryl 1,2,3-triazoles with two molecules of aryl alkynes in the presence of H$_2$O was disclosed by Li and co-workers[82] in 2015, which provides indenol[1,7-cd]azepin-1-ols **188** bearing a tertiary alcohol in good yields with excellent diastereoselectivity

(Scheme 56). Three equivalent of H$_2$O was found to be optimal to ensure a high yield. Replacing water with alcohols resulted in the corresponding ether products in moderate yields. A sulfonyl protecting group on the triazole was found to be crucial to the success of the reaction, while a benzyl protecting group prohibited the reaction. Since dual C(sp^2)—H functionalization was achieved in the reaction, for a substrate with a methyl occupying one of the ortho position of the benzene, only the [3+2] annulation resulting from single C(sp^2)—H functionalization was observed.
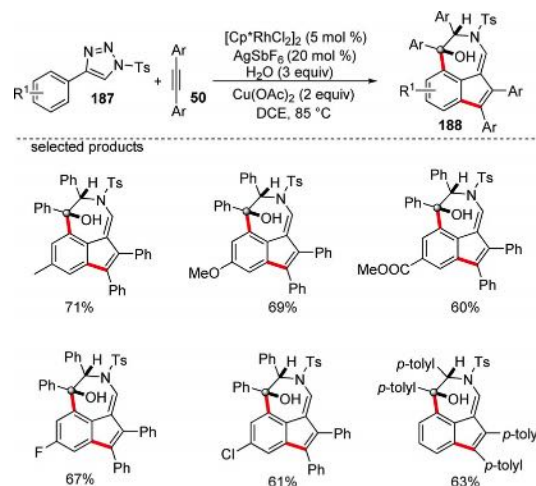
Scheme 56. Rh-catalyzed [3+2]/[5+2] annulation of 4-aryl 1,2,3-triazoles with aryl alkynes.

Formyl group is known to undergo transition-metal-catalyzed C—H activation for hydroformylation and related reactions.[83] In 2008, a rhodium-catalyzed asymmetric [4+2] annulation of benzene-linkered 4-alkynal **189** with isatins was disclosed by Tanaka and co-workers[84] for the generation of benzopyranones **190** bearing a spirocyclic quaternary center (Scheme 57). It was found that (R,R)-**191** could be used as the
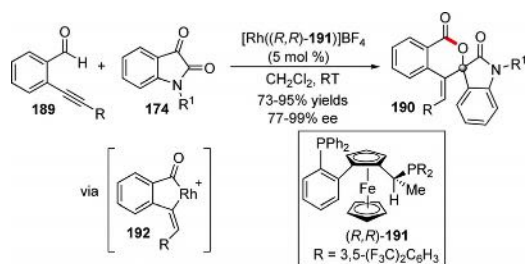
Scheme 57. Rh-catalyzed asymmetric [4+2] annulation of 4-alkynals with isatins.

Scheme 59. Rh-catalyzed [2+2+5] annulation of linked diynes with N-aryl nitrones.

optimal ligand, offering the spirocyclic benzopyranones in high yields and excellent enantioselectivities. A five-member rh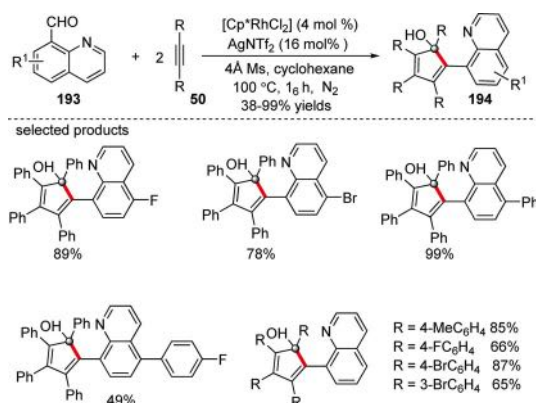odacycle **192** is proposed as the key intermediate that might be generated from the initial cleavage of the aldehyde C—H bond by rhodium and subsequent insertion into the alkyne. Subsequent migratory insertion to the carbonyl and reductive elimination then furnish the products.
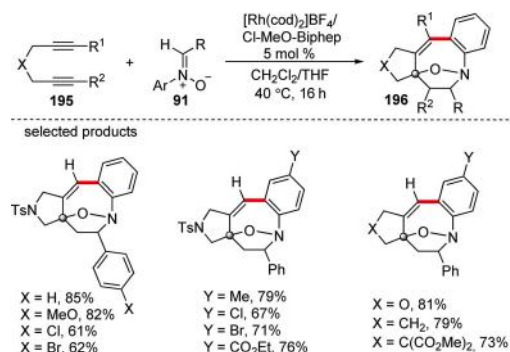
An interesting and challenge rhodium-catalyzed [2+2+1] annulation using 8-formylquinolines and two molecules of alkynes was recently reported by Li and co-workers (Scheme 58).[85] The reaction generated cyclopentadienols **194** with a quaternary center in good to excellent yields and a broad scope.

Scheme 58. Rh-catalyzed [2+2+1] annulation of 8-formylquinolines with ketones.

Wang and co-workers[86] in 2014 reported a rhodium-catalyzed [2+2+5] annulation of linked diynes with N-aryl nitrones to deliver bridged eight-membered heterocycles **196** containing a O-substituted quaternary center in good yields (Scheme 59). The nitrone group served as both a directing group for C—H activation and a five-atom unit in the annulation. Diynes with C-, O-, N-linkers are competent, and unsymmetrical diynes show excellent regioselectivity toward the annulation.

Similar to alkynes, allenes also participate in domino reactions initiated by transition-metal-catalyzed C—H activation to construct complex structural motifs. In 2015, Cheng and co-workers[87] developed a rhodium-catalyzed formal [4+1] annulation of aromatic carboxylic acids with allenes which provides

phthalide products **199** containing a quaternary center in good to excellent yields (Scheme 60). Internal allenes were also reactive giving high yields and good regioselectivities. In the same report, the authors extended the [4+1] annulation to include vinylic carboxylic acids with allenes to deliver 2-furanones in good yields with a quaternary center.
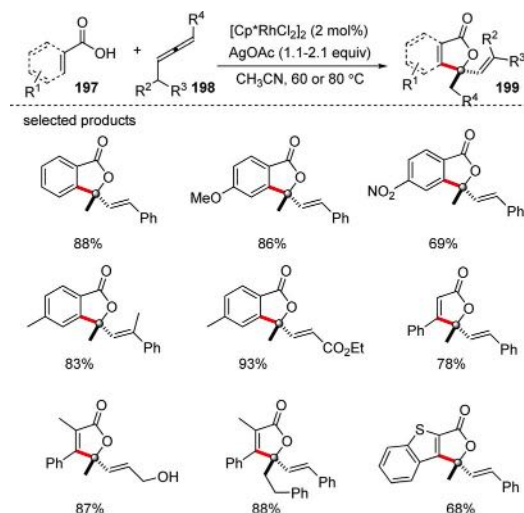
Scheme 60. Rh-catalyzed [4+1] annulation of aromatic or vinylic carboxylic acids with allenes.

A rhodium-catalyzed [5+1] annulation of alkenylphenols with allenes for the synthesis of 2,2-disubstituted 2H-chromenes **200** was reported by the group of Mascareñas and Guliías[88] in 2015 (Scheme 61). Good to excellent yields was obtained with a wide scope of substrates. Allenyl alcohols can also be used in the annulation which led to chromene products with a tethered ketone through enol-keto tautomerization. A triene intermediate **201** was observed when conducting the reaction at 40 °C, which converted into the chromene product upon heating at 60 °C within minutes (Scheme 62). This result then supports a mechanism that proceeds through rhodium-catalyzed alkene C—H addition to the allene to form the triene intermediate **201**, which undergoes a [1,7] sigmatropic hydrogen shift to generate an enone intermediate **202**.
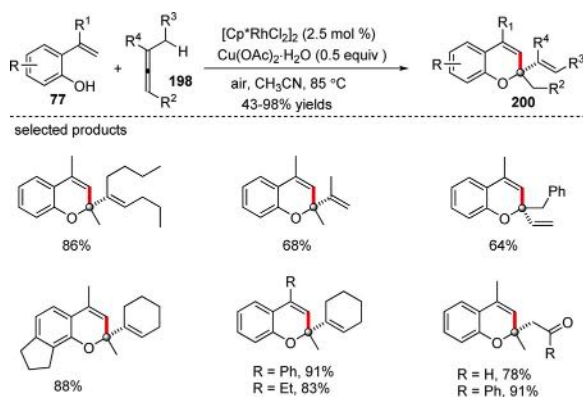
Scheme 61. Rh-catalyzed [5+1] annulation of alkenylphenols with allenes.
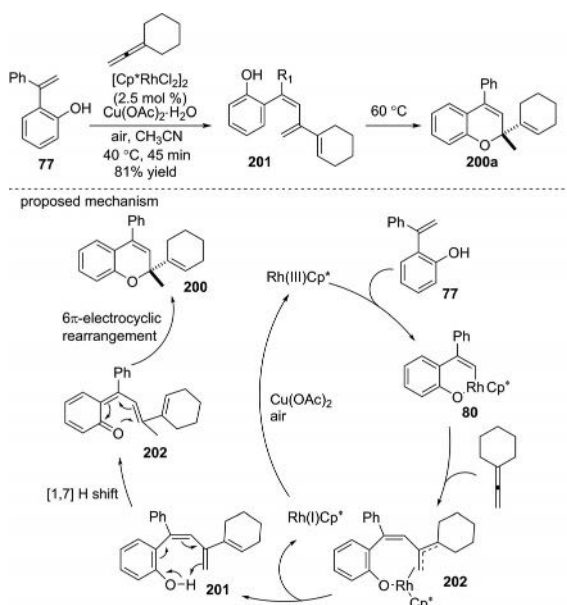
Scheme 62. Isolation of a key triene intermediate **201** and a possible mechanism.

A final 6π-electrocyclic ring closure then delivers the product (Scheme 62). Shortly after, Chen and co-workers[89] reported that cobalt also efficiently catalyze the [5+1] annulation of alkenylphenol with allenes to form chromenes in high yields with a broad scope.

3.3. Miscellaneous reactions

Main cyclopropenes are highly strained carbocycles and represent a type of versatile substrates in organic synthesis.[90] Wang and co-workers[91] in 2014 reported a mild rhodium-catalyzed redox-neutral transannulation of N-phenoxyacetamides with cyclopropenes (Scheme 63). The reaction provided 2H-chromenes **204** that contains an O-substituted quaternary center in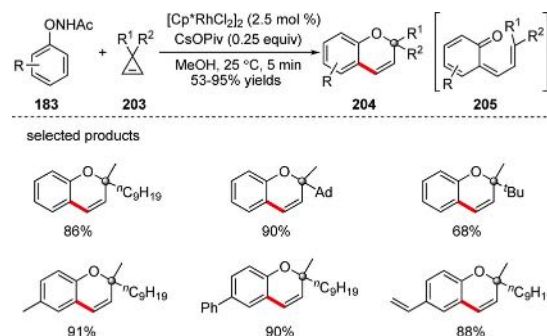 good to excellent yields with good functional group tolerance. Revealed by DFT calculations, Xia and co-workers[92] subsequently proposed that a dearomatized (E)-6-alkenylcyclohexa-2,4-dienone **205** serves as the key intermediate which generates the 2H-chromenes products via 6π-electrocyclization.

Scheme 63. Rh-catalyzed annulation of N-phenoxyacetamides with cyclopropenes.

A mild rhodium-catalyzed three component coupling of N-phenoxyacetamides, diazomalonates and alcohols was reported by Yi and Xu et al.,[93] which provides phenol derivatives with an ortho-substituted quaternary center in good yields (Scheme 64).
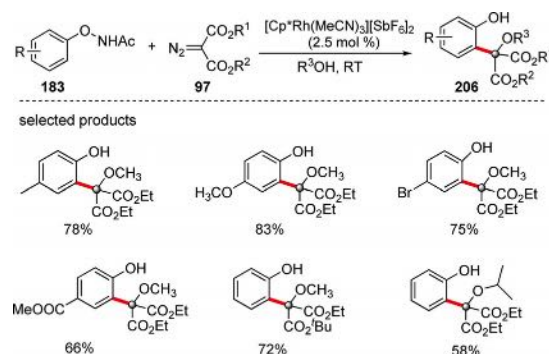
Scheme 64. Rh-catalyzed three components coupling reactions of N-phenoxyacetamides, diazomalonates, and alcohols.

The strained 7-oxabenzonorbornadienes **208** tend to undergo ring-opening due to the ring strain and the propensity to form aromatic naphthalenes under various conditions.[94] Liu and co-workers[95] recently disclosed an interesting coupling of alkynols **207** and 7-oxabenzonorbornadienes in the presence of H_2O via synergistic rhodium and scandium catalysis (Scheme 64). The reaction afforded spirocyclic dihydrobenzo[a]fluorenefurans **209** containing O-substituted quaternary center in good yields. A transient hemiketal group, formed through hydration of the alkynols, was proposed to serve as a directing group facilitating C−H activation to form intermediate **210**. Subsequent migratory insertion leads to the formation of intermediate **211**, which undergoes scandium-mediated dehydrative naphthylation to form hemiketal **212**. Final intramolecular Prins-type cyclization furnishes the products (Scheme 65).

4. N-Substituted Quaternary Centers

N-Substituted quaternary centers are key structural elements in pharmaceuticals and natural products.[96] Constructing N-substituted quaternary centers by C−H functionalization repre-
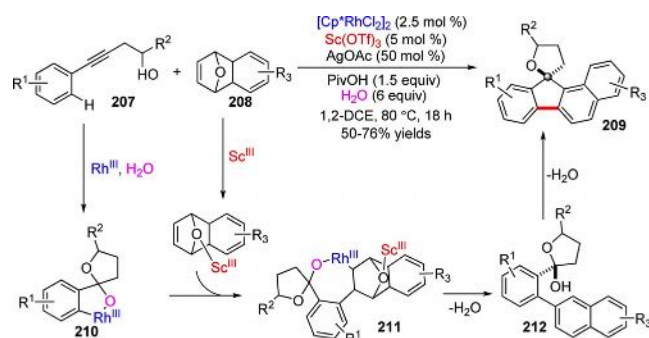
Scheme 65. Coupling of alkynols and 7-oxabenzonorbornadienes via rhodium and scandium co-catalysis.

sents a new and atom-economy approach; however, straightforward C−H addition to ketimines for this purpose is rarely reported, probably due to poor nucleophilicity of C-M intermediates resulting from C−H activation.[3c] Instead, a wide range of domino processes initiated by C−H activations are capable of converting ketimines into N-substituted quaternary centers.

4.1. [3+2] Annulation of aryl ketimines with unsaturated compounds

Ketimines are widely used as directing groups for *ortho*-C−H activation of arenes,[97] which, however, often participate in a follow-up [3+2] annulation with a range of unsaturated coupling partners such as alkenes, dienes, alkynes, and allenes to deliver cyclic N-substituted quaternary centers. A general mechanism for the [3+2] annulations of such process is outline in Scheme 66. Initial imine-assisted *ortho*-C−H activation of aro-
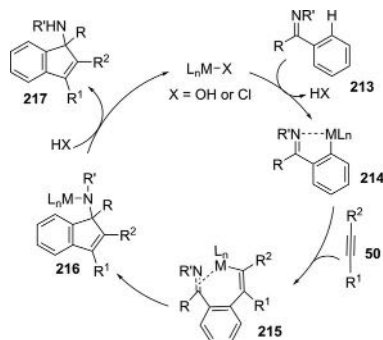

Scheme 66. A general mechanism for transition-metal-catalyzed [3+2] annulation of ketimines with alkynes.

matic ketimine **213** generates a five-membered cyclometalated complex **214**, which undergoes migratory insertion to the unsaturated bonds, for example, alkynes, to form an imine-chelated metal intermediate **215**. Then an intramolecular nucleophilic addition of C−M species to the ketimine gives an amido intermediate **216**, upon final protonolysis, which releases *tert*-carbinamine products **217** and regenerates the catalyst. In what follows, the annulations will be discussed according to the type of ketimines.

4.1.1. With free N−H aryl ketimines

In 2010, Zhao and co-workers[98] reported the first rhodium-catalyzed [3+2] annulaton of aryl N−H ketimines with alkynes for the generation of free amino indenes **217** with a N-substituted quaternary center [Scheme 67, Eq. (1)]. A relatively high tem-
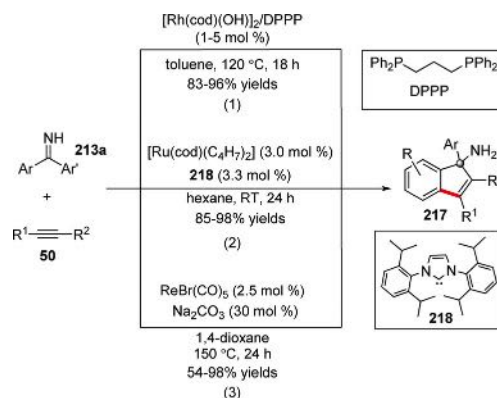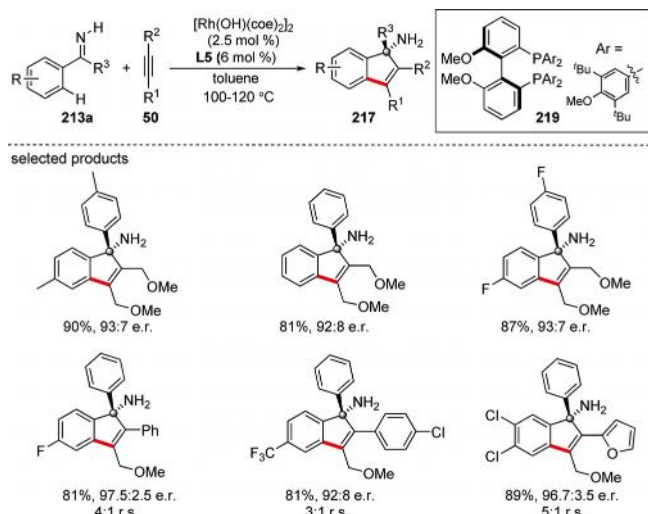

Scheme 67. [3+2] annulations of aryl N-H ketimines with alkynes via C−H activation.

perature is required to ensure a high yield of the products. The authors subsequently in 2013 improved this transformation by using ruthenium catalyst with NHC **218** as a ligand and considerably enhanced the reaction efficiency under mild conditions [Scheme 67, Eq. (2)].[99] This is likely due to the electronrichness of NHC ligand facilitating the insertion of Ru−C bond to the alkyne π-system. Afterwards in 2016, Wang and co-workers[100] also realized the [3+2] transformation using ReBr(CO)₅ catalyst without ligands, albeit with a high temperature [Scheme 67, Eq. (3)].

The enantioselective [3+2] annulations of aryl N−H ketimines with alkynes was first attempted in a single case by Zhao and co-workers[98] with rhodium catalyst and (*R*,*R*)-DIOP ligand, which only afforded a modest 51 % *ee*. Shortly after, the Cramer group[101] realized a rhodium-catalyzed highly enantioselective [3+2] annulation of free N−H ketimines with alkynes to deliver the indenamines **217** in good to high yields with excellent enantioselectivities by using **219** as the chiral ligand (Scheme 68).

Cramer and co-workers[102] extended the [3+2] annulations to include terminal allenes as effective coupling partners [Scheme 69, Eq. (1)]. Under rhodium catalysis with phosphine ligand **222**, the annulation delivered dihydroindenylamines **220** bearing an exocyclic alkene in good yields with high regio- and diastereoselectivity. When allenes bearing an ester group were applied, the newly formed amine group simultaneously cyclized with the ester to form fused lactams **221** in good yields. In 2013, the same group[103] reported the enantioselective [3+2] annulation of aryl N−H ketimines with 1,3-disubstituted allenes through a dynamic kinetic asymmetric transformation (DYKAT) approach [Scheme 69, Eq. (2)]. By employing [Rh(cod)(OH)]₂ and (*R*)-BINAP as a ligand, highly functionalized indenylamines **220** were isolated in good yields with excellent *E/Z*-, diastereo-, and enantioselectivities.

Scheme 68. Enantioselective [3+2] annulation of aryl N—H ketimines with alkynes.
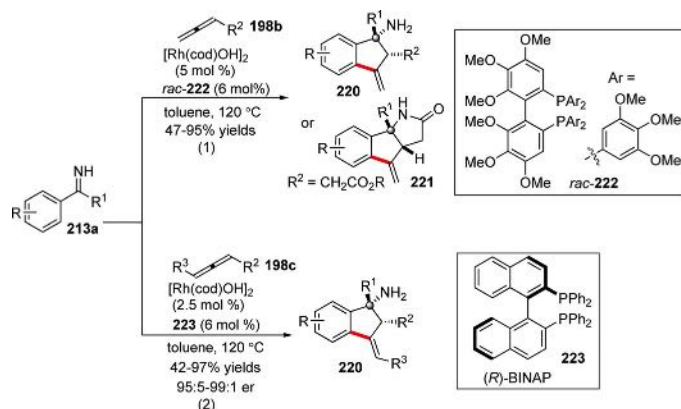
Scheme 69. Rh-catalyzed [3+2] annulation of aryl N—H ketimines with allenes.

4.1.2. With acyclic N-protected aryl ketimines

Other than N—H ketimines, a range of N-protected aromatic ketimines also efficiently participate in transition-metal-catalyzed [3+2] annulations with unsaturated coupling partners (Scheme 70). Takai and Kuninobu[104] in 2010 firstly published a rhenium-catalyzed [3+2] annulation of N-aryl or N-alkyl aromatic ketimine with terminal allenes to provide aminoindanes 220 [Eq. (1)]. In 2015, a manganese-catalyzed [3+2] annulation of N-aryl ketimines with alkenes was reported by Ackermann et al.[105] [Eq. (2)], and subsequently an iridium-catalyzed [3+2] annulation of N-sulfonyl ketimines with dienes was accomplished by Nishimura et al.[106] [Eq. (3)]. Around the same time, Li and co-workers[107] demonstrated that trifluoromethanesulfonyl alkynes could be applied in rhodium-catalyzed [3+2] annulation with O-methyl oximes to afford amino indene products 229 [Eq. (4)].
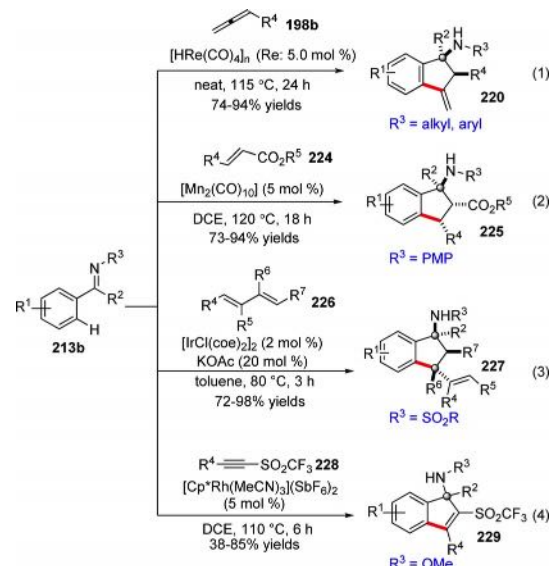
Scheme 70. [3+2] annulations between N-protected aromatic imines with allenes, alkenes, dienes, and alkynes.

4.1.3. With cyclic aryl ketimines

Main transition-metal-catalyzed [3+2] annulation of cyclic aryl ketimines with unsaturated coupling partners via C—H activation affords a promising way for construction of N-containing spirocyclic compounds. In this context, after Dong's first report[108] of rhodium-catalyzed [3+2] annulation of cyclic N-sulfonyl ketimines with alkynes, Wang et al.[109] subsequently in 2016 realized this transformation by using less-expensive cobalt catalyst. The enantioselective variant of the [3+2] annulations was developed in the same year by the Cramer group[110] by using a chiral rhodium catalyst 11, which generates the spirocyclic compounds 231 in high yields and enantioselectivities (Scheme 71). Mechanistic investigations indicated that the addition across the imine is the enantio-determining step in the catalytic cycle.
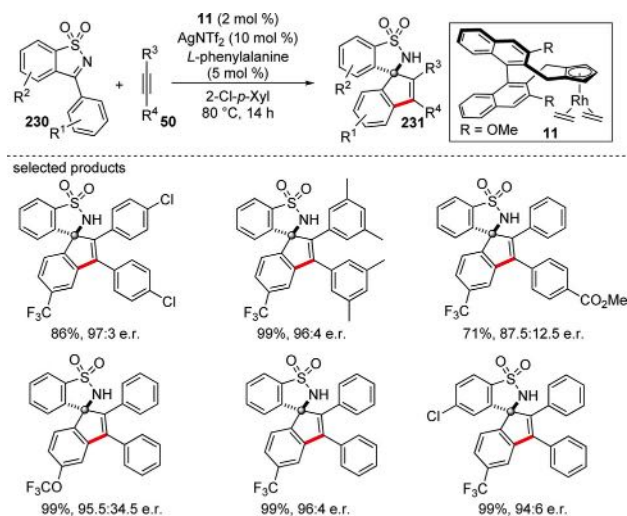
Scheme 71. Enantioselective [3+2] annulation of cyclic N-sulfonyl ketimines with alkynes.

By intercepting of aldehydes in the above [3+2] annulation, Dong, Qian, and co-workers[111] developed an interesting rhodium-catalyzed three-component annulation for the construction of polycyclic skeletons **241** in high yields with excellent diastereoselectivity (Scheme 72). Stoichiometric amount of (Boc)$_2$O
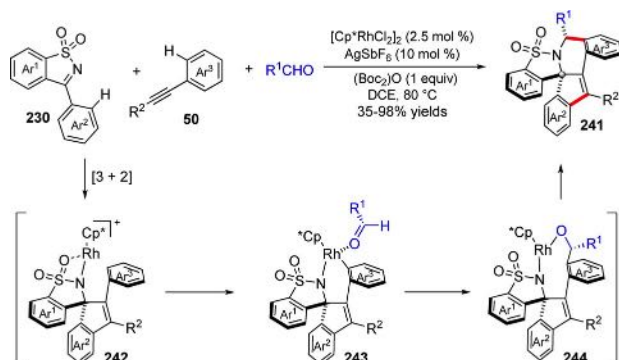
Scheme 72. Rh-catalyzed three-component reaction of imines, alkynes, and aldehydes.

was employed to promote the reaction. In a possible mechanism, the initial formed spirocyclic intermediate **242** through [3+2] annulation undergoes further sulfonamide-assisted C−H activation to form Rh-C species **243**. Addition of **243** to an aldehyde then generates a rhodium oxide species **244** that undergoes cyclization to give the product **241**. (Boc)$_2$O may act as a protecting reagent to facilitate a possible S_N1 cyclization of **244** to afford the final product.

In addition to alkynes, dienes and alkenes can be also applied in the [3+2] annulations with cyclic N-sulfonyl ketimines to synthesize highly functionalized spirocycles, as reported by the groups of Nishimura[112] and Li,[113] respectively (Scheme 73, eqs 1 and 2). Interestingly, with a successive double C−H activation process, Wei and co-workers[114] reported the use of thiophenes as the C2 partner in the rhodium-catalyzed [3+2] annulation with cyclic N-sulfonyl ketimines, which gives a rapid
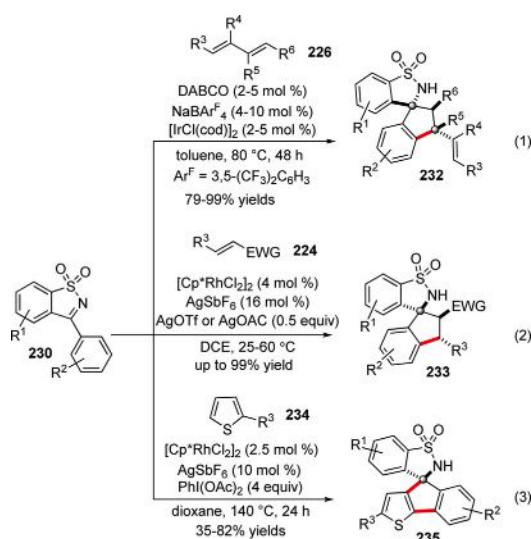
Scheme 73. [3+2] annulations of cyclic N-sulfonyl ketimines with dienes, allenes, and thiophenes.

access to spirocyclic sultams **235** in good yields [Scheme 73, Eq. (3)].

Cyclic N-acyl aryl ketimines, often existing as hydrate form, are also efficient precursors for transition-metal-catalyzed [3+2] annulations. In 2013, Nishimura and co-workers[115] developed a highly enantioselective [3+2] annulation of cyclic N-acyl ketimines with 1,3-dienes by using iridium catalyst with (S,S)-**238** as a chiral ligand [Scheme 74, Eq. (1)]. In 2016, the same group[116] reported a cationic iridium/BINAP system to catalyze the asymmetric [3+2] annulation of cyclic N-acyl ket-
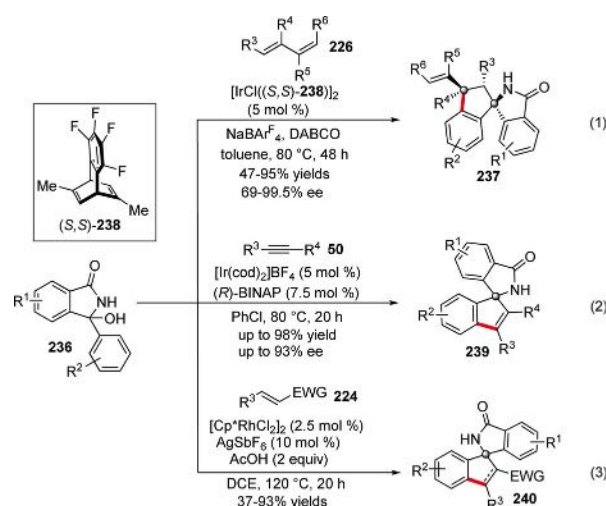
Scheme 74. [3+2] annulation using cyclic N-acyl ketimines.

imines with internal alkynes to achieve high yields and *ee* values [Eq. (2)]. Very recently, a rhodium-catalyzed [3+2] annulation of N-acyl ketimines with various activated olefins is described by the Kim group [Eq. (3)].[117] It was found that olefins of maleimides, maleates, fumarates, and cinnamates led to the formation of spiroindane products via the [3+2] annulation, while acrylates and quinones furnished unsaturated spiroindene products resulting from β-H elimination and subsequent Prins-type cyclization.

Cyclic enamines **245** were also employed in the rhodium-catalyzed [3+2] annulation with alkynes by the group of Li and Xia,[118] which provides spiro[indene-1,2′-pyrrolidine] compounds **246** in good yields with excellent functional group tolerance (Scheme 75). Mechanistically, initial enamine-directed C−H activation generates rhodium intermediate **247**, which undergoes insertion to the alkyne, followed by intramolecular addition of resulting vinyl C−Rh species to the C=C bond of the enamine leading to intermediate **250**. Final protonolysis of **250** then produces products **246** and regenerates the active rhodium catalyst with the aid of Cu(OAc)$_2$.

4.2. [4+1] Annulation of aromatic amides with unsaturated compounds

4.2.1. With aldehydes

Amides are efficient directing groups in transition-metal-catalyzed C−H functionalization, which, however, often participate
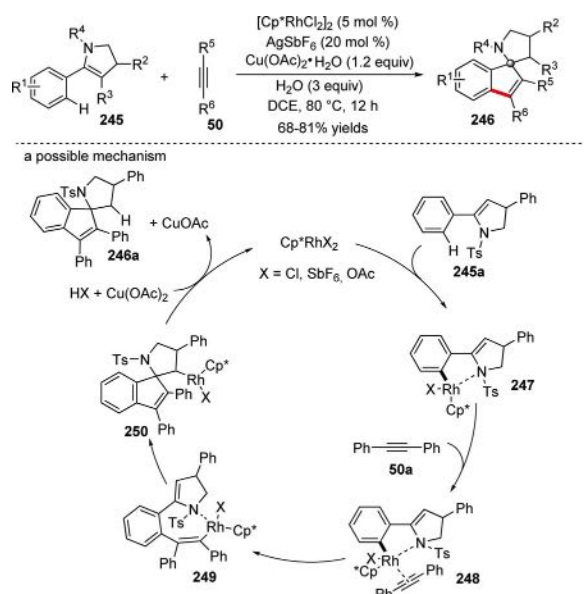
Scheme 75. Rh-catalyzed [3+2] annulations of cyclic N-sulfonyl enamines with alkynes.

broad scope [Scheme 77, Eq. (1)]. The quinones played a dual role as both one carbon component for the annulation and oxidant. Very recently, a cobalt-catalyzed [4+1] cyclization of benzimidates with maleimides was also reported by Zhang et al.[123] [Scheme 77, Eq. (2)]. Intriguingly, this transformation occurs in the absence of oxidant with the liberation of hydrogen instead. The resulting spirocyclic compounds **257** were prepared in generally high yields, and a wide variety of functional groups were well tolerated.
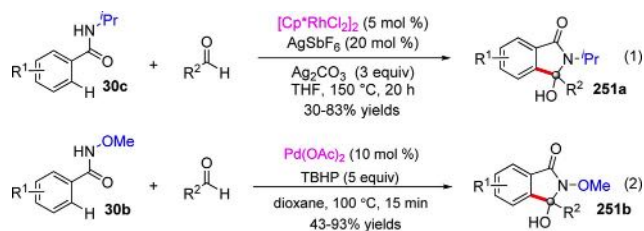

Scheme 77. [4+1] annulations using alkenes as one-carbon component.

in the coupling to generate various N-containing heterocycles.[119] A rhodium-catalyzed oxidative [4+1] annulation of benzamides **30c** with aldehydes was reported in 2012 by Kim and co-workers,[120] which provides hydroxyisoindolinones **251** in good yields with a broad scope [Scheme 76, Eq. (1)]. A high
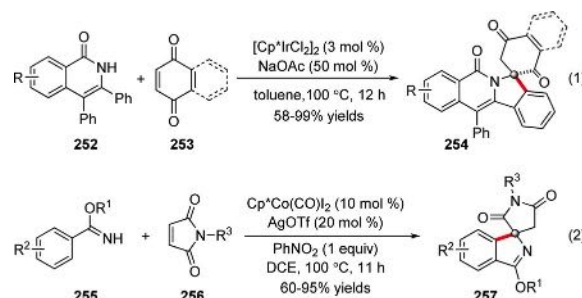

Scheme 76. [4+1] annulations of benzamides with aldehydes.

temperature (150 °C) was required for the reaction probably facilitating the rate-limiting insertion of aldehyde into a rhodacycle intermediate. In the following year, the [4+1] annulation of N-OMe benzamides **30b** with aldehydes was reported by Zhao and co-workers[121] by using palladium catalysis with TBHP as oxidant [Scheme 76, Eq. (2)]. This reaction proceeded under relatively mild conditions with short period of time; however, the mechanism was believed to proceed in radical process based on a set of control experiments.

4.2.2. With alkenes or allenes

Wang and co-workers[122] in 2015 demonstrated an interesting iridium-catalyzed oxidative [4+1] annulation of N—H isoquinolones **252** with 1,4-benzoquinones or 1,4-naphthoquinones, which afforded polycyclic compounds **254** containing a spiro N-substituted quaternary center in excellent yields with a

A regioselective rhodium-catalyzed [4+1] annulation of aromatic or vinylic amides with α-allenols was disclosed recently by the group of Lu and Liu,[124] which provides an efficient method for the synthesis of isoindolinones and 1,5-dihydropyrrol-2-ones bearing a N-substituted quaternary center in generally high yields (Scheme 78). The hydroxyl group on the allene substrate is essential in controlling the chemo- and regioselectivities probably by coordination to the rhodium catalyst.
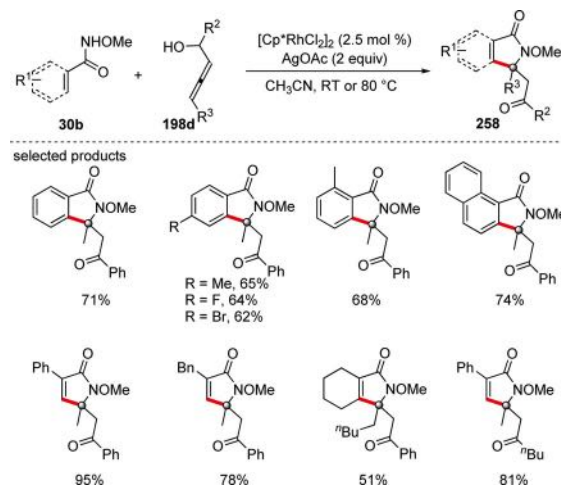
Scheme 78. Rh-catalyzed [4+1] annulation of aromatic or vinylic amides with α-allenols.

4.2.3. With alkynes

Propargyl alcohols as a one-carbon unit to participate in a redox-neutral [4+1] annulation with benzamides under either rhodium or ruthenium catalysis was disclosed recently by Liu,

Zhou, and co-workers (Scheme 79).[125] This transformation gave a series isoindolinones **258** with an N-substituted quaternary center in good yields.

Scheme 79. [4+1] annulation of benzamides with propargyl alcohols under rhodium or ruthenium catalysis.

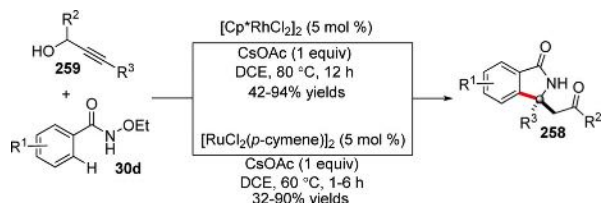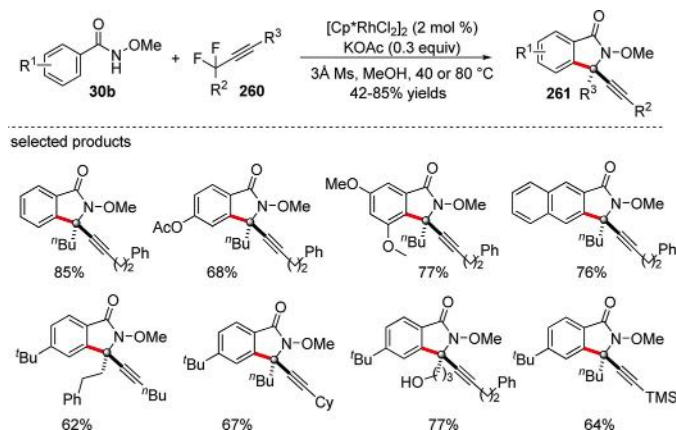An amazing and beautiful rhodium-catalyzed defluorinative [4+1] annulation reaction of benzamides with α,α-difluoromethylene alkynes was recently reported by Feng, Loh, and co-workers[126] for the construction of alkynyl-substituted isoindolin-1-ones **261** in high yields (Scheme 80). Intriguingly, the 2-


Scheme 80. Rh-catalyzed defluorinative [4+1] annulation of benzamides with α,α-difluoromethylene alkynes.

fold C−F bond cleavage offers an overall oxidant-free functionalization of C−H and N−H bonds, which resulted in net carbon-carbon triple bond relocation. In a simplified reaction pathway (Scheme 81), first chelation-assisted C−H bond cleavage of benzamide **41a** affords a five-membered rhodacycle **262**, which undertakes a regioselective migratory insertion to the alkyne to provide a seven-membered rhodacycle **263**. Cleavage of one of the C−F bonds takes place to afford allene **264**, which undergoes intramolecular aminorhodation to generate alkenyl rhodium intermediate **265**. At this stage, the second β-F-elimination occurs to account for the generation of desired product **258** accompanied by the catalyst regeneration.

Very recently, by tuning the electronic properties of Cp ligands, the Chang group[127] realized a divergent rhodium-catalyzed [4+1] and [4+2] annulations of conjugated enynones with benzamides, which provides isoindolinones **267** and tricyclic isoquinolinones **268**, respectively (Scheme 82). The presence of electron-withdrawing substituents on the Cp ligand
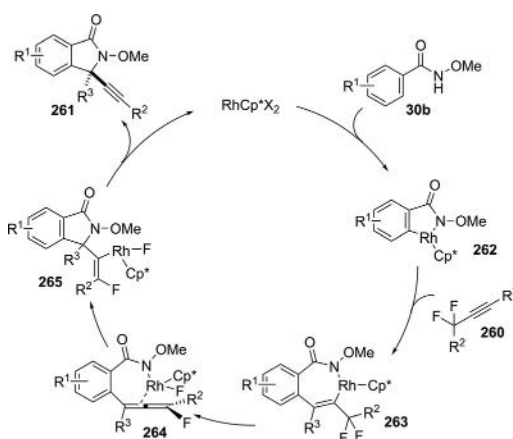
Scheme 81. A possible mechanism for Rh-catalyzed defluorinative [4+1] annulation.
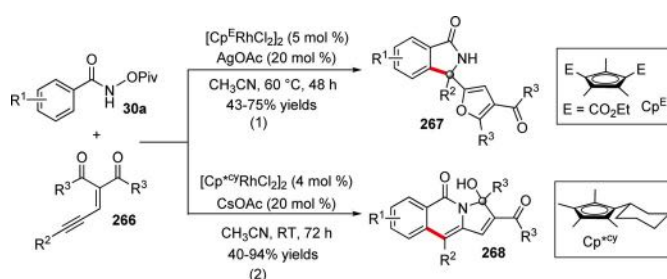
Scheme 82. Divergent Rh-catalyzed [4+1] and [4+2] annulations of conjugated enynones with benzamides.

(CpE) resulted in a formal carbene transfer facilitating the [4+1] cyclization, while electron-rich Cp ligand (Cp*cy) favors the triple bond insertion thus leading to the [4+2] annulation. It was proposed that the divergent reactivity may attribute to the change of the Lewis acidity of the resultant Cp-bound rhodium species.

4.2.4. With diazo compounds

Diazo compounds have been widely applied as one-carbon component in transition-metal-catalyzed [4+1] annulation via C−H functionalization. The Rovis group[128] in 2013 reported the first Rh-catalyzed [4+1] annulation of O-pivaloyl benzhydroxamic acids with donor/acceptor diazo compounds. Subsequently in 2014, Yu's group,[129] by using N-OAc amides as directing group, extended the scope of the annulation to include acceptor/acceptor diazo compounds. It is the Cramer group[130] that developed the asymmetrical version of the [4+1] annulation of benzamides with diazo compounds by employing a chiral rhodium catalyst **270**, which afforded a broad range of isoindolones **269** with quaternary carbon centers in good yields and excellent enantioselectivities (Scheme 83). The catalytic cycle is proposed to start with a chelation-assisted C−H activation to form a five-membered rhodacycle **271** (Scheme 84). The coordination of the diazo compounds with **271** forms a diazonium intermediate **272**, with the extrusion of N2 and 1,2-migratory insertion which converts into six-mem-
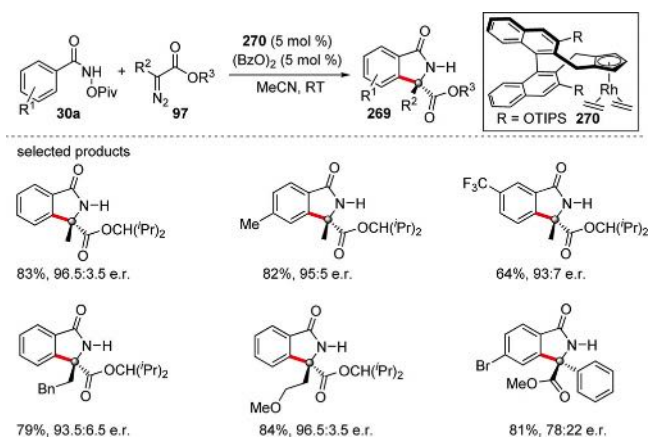
Scheme 83. Rh-catalyzed asymmetric [4+1] annulation of benzamides with diazo compounds.
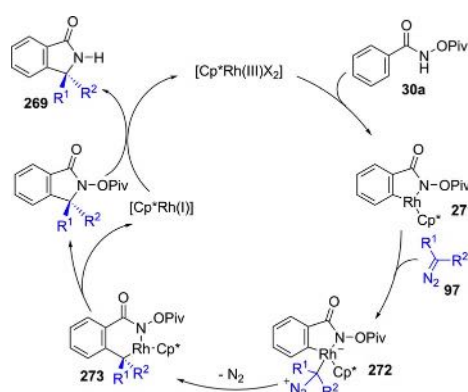
Scheme 84. Proposed mechanism for [4+1] annulations of benzamides with diazo compounds.

bered intermediate **273**. Final C−N reductive elimination lead to the formation of the [4+1] products and the N−OR serves as an internal oxidant to regenerate the catalyst with N−O bond cleavage.

Indoles and pyrroles, with *N*-OPiv amides directing groups, can also applied in C−H functionalization/[4+1] annulations

Scheme 85. Enantioselective [4+1] annulation of indoles/pyrroles with diazo compounds.

with diazo compounds to furnish highly functionalized fused heterocycles. Cui and co-workers[131] in 2014 firstly reported the racemic version of this reaction. Very recently, Song and co-workers[132] developed the enantioselective variant of the annulation by employing chiral rhodium ca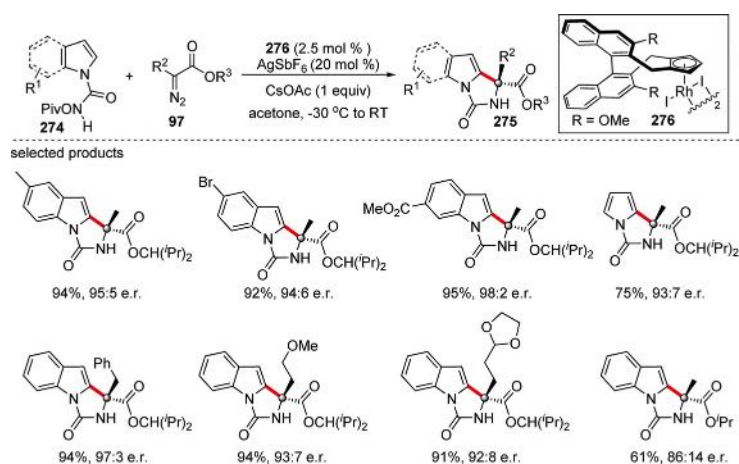talyst **276** (Scheme 85). The resulting 1,2-dihydro-3H imidazo[1,5-a]indol-3-one derivatives **275** having a N-substituted quaternary center could be obtained in high yields and excellent enantio-selectivities.

4.3. Miscellaneous reactions

Diazo compounds In 2005, by using $Ru_3(CO)_{12}/NH_4PF_6$ as the catalyst, an efficient C−H activation/hydroamination of benzo-cyclic secondary amines with two molecules of terminal al-kynes was developed by Yi and co-workers[133] for the synthesis of tricyclic quinoline derivatives **278** bearing an N-substituted quaternary center [Scheme 86, Eq. (1)]. Shortly after, the reac-
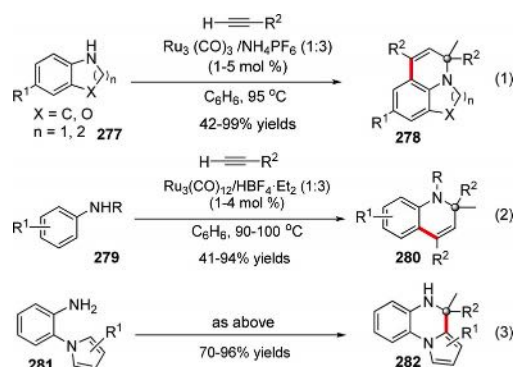
Scheme 86. Synthesis of quinoline and quinoxaline derivatives bearing an *N*-substituted quaternary center.

tion was extended by the same group with anilines as the C−H precursor to couple with terminal alkynes under the catalysis of $Ru_3(CO)_{12}/HBF_4\cdot OEt_2$, which produces quinolines **280** and quinoxalines **282** in good yields, respectively [Scheme 86, Eqs. (2) and (3)].[134]

It is proposed that an acetylide cationic complex **283** is initially generated from the reaction of ruthe-nium hydride with two molecules of terminal al-kynes. Hydroamination of the acetylide species **283** leads the formation of a cationic enaminyl species **284**, which undergoes *ortho*-arene C−H activation and reductive elimination to form *ortho*-metalated species **286**. Alkyne insertion occurs to give **287**, which is followed by alkene insertion/cyclization to produce a cationic Ru-alkyl species **288**. Final inter-ception with a terminal alkyne delivers the products **280** and regenerates the acetylide species **283** that enters into the catalytic cycle (Scheme 87).

N−S bonds as oxidizing directing groups are rarely introduced in transition-metal-catalyzed C−H func-tionalization, probably due to the lower oxidizing po-tential of a *N*-S bond.[135] Recently, Li and co-work-ers[136] disclosed a rhodium-catalyzed redox-neutral
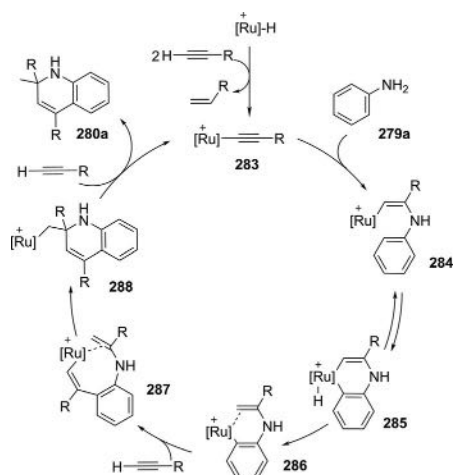
Scheme 87. Proposed mechanism for the Ru-catalyzed annulation of anilines with terminal alkynes.

annulation of *N*-sulfinyl ketoimines with two molecules of acrylates for the formation of 1*H*-isoindoles **292** bearing an *N*-substituted quaternary center, in which the cleavage of *N*-S bonds of *N*-sulfinyl ketoimines served as the oxidants (Scheme 88). A broad scope of substrates has been employed in the transformation to produce the products in good to excellent yields.
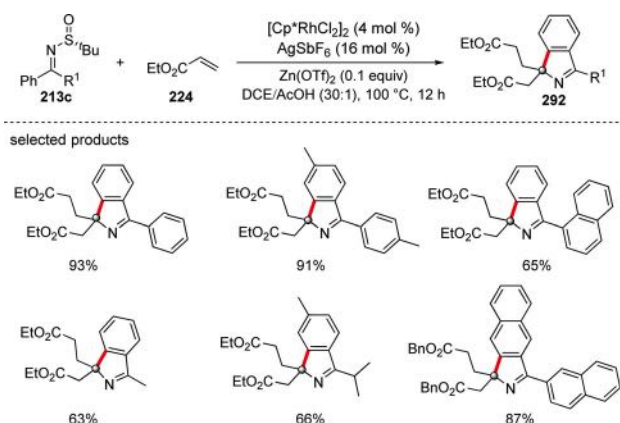
Scheme 88. Rh-catalyzed redox-neutral annulation of *N*-sulfinyl ketoimines with acrylates.

Very recently, Li, Xu, and co-workers[137] reported a rhodium-catalyzed redox-neutral annulation of 1,1-disubstituted alkenes **293** with *N*-aryloxyacetamides to afford 2,3-dihydrobenzofuran derivatives **294** with a quaternary carbon center in good yields (Scheme 89). An amide group on the alkenes was essential to the success of the annulation. Control experiments support a possible mechanism involving a Rh^III-Rh^V-Rh^III catalytic cycle (Scheme 90). Initially, a five-membered rhodacycle **295**, generated from the initial chelation-assisted C–H activation, undergoes insertion to the alkene to afford a seven-membered intermediate **296**. The rhodium center of **296** could be saturated via coordination by the amide thus avoiding unwanted β-elimi-

Scheme 89. Rh-catalyzed annulation of 1,1-disubstituted alkenes with *N*-aryl-oxyacetamides.
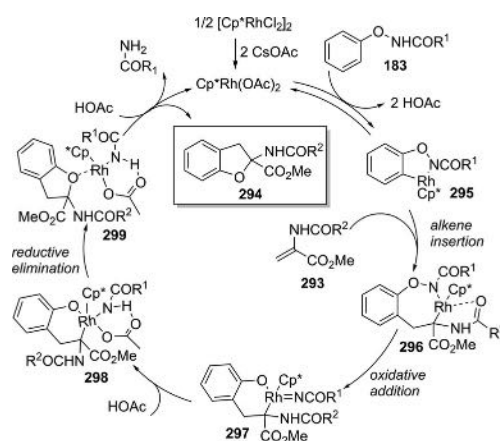
Scheme 90. Proposed mechanism for Rh-catalyzed annulation of alkenes **293** with *N*-aryloxyacetamides.
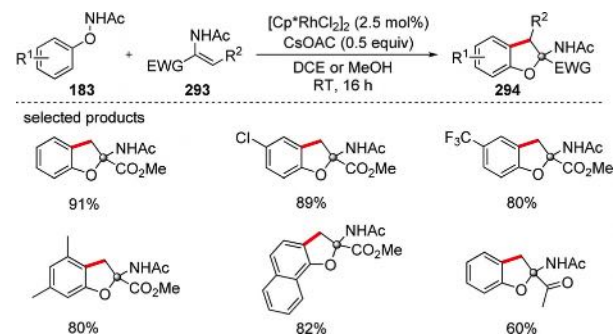
nation process. Oxidative addition of the rhodium to the N–O bond then leads to the formation of a Rh^V-intermediate **297**, which undergoes C–O reductive elimination with the aid of acetic acid to finally afford the products and release the catalyst.

5. Conclusion and Outlook

Quaternary carbon centers are ubiquitous structural units in a wide range of natural products and biologically active molecules; however, their construction has been a long-standing challenging endeavor in organic chemistry due to significant bulkiness often encountered in bond formations. Transition-metal-catalyzed C–H activation has attracted tremendous attention from chemists worldwide in the past decade, which offers an intriguing strategy for the generation of molecular complexity in a highly atom- and step-economic manner. Herein, the eclectic collection of recent development for the successful generation of quaternary centers via transition-metal-catalyzed C–H activation has been summarized. By employing various reaction patterns, a diverse array of simple to highly complex molecules containing quaternary centers have been synthesized. The methods summarized may provide a 'critical catalogue" of reactions to the synthetic chemist for grasping new ideas and choosing the best disconnections in

retrosynthetic analysis. Owing to the inherent advantage of transition-metal-catalyzed C—H activation, it can be anticipated that it will become a common and valuable tool for addressing many other synthetic challenges in organic chemistry in future.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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