Cp*M-Catalyzed Direct Annulation with Terminal Alkynes and Their Surrogates for the Construction of Multi-Ring Systems

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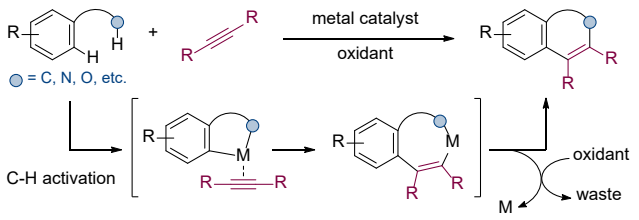
ABSTRACT: Transition-metal-catalyzed C–H activation followed by oxidative cyclization with unsaturated coupling partners has been a valuable synthetic tool for the multi-ring molecular scaffolds. This Perspective introduces the recent progress on the Cp*M-catalyzed (M = Co, Rh, and Ir) oxidative direct annulation of functionalized arenes with terminal alkynes and their equivalents through C–H bond cleavage. The highlighted examples are categorized according to the ten different types of reagents used in the transformations. The representative conditions, selected examples of the reaction scope, and key mechanistic aspects are briefly summarized.

1. Introduction

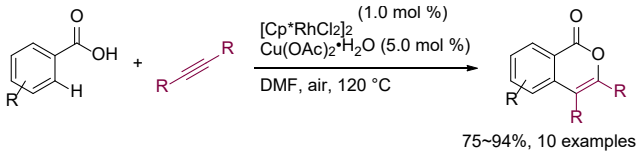
Poly(hetero)aromatic compounds are ubiquitous in various natural products, and are key structural motifs of manufactured functional molecules. To meet the increasing demand, the development of their efficient synthetic methods has been a substantial topic in the synthetic community. Over the last few decades, transition-metal-catalyzed C–H activation[1] and subsequent oxidative cyclization with unsaturated coupling partners[2] have been extensively studied due to the high efficiency and operational simplicity (Scheme 1). This strategy does not require the pre-functionalization of starting materials to ensure the cyclization, so that a variety of multi-ring systems can rapidly be assembled from readily available starting materials.

Scheme 1. Schematic Representation for Transition-Metal-Catalyzed Direct C–H Oxidative Annulation.



In 2007, Satoh and Miura firstly disclosed the utilization of a rhodium complex $[Cp^*RhCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) as catalyst for a direct oxidative annulation (Scheme 2).[3] Thus, a series of benzoic acids were successfully coupled with internal alkynes to produce the corresponding isocoumarins, and the catalyst turnover was achieved in the presence of catalytic or stoichiometric Cu(II) oxidant. This report has strongly motivated synthetic chemists to use Cp*Rh as well as relevant Co and Ir complexes to such annulative coupling reactions. The last twelve years witnessed the development of numerous reaction systems thus allowing us to construct fused-ring skeletons with simple manipulations; however, most of these reactions have been only applicable to internal alkynes. This limitation has brought a great challenge and, to overcome this problem, significant research interest has focused on the use of terminal alkynes and their equivalents to the catalysis.

Scheme 2. Cp*Rh-Catalyzed Annulation of Benzoic Acids with Internal Alkynes



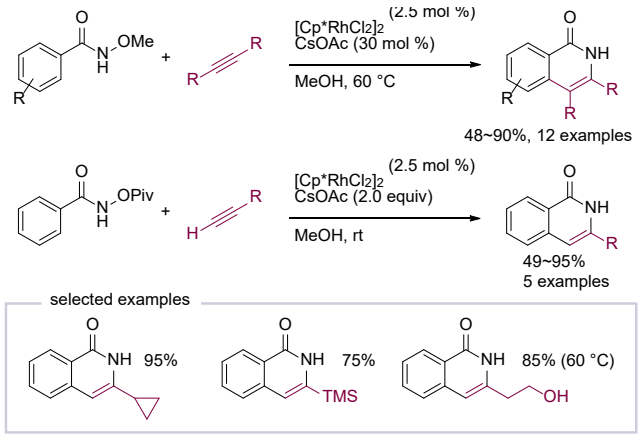
This Perspective concisely summarize the recent achievements on the Cp*M-catalyzed (M = Co, Rh, and Ir) oxidative annulation with terminal alkynes and their equivalents through the activation of C–H/X–H (X = C, N, and O) bonds. In this regard, reaction systems adopting Ru and CoX_2 complexes are beyond the scope of this Perspective, even though a number of effective annulation protocols have been established with the catalytic species.[4,5] The existing reports are herein categorized according to the type of coupling reagents used.[6]

2. Terminal alkynes

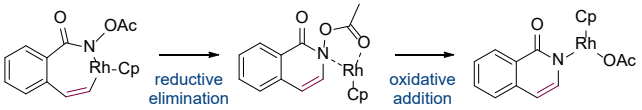
The "internal alkyne limitation" mentioned above stems from the presence of Cu(II) or Ag(I) species within the reaction systems, which are common external oxidants to ensure the catalyst turnover. The use of these reagents should be avoided because terminal alkynes preferentially dimerize under the oxidative conditions.[7] In 2010, Guimond and coworkers reported a Cp*Rh-catalyzed oxidative annulation of *N*-OMe-benzamides (hydroxamic acid derivatives) with internal alkynes (Scheme 3).[8] The N–O bond of the substrates acted as an internal oxidant to regenerate the catalytically active Rh(III) species probably via the oxidative addition. Accordingly, no external oxidant was required for this method, and further improvement in the reaction efficiency was achieved by replacing the *N*-OMe fragment with *N*-OPiv as reported from the same group in 2011.[9] The *N*-OPiv-benzamides could be coupled with terminal alkynes as

well as alkenes to access isoquinolones with various substitution patterns. These reports have raised *N*-OR-amides as the standard and productive oxidizing directing groups. DFT calculations were conducted to elucidate the reaction mechanism to find the C–N reductive elimination and C–O oxidative addition as a feasible sequence (Scheme 4).

Scheme 3. Rh-Catalyzed Annulation Utilizing *N*-OR Amides as Internal Oxidants

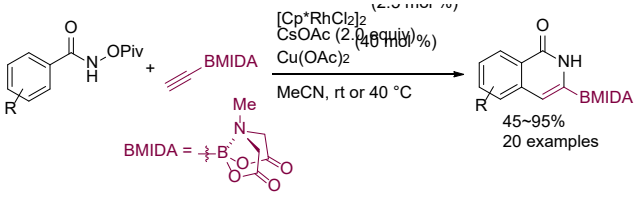


Scheme 4. Proposed Reaction Mechanism for the Annulation (Cp* and OPiv were Replaced by Cp and OAc to Simplify the Calculation)



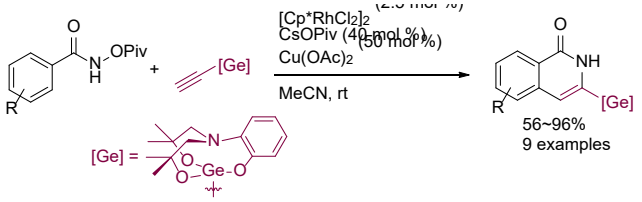
In 2012, Glorius and coworkers adopted *N*-OPiv-benzamides to the annulation with alkynyl MIDA (*N*-methyliminodiacetic acid) boronates (Scheme 5).[10] MIDA boronates, popularized by Burke and coworkers,[11] have been utilized as stable protected boronic acids, rendering the late stage functionalization under appropriate Suzuki-Miyaura coupling conditions.

Scheme 5. Rh-Catalyzed Annulation of *N*-OPiv Amides with Alkynyl MIDA Boronates



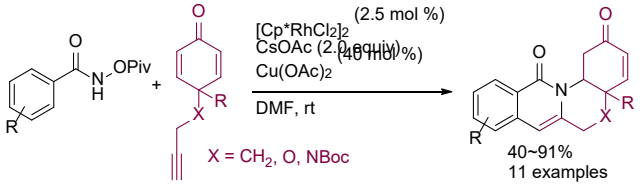
Recently, Xiao (2020) introduced alkynyl germatranes to the Rh-catalyzed annulation strategy to synthesize a series of germanium-substituted heterocyclic compounds (Scheme 6).[12] The alkynyl germanium reagents were prepared from the corresponding alkynyl Grignard reagents or parent terminal alkynes in one pot procedures. The masked germatrane group was inert under the standard cross-coupling conditions, whereas the annulated products could be coupled with haloarenes under TBAF (tetrabutylammonium fluoride) promoted Pd-catalyzed conditions.

Scheme 6. Rh-Catalyzed Annulation of *N*-OPiv Amides with Alkynyl Germatranes



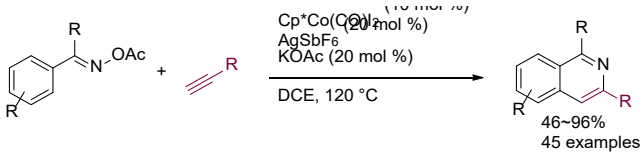
In 2014, Tian and Lin reported a cascade annulation of *N*-OPiv-benzamides with cyclohexadienone-based 1,6-enynes to directly construct tetracyclic skeletons, which are key structural motifs in many natural alkaloids (Scheme 7).[13] The reaction mechanism involves a sequential annulation with the terminal alkyne and intramolecular Michael addition onto the enone moiety.

Scheme 7. Rh-Catalyzed Arylative Cyclization of *N*-OPiv Amides with 1,6-Enynes



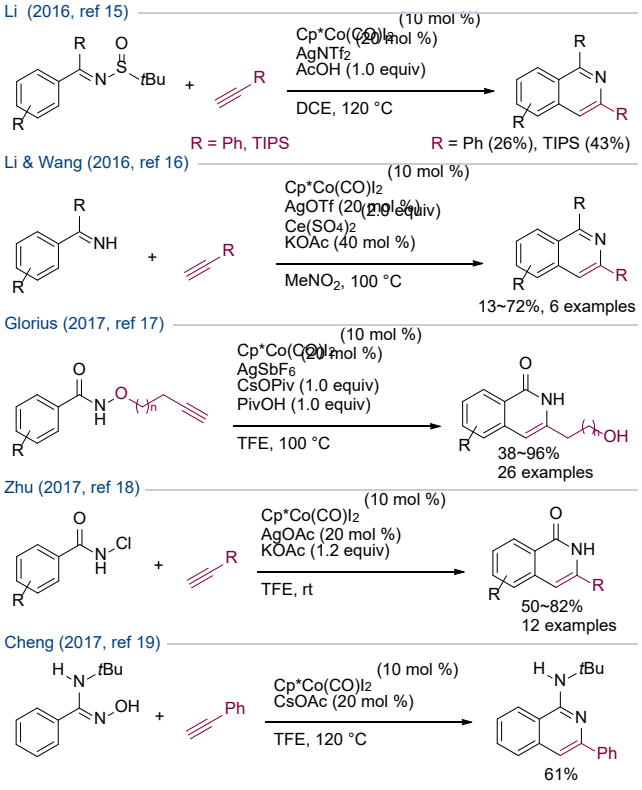
In 2015, Kanai and Matsunaga established a Cp*Co-catalyzed direct isoquinoline synthesis from *O*-acetyl oximes (Scheme 8).[14] Note that the N–O linkage within the oxime functionality acted as an internal oxidant. The Cp*Co catalyst exhibited much higher activity than the Cp*Rh to this transformation: Cp*Co afforded 82% product yield for the model reaction, whereas Cp*Rh gave 11% yield under identical conditions. In addition, superior site selectivity was observed for the Cp*Co catalysis when substituted oximes were employed probably due to the higher sensitivity to the steric hindrance.

Scheme 8. Co-Catalyzed Isoquinoline Synthesis with Terminal Alkynes



This report prompted several research groups to use Cp*Co catalyst for the annulation with terminal alkynes. The representative reactions are showcased in Scheme 9. Li and coworkers (2016)[15] adopted *N*-sulfinyl imines as oxidizing directing groups, and two terminal alkynes were examined in the report. Li and Wang (2016)[16] used $Ce(SO_4)_2$ as an external oxidant for the synthesis of isoquinolines. Glorius and coworkers (2017)[17] developed an intramolecular annulation of tethered alkynes. Zhu (2017)[18] and Cheng (2017)[19] adopted *N*-chloro amides and *N*-hydroxy amidines, respectively, as the internal oxidants.

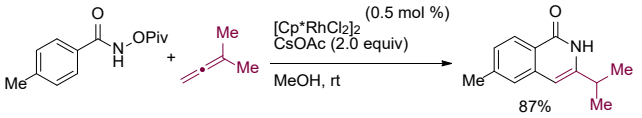
Scheme 9. Examples of Co-Catalyzed Oxidative Annulation with Terminal Alkynes



3. Allenes

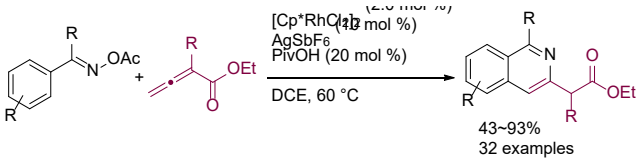
In 2012, Glorius demonstrated a coupling reaction of *N*-OPiv-benzamides with terminal allenes under the Cp*Rh catalysis (Scheme 10).[20] After the annulation event, the C–C double bond isomerized to form the thermodynamically most stable isomer. Some allenes produced 3-substituted isoquinolinones so that these formally can be regarded as terminal alkyne equivalents.

Scheme 10. Rh-Catalyzed Annulation of *N*-OPiv Amides with Terminal Allenes



Afterward, Yu and coworkers (2019) also developed a reaction of *O*-acetyl oximes with allenoates (Scheme 11).[21] The position of the C–C double within the product skeleton was primarily dictated by the aromatic stabilization, yielding 3-substituted isoquinolines as coupling products. The ester group on the allene was found to be essential to trigger the reaction efficiently.

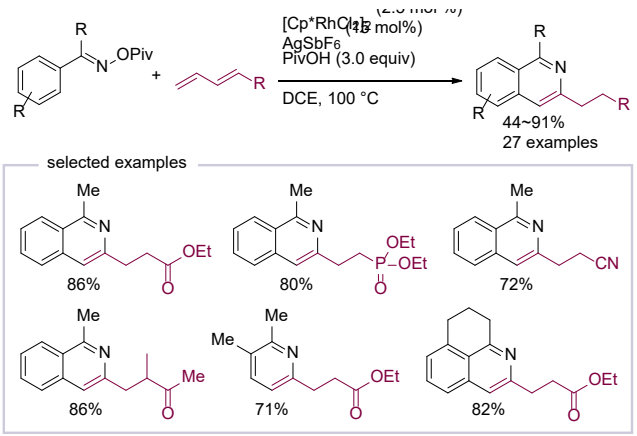
Scheme 11. Rh-Catalyzed Annulation of *O*-Ac Oximes with Terminal Allenes



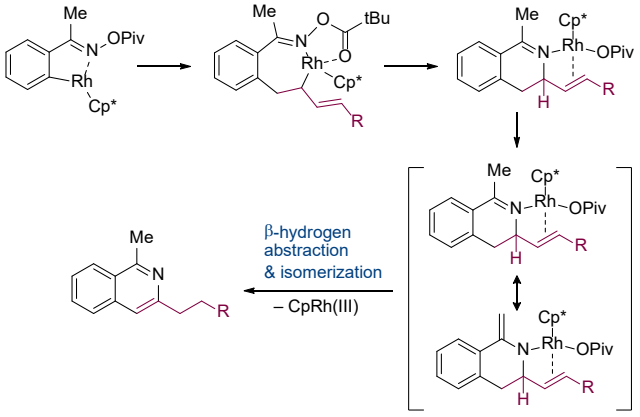
4. Dienes

In 2014, Glorius and coworkers established a synthetic method for 3-alkyl isoquinolines via C–H annulation and isomerization adopting 1,3-dienes as the coupling partners (Scheme 12).[22] A variety of electron deficient dienes could be utilized to the catalysis. The authors proposed a reaction mechanism illustrated in Scheme 13 according to deuterium-labeling experiments. After the C–N reductive elimination and oxidative addition into the adjacent N–O bond, β-hydrogen abstraction and isomerization may be effected to produce the aromatized product.

Scheme 12. Rh-Catalyzed Annulation of *O*-Piv Oximes with 1,3-Dienes



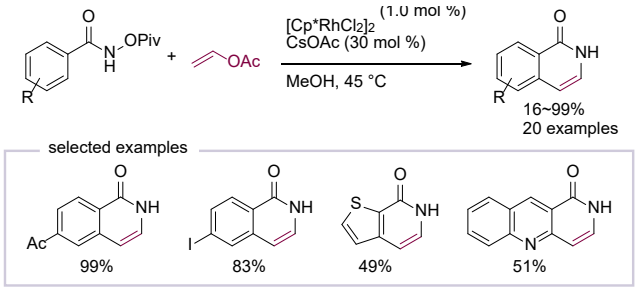
Scheme 13. Proposed Reaction Mechanism for the Annulation with 1,3-Dienes



5. Vinyl esters

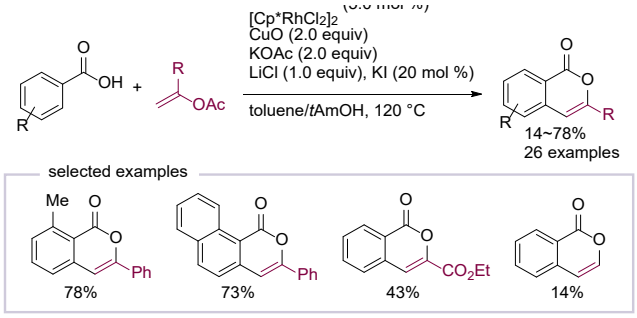
In 2014, Marsden and Raw described the use of vinyl acetate as an acetylene equivalent in the Cp*Rh-catalyzed annulation of *N*-OPiv-benzamides (Scheme 14).[23] It is notable that this offers an effective synthetic method for the construction of non-substituted vinylene-fused ring system without any specialized equipment for operating with acetylene gas in a safe manner.[24]

Scheme 14. Rh-Catalyzed Annulation of *N*-OPiv Amides with Vinyl Acetate



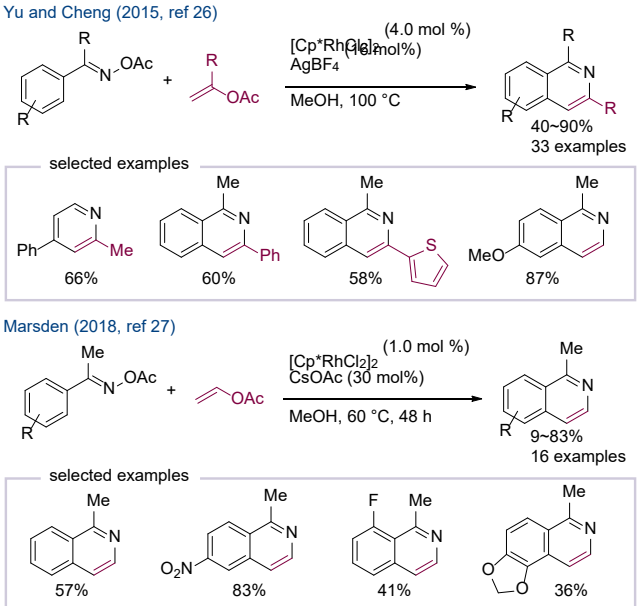
Just after this achievement, a similar reaction system was reported by Wen (2015).[25] Vinyl acetates could be coupled with benzoic acids to give the corresponding isocoumarins with the aid of stoichiometric Cu(II) oxidant (Scheme 15). The simple vinylene annulation was also possible upon treatment with simple vinyl acetate to give nonsubstituted isocoumarin, albeit with low (14%) product yield.

Scheme 15. Rh-Catalyzed Annulation of Benzoic Acids with Vinyl Acetates



Yu and Cheng (2015)[26] and Marsden (2018)[27] independently developed the Cp*Rh-catalyzed annulation of *O*-acetyl oximes with vinyl acetates (Scheme 16). This method afforded to produce various pyridines and isoquinolines in single operation, and could be utilized for the concise preparation of papaverine: a well-established opium alkaloid antispasmodic drug.

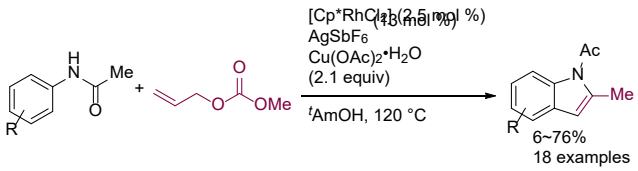
Scheme 16. Rh-Catalyzed Annulation of *O*-Ac Oximes with Vinyl Acetates



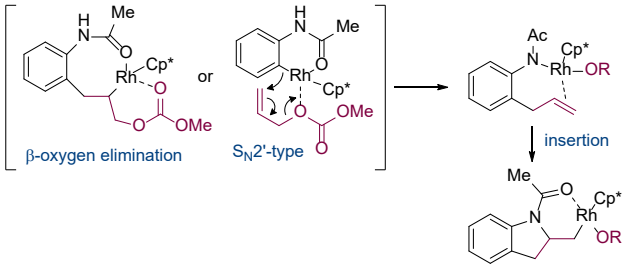
6. Allyl esters

In 2013, Saá and coworkers developed a reaction of acetanilides with an allyl carbonate in the presence of Cu(II) oxidant, yielding 2-methylindoles via the C–H/N–H oxidative annulation (Scheme 17).[28] Two possible mechanisms were postulated to explain the outcome (Scheme 18). After the directing-group-assisted C–H activation, allyl carbonate may regioselectively insert into the Rh–C bond with the help of the coordination of the carbonate moiety to the metal. The β-oxygen elimination was thereby effected to give an *ortho*-allylated intermediate. Alternatively, intramolecular S_N2'-type reaction would deliver the same intermediate. Subsequent olefin insertion, β-hydrogen elimination, and isomerization would give the coupling products.

Scheme 17. Rh-Catalyzed Annulation of Acetanilides with Allyl Carbonate

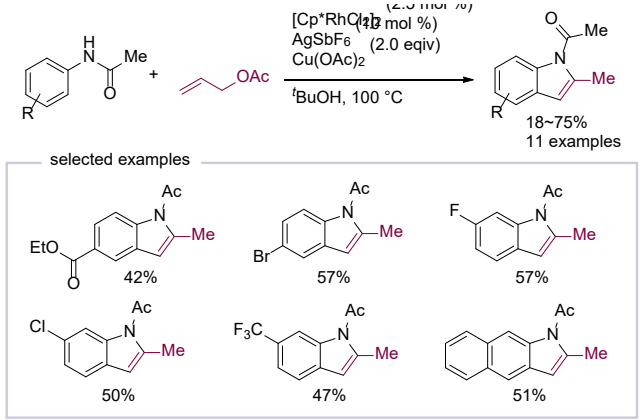


Scheme 18. Proposed Reaction Mechanism for the Annulation with Allyl Carbonate



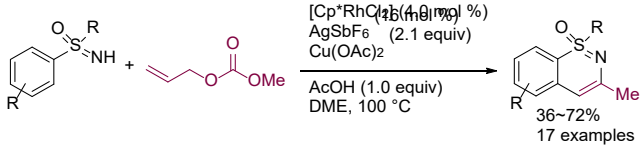
At the same period, Kim and coworkers (2013) reported a similar transformation using allyl acetates as the coupling partner (Scheme 19).[29] The scope with respect to the allyl esters was better examined in this work, and various 2-substituted indoles were synthesized with high *cis*-selectivity. The authors assumed that the pathway via the β-oxygen elimination was more favorable in this reaction, and the selectivity would be rationalized by adopting anti-elimination of the intermediate with an external acetoxy anion.

Scheme 19. Rh-Catalyzed Annulation of Acetanilides with Allyl Acetate

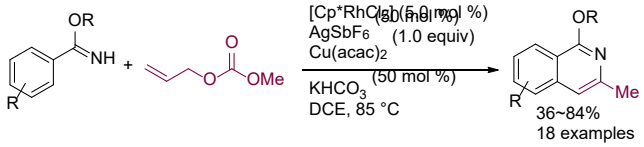


Bolm (2017)[30] and Dong (2020)[31] also established reaction systems using an allyl carbonate under the Cp*Rh-catalyzed conditions. Aryl sulfoximines (Scheme 20) and benzimidates (Scheme 21) were successfully converted into the corresponding benzothiazines and 1-alkoxyisoquinolines, respectively.

Scheme 20. Rh-Catalyzed Annulation of Sulfoximines with Allyl Carbonate



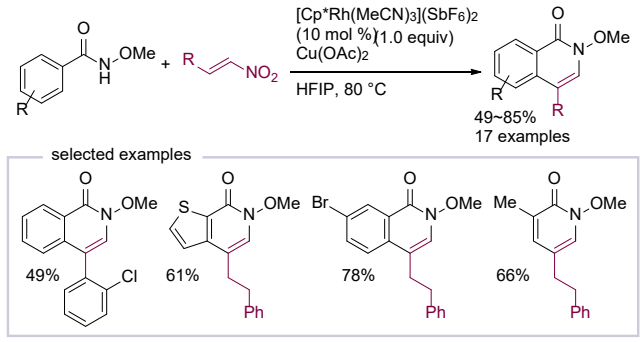
Scheme 21. Rh-Catalyzed Annulation of Imidates with Allyl Carbonate



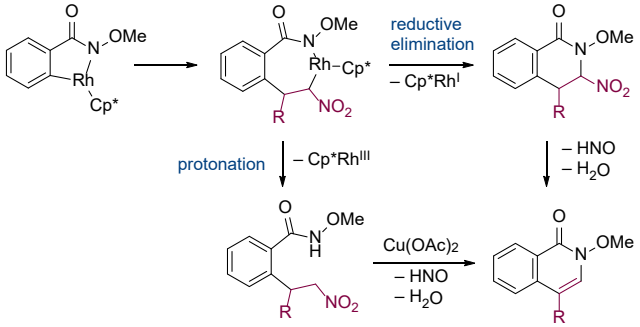
7. Nitro alkenes

In 2018, Ellman and coworkers found that a reaction of *N*-OMe-amides with nitroalkenes in the presence of a Cp*Rh catalyst and $Cu(OAc)_2$ oxidant resulted in the formation of 4-substituted isoquinolones (Scheme 22).[32] Notably, such a substitution pattern has not been accessible with other alkyne equivalents except for α-chloroaldehydes (see below). The authors proposed two pathways from a seven-membered Rh nitronate intermediate (Scheme 23). One possible mechanism involves C–N reductive elimination and denitration, in which the reduced Rh(I) species is oxidized by $Cu(OAc)_2$. The other one gives the corresponding nitroalkane as a primary product, and the subsequent $Cu(OAc)_2$-mediated cyclization would produce the coupling product.

Scheme 22. Rh-Catalyzed Annulation of Imidates with Nitro Alkenes



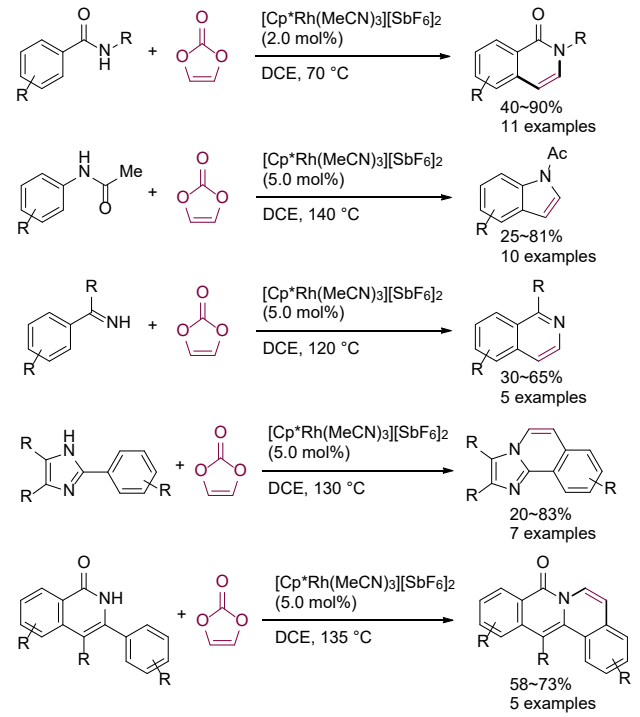
Scheme 23. Proposed Reaction Mechanism for the Annulation with Nitro Alkenes



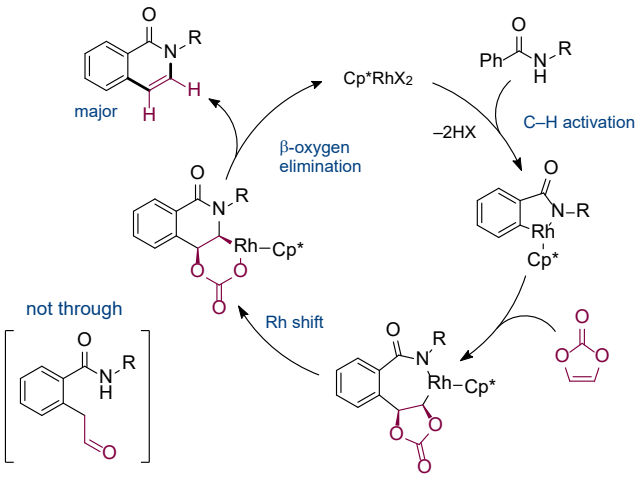
8. Vinylene carbonate

In 2019, Nishii and Miura disclosed a Cp*Rh-catalyzed annulation adopting vinylene carbonate as an acetylene surrogate (Scheme 24).[33] A notable feature of this reaction system is that no external oxidants and bases are required because the vinylene carbonate itself fulfills both functions. Various vinylene-fused N-heteroaromatics such as isoquinolones, indoles, benzimidazoles, isoquinolines, and benzothiazines were directly synthesized through the C–H/N–H oxidative cyclization. The authors proposed a reaction mechanism involving migratory insertion, Rh shift to the adjacent carbonate moiety, and β-oxygen elimination as illustrated in Scheme 25. The Rh shit step is assumed to be a redox-neutral concerted process or stepwise C–N reductive elimination and C–O oxidative addition mechanism. On the other hand, control experiments ruled out the mechanism through intramolecular dehydration of an aldehyde intermediate.

Scheme 24. Rh-Catalyzed N–H/C–H Oxidative Annulation with Vinylene Carbonate

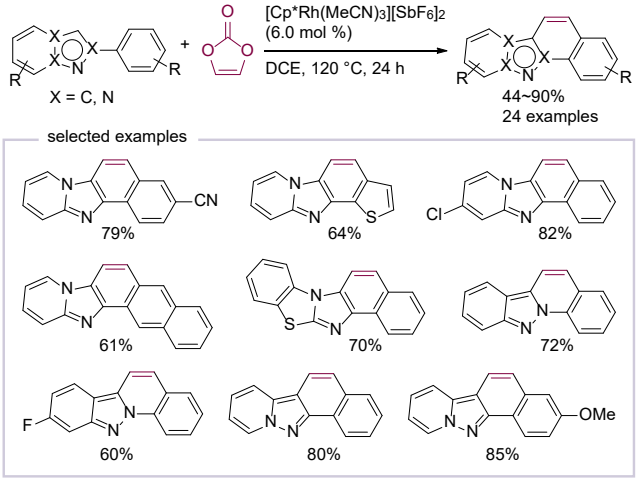


Scheme 25. A Proposed Reaction Mechanism for the Annulation with Vinylene Carbonate



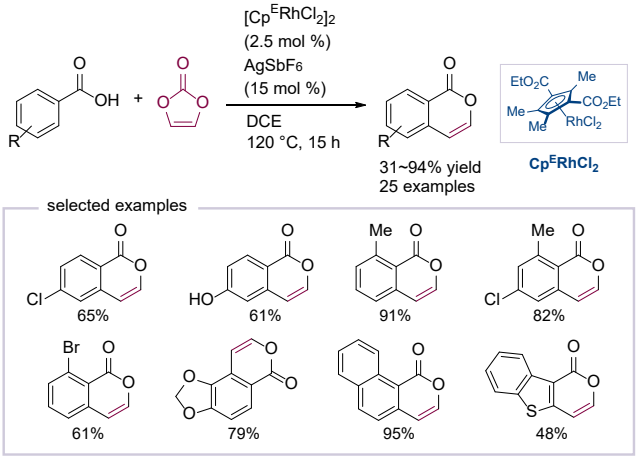
Upon the continuous research interest in this "vinylene transfer" reaction, they (2020) also achieved the catalytic C–H/C–H oxidative annulation of imidazole- and pyrazole-fused aromatics (Scheme 26).[34] The carbocyclization process was facilitated by the enriched nucleophilicity of the C3 positions of the substrates. The obtained polyaromatic compounds were considerably luminescent and exhibited well-ordered molecular packing structures in the solid state, which are unique characteristics of the unsubstituted vinylene-fused molecules.

Scheme 26. Rh-Catalyzed C–H/C–H Oxidative Annulation with Vinylene Carbonate

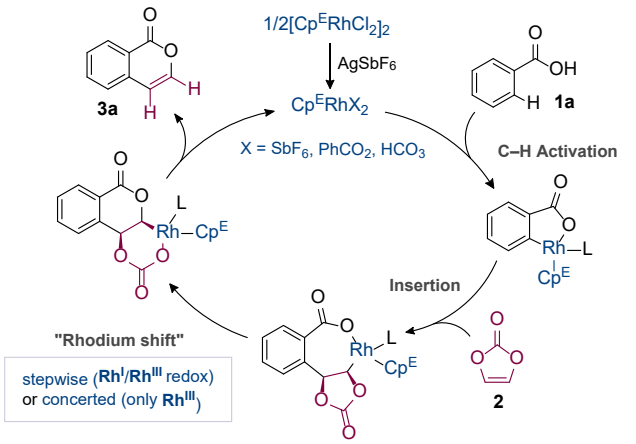


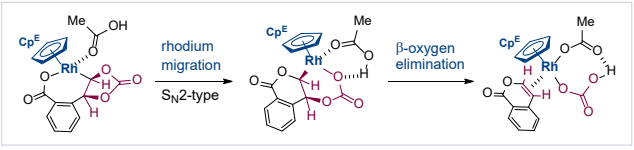
Very recently (2020), the same group established a direct annulation of benzoic acid derivatives through the activation of C–H/O–H bonds (Scheme 27).[35] The use of an electron deficient Cp^E ligand, which was developed by Shibata, Tanaka, and coworkers,[36] was essential to obtain the desired isocoumarin derivatives in reasonable product yields. This method achieved significant improvement in productivity as compared to that of the reaction adopting vinyl acetate as an acetylene surrogate (see Scheme 15). The reaction mechanism was proposed as similar to Scheme 25, and the authors conducted a computational study to characterize the Rh shit step (Scheme 28). As a result, a concerted S_N2-type reaction with the assistance of an intramolecular hydrogen bonding was found to be a possible pathway. The subsequent β-oxygen elimination is effected to produce the coupling product.

Scheme 27. Rh-Catalyzed C–H/O–H Oxidative Annulation with Vinylene Carbonate



Scheme 28. A Proposed Reaction Mechanism and Calculated Key Intermediates for the Isocoumarin Synthesis

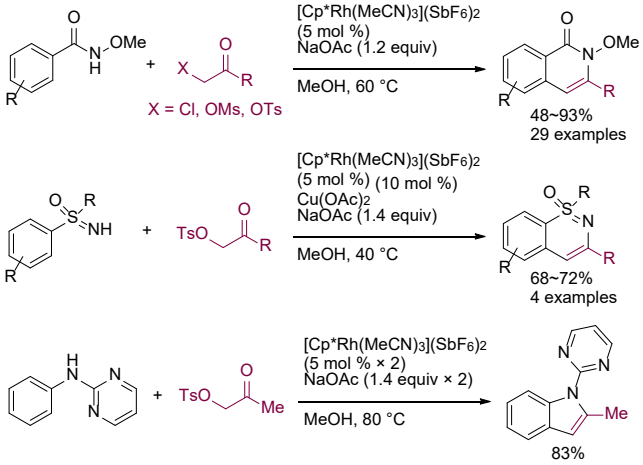




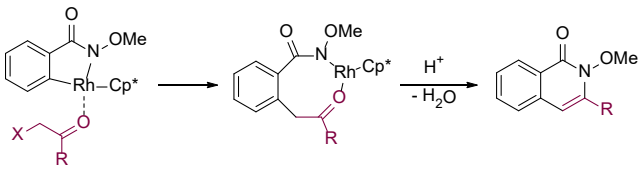
9. α-(Pseudo)halocarbonyls

In 2014, Glorius introduced α-(pseudo)haloketones as the equivalents of oxidized alkynes to the Cp*Rh-catalyzed annulation strategy (Scheme 29).[37] It was postulated that the α-(pseudo)halogen functionality could be substituted by nucleophilic aryl-Rh species to form α-arylketones, and further condensation with a proper nitrogen-based group would give the N-heterocycles (Scheme 30). Accordingly, a series of multi-ring products were synthesized without adopting external oxidants or oxidizing directing groups.

Scheme 29. Rh-Catalyzed N–H/C–H Oxidative Annulation with α-(Pseudo)haloketones

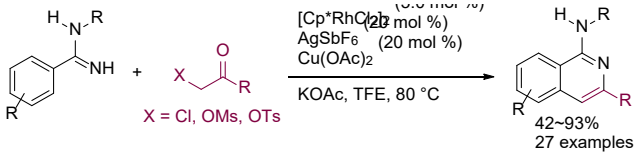


Scheme 30. Proposed Reaction Mechanism for the Rh-Catalyzed Annulation with α-(Pseudo)haloketones

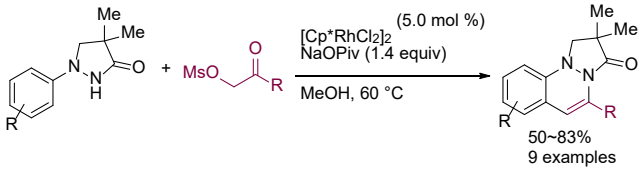


Afterward, Li and coworkers (2016) reported a reaction of imidines with α-(pseudo)haloketones to afford 1-aminoisoquinolines using Cp*Rh catalyst (Scheme 31).[38] In 2017, Chen and Huang also developed a catalytic annulation of pyrazolidinone with α-pseudohaloketones (Scheme 32).[39]

Scheme 31. Rh-Catalyzed Annulation of Imidines with α-(Pseudo)haloketones

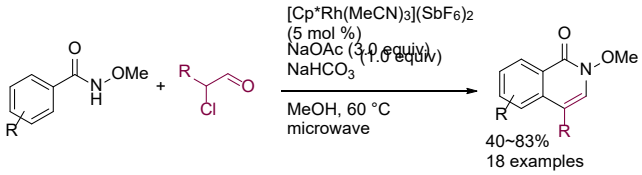


Scheme 32. Rh-Catalyzed Annulation of Pyrazolidinone with α-Pseudohaloketones



Bolm (2017) described the use of α-chloroaldehydes in the Cp*Rh-catalyzed annulation under microwave irradiation (Scheme 33).[40,41] The regioselectivity with respect to the substituent within the cyclized fragment was complementary to that of processes mentioned above. In particular cases, N,O-acetals, possible intermediates of the annulation, were obtained as major products.

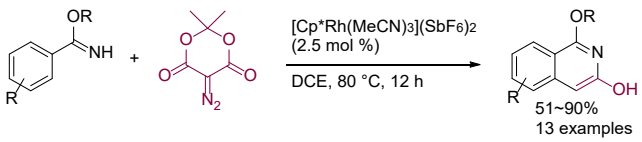
Scheme 33. Rh-Catalyzed Annulation of *N*-OMe Amides with α-Chloroaldehydes



10. Diazo compounds

Transition-metal-catalyzed carbenoid insertion reactions have emerged as powerful synthetic tools for C–C and C–heteroatom bond formation.[42] Although α-diazo carbonyls have been used as carbene precursors for the Cp*Rh-catalyzed annulation chemistry,[43] these could not be terminal alkyne equivalents due to the instability of mono-substituted diazo compounds. However, an interesting example reported by Liu and coworkers (2016) should be cited (Scheme 34).[44] They used a diazotized Meldrum's acid for the catalysis, thus producing 3-hydroxyisoquinolines with the release of an acetone and a CO_2 molecules. Overall, the diazotized acid acted as an ethynol equivalent.

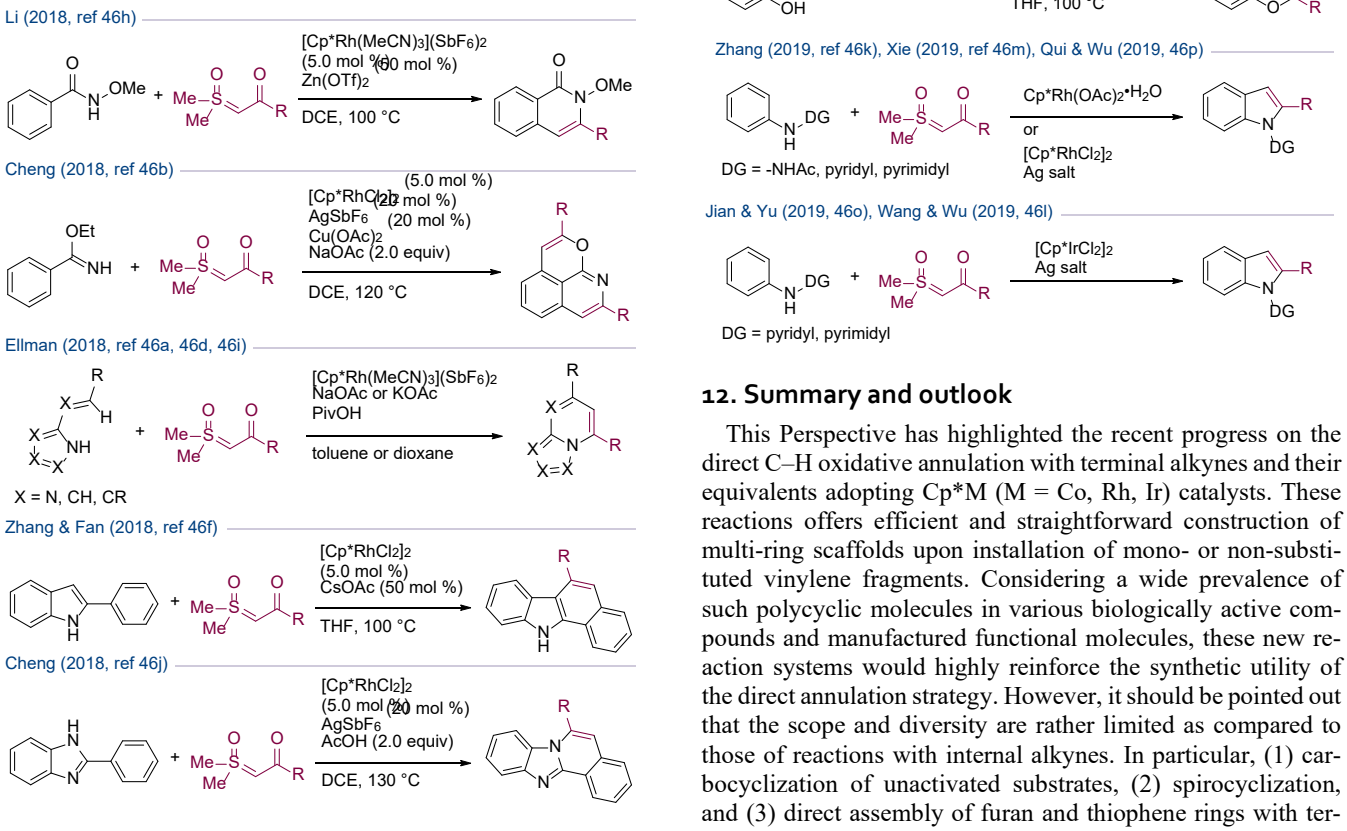
Scheme 34. Rh-Catalyzed Annulation of Imidates with Diazotized Meldrum's Acid

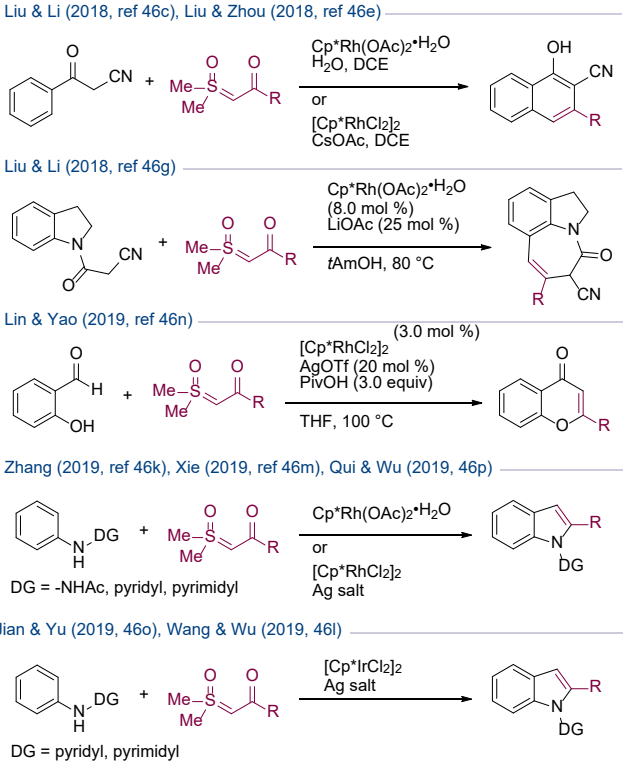


11. Sulfoxonium ylides

In 2017, the groups of Aïssa and Li independently utilized sulfoxonium ylides as carbene precursors for the Cp*Rh-catalyzed C–H functionalization chemistry to achieve direct acylmethylation of various arenes and heteroarenes.[45] As described in the reaction of α-(pseudo)halocarbonyls, the installed ketone groups may undergo further condensation in the presence of proper directing groups within the starting materials. Indeed, many research groups have adopted sulfoxonium ylides to the Cp*M-catalyzed direct annulation reactions which are summarized in Scheme 35.[46]

Scheme 35. Examples of Rh- and Ir-Catalyzed Annulation with Sulfoxonium Ylides





12. Summary and outlook

This Perspective has highlighted the recent progress on the direct C–H oxidative annulation with terminal alkynes and their equivalents adopting Cp*M (M = Co, Rh, Ir) catalysts. These reactions offers efficient and straightforward construction of multi-ring scaffolds upon installation of mono- or non-substituted vinylene fragments. Considering a wide prevalence of such polycyclic molecules in various biologically active compounds and manufactured functional molecules, these new reaction systems would highly reinforce the synthetic utility of the direct annulation strategy. However, it should be pointed out that the scope and diversity are rather limited as compared to those of reactions with internal alkynes. In particular, (1) carbocyclization of unactivated substrates, (2) spirocyclization, and (3) direct assembly of furan and thiophene rings with terminal alkynes or surrogates have not been achieved to the best of our knowledge. Obviously, there is a great demand for developing further effective catalytic protocols to address the remaining challenges, and thus it would be sufficiently interesting to follow the related works established in due course.

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Notes

The authors declare no competing financial interests.

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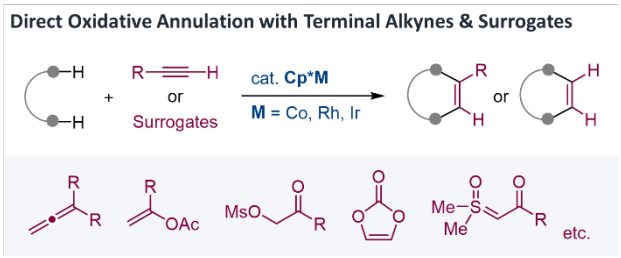
Direct Oxidative Annulation with Terminal Alkynes & Surrogates
H
H
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or
Surrogates
cat. Cp*M
M = Co, Rh, Ir
R
H
or
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