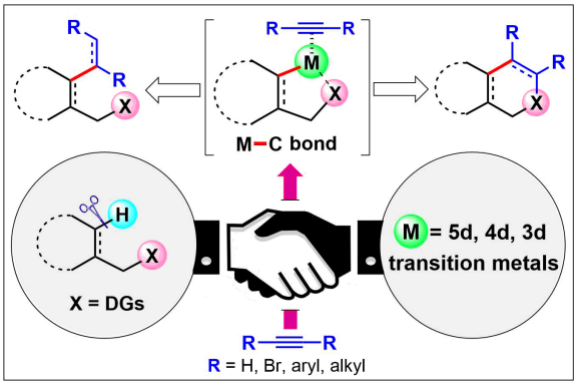
Reactivity of Alkynes with M-C Bonds generated through C-H Activation

Shyam Kumar Banjare, Pranav Shridhar Mahulkar, Tanmayee Nanda, Bedadyuti Vedvyas Pati, Lamphiza O Najiar and Ponneri C. Ravikumar*

ABSTRACT: Transition metal-catalyzed C-H activation and functionalization with various coupling partners is a well explored area of research. Among the various coupling partners used, alkynes occupy a prominent position on account of their varied reactivity. Due to their low steric demand and a high degree of unsaturation they effectively overlap with metal *d*-orbitals and form multiple bond-forming events giving rise to complex skeletons that are otherwise challenging to synthesize. This makes alkyne one of the most successful coupling partners in terms of the number of useful transformations. Remarkably, by changing the reaction conditions and transition-metals from 5d to 3d, the behaviors of alkynes also change. Despite enormous explorations with alkynes, there are still a lot more possible ways by which alkynes can be made to react with M-C bonds generated through C-H activation. Especially with the development of new high and low valent first-row metal catalysts, there is plenty of scope for this chemistry to evolve as one of the most explored areas of research in coming years. Therefore, a review on this topic is both timely and useful for synthetic chemists who are working in this area. In this review, we have highlighted the diverse reactivity of alkynes with various transition metals and their applications along with some of our thoughts on future prospects.



KEYWORDS: *Alkyne, M-C bond, C-H bond activation, alkenylation, annulation, alkylation, alkynylation.*

1. INTRODUCTION

The transition metal-catalyzed C-H bond activation and functionalization of the resultant M-C bond with various coupling partners for the formations of C-C, C-N, C-O, C-S, C-X bonds has emerged as a powerful tool in organic synthesis.[1] This step and atom economical strategy has been extensively applied for the synthesis of many bioactive heterocycles, natural products, agrochemicals, pharmaceuticals, and organic materials for optoelectronic devices.[2] Due to the ubiquitous nature of C-H bonds in organic molecules, often a directing group is used to address the issue of selective C-H bond activation.[3]

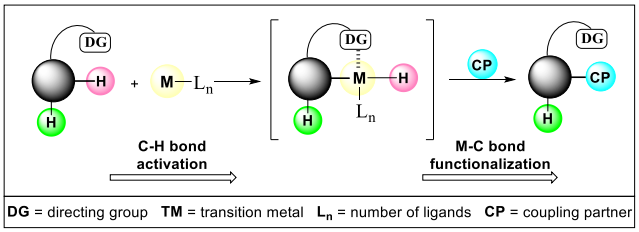


Fig. 1. The generalized concept of transition metal-catalyzed selective C-H bond activation and functionalization.

The generalized concept of C-H bond activation and functionalization is depicted in figure 1. Herein, the transition metal coordinates with the directing group (DG) and activates the proximal C-H bond through agostic interaction.[4] This process results in the formation of a cyclometallated intermediate involving a reactive M-C bond, which then reacts with a coupling partner and forms coupled product. The coupling partners such as alkenes,[5] allenes,[6] alkynes,[7] carbenes,[8] aryl/alkenyl/alkynyl/alkyl halides,[9] aryl/alkenyl/alkyl boronic acids[10,] etc. have been widely explored for the synthesis of useful organic molecules.

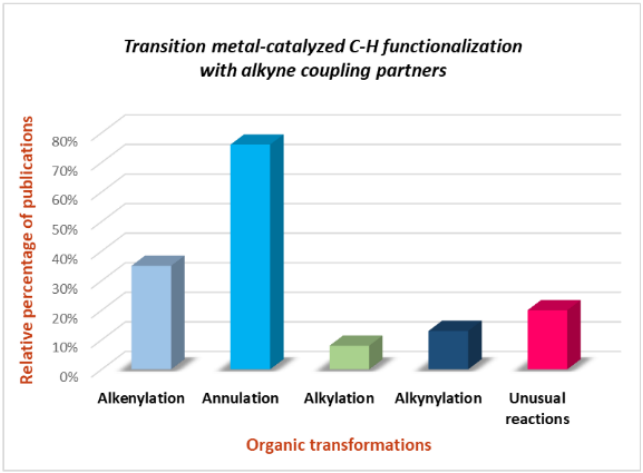
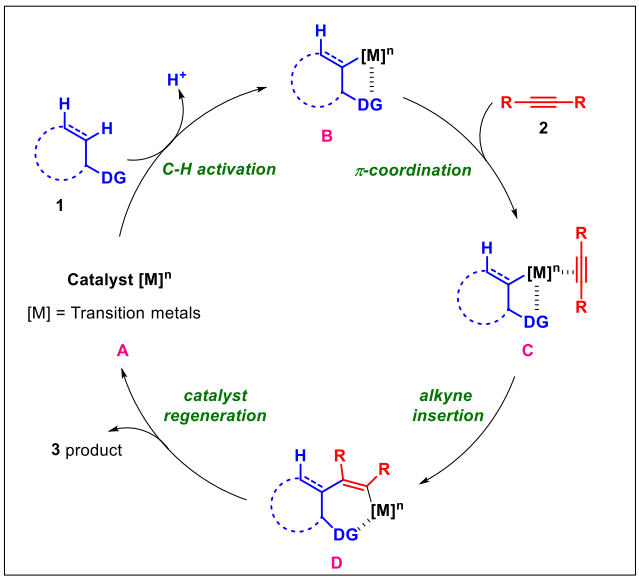


Fig. 2. Comparative reactivities of alkyne in C-H bond functionalization.

Among these coupling partners π-systems such as alkene, allene, and alkynes are widely employed on account of their ability to form multiple bonds in a single operation.[11] Moreover, these π-systems often give rise to unusual products that are unique and difficult to obtain by other methods. In this regard, alkynes occupy a very special place in terms of the number of unusual transformations. Even otherwise, alkynes are the most extensively explored coupling partner in transition metal-catalyzed C-H bond activation since the last two decades (Figure 2).[12] Numerous bioactive scaffolds and synthetically useful building blocks have been synthesized using alkynes, and hence their use as coupling partners occupies a prominent position in the area of C-H activation mediated chemical synthesis.[13] The varied reactivity of alkynes such as annulation, [14] alkylation, alkenylation, [15a-c] alkynylation,[15d] and many other unusual transformations have been well documented (Figure 2).[16]

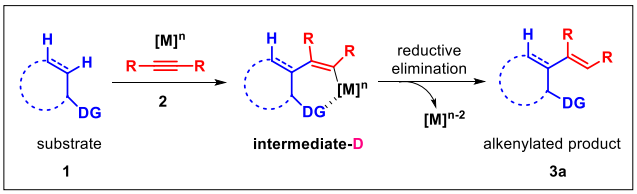
Among all these reactions, alkyne as an annulating agent in metal-catalyzed C-H bond activation is the most explored reaction. The diverse reactivity of alkyne as a coupling partner, has unlimited potential, particularly with the first-row metal catalysts. The number of unusual transformations with alkynes is continuously on the rise. With the development of new first-row metal catalysts in C-H activation reactions, exploratory work with alkynes is expected to grow significantly over the next decade. In this context, a perspective article covering the broad range of reactions that alkynes undergo with M-C bond obtained through C-H activation is both timely and useful for numerous synthetic chemists working in this area.

Scheme 1. Generalized catalytic cycle of C-H bond functionalization using alkyne.



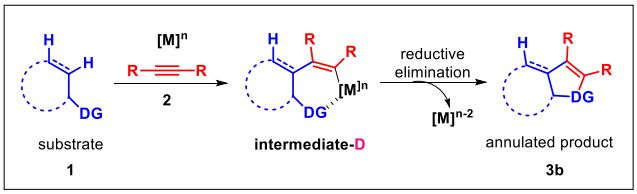
The generalized catalytic cycle of C-H bond functionalization using alkyne has been depicted in scheme 1. Initially, the active metal-catalyst **A** coordinates with the directing group of substrate **1**. Then the metal-catalyst activates the proximal C-H bond through agnostic interaction. This leads to the formation of a cyclometallated species **B**. Next, the cyclometallated intermediate **B** coordinates with alkyne **2** to give intermediate **C**. Further, alkyne insertion into the M-C bond leads to intermediate **D**. In this catalytic cycle, intermediate **D** is the key intermediate from which a variety of organic transformations such as alkenylation, annulation, cascade annulation, alkynylation have been achieved. The mechanistic aspects of each of these reactions is discussed independently and sequentially as follows.

Scheme 2. Transition metal-catalyzed alkenylation of C-H bond with an alkyne.



The Alkenylation process is one of the most common transformations from alkynes, where the alkyne is reduced to alkene. In this process, alkyne **2** undergoes insertion into the M-C bond to generate the intermediate **D**. Next, reductive elimination of species **D** leads to corresponding alkenylated product (scheme 2, **3a**) along with the extrusion of reduced metal catalyst [M]. The reduced metal catalyst will undergo re-oxidation to generate the active catalyst for the next catalytic cycle.

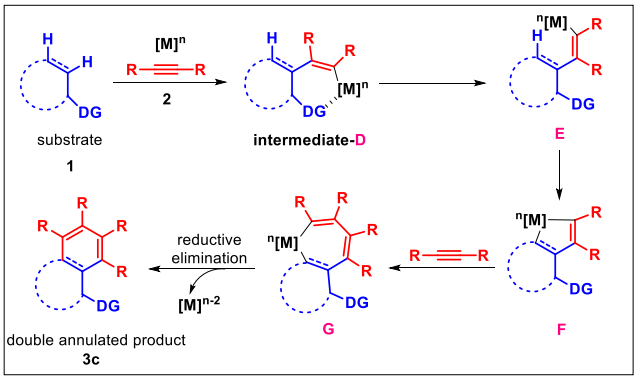
Scheme 3. Transition metal-catalyzed mono-annulation of C-H bond with an alkyne.



The annulation reactions with alkynes are one of the most prominent pathways, it is well explored in metal-catalyzed C-H activation reactions. In this process, alkyne **2** undergoes insertion into the M-C bond and generates intermediate **D**. Then, the reductive elimination gives the corresponding mono-annulated product (scheme 3, **3b**).

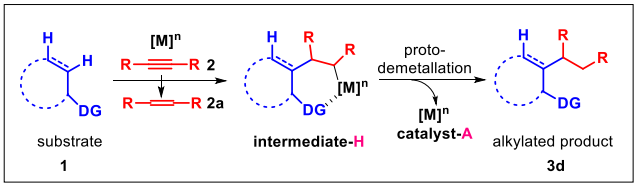
On similar lines, cascade C-H activation and annulation is a unique pattern of reaction that leads to a highly conjugated poly-aromatic scaffold through tandem C-H bond activations. The plausible pathway has been depicted in scheme 4. After the formation of cyclic intermediate **D**, the metal detaches itself from the DG and undergoes C-C bond rotation to develop proximity with the new C-H bond (Intermediate **E**).

Scheme 4. Transition metal-catalyzed cascade annulation of C-H bond with an alkyne.



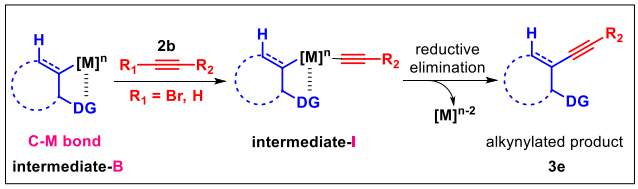
Activation of the proximal C-H bond in intermediate **E** leads to the formation of a new metallacycle intermediate **F**. Further alkyne **2** coordination and insertion into the new M-C bond gives rise to the intermediate **G** (scheme 4). Finally, reductive elimination of **G** gives the corresponding double annulated product **3c** and the reduced metal catalyst for further use in the catalytic cycle.

Scheme 5. Transition metal-catalyzed alkylation of C-H bond with an alkyne.



Compared to other transformations of alkyne, metal-catalyzed alkylation is quite challenging. For this, the alkyne **2** should first undergo hydrogenation to give the corresponding alkene **2a** (Scheme 5). Then, alkene gets inserted into the M-C bond and generates intermediate **H**. Finally proto-demetallation of intermediate **H** leads to the alkylated product **3d** and the active catalyst **A**.

Scheme 6. Transition metal-catalyzed Alkynylation of C-H bond with an alkyne.



In contrast to the previously discussed transformations, namely alkenylation and annulation, the alkynylation reactions have been developed using terminal alkynes **2b** (Scheme 6), which contain halogen/ hydrogen atom as a terminal substituent.

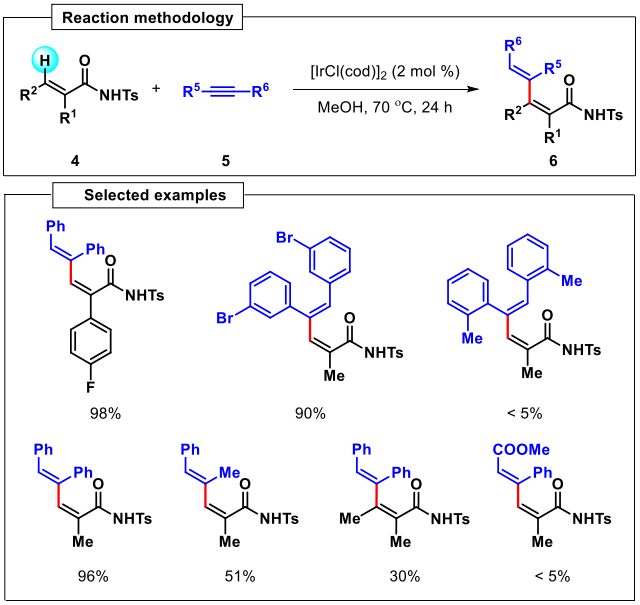
Initially, the M-C bond containing intermediate **B** is generated through metal-catalyzed C-H bond activation. With terminal alkynes containing halogen atoms, π-complexation followed by *β*-halide elimination produces the intermediate **I**. In the case of terminal alkynes with hydrogen atom, base-assisted deprotonation and metalation leads to intermediate **I**. Reductive elimination of intermediate **I** leads to alkynylated product **3e**.

Notably, apart from the typical reactivity of alkyne shown above. Alkynes are known to show unusual reactivity. These novel reactivities of alkynes are due to (i) intramolecular reactions of the alkyne (ii) *in-situ* hydration of alkynes, (iii) unusual ligand exchange in the catalytic process, (iv) novel substrate design, (v) the reactivity of different metals, and (vi) exploration of various reaction conditions. Such reactions are discussed in the unusual reactions section.

2. VARIOUS TRANSITION METAL-CATALYZED ALKENYLATION REACTIONS OF ALKYNES

The first report of iridium catalyzed alkene-alkyne cross-coupling reaction was demonstrated by Zhong *et al.* in 2019 (Scheme 7).[17]

Scheme 7. Iridium catalyzed cross-coupling of alkenes and alkynes.

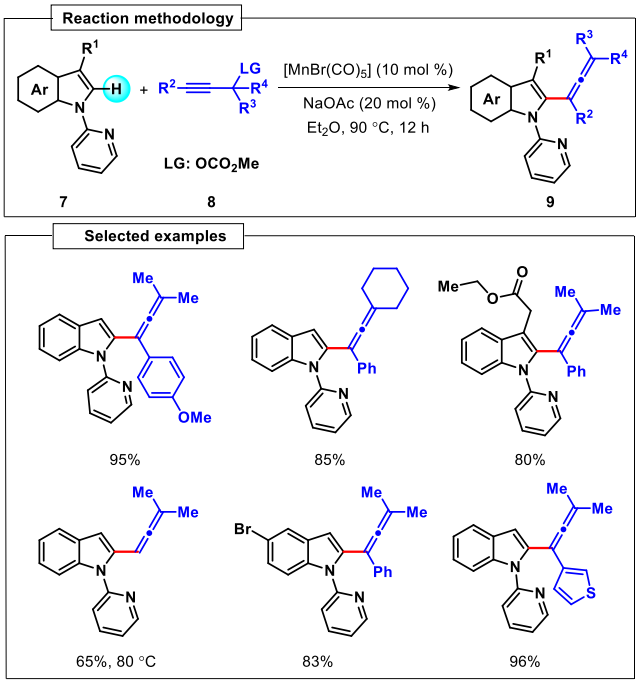


They have used *N*-substituted acrylamides **4** and various alkynes **5** to synthesize branched *Z*, *Z*-configured butadienes **6**. This reaction was carried out under ligand- and additive-free conditions, giving upto 98% yield with a high enantiomeric excess (99/1 ratio). The use of diphenylacetylene as the coupling partner gave impressive yields with many substrates. The aryl fluoride substituted acrylamide gives an excellent yield of 98% of the desired product, whereas methyl-substituted acrylamide with 4-bromo-substituted diarylacetylene produced 90% yield. Due to the electronic and steric factors, excellent regioselectivity was observed in the case of unsymmetrical alkyne. However, *ortho*-substituted and ester-derived diphenylacetylenes resulted in lower yields.

Prior to this report, Glorius *et al.*, in 2017, reported an Mn(I)-catalyzed regioselective C-H allenylation of various indole derivatives **7** with propargylic carbonate **8** to synthesize 2-allenylindoles **9** (Scheme 8).[18] This procedure is applicable for gram-scale synthesis under their optimized condition. The key feature of this methodology is that it allows the direct synthesis of ketones via earth-abundant Mn-catalyzed C-H activation strategy. Exploration of

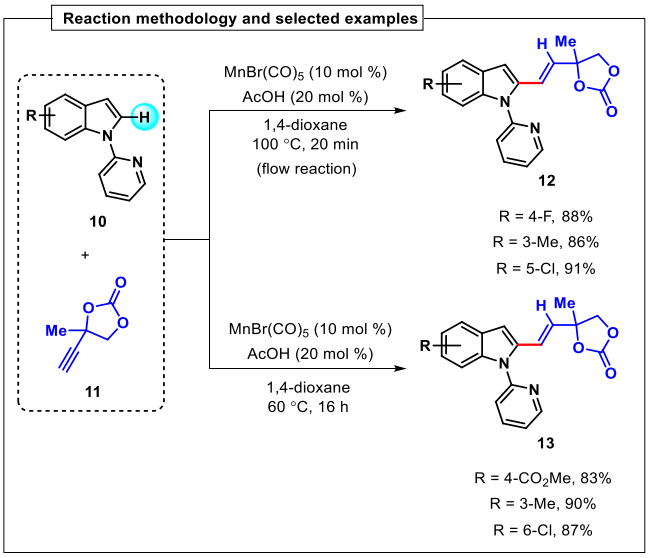
substrate scope revealed that the reaction gives high yields (>80%) of allenylindoles containing an aryl group at the *α*-position, including heteroarenes. The reaction also proceeded well with propargylic carbonate containing a cyclohexyl ring. Halo functionalities delivered the desired product in a selective fashion, which is otherwise prone to undergo several coupling reactions. Remarkably, trisubstituted allenes were achieved by employing this strategy, which is relatively unstable at high temperatures. Synthesis of allenylindoles containing an electron-withdrawing group, such as nitro, was also possible with the optimized condition. Moreover, this developed protocol provides a route to synthesize multi-substituted allenes, which show optical activity.

Scheme 8. Manganese catalyzed regioselective C-H allenylation.



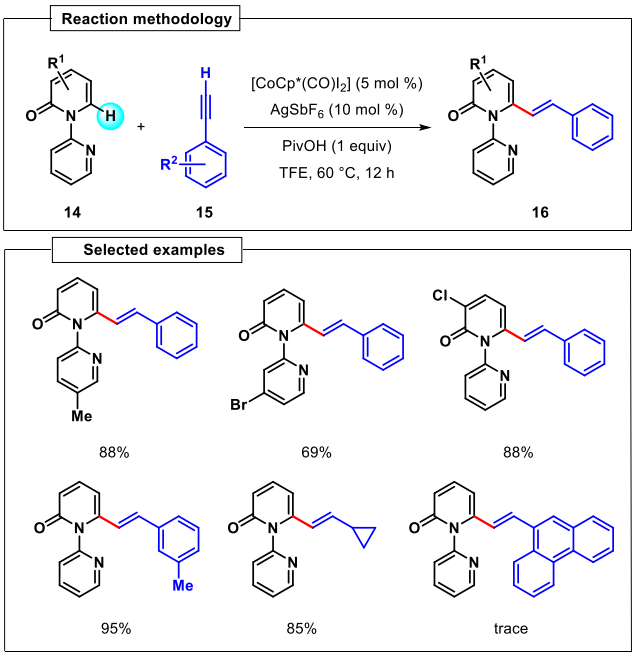
Further, in 2017, Ackermann *et al.* achieved chemo-selective hydroarylation **12**, **13** using Mn(I)-catalyst in a novel synergistic C-H activation strategy (Scheme 9).[19] They have used substituted alkynes **11** and various indoles **10** for this transformation. Notably, this reaction has been demonstrated via synergistic Brønsted acid/manganese(I) catalysis in a continuous flow, which allows efficient hydroarylation within 20 minutes. The generality of the demonstrated protocol has been tested with an ample range of substrates.

Scheme 9. Synergistic manganese(I) C-H activation catalysis in continuous flow.



It was observed that the reaction proceeded smoothly with electron-withdrawing functional groups, such as chloro-, bromo-, iodo-, ether, carboxylic acid, and ester. Moreover, the procedure offers products with excellent regioselectivity. Substrates other than indoles such as thiophenes, pyrroles, pyridones, and tryptophans were also amenable to this protocol.

Scheme 10. Cobalt catalyzed alkenylation of pyridones with terminal alkynes.

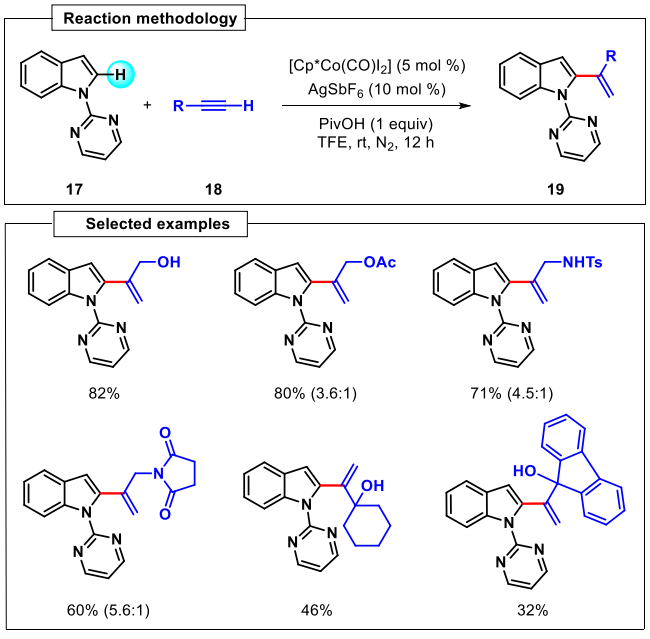


Recently, Ravikumar *et al.* have demonstrated the first report on cobalt catalyzed regioselective alkenylation of 2-pyridones **14** using terminal alkynes **15** (Scheme 10).[20] This Co(III)-catalyzed transformation was carried out in mild conditions and tolerated many valuable functionalities. Likewise, the protocol was very general, with a wide range of substrate scope. Substitution on the C3 position displayed varied reactivity, giving higher yields for electron-donating groups than withdrawing groups. The

operation of steric factors was also observed on C5 position, where increasing steric bulk gave lower yields. Remarkably, synthetically valuable functionalities such as bromo-, chloro-, and cyano- were well tolerated without affecting the yields.

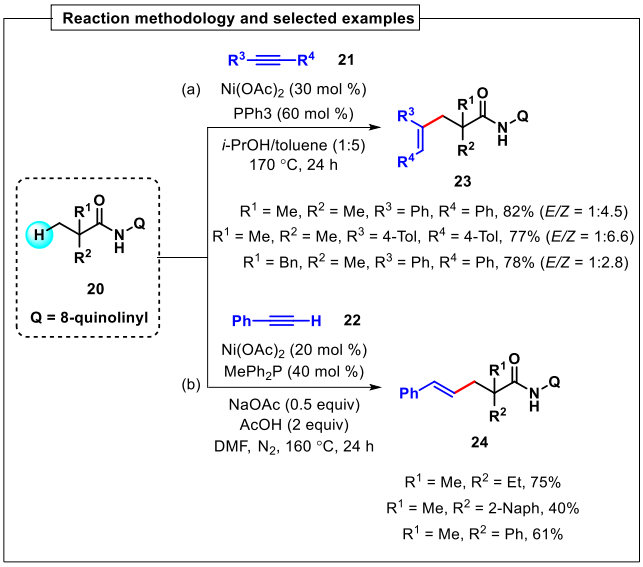
In 2017, an inexpensive and highly regioselective method of inserting indoles **17** into terminal alkynes **18** was devised by Li *et al.* (Scheme 11).[21] This Co-catalyzed reaction affords efficient synthesis of *α-gem*-vinylindoles under mild conditions. As evident, propargyl alcohols and propargyl esters reacted to give high yields, whereas ethers gave moderate yields. Notably, excellent selectivity was observed in various 1,1-disubstituted propargyl alcohols, which is associated with hydrogen bonding with the solvent. For the first time, the addition-type alkenylation of unreactive *β*-C(sp^3)-H bonds of aliphatic amides **20** using internal alkynes **22** was reported by You *et al.* in 2015 (Scheme 12a).[22] This method was applied to synthesize *γ,δ*-unsaturated carboxylic amide derivatives **23**, which can be further converted to *γ*-butyrolactones. Various 2,2-disubstituted propanamide containing both linear and cyclic chains were employed in the reaction, which gave moderate to good yields. Notably, in the case of 2-phenyl substituted amides, alkenylation occurred only at the C(sp^3)-H bond, while the C(sp^2)-H bond remained intact. The reaction condition was applicable on aromatic rings bearing both electron-withdrawing and -donating groups and offered an *E/Z* ratio up to 1:20. Moreover, the reaction was not affected by steric hindrance in the case of 1,2-di(naphthalen-2-yl)ethyne and gave 73% yield.

Scheme 11. Cobalt catalyzed hydroarylation of alkynes via C-H bond activation.



Internal alkynes containing a heteroaromatic ring were also amenable to the reaction. On similar lines, Zhang *et al.* reported alkenylation of unactivated *β*-C(sp^3)-H bonds of aliphatic amides **20** using terminal alkynes **22** using an inexpensive nickel catalyst (Scheme 12b).[23] The resulting product **23** can be further transformed into *β*-styrylcarboxylic acid derivatives. On reacting various substrates, a general trend was observed *β*-methyl containing aliphatic amides were well tolerated in the reaction. The resultant products were obtained in *E*-configuration, implying the transformation in highly selective.

Scheme 12. Nickel catalyzed C(sp^3)-H alkenylation of aliphatic amides with terminal and internal alkynes.

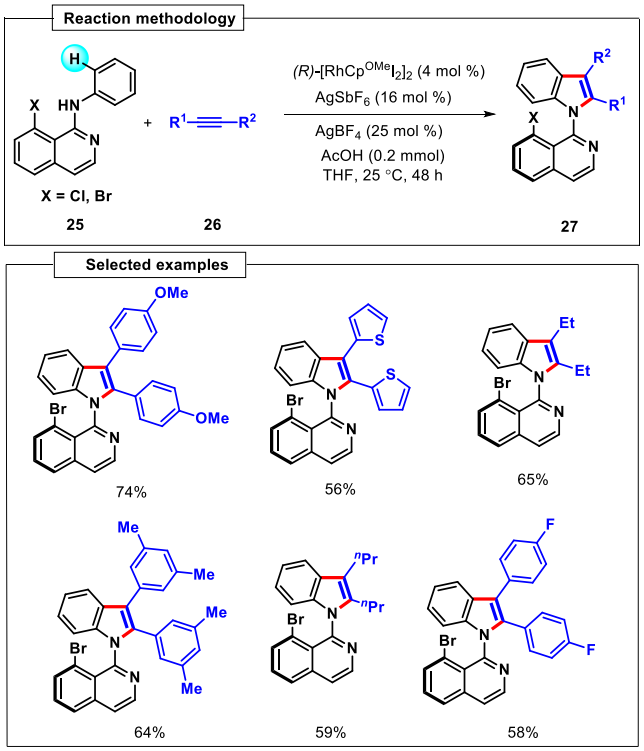


Different *α*-substituted aliphatic amides such as long-chain alkyl, benzyl, and phenyl amides were tried, all of which have given good yields. Notably, the functionalization occurred exclusively at the *β*-methyl group, while the *β*-methylene and γ-methyl groups remained intact. Moreover, α-cyclic substituted amide derivatives could also be manufactured in moderate yields using this reaction condition.

3. VARIOUS TRANSITION METAL-CATALYZED ANNULATION REACTIONS OF ALKYNES

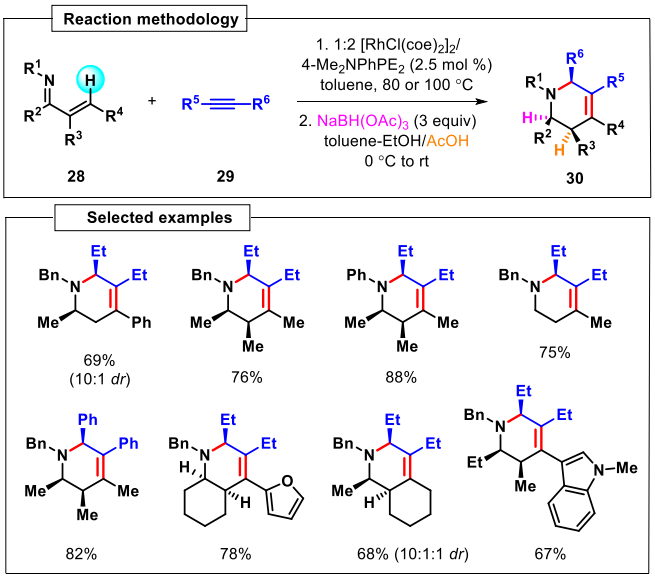
Annulation reaction of alkynes is one of the most successful transformations; in this regard, Li *et al.* devised a method to synthesize indoles **27** via C-H bond activation of anilines containing an *N*-isoquinolyl group **25** by oxidative [3+2] annulation with alkynes **26** (Scheme 13).[24] During the exploration of this methodology, they observed high enantioselectivity with *para*-substituted symmetrical diarylalkynes containing electron-donating as well as halogen groups in good yields. *meta*-Substitution offered products with similar efficiency; however, *ortho*-substitution hampered the reaction due to the steric effect. Heteroaryl alkynes were also coupled to deliver the product, whereas alkyl-aryl alkynes could not sustain under the reaction condition. While screening different anilines, it was observed that chloro, methyl, or phenyl substitution on the C-8 position offered better yields with high enantioselectivity. Also, alkyl, aryl, and halogen substitutions at *meta* and *para* positions were tolerable, giving highly enantioselective products.

Scheme 13. Rhodium catalyzed atroposelective synthesis of indoles via C-H bond activation.



In 2012, Ellman *et al.* reported a Rh-catalyzed annulation of *α,β*-unsaturated imines **28** with alkynes **29** for the synthesis of 1,2-dihydropyridines **30** (Scheme 14).[25] The reaction proceeds in the presence of a pre-catalyst $[RhCl(coe)_2]_2$ in a cascade annulation manner. Depending on the substrate, it delivers the desired product with one, two, or three stereogenic centers. Aryl and alkyl-substituted imines smoothly participated in the reaction and gave excellent yields. This procedure also offered bicyclic compounds and heterocyclic derivatives such as furans and indoles in good yields with high stereoselectivity.

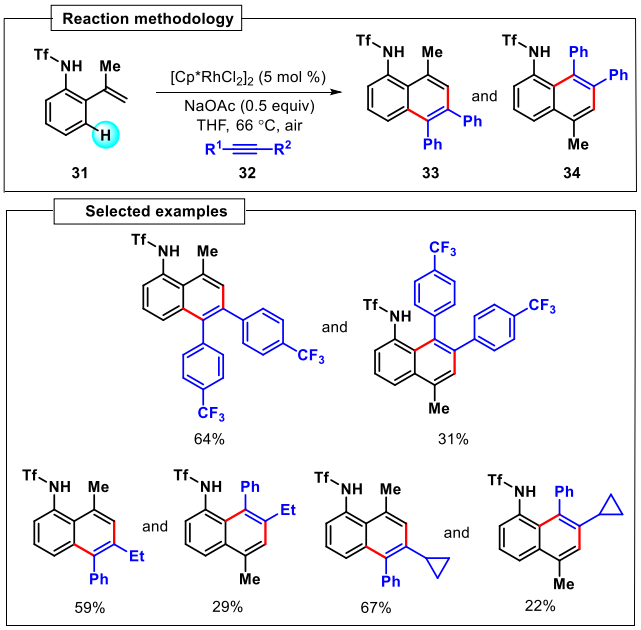
Scheme 14. Rhodium catalyzed synthesis of dihydropyridines via C-H bond annulation.



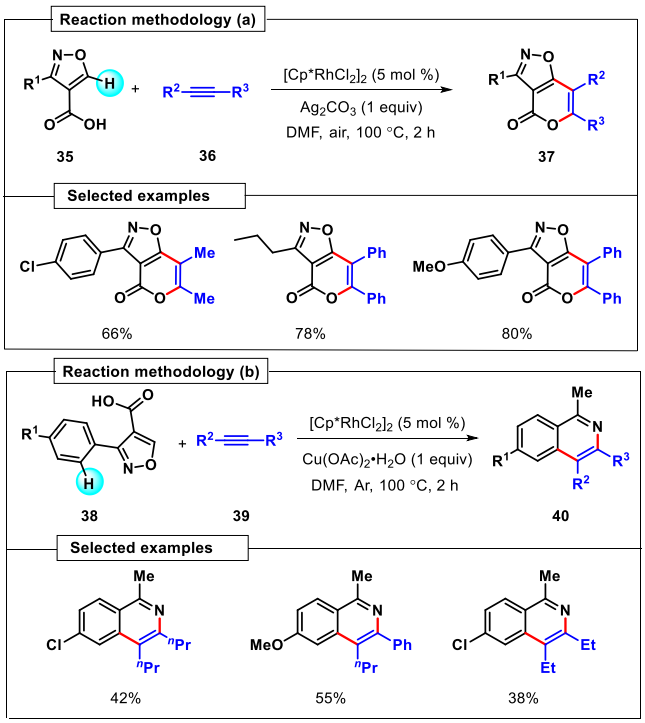
An interesting annulation was reported by Gulias *et al.* in 2019, which involved *O*-alkenyl *N*-triflylanilides **31** and alkynes **32** to produce various naphthylamides **33** (Scheme 15).[26] Apart from the traditional [4+2] cycloaddition products, this reaction also features the production of isomeric naphthylamides **34**, following the migration of alkenyl moiety from the *ortho* to *meta* position. The procedure applied to symmetrical diaryl acetylenes bearing both electron-withdrawing and -donating groups. Asymmetrical alkyl aryl alkyne but-1-yn-1-ylbenzene furnished selectively a single regioisomer. It is noteworthy that, in the case of aliphatic alkynes, the rearranged product was observed as major owing to a change in selectivity. Different substituted alkenyl triflylanilides were subjected to standard conditions, among which corresponding *meta*- and *para*-substituted products were obtained in moderate to good yields.

In 2019, Nakamura *et al.* demonstrated an oxidative [4+2] annulation reaction of isoxazolyl-4-carboxylic acids **35** and its 3-aryl substituted derivatives **38** with internal alkynes **36** and **39** (Scheme 16a,b).[27] The methodology (a) depicts the synthesis of pyranoisoxazolone derivatives **37**. The method worked well for symmetric alkynes with electronically distinct substituents, which furnished products in good yields. High regioselectivity was also observed in the case of asymmetrical alkynes with a single regioisomer. Reaction methodology (b) describes the synthesis of isoquinolines **40**. Similar to the previous case, both symmetrical and asymmetrical alkynes underwent annulation to give the respective products, which shows high regioselectivity with unsymmetrical alkynes.

Scheme 15. Rhodium catalyzed annulation of *ortho*-alkenyl anilides with alkynes.

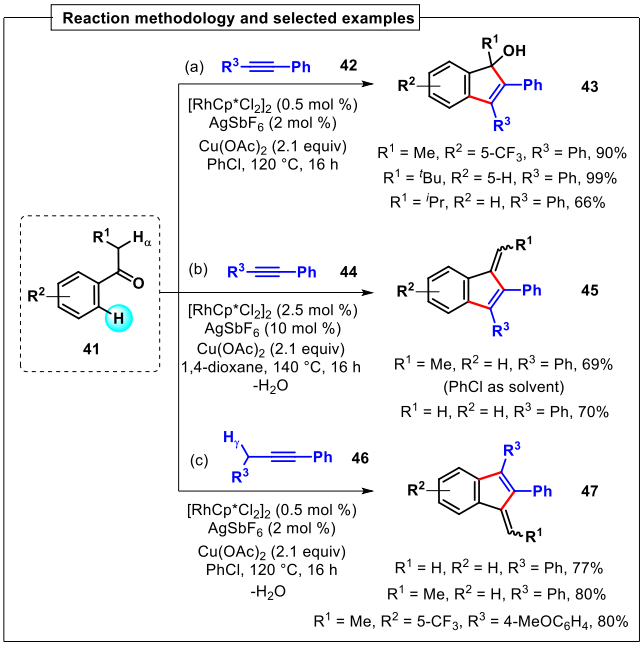


Scheme 16. Rhodium catalyzed carboxylate-directed C-H functionalization of isoxazoles with alkynes.



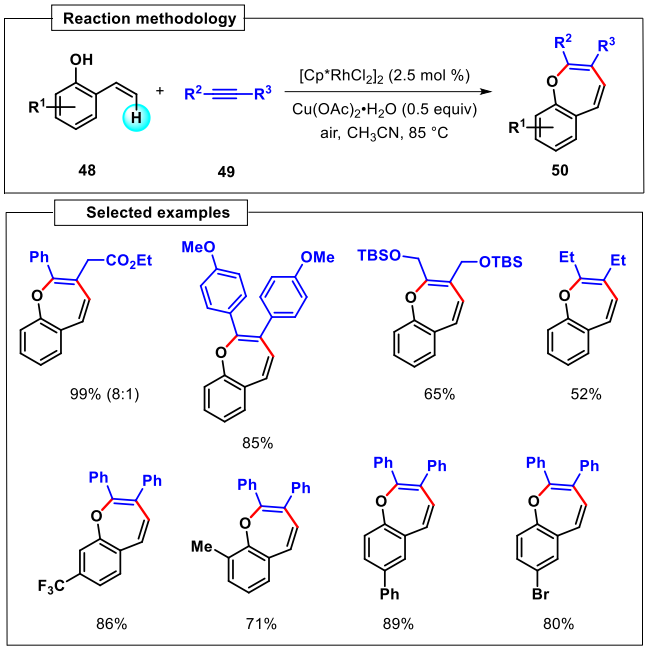
Glorius *et al.* devised a method to synthesize indenols and fulvenes (Scheme 17).[28] This method involved C-H activation of aryl ketones **41** using a rhodium catalyst, then coupling with internal alkynes **42**. This transformation leads to product formation **43**, which involves either an α or γ dehydration step. Pivalophenone proved to be an exemplary substrate and coupled with diphenylethyne to give the product indenol in excellent yields. The oxidant $Cu(OAc)_2$ was found to improve the reactivity of the substrate. Notably, electrophilic phenones led to indenol products against the expected fulvene derivatives, whereas neutral and electron-donating phenones gave the expected fulvenes. It was revealed that cleavage of γ-H is more feasible than the α-H to obtain the product **47**, following which the authors could use milder conditions and obtain higher yields. Control over both processes provides access to regioselective fulvenes containing various functional groups. Some fulvenes could be easily accessed through the α-pathway but were challenging to synthesize through the γ-pathway, and vice-versa for other fulvenes. This procedure also showed high tolerance towards halides and heterocycles.

Scheme 17. Rhodium catalyzed coupling of aryl ketones with internal alkynes.



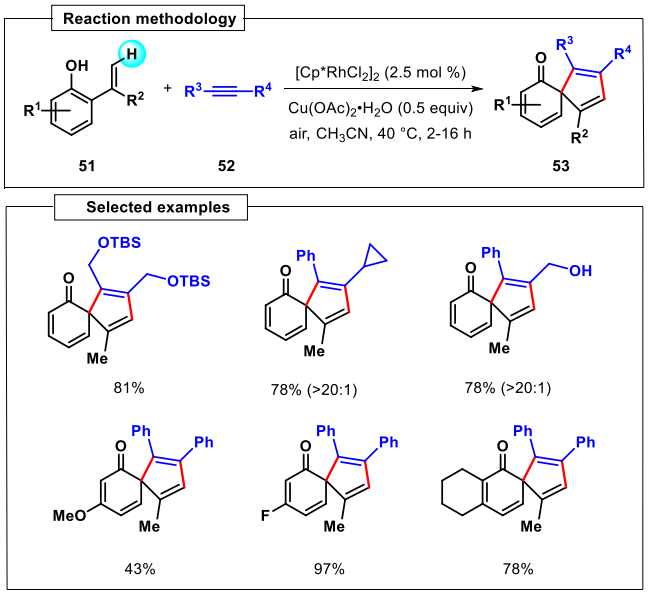
In this series, M. Gulias *et al.* demonstrated another example of Rh-catalyzed annulation of *o*-vinylphenols **48** with internal alkynes **49** (Scheme 18).[29] This procedure uses $Cu(OAc)_2$ as an oxidant along with the catalyst to furnish benzoxepine skeletons **50** via a [5+2] cycloaddition step. Symmetrical diaryl alkynes containing both electron-withdrawing and -donating groups smoothly participated in the reaction to give good yields. Asymmetrical alkynes furnished the products in high regioselectivity. Substrates containing substituents *para* to the hydroxyl group such as bromo-, methoxy, or ester groups were well tolerated in the reaction and gave products in excellent yields. Similarly, *ortho*- and *meta*-substituted vinylphenols also coupled consistently, giving good yields. Notably, substrates bearing alkyl substituents at the terminal position of alkene could not tolerate the reaction condition and decomposed into other products.

Scheme 18. Rhodium catalyzed C-H functionalization of *o*-vinylphenols.



In addition to their previous work, M. Gulias *et al.* have reported a [3+2] cycloaddition of 2-alkenylphenols **51** with alkynes **52** (Scheme 19).[30] The reaction features a rhodium(III)-catalyst towards forming dearomatized spirocyclic skeletons **53**. Substrate scope studies suggest that symmetrical alkynes containing electronically distinct aryl substituents participated in this transformation. Similarly, symmetrical dialkyl substituted alkynes also afforded products in good yields. The reaction showed high regioselectivity.

Scheme 19. Rhodium catalyzed dearomatizing [3+2] annulation of substituted alkenylphenols and alkynes.

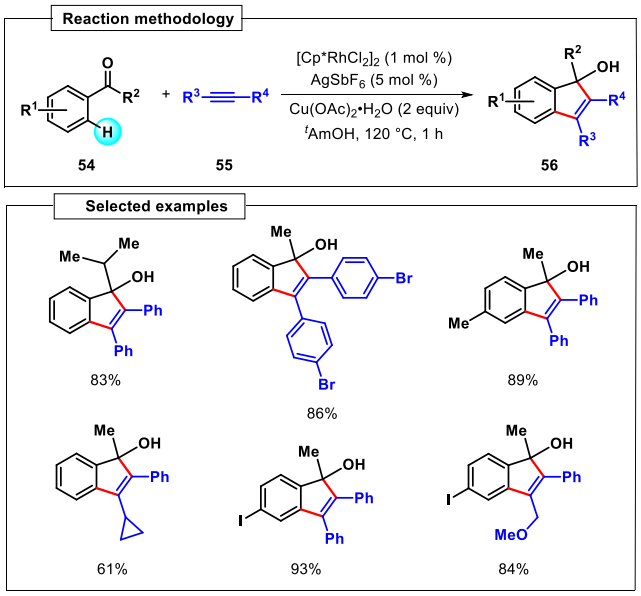


They have also employed 2-alkenylphenols containing substituents other than methyl at the internal position of the alkene. Notably, it was observed that the substrates bearing aryl groups decreased the reaction rates, hence requiring elevated temperatures to undergo further transformation. This method also worked well with electron-donating as well as withdrawing *para*-substituted alkenylphenols, giving good to excellent yields, respectively. Notably, alkyne with free hydroxyl group substituent could withstand the reaction condition and remain intact throughout the transformation.

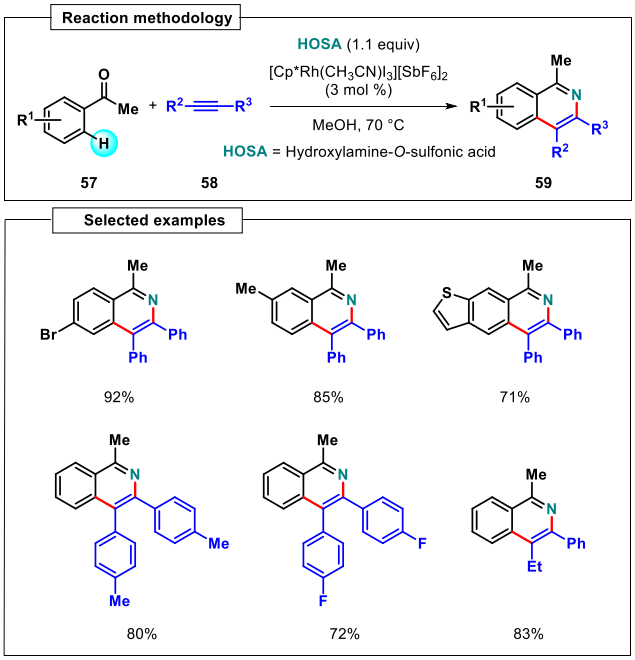
Further, Cheng *et al.* reported a carbocyclization reaction of aryl ketones **54** and alkynes **55** using an Rh(III)-catalyst (Scheme 20).[31] This method efficiently afforded substituted indenols **56** in the presence of a copper oxidant. Aryl ketones bearing both electron-rich and -deficient groups reacted well in the optimized reaction condition. Acetophenones with the halogen-containing aromatic ring also tolerated the reaction. Also, the authors have studied the effect of changing the methyl group of acetophenone to other alkyl groups such as ethyl and isopropyl and obtained satisfactory amounts of respective products in both cases. Moreover, alkynes containing sensitive functional groups such as bromo-substituent tolerated the reaction condition and transformed efficiently. The reaction proceeded in excellent regioselectivity with asymmetrical alkynes such as phenyl-cyclopropyl acetylene and propargylic ether, which leads to their respective indenol products.

In 2020, Ravikumar *et al.* disclosed a new reactivity of hydroxylamine-*O*-sulfonic acid (HOSA) as an aminating agent with alkynes **58** towards the synthesis of isoquinolines **59** (Scheme 21).[32] This is the first report wherein the *in-situ* formed directing group acts as the acid additive as well as an internal oxidant. During substrate scope studies, it was observed that *ortho*-substitution hampered the reaction, giving lower yields. Apart from these results, most of the substituents were compatible with optimized conditions, affording good yields. The scope of benzophenones was also vast, and most of the substitutions were tolerated successfully.

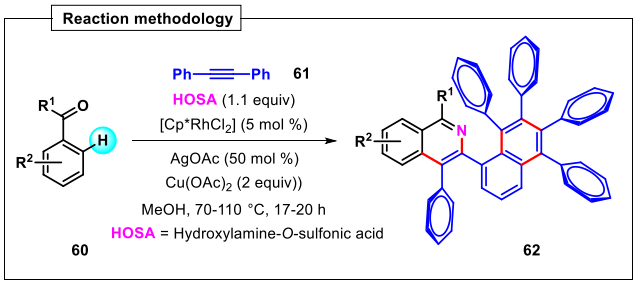
Scheme 20. Rhodium catalyzed carbocyclization of aryl ketones and alkynes.

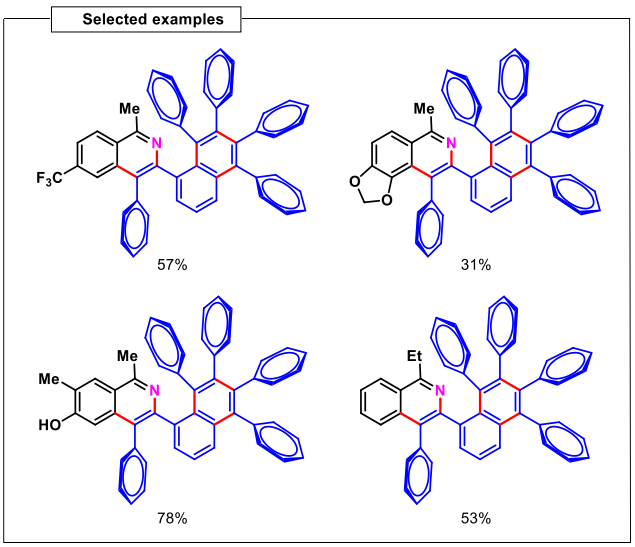


Scheme 21. Rhodium catalyzed synthesis of isoquinolines from arylketones.



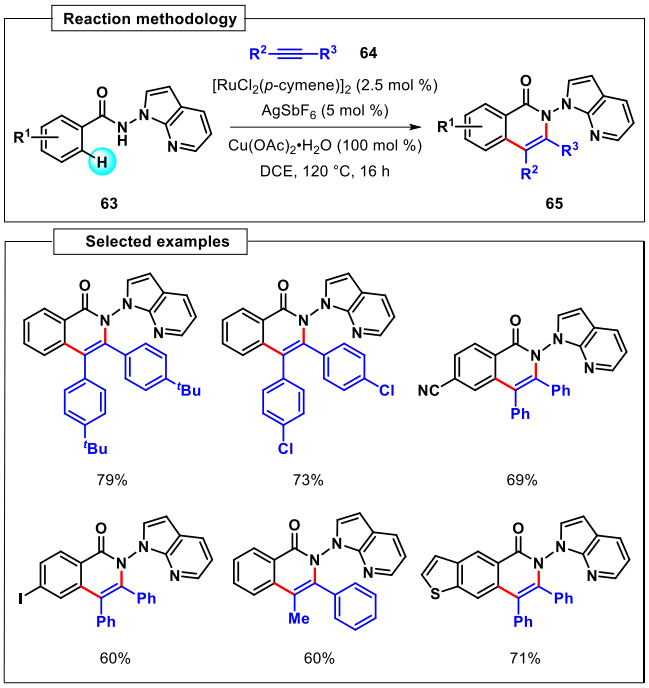
Scheme 22. Rhodium catalyzed triple C-H bond activation of aryl ketones using alkynes.





Following their work on the application of hydroxylamine-*O*-sulfonic acid to form iso-quinolines, Ravikumar *et al.* recently reported the synthesis of *aza*-polycyclic aromatic hydrocarbons **62** via triple C-H bond activation of aryl ketones **61** and internal alkynes **63** (Scheme 22).[33] This Rh(III)-catalyzed transformation also demonstrated the annulation of two different alkynes in a regioselective manner. The substrate scope for this reaction was generalized with a wide range of substituents. Various substitutions on different positions were amenable such as *p*-Me, *p*-OMe, *m*-Me, and *o*-OMe. Moreover, heteroaromatic aryl ketones including thiophene, furan, and indole could be successfully tolerated in this reaction condition. Further, Ravikumar *et al.* described a Ru(II)-catalyzed directing group-assisted annulation of *N*-substituted benzamides **63** with internal alkynes **64** (Scheme 23).[34] The authors found that *para*-substituted symmetrical diaryl alkynes offered very good yields. Likewise, aliphatic symmetrical alkynes are also coupled consistently to provide good yields. As observed in most annulation reactions, asymmetrical alkynes showed high regioselectivity exclusively resulted in a single isomer. Also, the scope of benzamides was found to tolerate a wealth of synthetically valuable functionalities. Notably, the protocol could be extended to heteroarylamides, and even sensitive groups such as chloro- and bromo- were tolerated.

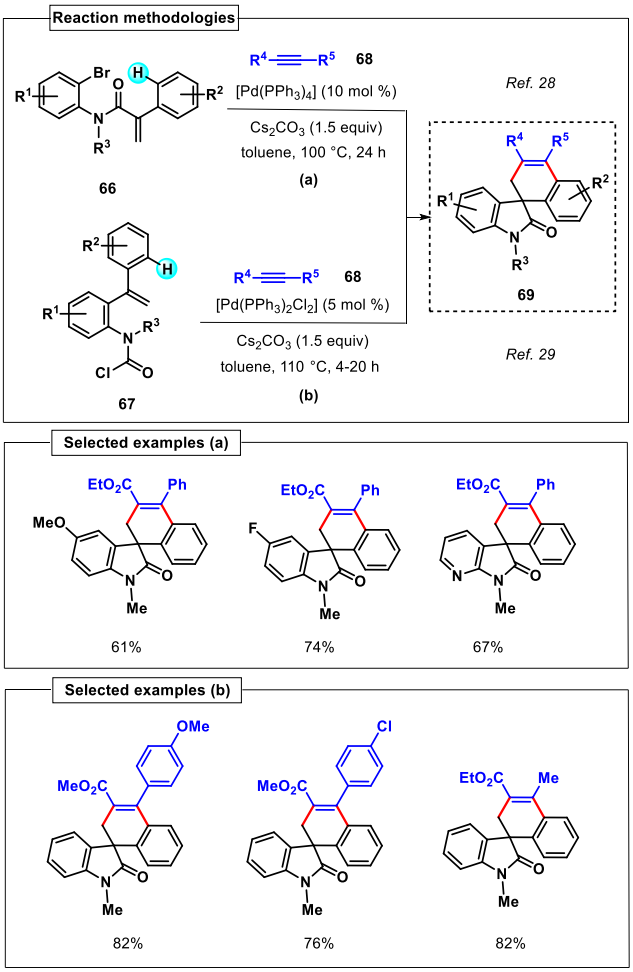
Scheme 23. Ruthenium catalyzed oxidative annulation of benzamides with alkynes.



In 2017, Lautens *et al.* reported the annulation reaction between aromatic acrylamides **66** and alkynes **68** to synthesize spirooxindoles **69** (Scheme 24a).[35] The effect of substituents on the substrate was examined. They observed that electron-deficient substituents such as fluoro provided better results than electron-rich substituents. The protocol was also compatible with heterocyclic substituents such as the pyridyl group, which provided good yields.

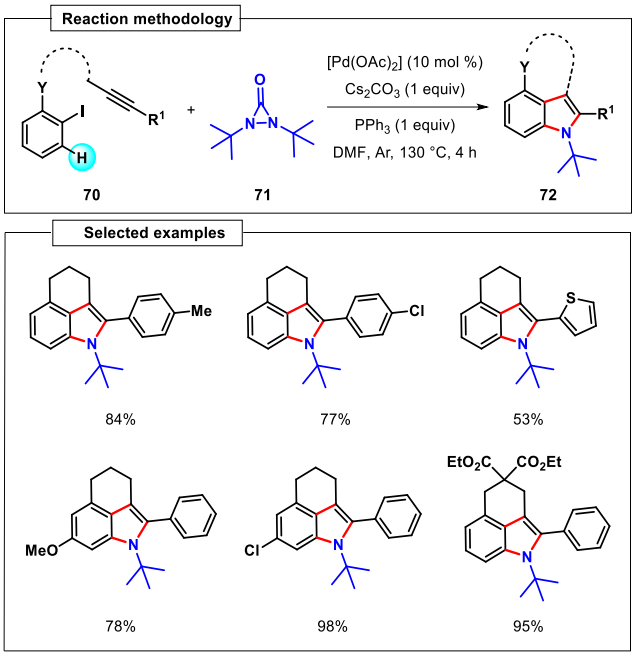
A similar transformation was also reported by Chen *et al.* to achieve the synthesis of spirooxindoles **69** from carbamoyl chlorides **67** with alkynes **68** (Scheme 24b).[36] Substrate scope studies revealed that the reaction could tolerate carbamoyl chlorides containing both electron-rich and -deficient substituents, including sensitive groups such as halogens. A variety of alkynes were tested against the condition to determine the alkyne scope. Alkyl aryl alkynes containing electron-donating as well as electron-withdrawing groups were amenable and gave good yields. Moreover, dialkyl alkynes such as ethyl but-2-ynoate also coupled smoothly and provided the desired products in satisfactory yields.

Scheme 24. Palladium-catalyzed spirocyclization to generate spirooxindoles.



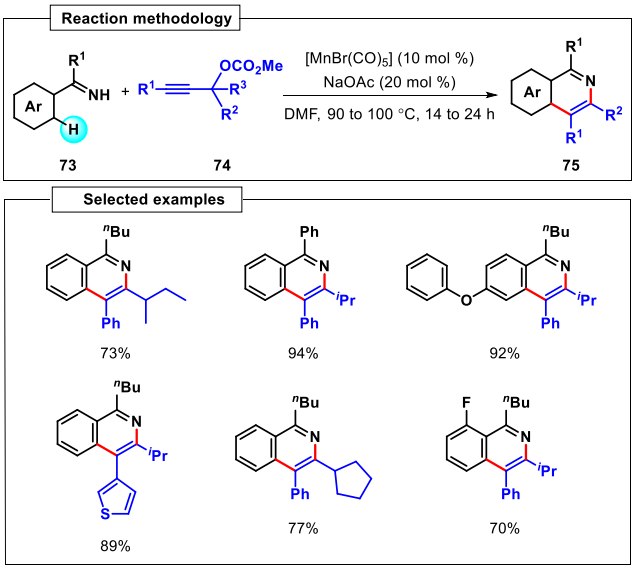
In 2020, Yu *et al.* reported an unforeseen intramolecular [2+2+1] annulation reaction of alkyne-tethered aryl iodides **70** with diaziridone **71**, giving 3,4-fused tricyclic indoles **72** as the product (Scheme 25).[37] Upon varying the substitution pattern on the substrate, electron-deficient substituents were found to be more effective than electron-rich substituents. Substitution on the aromatic ring attached to the alkyne moiety was also carried out, wherein it was observed that both electron-donating and -withdrawing groups gave the respective products in good yields. Moreover, heterocycles such as thienyl could also be tolerated, albeit in a lower yield. Following the work of the Wang group, Glorius *et al.* in 2017 reported a similar transformation using alkyl aryl imines **73** and alkynes containing a traceless directing group **74** (Scheme 26).[38] The main feature of this reaction is its high regioselectivity, which was observed for the first time with Mn(I). This method was remarkably effective with unsymmetrical alkynes, which were challenging to couple previously. Various substrates bearing electronically distinct substituents were reacted with alkynes, giving reasonable amounts of products. In the case of *meta*-substituted imines, the C-H bond that is sterically less crowded, was activated, leading to the corresponding isoquinolines in moderate yield.

Scheme 25. Palladium-catalyzed intramolecular annulation of alkyne-tethered aryl iodides with diaziridone.



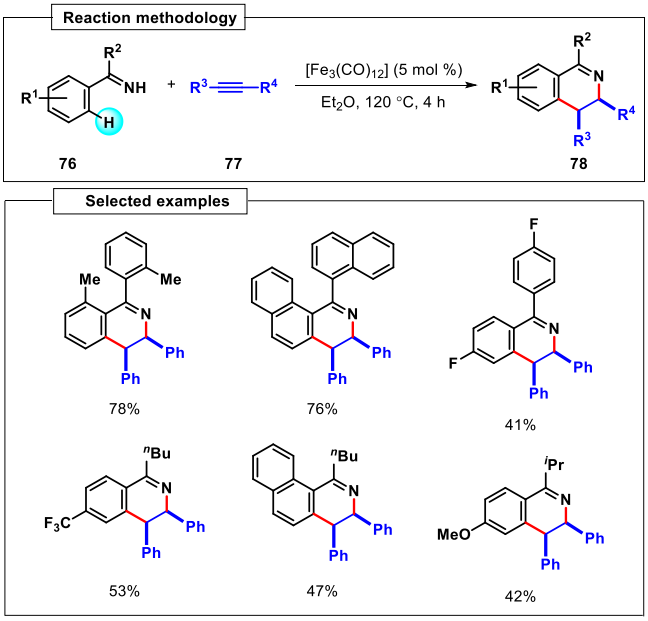
In comparison, *ortho*-substitution on the imine gave a slightly better yield. Diaryl ketimines also participated smoothly and gave the respective products in high amounts. Aryl imidates were well tolerated under the reaction condition and furnished high yields. Furthermore, this method was successfully extended to heterocycles such as thiophene and benzothiophene.

Scheme 26. Manganese catalyzed regioselective annulation of aromatic imines with alkynes.

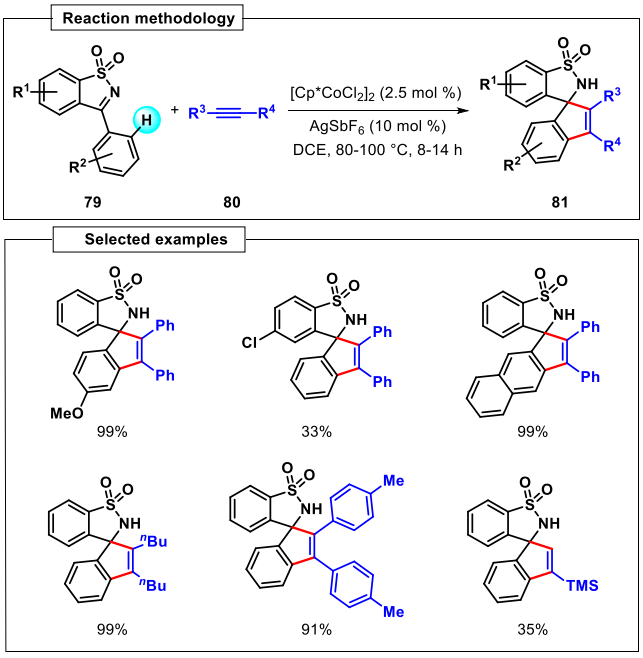


The first case of iron-carbonyl-catalyzed C-H activation of arenes was reported by Wang *et al.* in 2016 (Scheme 27).[39] The reaction featured various substituted *N-H* imines **76** and internal alkynes **77** for the synthesis of *cis*-3,4-dihydro isoquinolines **78**. Looking at the effect of introducing substituents on the imine, the authors found that the reaction tolerated both electron-withdrawing and -donating substituents. Also, *meta*-substitution allowed selective activation of the less sterically hindered C-H bond. However, the steric bulk arising due to *ortho*-substitution did not significantly affect the formation of the product. The use of asymmetrical diarylimine offered the respective product with excellent regioselectivity. Notably, aromatic alkynes containing halogen moieties were applied to the procedure and coupled consistently to give the desired dihydro isoquinolines. These halogen groups allowed further functionalization of the products, which is more synthetically useful.

Scheme 27. Iron catalyzed redox-neutral [4+2] annulation of *N-H* imines and internal alkynes.



Scheme 28. Cobalt catalyzed annulation of *N*-sulfonyl ketimines with alkynes.

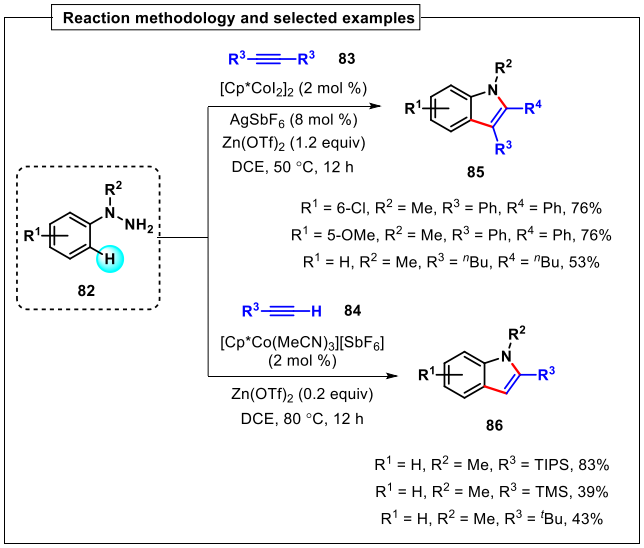


Wang *et al.* described the synthesis of spiro indenyl benzosultams **81**. The synthetic procedure involved *N*-

sulfonyl ketimines **79** with internal and terminal alkynes **80** (Scheme 28).[40] The authors examined the substitution effects on the phenyl ring by varying R^2-substituents. Substitution with electron-rich species such as methyl and methoxy favored the reaction. Moreover, it was observed that the effect of substitution at different positions was significant. For example, methoxy substitution at the *para*-position gave a significantly greater yield than substitution at *ortho*-position. On observing the yield of the product obtained by reacting ketimine containing an *ortho*-phenyl group, it was confirmed that steric factors played a major role in determining the rate of reaction. Substrates with different R^1-groups were also tried, giving moderate to good results. Next, the authors employed different alkynes to test their scope. *para*-substituted symmetrical diaryl alkynes furnished the desired products in good amounts. An alkyne containing sensitive nitro- group was also identified as amenable, affording products in excellent yields. Moreover, asymmetrical alkynes were tolerated under reaction condition, albeit in a lower yield.

In 2016, Zhu *et al.* disclosed the procedure for the synthesis of indoles **85**, **86** via C-H annulation of *N*-substituted phenylhydrazines **82** with internal **83** and terminal alkynes **84** (Scheme 29).[41] The generality of the developed methodology has been tested with the various substrate by varying the substitution pattern on phenyl-hydrazine. The steric effect was a major factor in determining the product's yields. Increasing bulkiness around nitrogen leads to decreasing yields; thus, lower yields were observed when methyl was replaced with ethyl and isopropyl groups.

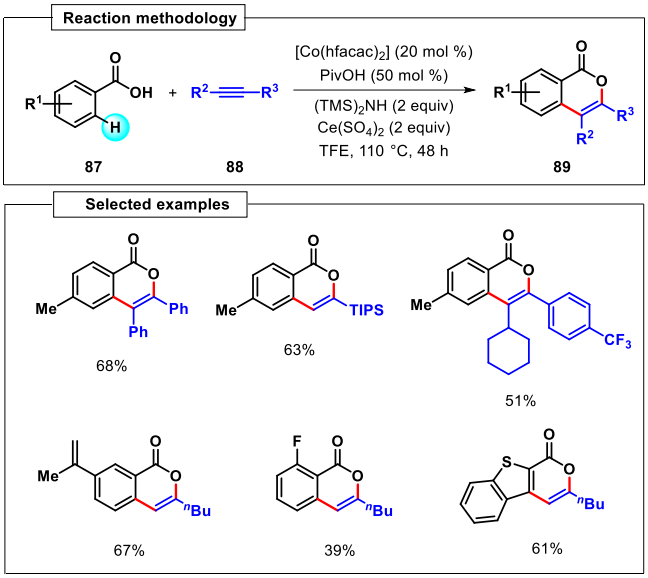
Scheme 29. Cobalt catalyzed C-H annulation of *N*-substituted phenylhydrazines with alkynes.



ortho-Substitution with electrophilic groups afforded products in moderate yields, while *meta*-substitution offered highly regioselective products, giving only a single isomer. Astonishingly, the authors observed a direct relation of product yield with the bulkiness of the silyl group in silyl-substituted alkynes.

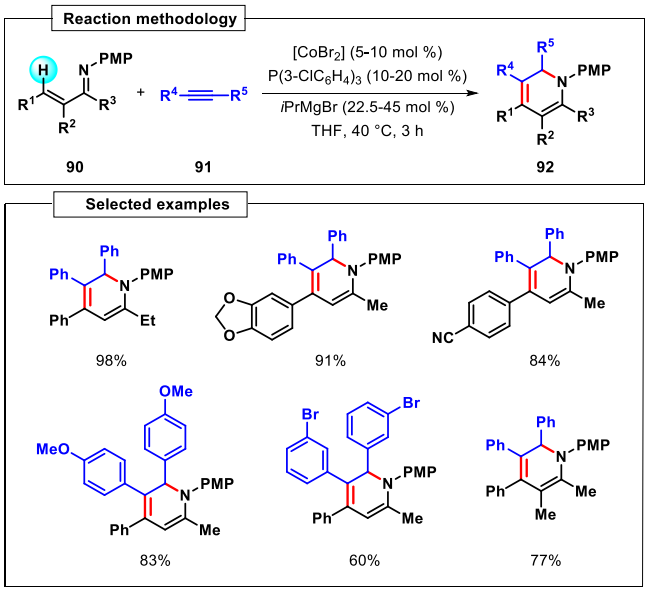
In this series, Daugulis *et al.* presented a Co(II)-catalyzed, carboxylate-directed C-H annulation of methyl benzoic acids **87** with alkynes **88** (Scheme 30).[42] The procedure required the presence of a base, an oxidant, and cerium sulfate as co-oxidant. Substrates containing both electron-donating and -withdrawing substituents were compatible in this protocol. The transformation selectively functionalized less sterically hindered C-H bonds, thereby offering highly regioselective iso-chromones **89**. Benzoic acids containing a broad range of functionalities such as methoxy, chloro-, fluoro-, vinyl, and some heterocycles were identified as amenable.

Scheme 30. Cobalt catalyzed annulation of benzoic acid with alkynes for the synthesis of iso-chromones.



The method tolerated alkynes containing a wealth of synthetically valuable functionalities such as cyanide, phthalimide, and olefins. Silyl and aryl acetylenes also coupled efficiently to give the corresponding iso-chromone products. Moreover, some internal alkynes, such as 1-phenyl-1-propyne, exclusively produced a single regio-isomer in moderate yields.

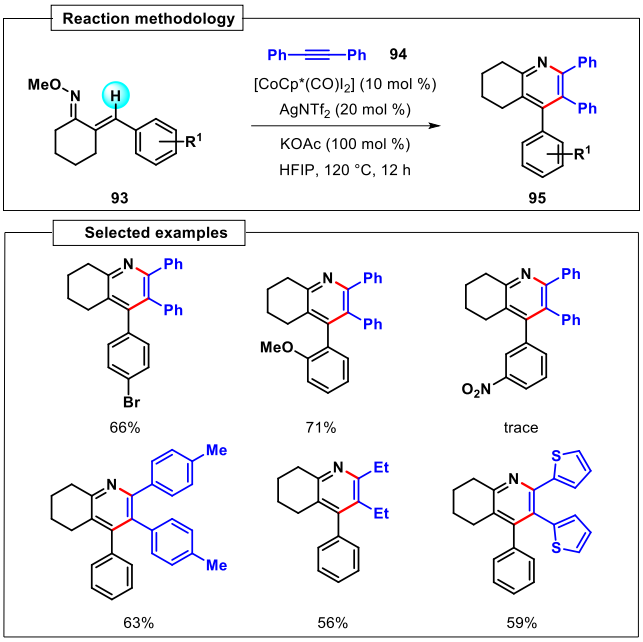
Scheme 31. Cobalt catalyzed olefinic annulation of *α,β*-unsaturated imines.



On similar lines, Yoshikai *et al.* have reported a transformation for synthesizing poly-substituted dihydropyridine derivatives **92** using cobalt-catalyst (Scheme 31).[43] The scheme featured *α,β*-unsaturated imines **90** along with alkynes **91** in the presence of cobalt and Grignard reagent. The substrate scope for the reaction was studied, in which imines with varied substitution patterns were reacted with diphenylacetylene. Also, various conjugated imines were efficiently converted to the desired products and tolerated with many functionalities such as methoxy-, and cyano- groups. The reacting partner alkyne was also well tolerated in the optimized reaction conditions and gave good yields.

Recently, Ravikumar *et al.* described a Co(III)-catalyzed annulation of *α,β*-unsaturated oxime ethers **93** with alkynes **94** (Scheme 32).[44] This redox-neutral method afforded multi-substituted pyridines in good yields. *para*-Substitution on the substrate resulted in good yield, however, a trace amount of product was observed for *meta*-substituted nitro substrate. In contrast, *ortho*-substitution provided 71% yield of the desired product. Owing to the electronic effects, electron-donating groups were preferred over electron-withdrawing groups.

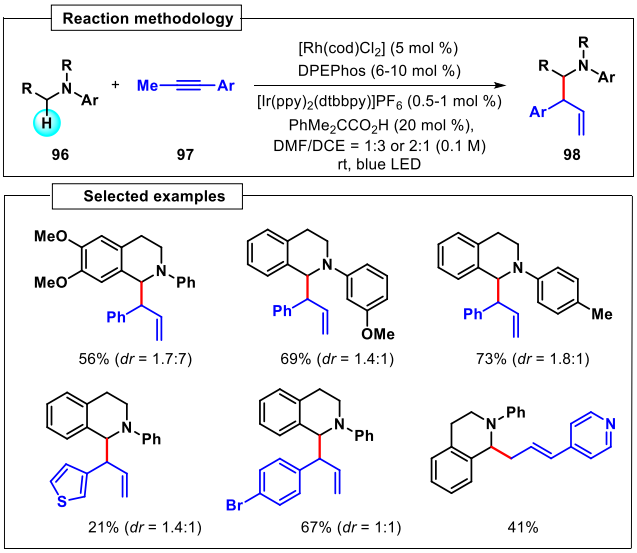
Scheme 32. Cobalt catalyzed annulation of α,β-unsaturated oxime ethers with alkynes.



4. VARIOUS TRANSITION METAL-CATALYZED ALKYLATION REACTIONS OF ALKYNES

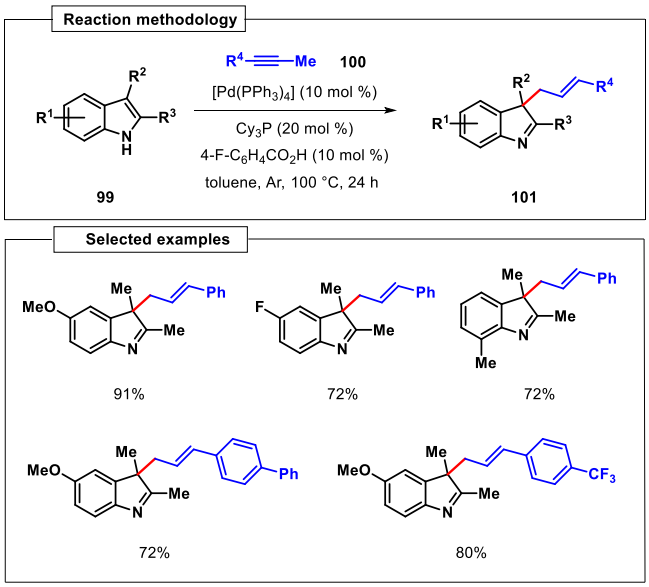
The transition metal-catalyzed alkylation reaction using alkyne as an alkylating surrogate is quite a challenging and underdeveloped area. This is because of the favorable possibility of conversion of the alkyne to allene or olefin after undergoing *in-situ* reduction. In this regard, Breit *et al.* described a regio-divergent *α*-allylation reaction of amines **96** using rhodium/photoredox dual catalysis method (Scheme 33).[45] This novel pathway requires alkynes **97** as electrophilic carriers against the traditional transition-metal catalyzed allylation method.

Scheme 33. Regiodivergent hydroaminoalkylation of alkynes and allenes using rhodium and photoredox catalysis.



In general, it was observed that *para*-substituted phenyl rings on the nitrogen atom smoothly participated in the reaction, giving moderate to good yields with excellent regioselectivity. On the contrary, *meta*-substitution with electron-withdrawing groups did not tolerate the reaction. Moreover, *α*-amino ethyl esters and ketones were also amenable to the reaction. Both *meta*- and *para*-substituted aryl propynes furnished products in good yields. Aromatic rings bearing heteroatoms were also tolerated, albeit in lower yields. Also, Yao *et al.* successfully synthesized indolenins with C-3 quaternary centers **101** via dearomative allylic alkylation of indoles **99** and alkynes **100** (Scheme 34).[46]

Scheme 34. Palladium-catalyzed allylic alkylation of indoles with alkynes.

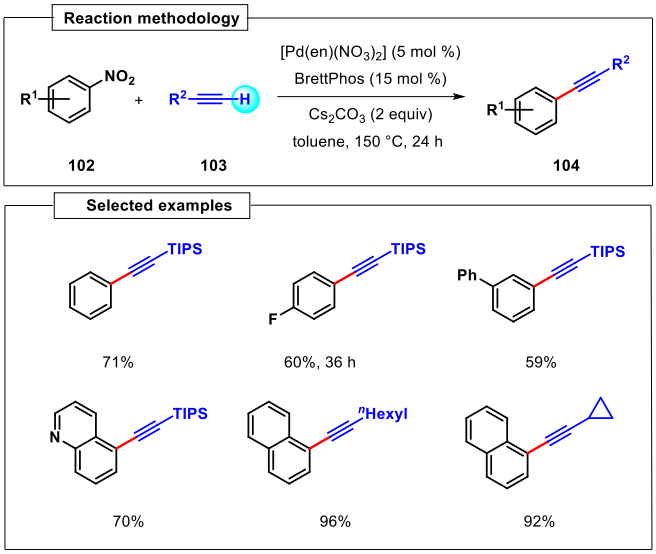


Substrate scope studies indicated that indoles containing electron-donating groups on C-5 as well as C-7 positions were efficiently converted to the desired indolenins. Fluoro-substitution on the C-5 position also produced the corresponding product in good yield. As far as alkyne scope is concerned, alkynes containing one aromatic substituent were compatible. Alkynes with an electron-deficient species substituted to the phenyl ring displayed better suitability towards the transformation than those bearing electron-rich species. Moreover, this alkylation using alkyne led to the synthetically useful quaternary center bearing indole derived-product **101**.

5. VARIOUS TRANSITION METAL-CATALYZED ALKYNYLATION REACTIONS OF ALKYNES

The alkynylation reaction is one of the well-known reactivity of alkyne, which could be achieved using terminal alkynes as a reacting partner. In this context, You *et al.* recently reported the alkylation reaction between nitro-benzenes **102** and terminal alkynes **103**, offering C(sp^2)-C(sp) bond formation **104** (Scheme 35).[47] On examining the substrate scope, the authors observed that electron-deficient nitro-benzenes yielded better results than electron-rich substrates. Substrates containing substituents at the *ortho-, meta-, and para-* positions of the phenyl ring were found to be successful. A broad range of functionalities such as ketone, methoxy, and heterocycles such as pyridine rings were able to withstand the condition.

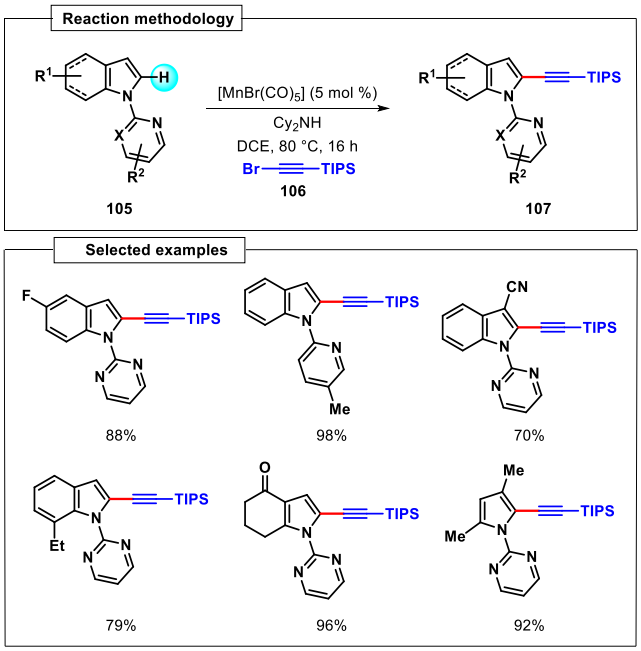
Scheme 35. Palladium-catalyzed cross-coupling of nitrobenzene with terminal alkynes.



Apart from silyl-containing alkynes, aliphatic alkynes containing cyclic and acyclic groups also coupled smoothly, giving the desired products in excellent yields. Remarkably, using terminal alkynes, the palladium-catalyzed *ipso*-alkynylation has been achieved, which is quite challenging in the presence of the -NO_2 group.

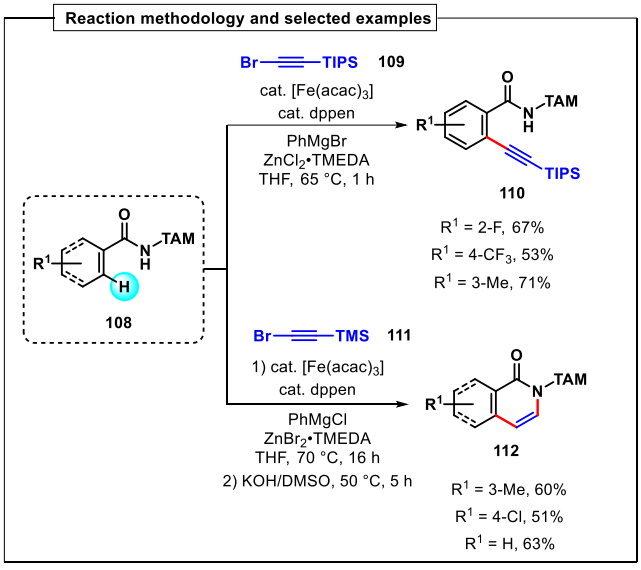
In this series, Ackermann *et al.* successfully achieved Mn(I)-catalyzed alkynylation of *N*-substituted indoles **105** with silyl haloalkynes **106** (Scheme 36).[48] The authors applied this transformation to set the stage for synthesizing various cyclic and acyclic peptides. Substrate scope studies revealed that substitution on the phenyl ring of indole with both electron-donating and -withdrawing groups resulted in very good yields. Likewise, substituting the pyrimidyl ring also afforded respective alkynylated products in excellent yields. Notably, sensitive groups such as bromo-, ester, cyano, and nitro were also well-tolerated and remained unaffected throughout the transformation.

Scheme 36. Manganese catalyzed alkynylation of *N*-substituted indoles.



Further, Ackermann *et al.* gave the first report on iron-catalyzed alkynylation of arenes, heteroarenes, and alkenes using triazolyldimethyl-amine as a directing group (Scheme 37).[49] This method employed substituted benzamides **108** and bromoalkynes **109** along with [Fe(acac)$_3$] and *dppen* in catalytic amounts. Substitution on all three positions, *ortho*, *meta,* and *para* was successful, and the desired products were obtained in good yields. *meta*-Substitution afforded products with high positional selectivity, wherein the less sterically crowded C-H bond was activated. Heterocycles such as pyrroles also tolerated the reaction smoothly.

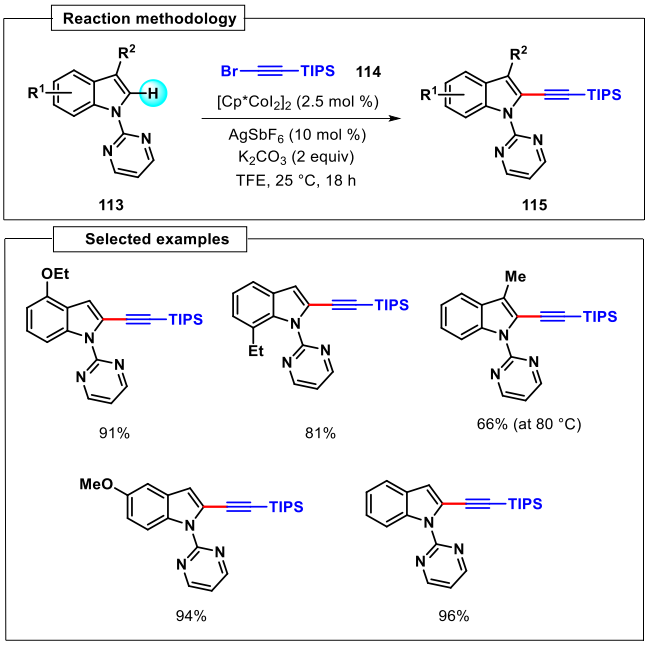
Scheme 37. Iron catalyzed triazole assisted alkynylation of aromatic amides.



Remarkably, this procedure has been applied on alkenes, giving substituted olefins in a highly diastereoselective manner. The synthesized products could be further transformed into isoquinolones **112** by treating with a base. Various substituted benzamides smoothly participated in the transformation, and a broad range of functionalities were tolerated in this reaction condition. Moreover, the authors also described the removal of the triazolyldimethyl-amine (TAM) group.

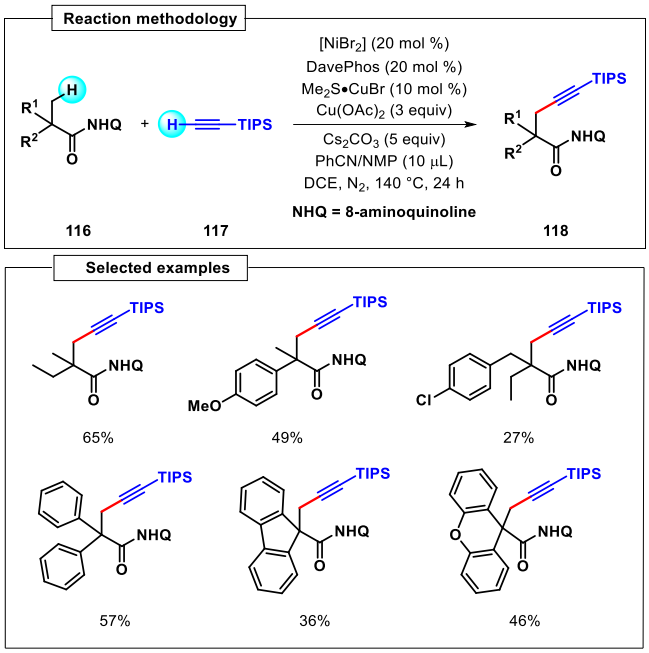
The same group has described a Co(III)-catalyzed alkynylation of *N*-substituted indoles **113** with bromoalkynes **114** (Scheme 38).[50] This reaction has been carried out in very mild conditions and ambient temperatures. Indoles substituted with electrophilic functional groups smoothly participated in the reaction and provided excellent yields. Bulky substitutions on the substrate also could withstand the condition, readily affording the alkynylated indoles. Apart from indoles, the procedure was successfully extended to pyrroles, which underwent alkynylation in identically mild conditions. This protocol could also tolerate a valuable ketone substrate, thus expanding its substrate scope and synthetic probability of this methodology.

Scheme 38. Cobalt catalyzed alkynylation of indoles with bromoalkynes.



A Ni(II)-catalyzed oxidative alkynylation of aliphatic amides **116** exclusively with terminal alkynes **117** for the production of alkyl-substituted internal alkynes **118** was reported by Shi *et al.* in 2017 (Scheme 39).[51] The reaction was carried out in the presence of copper oxidant and Me$_2$S·CuBr as the additive. Different amides containing electron-rich groups such as alkyl, phenyl, or benzyl effectively gave the desired products. Also, cyclic and acyclic amides were found to be compatible with the optimized condition. Notably, amides containing a phenyl group substituted with electrophilic moieties were observed to be more effective than their nucleophilic counterparts.

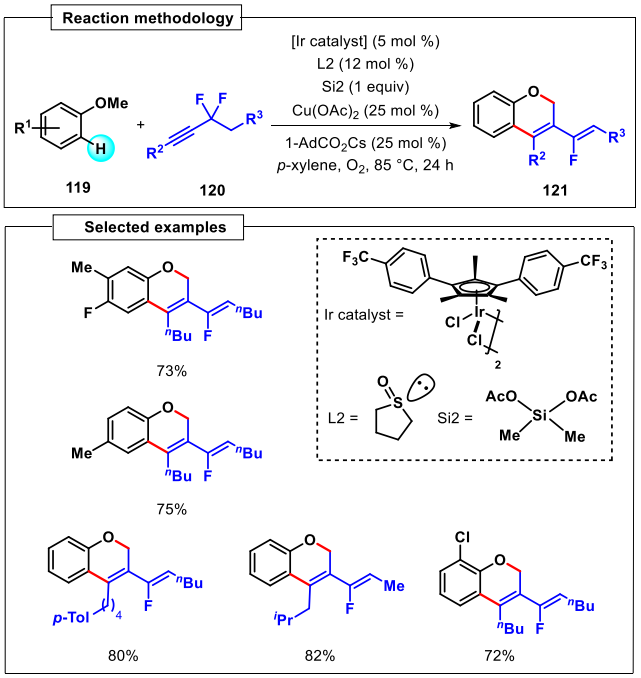
Scheme 39. Nickel catalyzed alkynylation of aliphatic amides with terminal alkynes.



6. VARIOUS TRANSITION METAL-CATALYZED UNUSUAL REACTIONS OF ALKYNE

This section covers various unusual reactivities of alkyne toward the M-C bond. Rovis *et al.* demonstrated the novel reactivity of anisole **119** with difluoroalkynes **120** in the presence of an electrophilic Ir(III)-catalyst (Scheme 40).[52] The reaction proceeded by generating a reactive metallacycle, which produced chromenes **121** as the products after alkyne insertion.

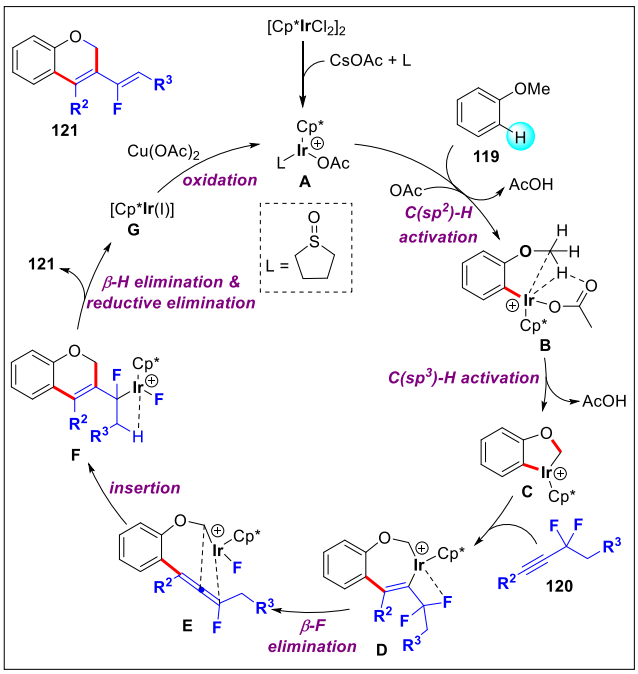
Scheme 40. Iridium catalyzed carbo-carbation of difluoroalkynes using anisole.



The authors employed a broad range of substituted anisoles to determine the substrate scope, wherein the anisoles derivatives with various electronic nature were found to be amenable. A single regioisomer has been observed exclusively with *meta*-substituted anisoles due to C-H activation occurring at the less sterically hindered position. Linear as well as branched alkynes coupled smoothly and gave the corresponding products in good yields. The key feature of this reaction is that it is highly regioselective as well as stereoselective, giving the *Z*-isomer exclusively. Remarkably, sensitive functional groups such as chloro- and cyclopropyl rings could withstand the reaction.

Further, the proposed catalytic cycle has been depicted in scheme 41, where the reaction was initiated with the generation of active Ir-catalyst **A**, from the Ir-dimer complex. Then (sp^2)-H activation of anisole **119** leads to the formation of intermediate **B** after which sequential (sp^3)-H activation gives cyclometallated intermediate **C**.

Scheme 41. Catalytic cycle of Iridium catalyzed sp^2 and sp^3 C-H bonds activation.

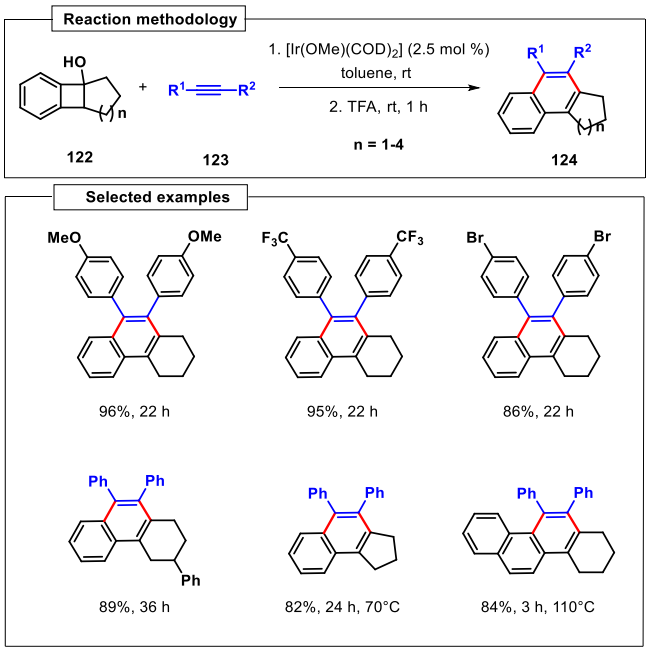


Then alkyne **120** coordination followed by insertion affords intermediate **D**, which leads to the allene-based intermediate **E** after *β*-fluoride elimination of species **D**. Further, insertion of M-C bond into the allene center gives intermediate **F**. From this intermediate, the desired product **121** is produced through *β*-hydride followed by reductive elimination, along with the generation of reduced species **G**. The intermediate **G** is re-oxidized in the presence of copper to regenerate the active catalyst **A** for the next catalytic cycle.

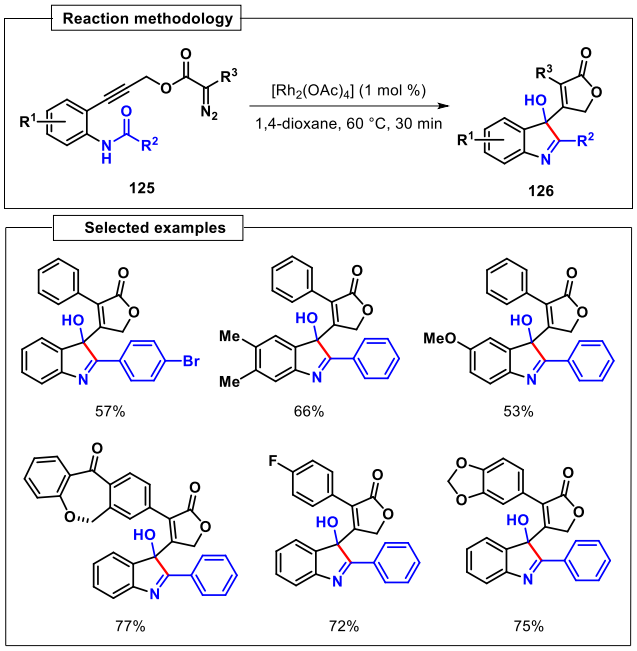
Zhu *et al.,* in 2016, unraveled the first report on Ir-catalyzed intermolecular annulation of ring-fused benzocyclobutenols **122** with alkynes **123** to afford different polycyclic aromatic hydrocarbons **124** (Scheme 42).[53] Where the metal coordinates through free -OH for the insertion between C-C bond to generate the M-C bond. The authors examined the scope of the reaction, which revealed the general trend in the reactivities of the substrates and

alkynes. They observed that electron-rich alkynes gave better results than electron-deficient alkynes. Apart from these, halogen-containing alkynes also offered remarkable yields. For instance, alkynes containing fluoro and CF_3 groups gave the desired products in excellent yields. Notably, these halogen moieties remained unreacted throughout the transformation and set the stage for further functionalization. Regarding the cyclobutenols, it was found that the reaction could tolerate substrates containing an aryl or alkyl group on the phenyl ring. Remarkably, this methodology could also afford five, seven, and eight-membered ring-fused products, which are otherwise challenging to synthesize.

Scheme 42. Iridium catalyzed annulation of benzocyclobutenol with alkynes.



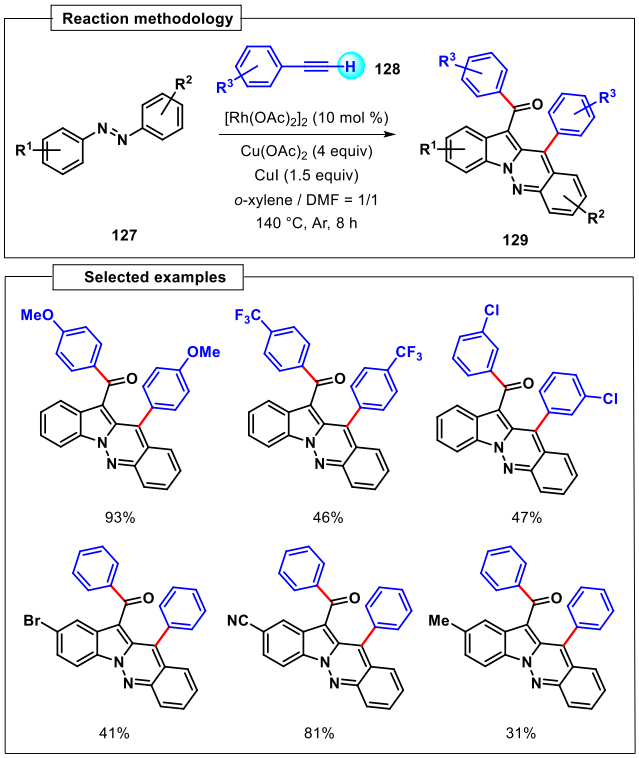
Scheme 43. Rhodium catalyzed formal C-O insertion reaction for the synthesis of indol-3-ol skeletons.



A novel method for synthesizing 3*H*-indol-3-ol skeletons **126** was reported by Hu *et al.* in 2019 (Scheme 43).[54] This intramolecular C-O insertion reaction featured alkyne-tethered diazo compounds **125** in the presence of an Rh(II) acetate catalyst. The scope of the reaction was determined by varying the substitution patterns on the substrate. Substrates bearing substituents with diverse electronic nature could tolerate the reaction, giving products in good yields. Bulky groups such as 2-naphthyl and other heterocycles did not hamper the efficiency of the reaction, suggesting that steric effects do not have a significant effect in determining the product yield. On varying the R^3 group on the substrate, moderate yields were observed. Further studies were also carried out to determine the scope of late-stage functionalization.

Further, Yuan et al. observed another novel reactivity of alkynes in 2019, where they have reported a method to synthesize indolo[1,2-*b*]cinnolies **129** via C-H activation of azobenzenes **127** with terminal alkynes **128** (Scheme 44).[55] *para*-Substitution on the phenyl ring of asymmetrical azobenzenes with electrophilic groups delivered the desired product in moderate to good yields. In these cases, the metal preferably chose to coordinate with the electrophilic substituents, which is unconventional. Regarding alkynes, the authors observed that substitution position on phenylacetylenes was crucial for determining the fate of the reactants. *meta*-Substitution on the phenyl ring hampered the reaction rate, while *ortho*-substitution failed to give the products, reflecting the operation of steric effect.

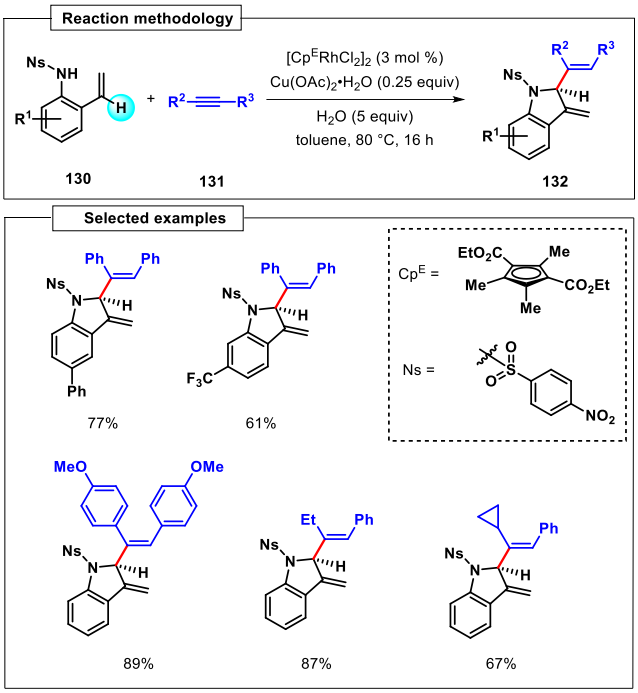
Scheme 44. Rhodium catalyzed cascade annulation of azobenzenes with terminal alkynes.



In 2018, Gulias *et al.* disclosed the unforeseen reactivity of 2-alkenyl anilides **130** with alkynes **131** (Scheme 45).[56] The reaction featured an electrophilic Rh-catalyst giving 2-substituted indolines **132** as products. Careful examination of the substrate scope revealed that anilides bearing electron-donating groups were more effective than those containing electron-withdrawing groups. A similar pattern was observed while studying the alkyne scope. Asymmetrical alkynes offered exclusively a single regioisomer in which the aryl substituent was present at the terminal carbon of the alkene. The condition could also tolerate alkynes containing strained ring systems such as cyclopropane.

Further, in 2020, Lin *et al.* reported a novel method for selective trans-exo arylative cyclization of 1,6-enynes **134**. The reaction was carried out in the presence of an Rh-catalyst and *N*-heterocyclic directing group **133** (Scheme 46).[57] Enynes containing sterically crowded aryl groups as R^3-substituents showed lesser yields than those containing less crowded aliphatic groups. Remarkably, enynes bearing sensitive groups such as bromo- could also be tolerated in good yields. Next, the scope of directing group was studied. It was observed that aryl-pyridines containing electron-donating groups at the *para* position on the phenyl ring gave good yields. Substitution on the pyridyl ring was also experimented with, wherein substituting electron-rich groups led to products with high yield. Additionally, the protocol was also appropriate with heterocyclic moieties such as thiophene.

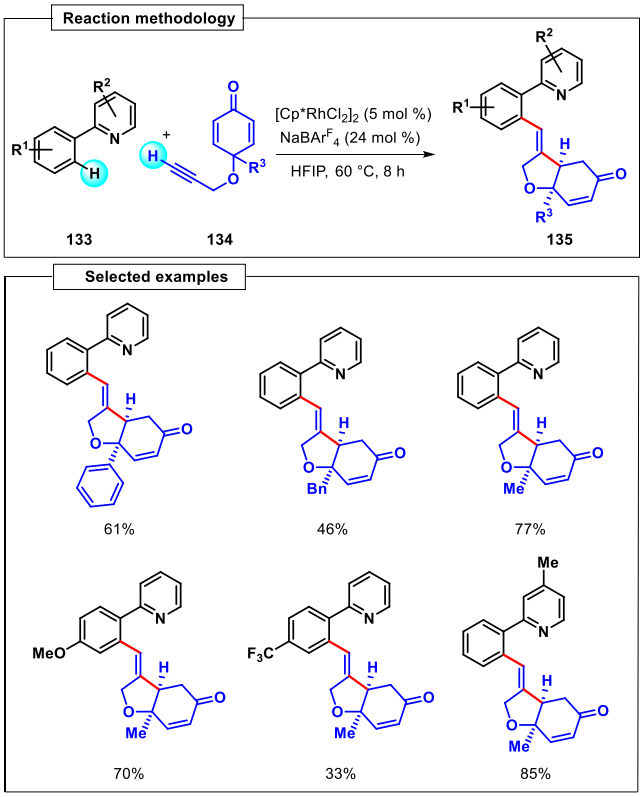
Scheme 45. Rhodium catalyzed annulation of 2-alkenyl anilides with alkynes.



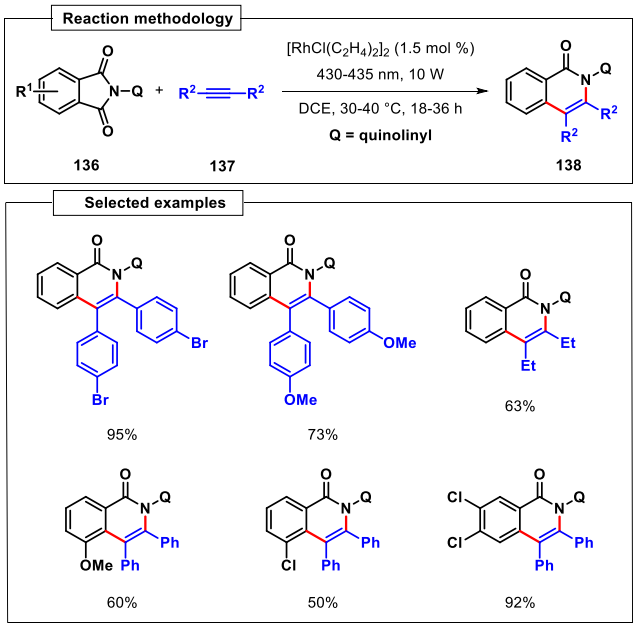
Recently, Chen *et al.* reported an Rh-catalyzed visible-light-induced decarbonylative coupling of imides **136** with alkynes **137** to form isoquinolones **138** (Scheme 47).[58] Careful examination of the reaction scope showed that aryl alkynes containing electron-withdrawing groups such as bromo- and trifluoromethyl were preferred over electron-donating groups such as methoxy. Additionally, symmetrical aliphatic alkynes are coupled consistently, giving products in moderate yields. The desired product was not obtained in the case of cyano substitution due to the coordinating capability of nitrogen with the metal catalyst. Next, the scope of imides was studied. The effect of substitution on imides was the opposite of alkynes, as electron-donating groups gave better yields than electron-withdrawing groups. Di-substituted imides could also participate in the reaction, providing excellent yields. It is noteworthy that terminal alkynes could produce the desired isoquinolones in significant yields, despite the strong possibility of the reactants undergoing [2+2+2] cycloaddition.

Further, Shi *et al.* reported the synthesis of biarylphosphines **142** and **143** via direct hydroarylation of alkenes **140** and alkynes **141** with tertiary phosphines **139** (Scheme 48).[59] The first method corresponds to di-substituted alkylated products. Various substitution patterns were applied to determine its substrate scope. Both electron-rich and -deficient substitutions were amenable and gave products in moderate to good yields. The second method represents the formation of hydroarylation adduct. In this case, it was found that electron-withdrawing substituents attached to the phenyl ring hampered the efficiency of the reaction, thereby giving less yield. In contrast, substitution with electron-rich groups gave the corresponding products in moderate to good yields.

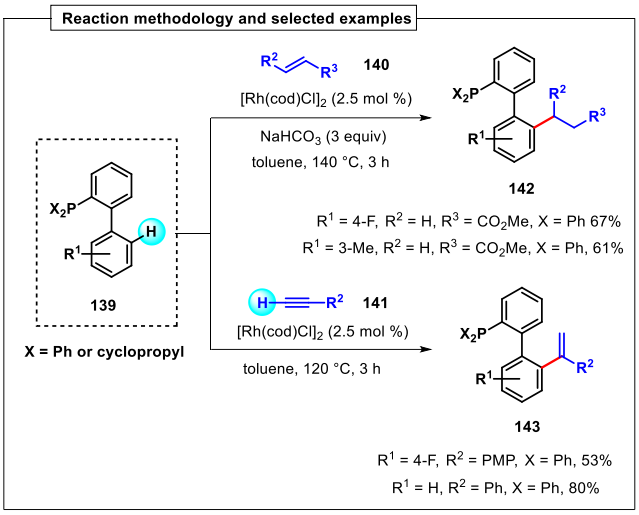
Scheme 46. Rhodium catalyzed cyclization of alkene-tethered cyclohexadienones.



Scheme 47. Rhodium catalyzed decarbonylative coupling of imides with alkynes.

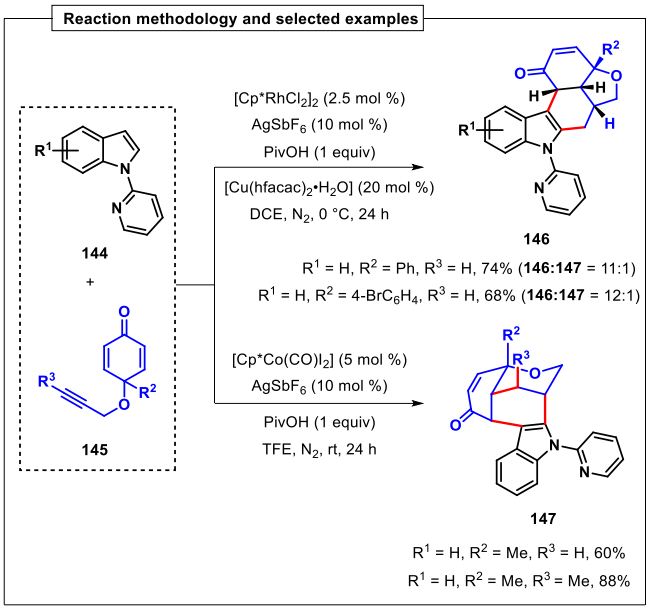


Scheme 48. Rhodium catalyzed hydroarylation of alkenes and alkynes.



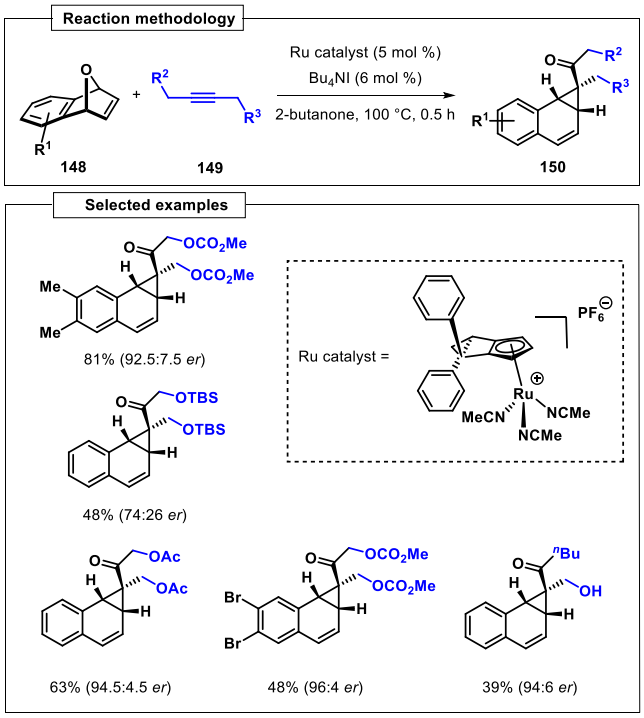
In this series, Li *et al.* reported an alkyne insertion reaction between *N*-substituted indoles **144** and 1,6-enynes **145** using rhodium and cobalt catalysts (Scheme 49).[60] The authors observed a well-known type-I intramolecular Diels-Alder reaction in the case of a rhodium catalyst, whereas a rare type-II intramolecular Diels-Alder reaction when cobalt catalyst was employed. The products obtained in each case were [6,5]-fused cycles **146** and bridged [3,3,1]-cycles **147** respectively.

Scheme 49. Rhodium and cobalt catalyzed alkyne insertion in indoles.



To determine the scope of the rhodium-catalysed reaction, enynes containing electron-donating groups were used, along with a few examples of electron-withdrawing groups. *para*-Bromo substituted phenyl ring gave a slightly better result than an unsubstituted phenyl ring. In the cobalt catalyzed reaction, most of the reactions were carried out using enynes bearing electron-donating groups, out of which two examples are shown in scheme 49.

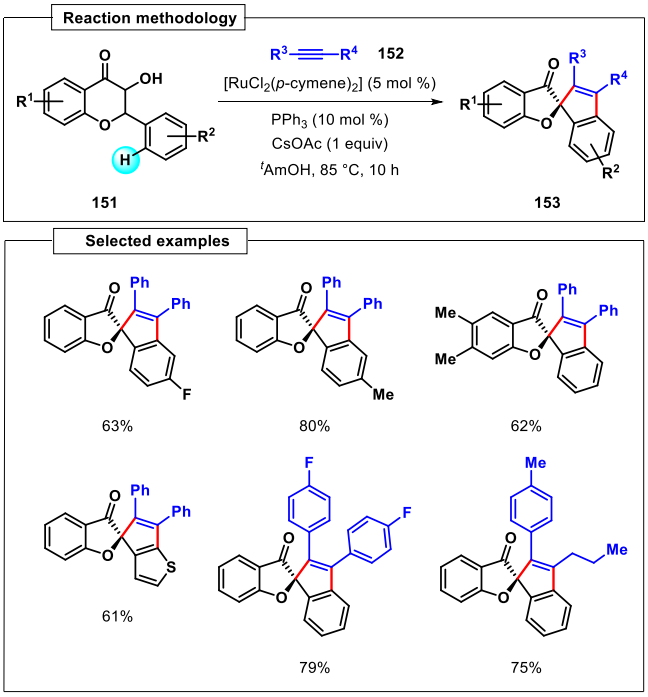
Scheme 50. Ruthenium catalyzed coupling of oxabenzonorbornadienes with alkynes.



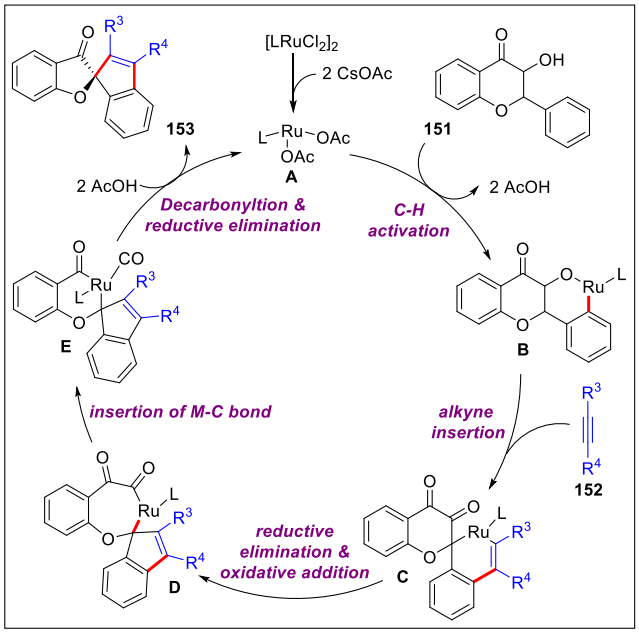
In 2019, Cramer *et al.* described the synthesis of benzonorcaradienes **150** from oxabenzonorbornadienes **148** and alkynes **149** (Scheme 50).[61] The reaction scope was studied by varying the substitution patterns on the substrate. Oxabenzonorbornadiene with two methyl groups reacted very efficiently, giving the desired product in high yield. Subsequently, the substrate containing two bromo-groups showed excellent enantioselectivity, although reacted to give only moderate yield. Next, the scope of alkynes was studied; the symmetrical alkynes containing electron-withdrawing groups coupled smoothly to give the corresponding products in moderate to good yields. Apart from these, the reactivity of various asymmetrical alkynes was also tested, all of which showed high enantioselectivities.

Further, Gogoi *et. al.* described the synthesis of spiro-indene benzofuranones **153** via decarbonylative annulation of 3-hydroxy-2-phenyl-chromones **151** with alkynes **152** (Scheme 51a).[62] On studying the substrate scope for the reaction, it was found that both electron-withdrawing and donating substitution at the *R²*-position were tolerable; however, electron-donating groups showed better reactivity. Similarly, substituents of different electronic nature at the *R¹*-position successfully gave the desired products in good yields. Notably, substitution with heterocycle at the *R²*-position was also successful, albeit in moderate yields. The scope of alkynes has been expanded, and various symmetrical di-aryl alkynes were subjected to the standard reaction condition. Here, di-aryl alkynes bearing substituents of varied nature displayed similar reactivity, indicating that electronic effects do not play a significant role in affording the desired products. Moreover, the procedure could also be extended to various alkyl aryl alkynes and heteroaromatic alkynes.

Scheme 51a. Ruthenium catalyzed synthesis of spirobenzofuranones.



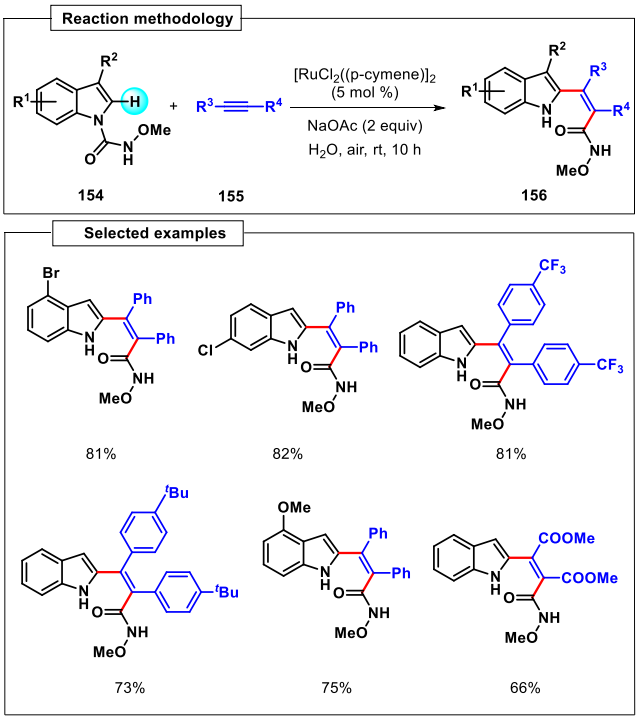
Scheme 51b. Catalytic cycle for ruthenium-catalyzed synthesis of spirobenzofuranones.



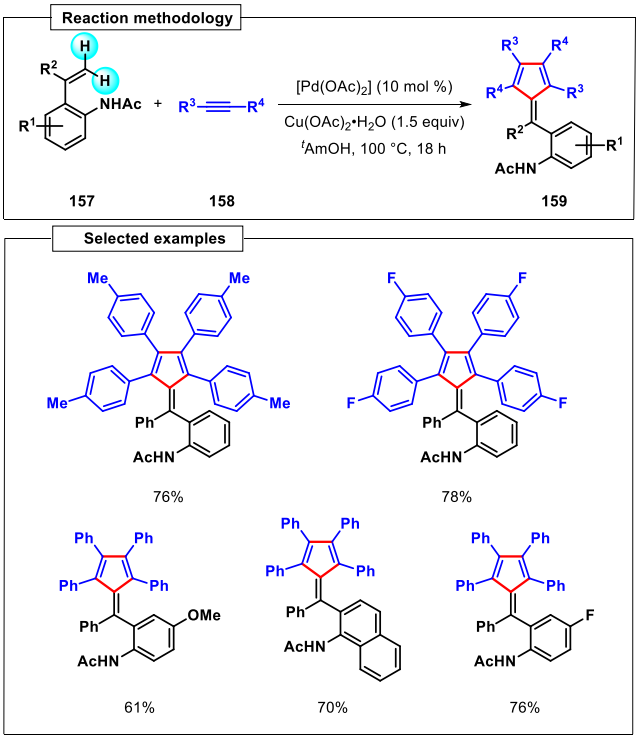
Further, the mechanism for the synthesis of spirobenzofuranones has been depicted in scheme **51b**. Initially, the active metal-catalyst **A** coordinates with substrate **151**, which resulted in the intermediate **B** after selective C-H bond activation. Then the insertion of alkyne **152** into M-C bond gives intermediate **C**. Further reductive elimination followed by oxidation of metal-catalyst leads to the formation of species **D**. Then the further insertion of M-C bond into carbonyl gives intermediate **E**. Consequently, de-carbonylation followed by reductive elimination leads to the desired product formation **153** along with the generation of active catalyst **A** for the next catalytic cycle.

Recently, Zhang *et al.* have reported a method to synthesize tetrasubstituted alkenes **156** via olefination of indoles **154** and alkynes **155** (Scheme 52).[63] The amide directing group attached at the nitrogen atom of the indole moiety promotes this Ru-catalyzed transformation under aqueous conditions, Substrate scope studies revealed that indoles containing varied substitution patterns were amenable to the reaction condition. For instance, 4-methoxy as well as 4-bromo- indole was successfully converted to the respective products in good yields. However, the protocol was not suitable for electron-withdrawing groups. Also, substitution at the C-5 position was reported to be successful. Next, the scope of alkynes was determined. Aromatic alkynes bearing both electron-rich and -deficient groups were effective. Moreover, the condition was applicable on aliphatic alkynes too, which readily furnished the desired products in satisfactory yields. Remarkably, this transformation was also appropriate with some natural product derivatives.

Scheme 52. Ruthenium catalyzed olefination of indoles with alkynes.



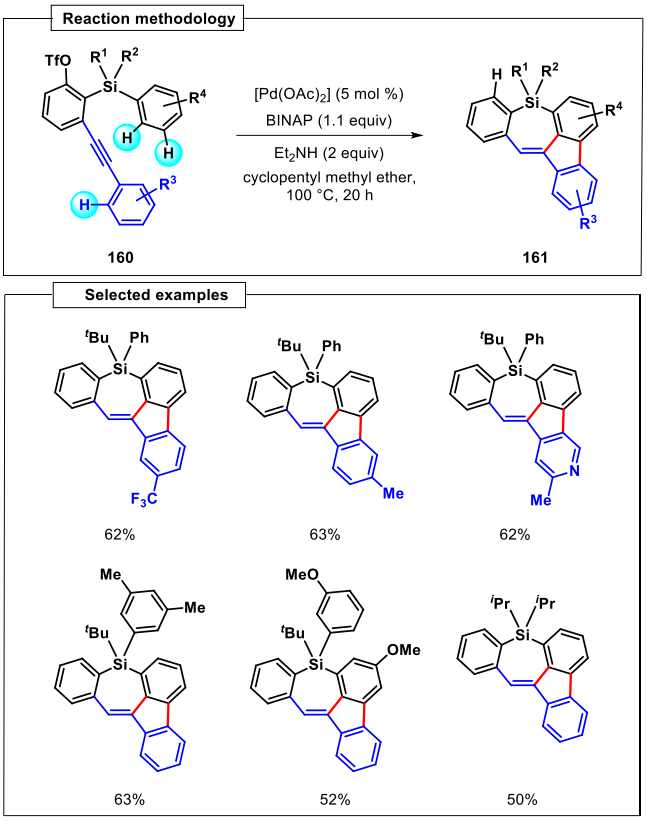
Scheme 53. Palladium-catalyzed double annulation of vinylic compounds.



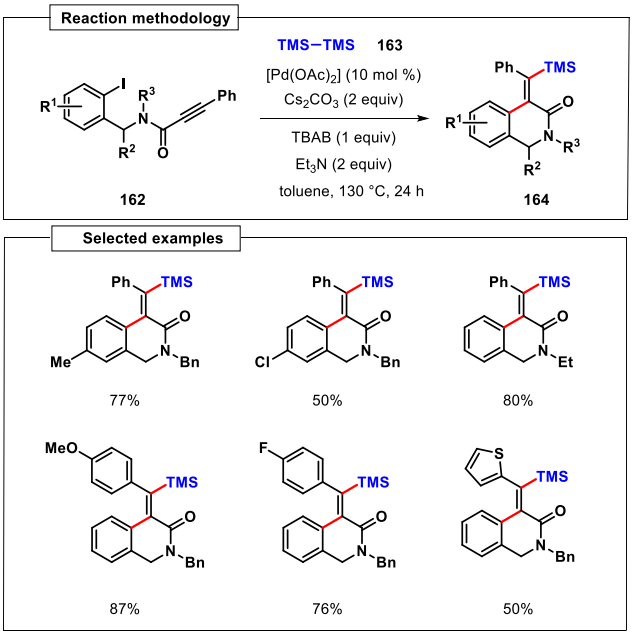
Notably, In 2020, Gogoi *et al.* demonstrated the first report on transition-metal catalyzed double annulation of vinylic geminal C(sp^2)-H of aryl acetamides **157** with di-substituted alkynes **158** (Scheme 53).[64] This protocol was promoted by Pd(II)-catalyst and successfully applied for the synthesis of penta-fulvenes **159**. The symmetrical diaryl alkynes with diverse substituents participated smoothly and afforded the desired products in good yields. The effect of substituents on the phenyl ring of the substrate was also examined. The electron-withdrawing group *para* to the acetamide moiety was responsible for providing better yields than its electron-donating analog. Moreover, naphthyl-containing acetamide was identified as amenable and provided the corresponding product in a satisfactory amount.

Shintani *et al.* reported an unforeseen method for synthesizing dibenzosilepins **161** from silyl-containing aryl triflates **160** (Scheme 54).[65] The reaction proceeded via 1,*n* migration of palladium followed by *anti*-carbopalladation of the attached alkyne moiety. The scope of this transformation was determined by studying the electronic effects of substituents. The use of an electron-donating group on R^2 favored the reaction. Various heterocycles such as naphthyl and pyridyl were also compatible, which provided good yields. Further, Zhang *et al.* have also demonstrated their work on palladium-catalyzed *anti*-carbosillylation of alkynes **162** using hexamethyldisilane **163** to afford isoquinoline-containing exocyclic vinylsilanes **164** (Scheme 55).[66] The reaction was carried out with different substituted substrates to determine the generality of the demonstrated reaction condition. Substrates containing electron-rich groups proved to be more successful than their electron-withdrawing group containing analogs. Alkyl substitution on nitrogen instead of an aryl group further improved the yield. A similar effect of substituents was observed on the phenyl ring attached to the alkyne, although the effect was less pronounced. Apart from phenyl, other heterocycles such as 2-thienyl could also be tolerated, albeit in a lower reactivity.

Scheme 54. Palladium-catalyzed *anti*-carbopalladation of alkyne.



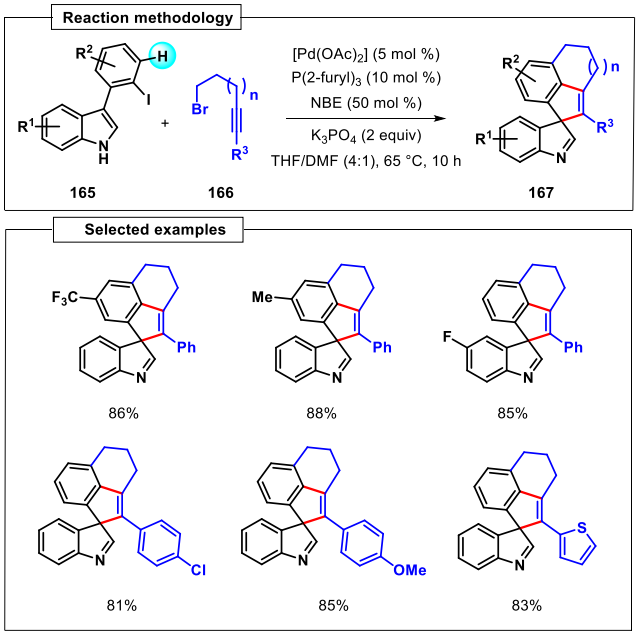
Scheme 55. Palladium-catalyzed carbosilylation of alkynes to produce exocyclic vinylsilanes.



Also, Luan *et al.* described the synthesis of spiro-indolenin containing pentacyclic frameworks **167** via intermolecular domino annulation of biaryl indoles **165** with bromo-alkyl alkynes **166** (Scheme 56).[67] Overall, the authors observed good compatibility of a diverse range of substrates containing electron-withdrawing and -donating groups. Substitution on the phenyl ring at the C-3 position with -CF_3 and methyl groups yielded reasonable products. Similarly,

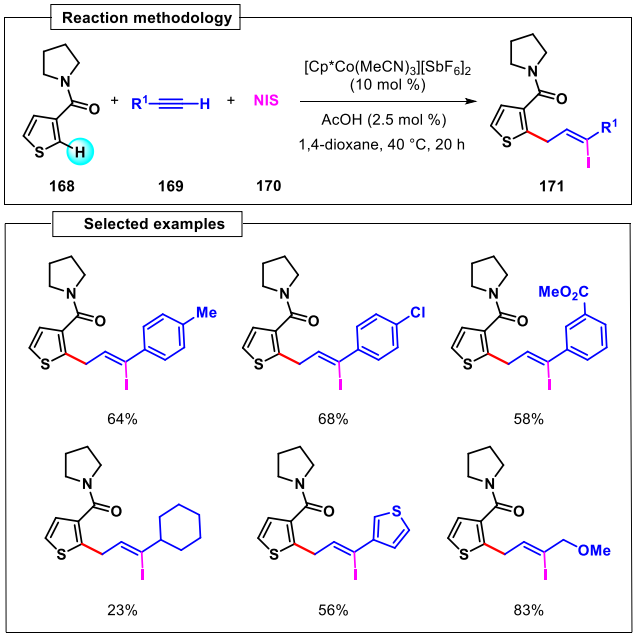
various substitution patterns were also tried on the phenyl ring of indole, which gave good yields. The authors have also tested various electronically distinct alkynes to determine their scope.

Scheme 56. Palladium-catalyzed annulation of indoles to afford spiro-indolenins.



All alkynes smoothly coupled with the substrate under the given condition in good yields, irrespective of their electronic nature. Moreover, alkynes containing heteroaromatic rings such as thiophene could also be tolerated, efficiently giving the corresponding product in good yields.

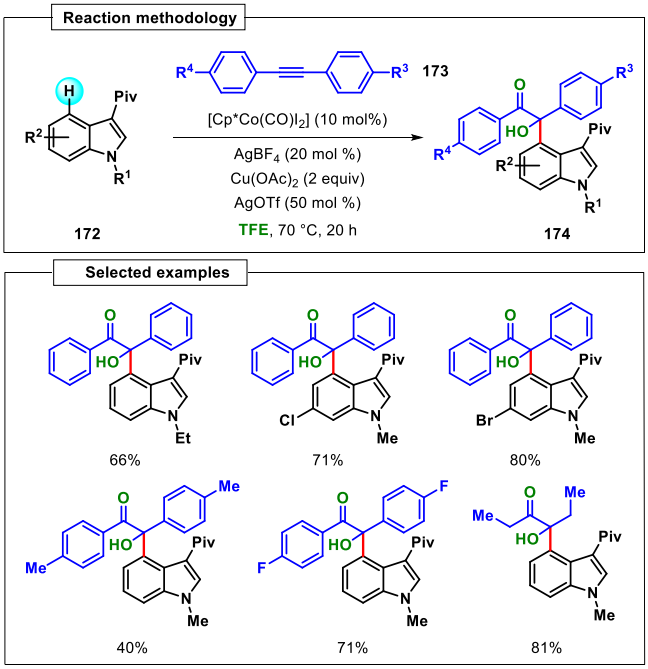
Scheme 57. Cobalt catalyzed a three-component addition reaction for the synthesis of alkenyl halides.



In 2017, Ellman *et al*. reported an unusual three-component addition reaction between pyrrolidin-1-yl(thiophen-3-yl)methanone **168** terminal alkynes **169** and halogenating agents **170** giving functionalized alkenyl halides **171** as the product (Scheme 57).[68] After optimizing the reaction condition, the substrate scope was determined. A broad range of alkyl and aryl terminal alkynes were compatible with the reaction condition. Alkynes containing electronically distinct substituents such as *p*-tolyl and *p*-chlorophenyl gave comparable yield. *meta*-Carbonyl substituted alkyne was also tested, which provided the desired product in moderate yield. Apart from these, heterocycles such as 3-thienyl were also compatible and gave reasonable yields. Moreover, aliphatic alkynes containing cyclohexyl ring and a methoxy group were identified as amenable, although the former alkyne displayed poor reactivity.

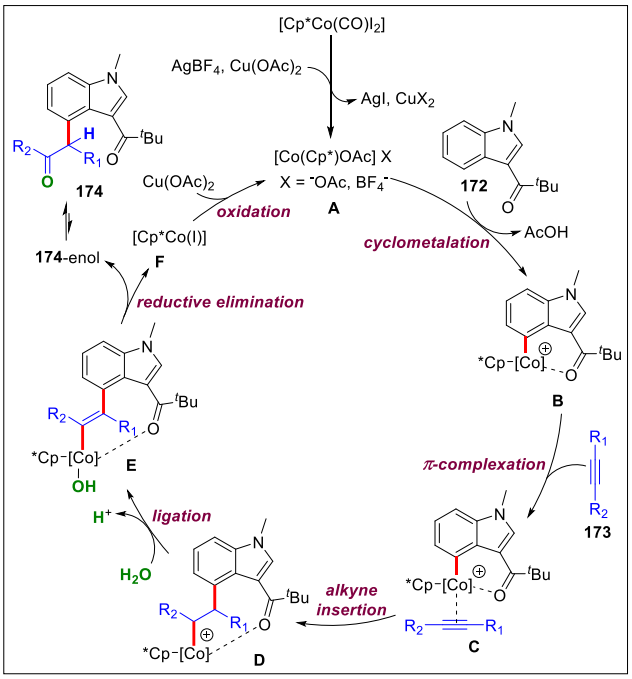
Recently, another novel reactivity of alkyne has been observed by Ravikumar *et al.* They have disclosed the cobalt-catalyzed regioselective C(4)-H functionalization of indoles **172** with alkynes **173** for the formation of *α*-hydroxy ketones **174** (Scheme 58a).[69] This work was promoted by chelation of pivaloyl directing group with metal towards formation of an M-C bond in a weakly coordinating manner. Remarkably, TFE acts as the source of *in-situ* generated water, forming the *α*-hydroxy ketone.

Scheme 58a. Cobalt catalyzed regioselective C(4)-H functionalization of indoles.



The substrate scope of this reaction was studied after optimizing the condition. The indoles containing halogens at the C-6 position were successfully converted to the desired products in good yields. In addition, varying substitution on nitrogen was compatible with the reaction apart from the methyl group. Regarding alkynes, it was found that aromatic alkynes bearing electron-withdrawing groups were more effective than those containing electron-donating groups.

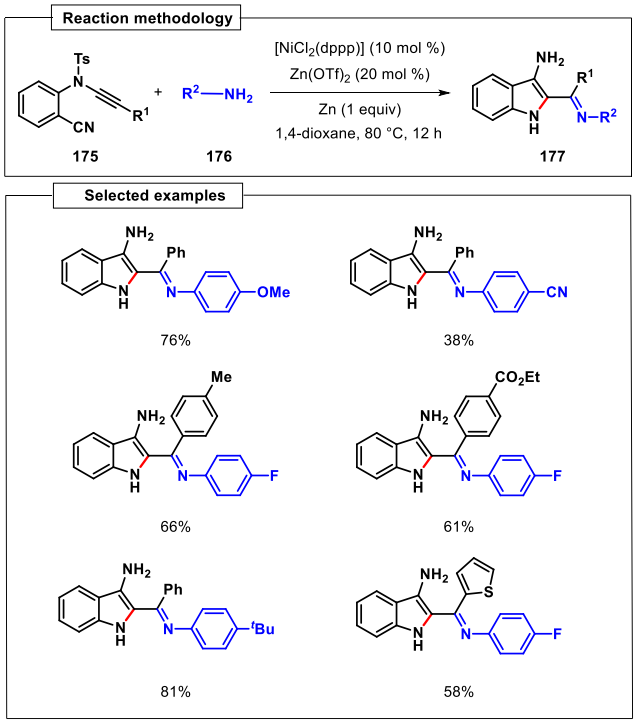
Scheme 58b. Cobalt catalyzed regioselective C(4)-H functionalization of indoles.



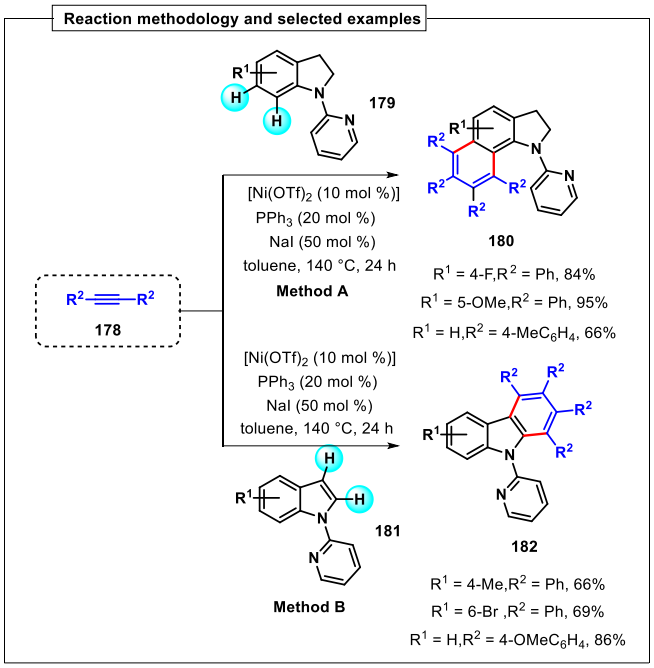
Moreover, aliphatic alkynes were also identified as amenable and gave the corresponding products in good yields. Notably, the unsaturated ketone has been obtained with an asymmetrical alkyne with this protocol. The mechanism for regioselective indole C(4)-H functionalization has been depicted in scheme 58b. The active catalyst **A** is generated in the presence of silver salt and copper acetate, which affords the cyclometelated intermediate **B** after regio-selective C-H bond activation of 3-pivaloyl indole **172**. Then alkyne **173** coordination followed by insertion gives species **D**. Further, the ligation of species **D** forms intermediate **E**. Next, reductive elimination of intermediate **E** produces the desired product **174** after keto-enol tautomerization along with reduced species **F**. The active catalyst **A** is regenerated in the presence of copper salt for the next catalytic cycle.

In 2021, Liu *et al.* described a unique and efficient method for the synthesis of 3-aminoindoles **177** via regio-selective cyclization of ynamide-nitriles **175** and amines **174** (Scheme 59).[70] The electron-donating substituents on the amine significantly increased its nucleophilicity, which elevated its reactivity. *para*-Substitution with an *N*,*N*-dimethyl group resulted in a reduced yield due to the coordinating ability of nitrogen being reduced with the metal. This might be responsible for quenching the reactivity of the catalyst. The authors also observed the operation of steric factors to a significant degree. Also, the ynamides containing electron-withdrawing groups were favored, which resulted in excellent yields. An unwanted [2+2+2] cycloaddition reaction was observed for alkyl-substituted ynamides, thus giving lower yields.

Scheme 59. Nickel catalyzed cyclization of ynamide-nitriles with amines.



Scheme 60. Nickel catalyzed annulation of indole and indoline.



Further, in 2021 Ravikumar *et al.* demonstrated the synthesis of poly-heterocyclic indoline **181** and bioactive carbazole motifs **182** via sequential C-H bond activation of indoline **179** and indoline **180** using alkynes **178** (Scheme 60).[71] This selective functionalization of indole, even in the presence of C7-H, makes this approach unique. The reaction condition was optimized, following which the scope of the reaction was examined. The protocol was appropriate with indolines substituted with halogens at the C4 position and electron-releasing groups at the C5 position. However, substitution using electron-withdrawing groups seemed to decrease the nucleophilicity of the M-C bond, thus failing to deliver the products. Moreover, sequential C6/C7 functionalization of indoline successfully provided numerous heteropolycyclic scaffolds.

In contrast to the substitution pattern observed for indolines, C4 substitution with electrophilic groups afforded good yields. The position of substitution was also experimented with, which indicated that C5, C6, and C7 substitution provided good to very good yields. Moreover, photophysical studies have been demonstrated to show the applicability of these molecules in material science.

6. CONCLUSIONS AND FUTURE ASPECTS

The transition metal-catalyzed C-H bond activation and functionalization has become an useful tool to synthesize molecules for medicinal and material chemistry applications. Alkyne as a reacting partner in this process has many advantages. It adds value to the chemist's toolbox by displaying new reactivity and novel transformations. The reactivity of alkyne varies with the catalytic potential of high-valent as well as low-valent transition metals (3d, 4d, 5d). The first-row transition metal-catalysts are gaining significance in recent years due to their cost-effectiveness, abundance and eco-friendly nature. Numerous transformations involving novel reactivities with the 3d transition metals (Mn, Fe, Co, Ni) have been well documented.

Despite extensive studies and reports, the chemistry of alkynes in C-H activation reactions is still in its infancy. The design and development of intramolecular reactions involving alkynes have no limit. Alkyne tethered with other functional groups such as enones, halides, esters, carbenes and ketones have undergone cascade process to produce complex skeletons that are otherwise very difficult to synthesize. There is enormous room to develop this approach for the synthesis of complex organic molecules. The use of aliphatic and terminal alkynes had been limited. The reactivity of alkynes with low-valent transition metals such as Pd (0), Co(0/I), Fe (0), Ni (0), as well as simple salts like $RhCl_2$, $RuCl_2$, $CoBr_2$ also needs to be explored further. The alkenylation and annulation reactions of alkynes are well documented. However, alkyne-derived alkylation is still challenging because of the favorable possibility of *β*-hydride elimination. The enantioselective metal-catalyzed C-H functionalization using alkynes as the coupling partner is still countable. Hence the development of efficient enantiomeric protocols is desirable in the future. Furthermore, the reactivity of alkynes in multicomponent C-H bond activation is also limited, which needs to be developed.

We fully expect that this perspective will help readers get a broad idea about the reactivity of alkynes with M-C bonds generated through C-H bond activation. We also hope that this perspective would inspire chemists to work on unexplored and less explored areas stated above in the near future.

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Notes

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ABBREVIATIONS

DCM (Dichloromethane), TFE (Trifluoroethanol), AcCl (Acetyl chloride), PivCl (Pivaloyl chloride), AcOH (Acetic acid), EtOAc (Ethyl acetate), DCE (1,2-Dichloroethane), HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol), DCB (1,2-Dichlorobenzene), TFT (Trifluorotoluene), THF (Tetrahydrofuran), DMF (Dimethylformamide), Cp* (1,2,3,4,5-Pentamethylcyclopentadiene), coe (Cyclooctene), ^{t}AmOH (tert-Amyl alcohol), HOSA (Hydroxylamine-*O*-sulfonic acid), Et_2O (Diethyl ether), TMS (Trimethylsilyl), cod (Cyclooctadiene), dtbbpy (4,4′-Di-tert-butyl-2,2′-dipyridyl), ppy (2-Phenylpyridine), Cy (cyclohexyl), en (Ethylenediamine), NMP (*N*-Methyl-2-pyrrolidone), dppen (1,2-Bis(diphenylphosphino)ethylene), TBAB (Tetrabutylammonium bromide), NBE (norbornene), BINAP (2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene), TFA (Trifluoroacetic acid), hfacac (Hexafluoroacetylacetone), OTf (trifluoromethanesulfonate), Et_3N (Triethylamine), PMP (*p*-methoxy phenyl), TIPS (Triisopropylsilane), (rt (Room temperature).

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