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Diverse reactivity of alkynes in C–H activation reactions

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Alkynes occupy a prominent role as a coupling partner in the transition metal-catalysed directed C–H activation reactions. Due to low steric requirements and linear geometry, alkynes can effectively coordinate with metal d-orbitals. This makes alkynes 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 pattern of reactivity of alkynes also changes. Due to the varied reactivity of alkynes, such as alkenylation, annulation, alkylation, and alkynylation, they have been extensively used for the synthesis of valuable organic molecules. Despite enormous explorations with alkynes, there are still a lot more possible ways by which they can be made to react with M–C bonds generated through C–H activation. Practically there is no limit for the creative use of this approach. In particular 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 the coming years. Therefore, a highlight article about alkynes is both timely and useful for synthetic chemists working in this area. Herein, we have highlighted the diverse reactivity of alkynes with various transition metals (Ir, Rh, Ru, Pd, Mn, Fe, Co, Ni, Cu) and their applications, along with some of our thoughts on future prospects.

1. Introduction

The transition metal-catalysed C–H bond activation and functionalisation of the resultant M–C bond with various coupling partners such as alkenes,[1] allenes,[2] alkynes,[3] carbenes,[4]

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aryl/alkenyl/alkynyl/alkyl halides,[5] and aryl/alkenyl/alkyl boronic acids,[6] has emerged as a powerful tool in organic synthesis.[7–10]

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] Among the π-systems, alkynes have been the most extensively explored coupling partner in transition metal-catalysed C–H bond activation over the last two decades (Fig. 1).[12] On account of their high degree of unsaturation, small size, and linear geometry, they effectively bind to metal d orbitals and participate in various catalytic pathways. The varied reactivity of alkynes, such as annulation,[13] alkylation,[14] alkenylation,[15a–c] alkynylation,[15d] and many other unusual transformations, has been well documented (Fig. 1).[16]

Numerous bioactive scaffolds and synthetically useful building blocks have been synthesized using alkynes. Hence, their use as a coupling partner occupies a prominent position in the area of C–H activation-based chemical synthesis.

The generalized catalytic cycle of C–H bond functionalisation using alkynes has been depicted in Scheme 1. Initially, the active metal-catalyst **A** coordinates with the directing group of substrates **1**.

Then, the metal-catalyst activates the proximal C–H bond through agostic interaction. This leads to the formation of a cyclometalated species **B**. Next, the cyclometalated

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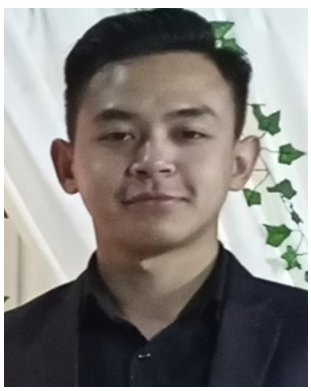

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Ponneri C. Ravikumar

Dr Ponneri C. Ravikumar (also known as P. C. Ravikumar) obtained his PhD degree in Organic Chemistry at the IISc Bangalore, with Professor A. Srikrishna. In 2007, he moved to the USA for a postdoctoral position with Prof. Fraser F. Fleming at Duquesne University, Pittsburgh, USA. Later, in 2009, he moved to Yale University for a second postdoctoral position with Prof. Seth B. Herzon. He started his independent research career as an Assistant Professor at the School of Basic Sciences, IIT Mandi, Himachal Pradesh, India in 2010. Currently, he is an Associate Professor in the School of Chemical Sciences at the National Institute of Science Education and Research (NISER) Bhubaneswar. His research focuses on "Transition metal-catalyzed synthetic methodologies involving C–H, C–C and C–N bond activation."

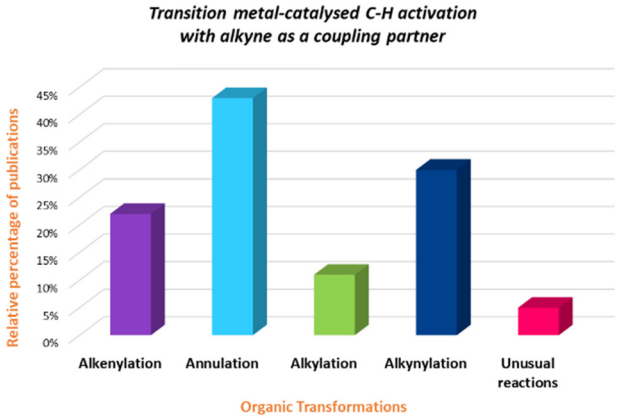
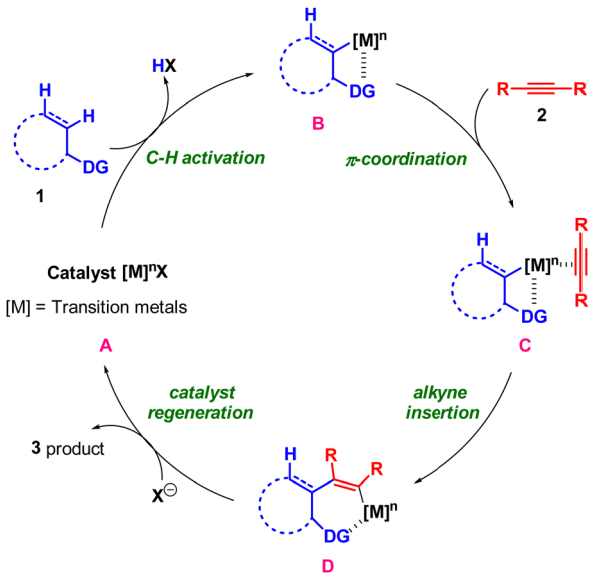


Fig. 1 Comparative reactivities of alkynes in C–H bond functionalisation.[12d]

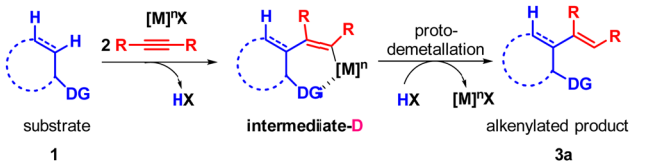


Scheme 1 Generalized catalytic cycle of C–H bond functionalisation using alkynes.

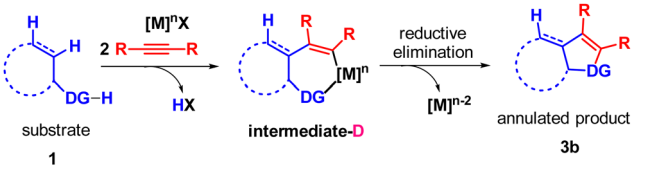
intermediate **B** coordinates with alkyne **2** to give intermediate **C**. Further, alkyne insertion into the M–C bond leads to intermediate **D**. In this catalytic cycle, intermediate **D** is the key intermediate from which a variety of organic transformations such as alkenylation, annulation, cascade annulation, and alkynylation have been achieved. The mechanistic aspects of each of these reactions are discussed independently and sequentially as follows.

The alkenylation process is a common transformation of alkynes, where they are reduced to an alkene. In this process, alkyne **2** undergoes insertion into the M–C bond to generate the intermediate **D**. Next, proto-demetallation of species **D** leads to the corresponding alkenylated product (Schemes 2, **3a**).

The annulation reactions with alkynes are one of the most prominent pathways and are well explored in metal-catalysed C–H activation reactions. In this process, alkyne **2** undergoes



Scheme 2 Transition metal-catalysed alkenylation of a C–H bond with an alkyne.

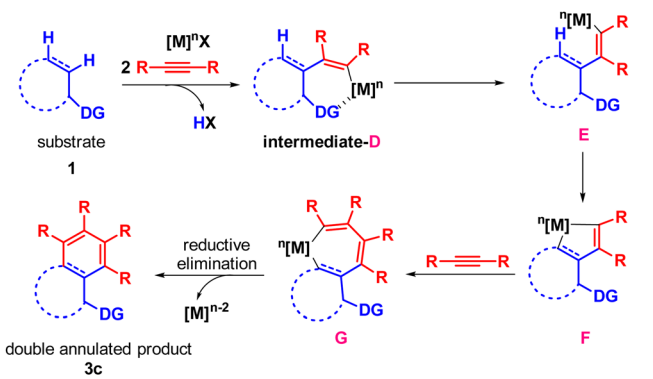


Scheme 3 Transition metal-catalysed mono-annulation of a C–H bond with an alkyne.

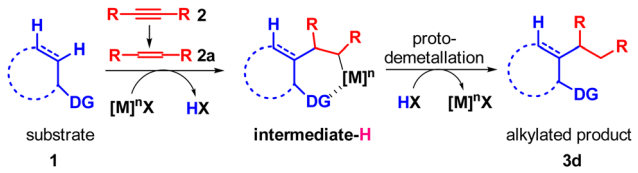
insertion into the M–C bond and generates intermediate **D**. Then, the reductive elimination gives the corresponding mono-annulated product (Schemes 3, **3b**). Along with the extrusion of the reduced metal catalyst [M]. The reduced metal catalyst will undergo re-oxidation to generate the active catalyst for the next catalytic cycle.

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 activation. The plausible pathway has been depicted in Scheme 4. After the formation of the cyclic intermediate **D**, the metal detaches from the DG and undergoes C–C bond rotation to develop proximity with the new C–H bond (intermediate **E**).

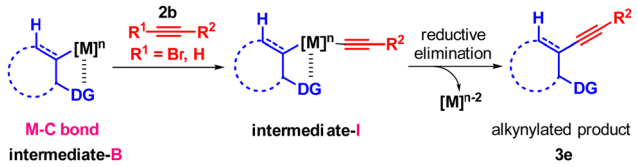
Activation of the proximal C–H bond in intermediate **E** leads to the formation of a new metallacycle intermediate **F**. Further alkyne **2** coordination and insertion into the new M–C bond gives rise to the intermediate **G** (Scheme 4). Finally, reductive elimination of **G** gives the corresponding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



Scheme 4 Transition metal-catalysed cascade annulation of a C–H bond with an alkyne.



Scheme 5 Transition metal-catalysed alkylation of a C–H bond with an alkyne.



Scheme 6 Transition metal-catalysed alkynylation of a C–H bond with an alkyne.

Compared to other transformations of alkynes, metal-catalysed alkylation is quite challenging. For this, the alkyne **2** should first undergo hydrogenation to give the corresponding alkene **2a** (Scheme 5). Then, the alkene gets inserted into the M–C bond and generates intermediate **H**. Finally, proto-demetalation of intermediate **H** leads to the alkylated product **3d** and the active catalyst **[M]^{n}X**.

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

Initially, the M–C bond-containing intermediate **B** is generated through metal-catalysed C–H bond activation. For terminal alkynes containing halogen atoms, π-complexation followed by β-halide elimination produces the intermediate **I**. In the case of terminal alkynes with the 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 alkynes shown above, alkynes are also 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.

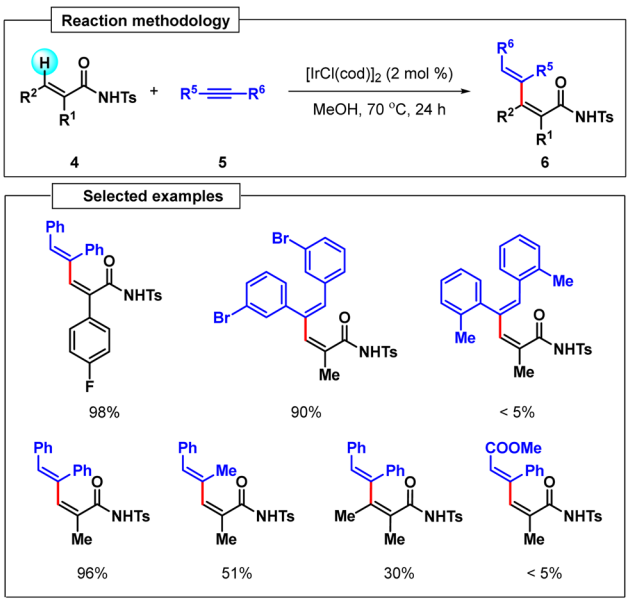
The diverse reactivity of alkynes as a coupling partner has unlimited potential, particularly with the first-row metal catalysts. The number of unusual transformations with alkynes is continuously on the rise on account of their ability to form multiple bonds. With the development of new first-row metal catalysts in C–H activation reactions, exploratory work with alkynes is expected to grow significantly over the next decade. In this context, a highlight article covering the broad range of reactions that alkynes undergo with M–C bonds obtained through C–H activation is both timely and useful for numerous synthetic chemists working in this area.

In the following sections, we will discuss some of the key reports demonstrating the various reactivities of alkynes towards M–C bonds in the same order as mentioned above. Furthermore, the reports in each section are discussed according to the metal used for the transformation, going from 5d to 3d metals.

2. Various transition metal-catalysed alkenylation reactions of alkynes

Alkenylation is the second most explored reactivity of alkynes towards the M–C bond after annulation. It has a wide range of applications in synthetic chemistry, including the synthesis of many bioactive molecules. The first report of iridium catalysed alkene-alkyne cross-coupling reaction was demonstrated by Zhong *et al.* in 2019 (Scheme 7).[17] 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 up to 98% yield. The use of diphenylacetylene as the coupling partner gave impressive yields with many substrates. The aryl fluoride substituted acrylamide gave 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 alkynes. However, *ortho*-substituted and ester-derived diphenylacetylenes resulted in lower yields.

Prior to this report, Glorius *et al.*, in 2017, reported an Mn(I)-catalysed regioselective C–H allenylation of various indole derivatives **7a** with propargylic carbonate **8a** to synthesize 2-allenylindoles **9a** (Scheme 8a).[18a] This procedure is applicable for gram-scale synthesis under optimized conditions. The key

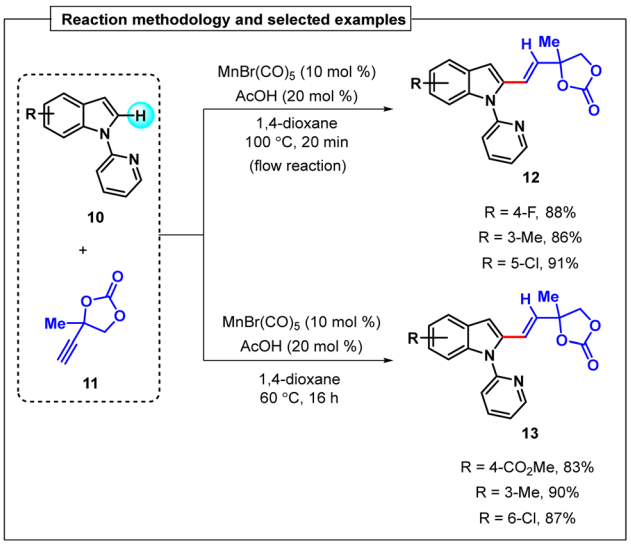


Scheme 7 Iridium-catalysed cross-coupling of alkenes and alkynes.

feature of this methodology is that it allows the direct synthesis of ketones *via* an earth-abundant Mn-catalysed C–H activation strategy.

Exploration of the 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. Moreover, this developed protocol provides a route to synthesize multi-substituted allenes, which show optical activity. Furthermore, Glorius *et al.*, in 2019, reported the synthesis of 1,3-enynes **9b** in high regioselectivity (Scheme 8b).[18b] Similar to the earlier report in this method, a manganese catalyst has been utilized with indole **7a** and 1,3-diyne **8a** giving rise to the desired product in good yields. Moreover, this protocol is quite generalized with a broad variety of indole substituents as well as symmetrical and unsymmetrical alkynes.

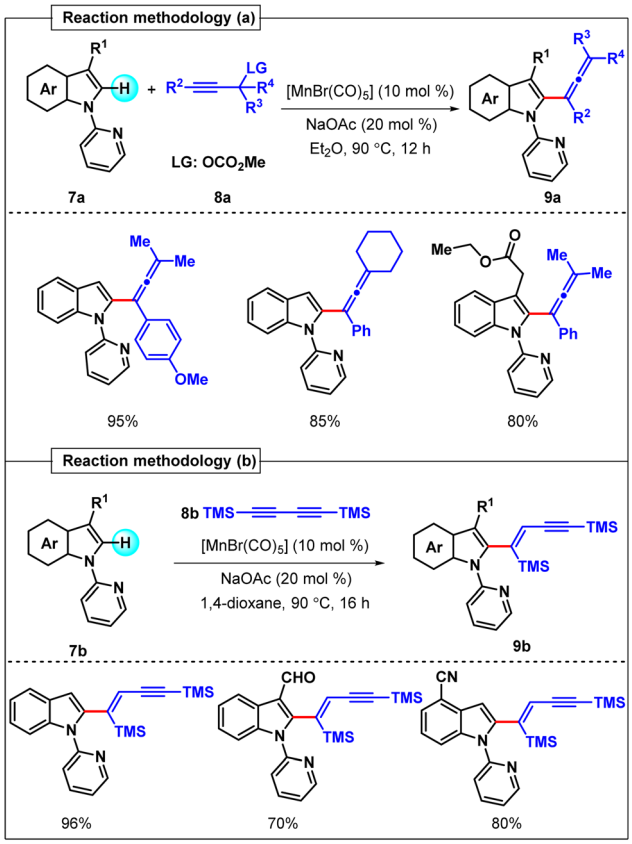
Furthermore, in 2017, Ackermann *et al.* achieved chemoselective hydroarylation of **12** and **13** using a Mn(I)-catalyst in a novel synergistic C–H activation strategy (Scheme 9).[19] They have used substituted alkynes **11** and various indoles **10** for this transformation. Notably, this reaction 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. 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 offered products with excellent regioselectivity. Substrates other than indoles such as thiophenes, pyrroles, pyridones, and tryptophans were also amenable to this protocol.



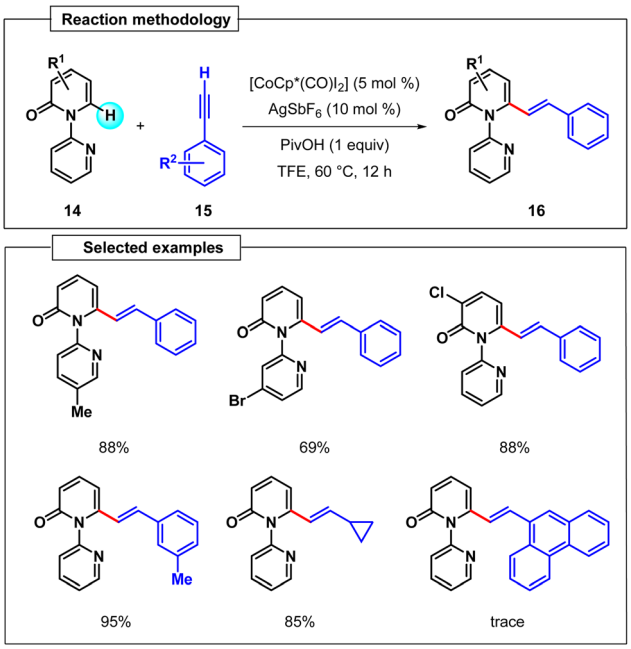
Scheme 9 Synergistic manganese(I) C–H activation catalysis in continuous flow.

Recently, Ravikumar *et al.* have demonstrated the first report on cobalt-catalysed regioselective alkenylation of 2-pyridones **14** using terminal alkynes **15** (Scheme 10).[20] This Co(III)-catalysed 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 the C5 position, where increasing the steric bulk gave lower yields. Remarkably, synthetically valuable functionalities such as bromo-, chloro-, and cyano- were well tolerated without affecting the yields.

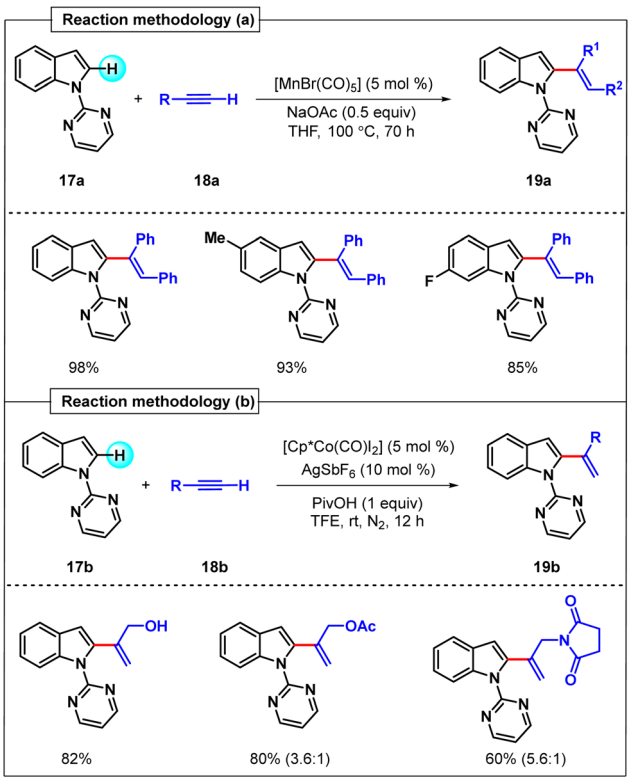
Rueping *et al.* in 2018 reported the selective alkenylation of indole using a manganese catalyst (Scheme 11a).[21a] This method is quite applicable for a wide range of alkyne and indole substituents. However, this protocol takes almost 70 h for the completion of the reaction. In 2017, a complementary and highly regioselective method of inserting indoles **17b** into terminal alkynes **18b** was devised by Li *et al.* (Scheme 11b).[21b] This Co-catalysed 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



Scheme 8 Manganese catalysed regioselective C–H bond activation.



Scheme 10 Cobalt-catalysed alkenylation of pyridones with terminal alkynes.



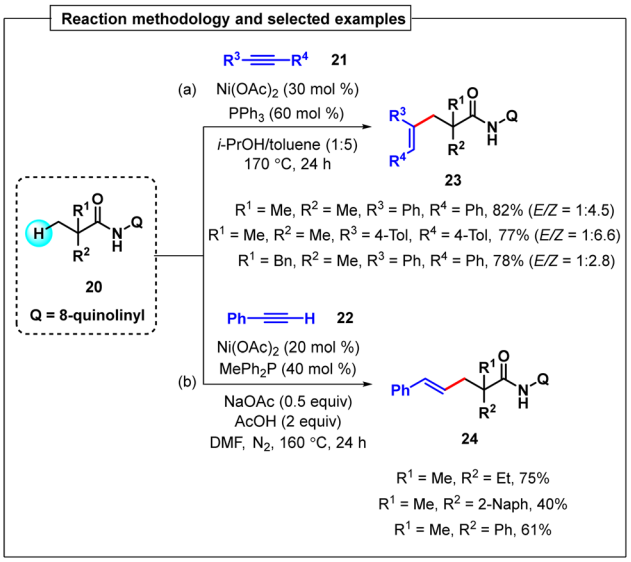
Scheme 11 Manganese and cobalt-catalysed hydroarylation of alkynes *via* C–H bond activation.

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 propanamides 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 conditions were 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. 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** with 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 that β-methyl containing aliphatic amides were well tolerated in the reaction. The resultant products were obtained in the *E*-configuration, implying that the transformation is highly selective. 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 functionalisation 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.

On studying the above reports of alkenylation on various substrates using alkyne as a coupling partner, we observe



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

limited reports on alkenylation using internal alkynes as coupling partners. However, terminal alkynes seem to be more effective in giving alkenylated products due to sterically favourable 1,2-insertion. Also, extensive work using indole as a substrate has been done. In contrast, other substrates, such as indoline, remain unexplored. Thus, employing various other substrates for alkenylation using alkynes would be the future interest of chemists. Furthermore, the majority of alkenylation reactions have been done using only strong coordination (chelation using N-heterocycles). Thus, determining the scope of this transformation using weak coordination marks the need of the hour.

3. Various transition metal-catalysed annulation reactions of alkynes

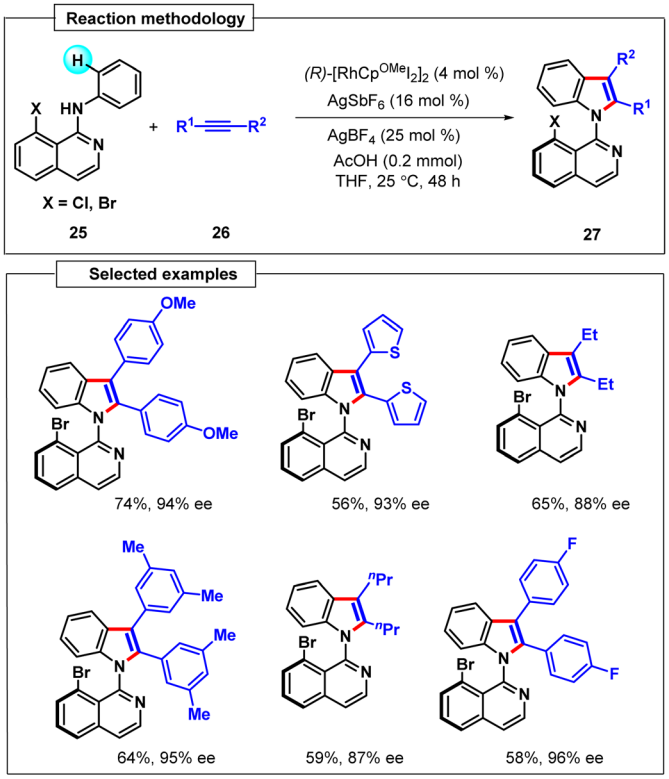
Annulation reaction of alkynes is one of the most successful transformations in the context of C–H activation. A wide range of directing groups have been used to date for selective C–H activation strategies. In this regard, Li *et al.* devised a method to synthesize indoles **27** *via* C–H bond activation 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 be sustained under the reaction conditions. 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 the *meta* and *para* positions were tolerable, giving highly enantioselective products.

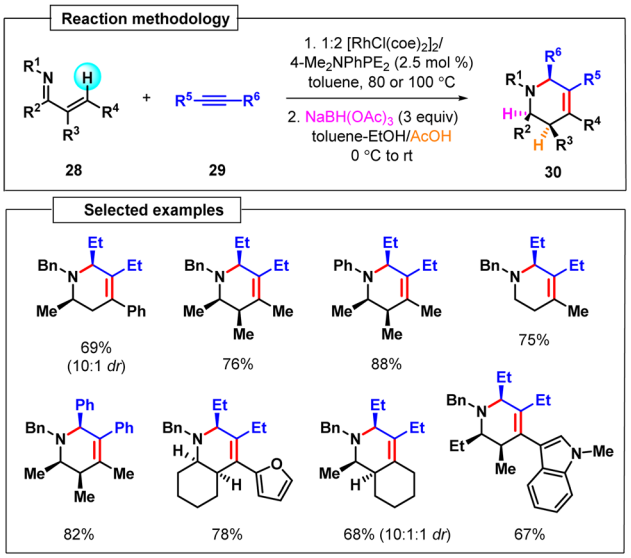
In 2012, Ellman *et al.* reported an Rh-catalysed annulation of α,β-unsaturated imines **28** with alkynes **29** for the synthesis of 1,2-tetrahydropyridines **30** (Scheme 14).[25] The reaction proceeds in the presence of a pre-catalyst $[RhCl(coe)_2]_2$ in a cascade annulation manner. Depending on 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.

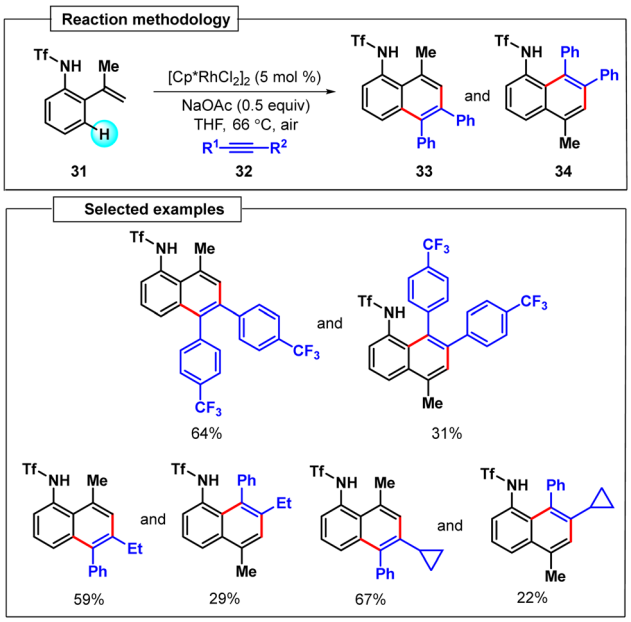
An interesting annulation reaction was reported by Gulias *et al.* in 2019, which involved *O*-alkenyl *N*-triflylanilides **31** and alkynes **32** to produce various naphthylamides **33** (Scheme 15).[26] Apart from the traditional [4+2] cycloaddition products, this reaction also features the production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



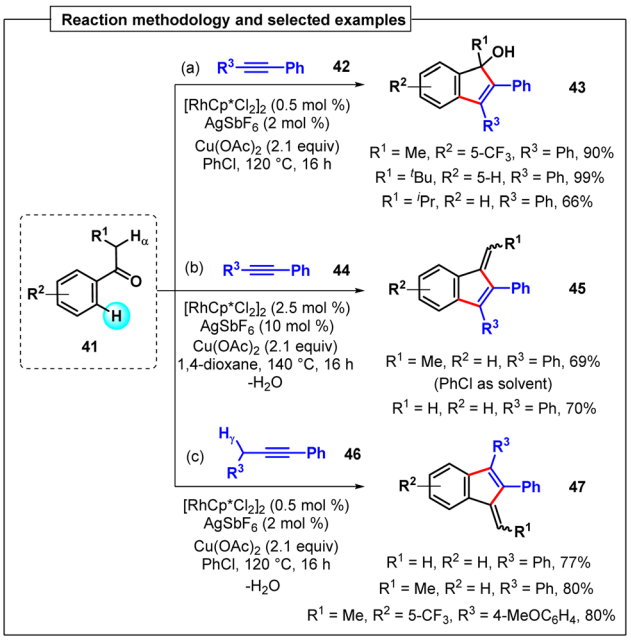
Scheme 13 Rhodium-catalysed atroposelective synthesis of indoles *via* C–H bond activation.



Scheme 14 Rhodium-catalysed synthesis of tetrahydropyridines *via* C–H bond annulation.

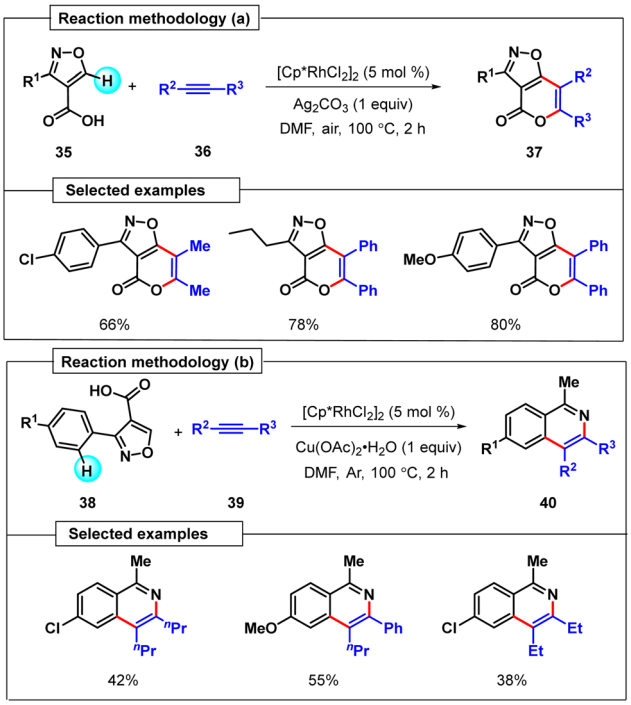


Scheme 15 Rhodium-catalysed annulation of *ortho*-alkenyl anilides with alkynes.



Scheme 17 Rhodium-catalysed coupling of aryl ketones with internal alkynes.

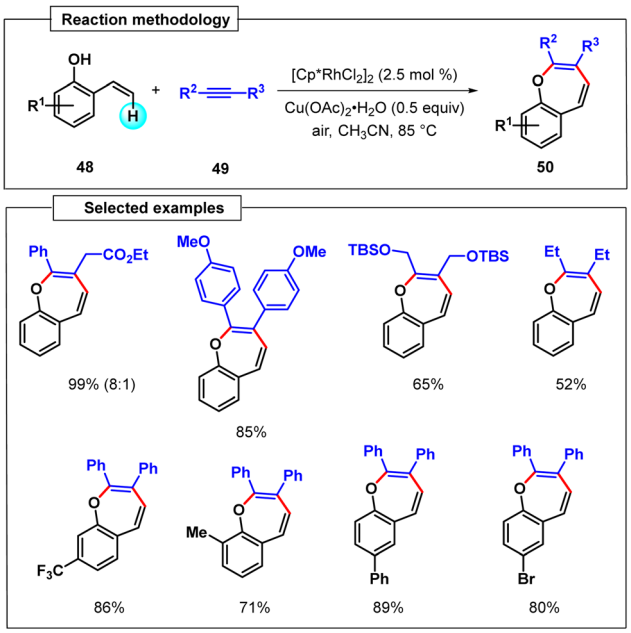
In 2019, Nakamura *et al.* demonstrated an oxidative [4+2] annulation reaction of isoxazolyl-4-carboxylic acids **35** and its 3-aryl substituted derivatives **38** with internal alkynes **36** and **39** (Scheme 16a and b).[27] The methodology (a) depicts the synthesis of pyranoisoxazolone derivatives **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 unsymmetrical alkynes with a single regioisomer. Reaction methodology (b) describes the synthesis of isoquinolines **40**. Similar to the previous case, both symmetrical and unsymmetrical alkynes underwent annulation to give the respective products, which shows high regioselectivity with unsymmetrical alkynes.



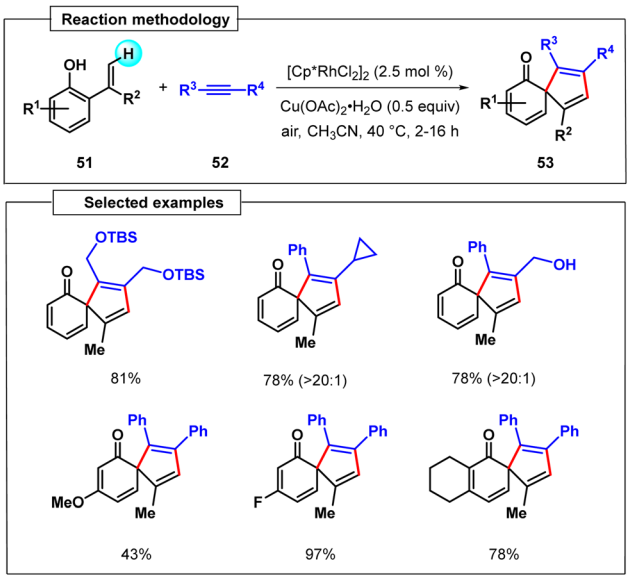
Scheme 16 Rhodium-catalysed carboxylate-directed C–H functionalisation of isoxazoles with alkynes.

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, followed by 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, electron deficient 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. In this series, Gulias *et al.* demonstrated another example of Rh-catalysed 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.



Scheme 18 Rhodium catalysed C–H functionalisation of *o*-vinylphenols.



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

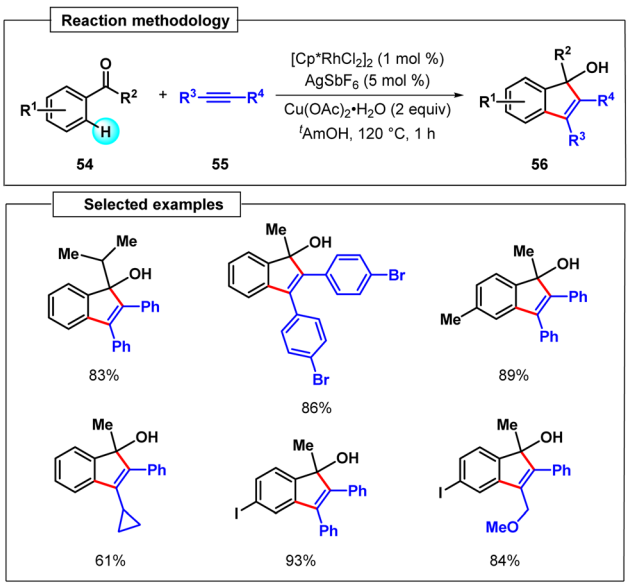
Symmetrical diaryl alkynes containing both electron-withdrawing and -donating groups smoothly participated in the reaction to give good yields. Unsymmetrical alkynes furnished the products in high regioselectivity. Substrates containing substituents *para* to the hydroxyl group such as bromo-, methoxy, 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 conditions and decomposed into other products.

In addition to their previous work, 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 the products in good yields. The reaction showed high regioselectivity.

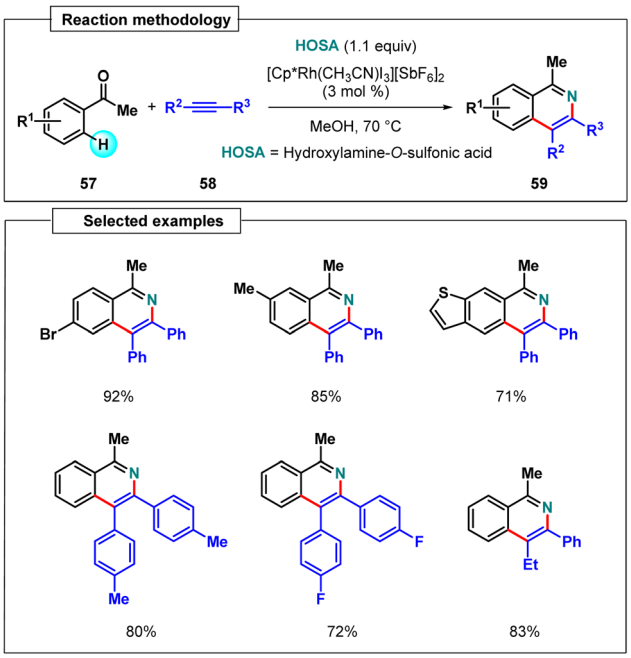
They have also employed 2-alkenylphenols containing substituents other than methyl at the internal position of the alkene. Notably, it was observed that the substrates bearing aryl groups decreased the reaction rates, hence requiring elevated temperatures to undergo further transformation. This method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

The behavior of alkynes in the above two cases is of profound interest. We observe a stark variation in the reactivity of the alkyne towards a structurally similar substrate with just a slight change in the reaction conditions, which gives rise to entirely different products, benzoxepines and spirotetraenones.

Furthermore, 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 conditions. 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



Scheme 20 Rhodium-catalysed carbocyclization of aryl ketones and alkynes.

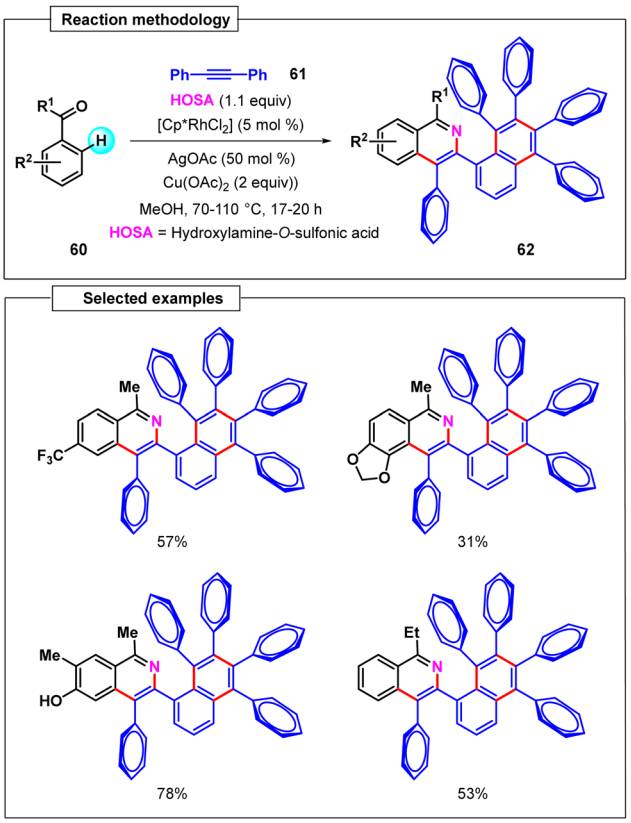


Scheme 21 Rhodium-catalysed synthesis of isoquinolines from arylketones.

isopropyl and obtained satisfactory amounts of respective products in both cases.

Moreover, alkynes containing sensitive functional groups such as bromo-substituents tolerated the reaction conditions and transformed efficiently. The reaction proceeded in excellent regioselectivity with unsymmetrical alkynes such as phenyl-cyclopropyl acetylene and propargylic ether, which leads to their respective indenol products. An analogous transformation was reported by Glorius *et al.* with similar conditions described above in Scheme 17.

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 the optimized conditions, affording good yields. The scope of benzophenones was also vast, and most of the substitutions were tolerated successfully. Following their work on the application of hydroxylamine-*O*-sulfonic acid to form isoquinolines, 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)-catalysed transformation also demonstrated the annulation of two different alkynes in a regioselective manner. The substrate scope for this reaction was generalised 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



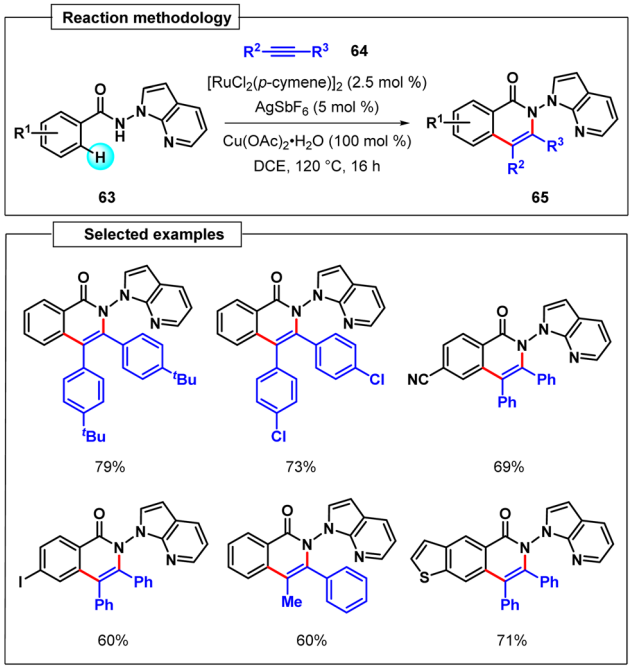
Scheme 22 Rhodium-catalysed triple C–H bond activation of aryl ketones using alkynes.

ketones including thiophene, furan, and indole could be successfully tolerated in this reaction condition.

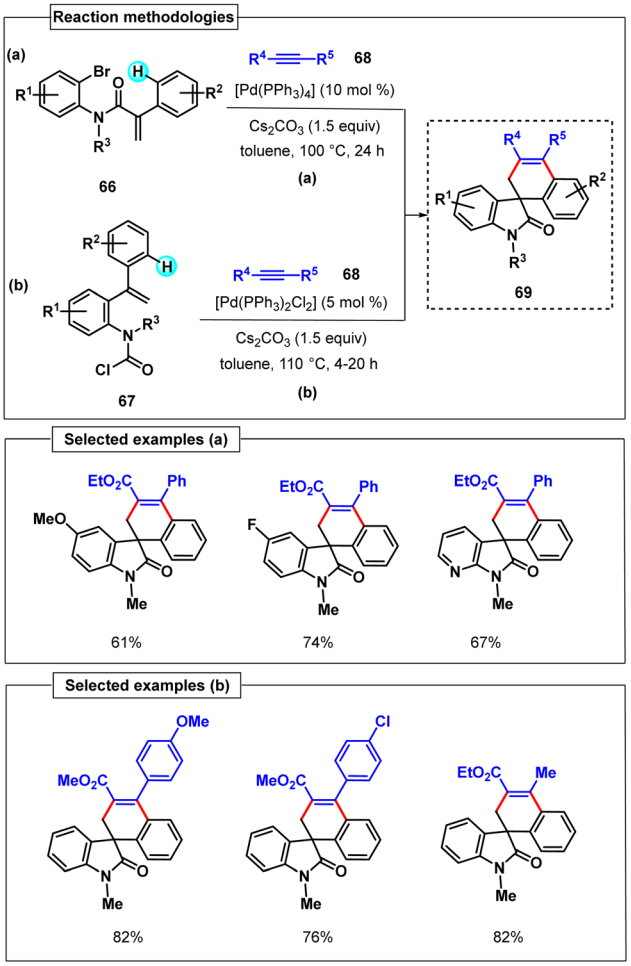
Further, Ravikumar *et al.* described a Ru(II)-catalysed directing group-assisted annulation of *N*-substituted benzamides **63** with internal alkynes **64** (Scheme 23).[34] The authors found that *para*-substituted symmetrical diaryl alkynes offered very good yields. Likewise, aliphatic symmetrical alkynes are also coupled consistently to provide good yields. As observed in most annulation reactions, unsymmetrical alkynes showed high regioselectivity exclusively resulting 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.

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



Scheme 23 Ruthenium-catalysed oxidative annulation of benzamides with alkynes.



Scheme 24 Palladium-catalysed spirocyclization to generate spirooxindoles.

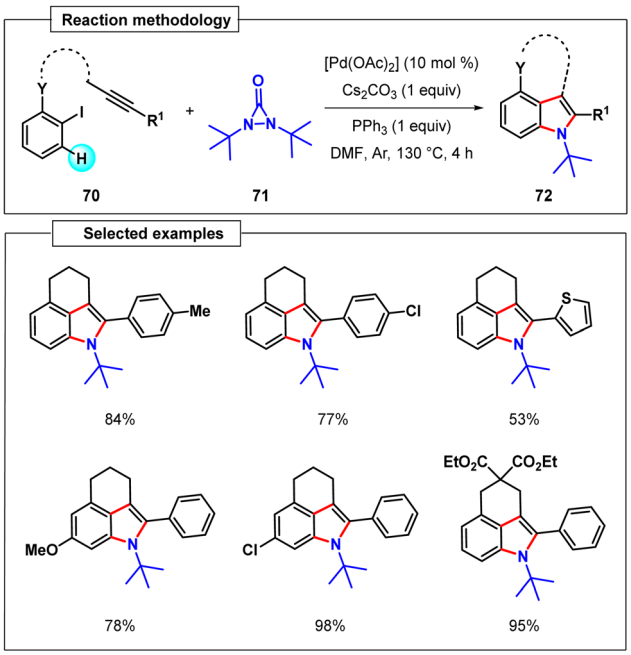
chlorides containing both electron-rich and -deficient substituents, including sensitive groups such as halogens. A variety of alkynes were tested against the conditions to determine the alkyne scope. Alkyl aryl alkynes containing electron-donating as well as electron-withdrawing groups were amenable and gave good yields. Moreover, dialkyl alkynes such as ethyl but-2-ynoate also coupled smoothly and provided the desired products in satisfactory yields.

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.

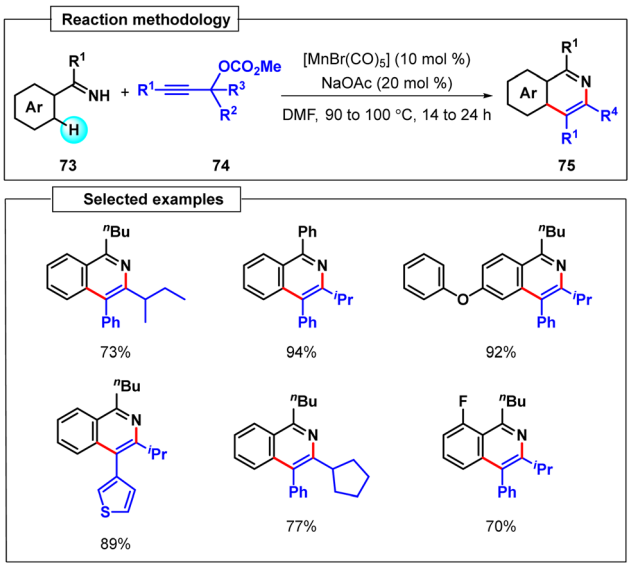
Following the work of the Wang group, Glorius *et al.* in 2017 reported a similar transformation using alkyl aryl imines **73** and alkynes containing a traceless directing group **74** (Scheme 26).[38] The main feature of this reaction is its high regioselectivity, which was observed for the first time 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. 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 conditions and furnished high yields. Furthermore, this method was successfully extended to heterocycles such as thiophene and benzothiophene.

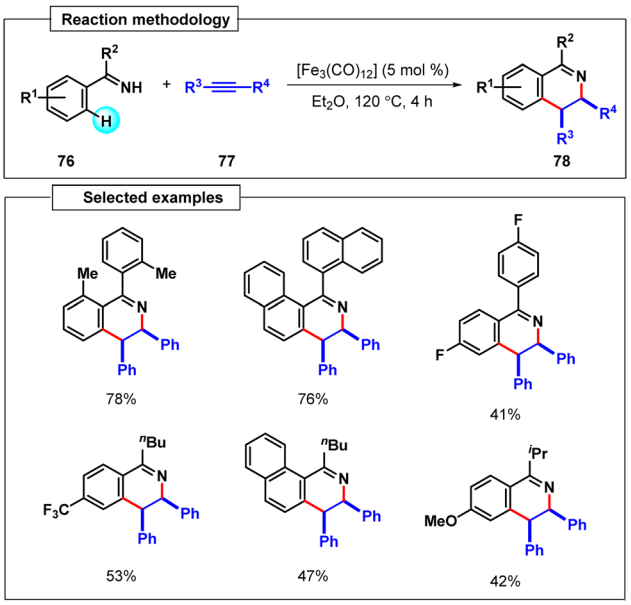
The first case of iron-carbonyl-catalysed C–H activation of arenes was reported by Wang *et al.* in 2016 (Scheme 27).[39] The reaction featured various substituted N–H imines **76** and internal alkynes **77** for the synthesis of *cis*-3,4-dihydro isoquinolines **78**. Looking at the effect of introducing 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 unsymmetrical 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 functionalisation of the products, which is more synthetically useful.



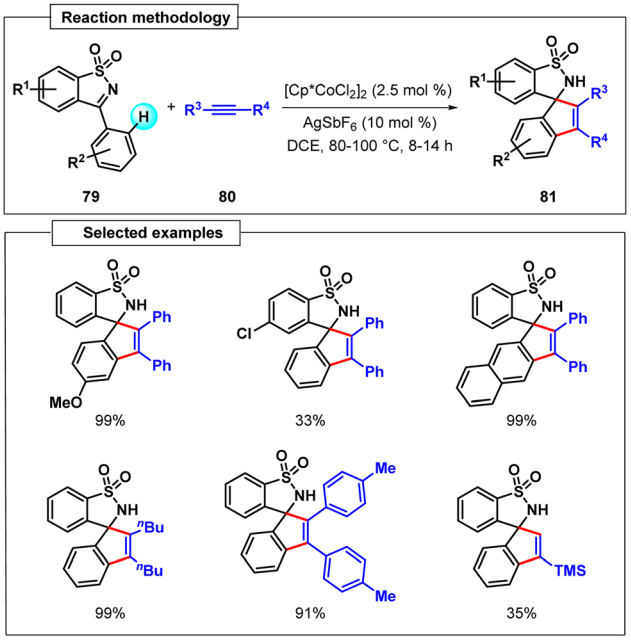
Scheme 25 Palladium-catalysed intramolecular annulation of alkyne-tethered aryl iodides with diaziridone.



Scheme 26 Manganese-catalysed regioselective annulation of aromatic imines with alkynes.

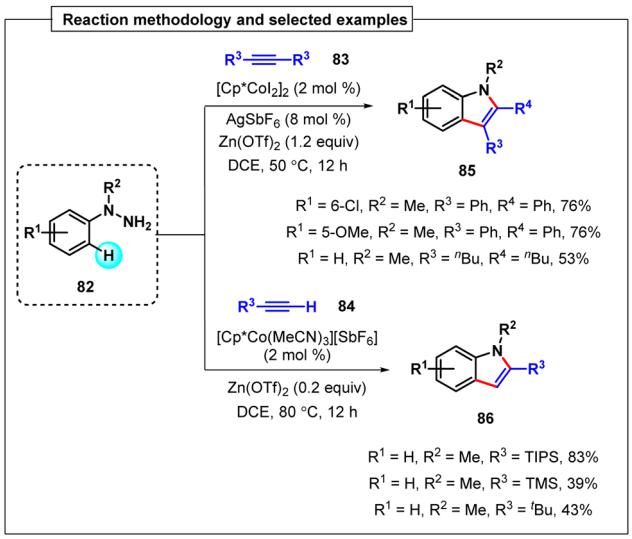


Scheme 27 Iron catalysed redox-neutral [4+2] annulation of N–H imines and internal alkynes.

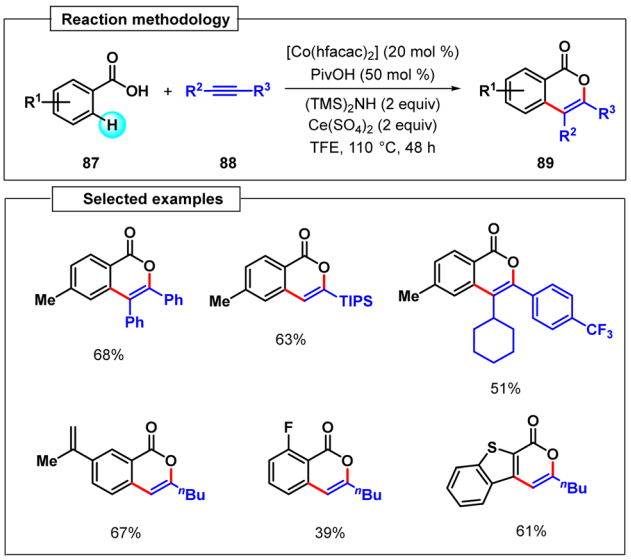


Scheme 28 Cobalt-catalysed annulation of *N*-sulfonyl ketimines with alkynes.

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 the *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



Scheme 29 Cobalt-catalysed C–H annulation of N-substituted phenyl-hydrazines with alkynes.



Scheme 30 Cobalt-catalysed annulation of benzoic acid with alkynes for the synthesis of Isocoumarin.

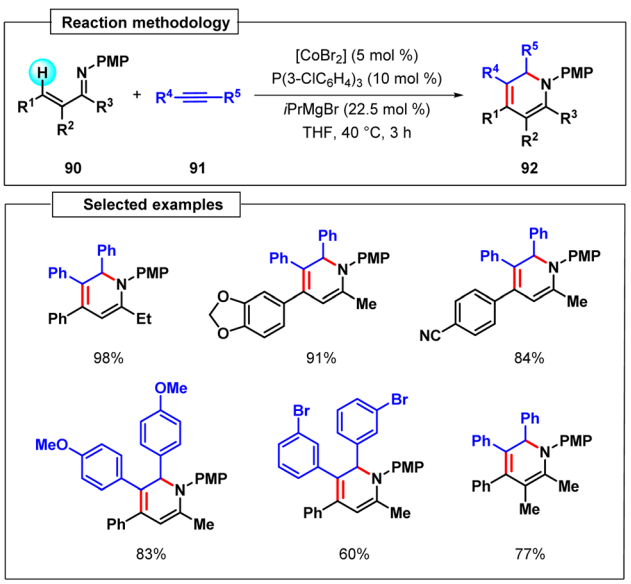
containing a sensitive nitro-group was also amenable, affording products in excellent yields. Moreover, unsymmetrical alkynes were tolerated under the reaction conditions, albeit in a lower yield.

In 2016, Zhu *et al.* disclosed the procedure for the synthesis of indoles **85** and **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 substrates by varying the substitution pattern on phenyl-hydrazine. The steric effect was a major factor in determining the product yields.

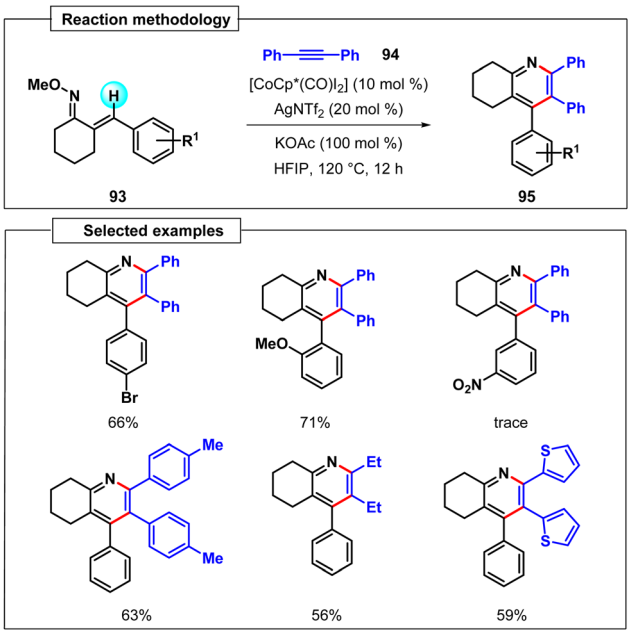
Increasing bulkiness around the nitrogen leads to decreasing yields; thus, lower yields were observed when methyl was replaced with ethyl and isopropyl groups. *ortho*-Substitution with electrophilic groups afforded the products in moderate yields, while *meta*-substitution offered highly regioselective 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)-catalysed, 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 a co-oxidant. Substrates containing both electron-donating and -withdrawing substituents were compatible in this protocol. The transformation selectively functionalised less sterically hindered C–H bonds, thereby offering highly regioselective Isocoumarin **89**. Benzoic acids containing a broad range of functionalities such as methoxy, chloro-, fluoro-, vinyl, and some heterocycles were identified as amenable.

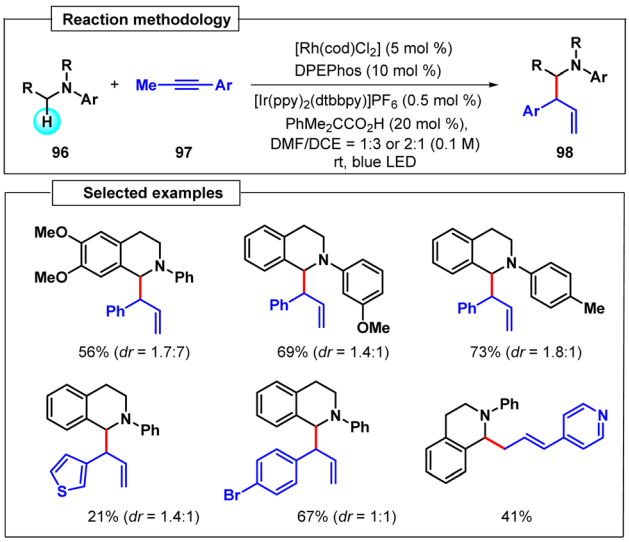
The method tolerated alkynes containing a wealth of synthetically valuable functionalities such as cyanide, phthalimide, and olefins. Silyl and aryl acetylenes also coupled efficiently to give the corresponding iso-chromone products. Moreover, some internal alkynes, such as 1-phenyl-1-propyne, exclusively produced a single regio-isomer in moderate yields. On similar lines, Yoshikai *et al.* have reported a transformation for synthesizing poly-substituted dihydropyridine derivatives **92** using a 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



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



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



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

also well tolerated in the optimized reaction conditions and gave good yields.

Recently, Ravikumar *et al.* described a Co(III)-catalysed 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 the *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.

On studying the above reports of annulation on various substrates using alkynes as coupling partners, we observed that the majority of the work has been done on aromatic substrates, while aliphatic substrates remain unexplored for this transformation. Furthermore, we observe the wide use of unsymmetric alkynes to carry out the annulation. This is quite remarkable as unsymmetric alkynes are a challenging reacting partner in terms of controlling the regioselectivity of the obtained product. Still, there is plenty of scope to further improve the selectivity in such annulation reactions, which will enhance the value of the products as well as the transformation. Moreover, there is no report on the use of iridium and nickel for annulation reaction with alkyne. Hence, the next step would be to employ these metals and look for more efficient and sustainable conditions for carrying out the transformation.

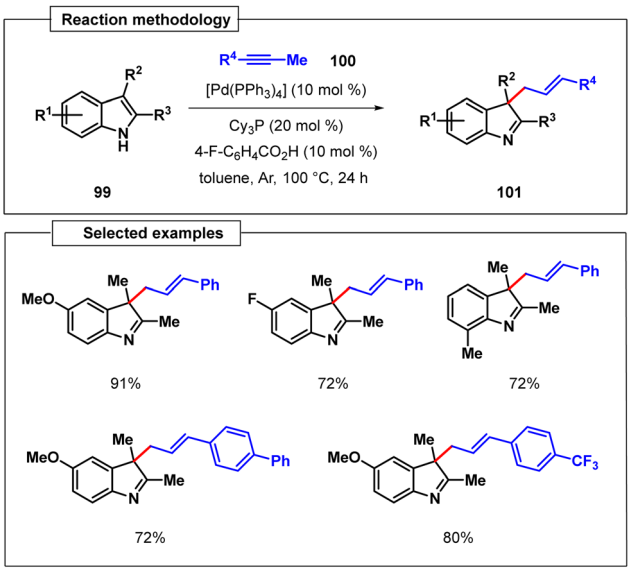
4. Various transition metal-catalysed alkylation reactions of alkynes

The transition metal-catalysed 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 a rhodium/photoredox dual catalysis method (Scheme 33).[45] This novel pathway requires alkynes **97** as electrophilic carriers against the traditional transition-metal catalysed allylation method.

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]

Substrate scope studies indicated that indoles containing electron-donating groups on the 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 on the phenyl ring displayed better suitability towards the transformation than those bearing electron-rich species. Moreover, this alkylation using alkynes led to the synthetically useful quaternary center bearing indole derived-product **101**.

As we observe, transition metal-catalysed alkylation using alkynes has been reported using precious metals such as rhodium and palladium. Hence, the next challenge to overcome would be to carry out the transformation using cheaper and

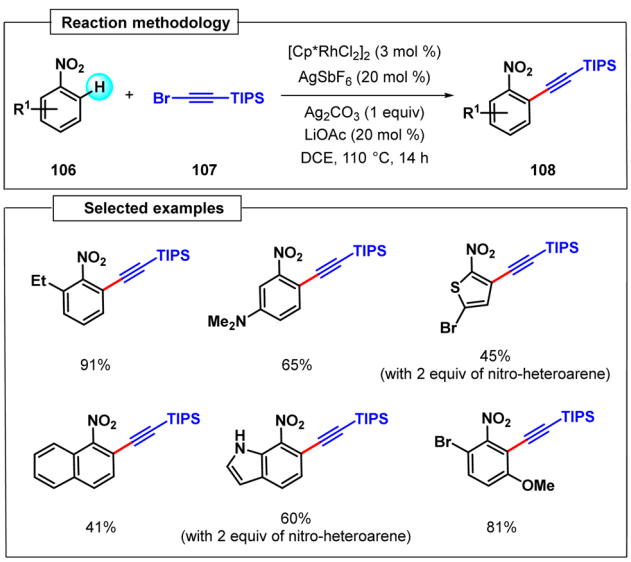


Scheme 34 Palladium-catalysed allylic alkylation of indoles with alkynes.

eco-friendly base metal catalysts such as cobalt, nickel, manganese *etc.*

5. Various transition metal-catalysed alkynylation reactions of alkynes

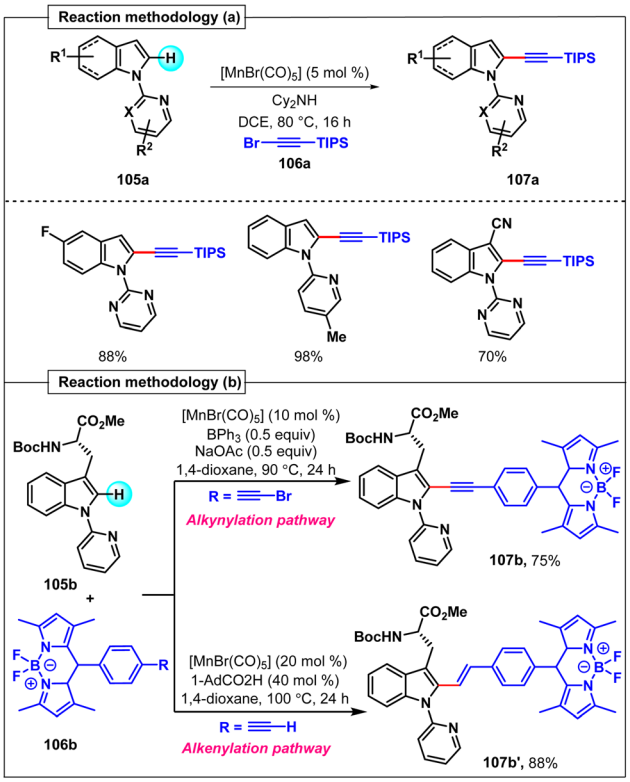
The reactivity of alkynes further needs to be revealed towards the M–C bond to generate alkynylated products, which is an underdeveloped and challenging task. This can be overcome by using the terminal alkyne as the coupling partner containing terminal bromide. Echavarren *et al.* recently reported Rh(III)-catalyzed *ortho*-alkynylation of nitroarenes **106** using bromoalkyne **107** in a regioselective manner (Scheme 35).[47]



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

Unsubstituted nitrobenzene offered a mixture of mono- and dialkynylated products in 4 : 1 ratio, whereas *ortho*-substituted nitrobenzene resulted in monoalkynylation. High site-selectivity was observed in the case of *meta*-substituted nitrobenzenes, offering functionalization at the least hindered site in the case of methyl, dimethyl and some other substituents. Remarkably, the authors achieved complete dialkynylation using two equivalents of the bromoalkyne. The protocol was applicable on a broad range of functionalities such as methoxy, bromo, nitro and heterocycles such as thienyl and indole. Notably, the methodology was also applied to synthesize complex chiral indole motifs. 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-catalysed *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)-catalysed alkynylation of N-substituted indoles **105a** with silyl haloalkynes **106a** (Scheme 36a).[48a] 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



Scheme 36 Manganese-catalysed alkynylation and alkenylation of N-substituted indoles.

also well-tolerated and remained unaffected throughout the transformation.

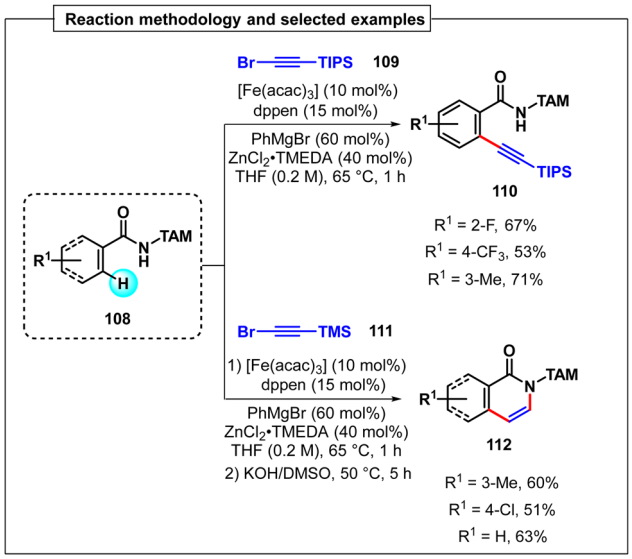
Similar to the earlier report, Ackermann *et al.* have recently reported chemo-divergent manganese catalysed sp^2 C–H bond activation of peptide derivatives **105b** (Scheme 36b).[48b] This method is highly effective in terms of its chemoselectivity, and has great potential from a pharmaceutical point of view. Notably, in this protocol, alkyne derived fluorinated Boron-Dipyrromethene (BODIPY) **106b** has been used as a reacting partner, which can be used in molecular imaging applications. A switchable reactivity was observed by changing the reaction conditions and coupling partner leading to alkynylation **107b** and alkenylation **107b′** reactions. In addition, this method also has potential towards the development of fluorophores through C–H bond activation using an earth abundant Mn(I)-catalyst in a chemo-divergent manner.

Furthermore, Ackermann *et al.* gave the first report on iron-catalysed 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. 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 these reaction conditions. Moreover, the authors also described the removal of the triazolyldimethyl-amine (TAM) group.

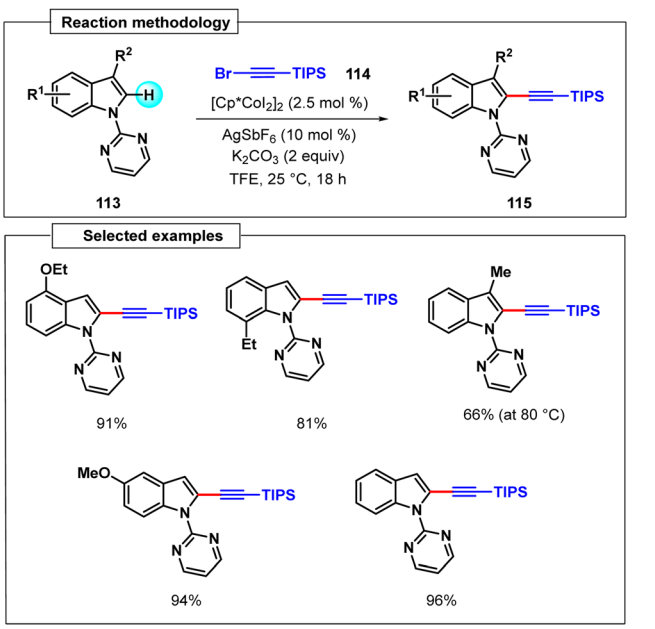
The same group has described a Co(III)-catalysed alkynylation of N-substituted indoles **113** with bromoalkynes **114** (Scheme 38).[50] This reaction has been carried out in very mild conditions and ambient temperatures. Indoles substituted with electrophilic functional groups smoothly participated in the reaction and provided excellent yields. Bulky substitutions on the substrate could also withstand the conditions, 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 the synthetic probability of this methodology.

A Ni(II)-catalysed 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 $Me_2S{\cdot}CuBr$ 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 conditions. Notably, amides containing a phenyl group substituted with electrophilic moieties were observed to be more effective than their nucleophilic counterparts.

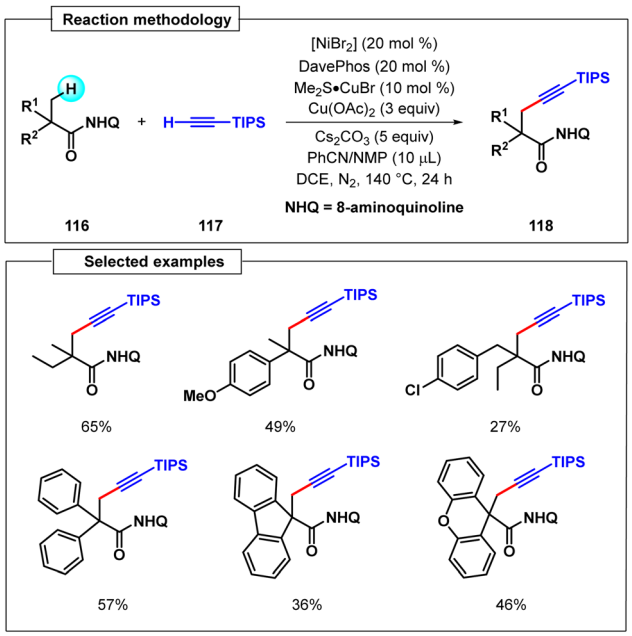
On studying the above alkenylation reports using alkyne, we observe that the use of aliphatic substrates for alkynylation has been done to a limited extent. Similar to the reports on alkenylation reactions, the alkynylation reports presented above are mostly aided by strongly coordinating directing groups. Keeping in mind the advantages of weak coordination, such alkynylation strategies *via* weak coordination would be



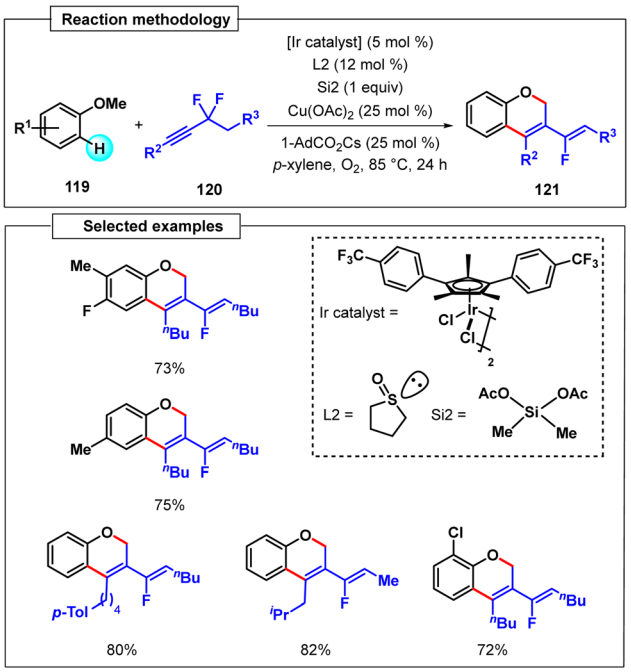
Scheme 37 Iron-catalysed triazole-assisted alkynylation of aromatic amides.



Scheme 38 Cobalt-catalysed alkynylation of indoles with bromoalkynes.



Scheme 39 Nickel-catalysed alkynylation of aliphatic amides with terminal alkynes.



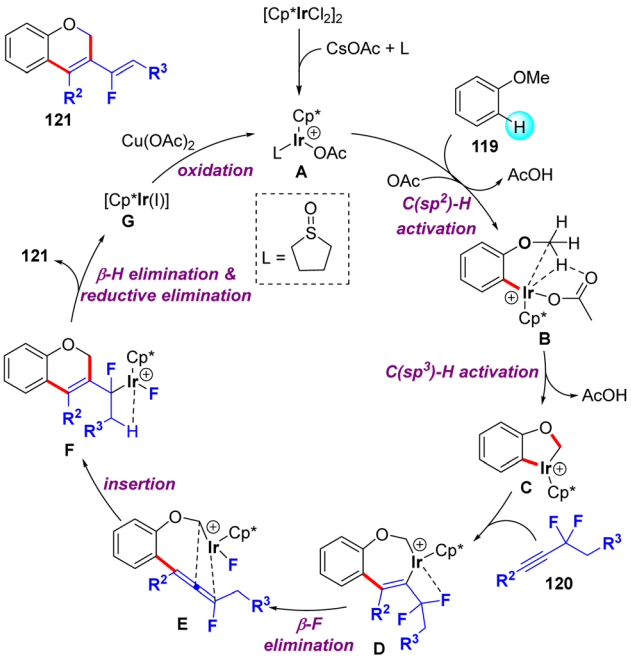
Scheme 40 Iridium-catalysed carbo-carbation of difluoroalkynes using anisole.

desirable. Thus, the search for efficient and sustainable methodologies can be extended with the use of weak coordination.

6. Various transition metal-catalysed unusual reactions of alkynes

This section covers various unusual reactivities of alkynes toward the M–C bond. This has provided wide applications in organic transformations and synthesis of many bioactive molecules. 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. The authors employed a broad range of substituted anisoles to determine the substrate scope, wherein anisole derivatives with various electronic natures 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.

Furthermore, 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 cyclometalated intermediate **C**.

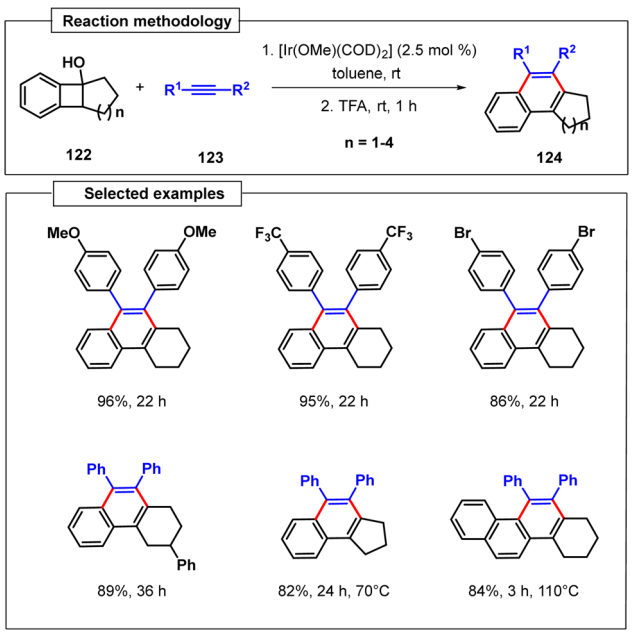


Scheme 41 Catalytic cycle of iridium-catalysed sp^2 and sp^3 C–H bond activation.

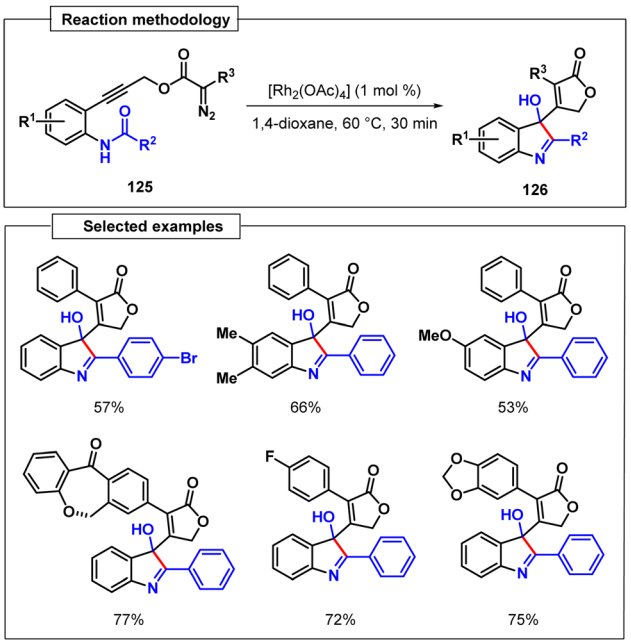
Then, alkyne **120** coordination followed by insertion affords intermediate **D**, which leads to the allene-based intermediate **E** after β-fluoride elimination of species **D**. Furthermore, insertion of the M–C bond into the allene center gives intermediate **F**. From this intermediate, the desired 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-catalysed intermolecular annulation of ring-fused benzocyclobutenols **122** with alkynes **123** to afford different polycyclic aromatic hydrocarbons **124** (Scheme 42).[53] Herein, the metal coordinates through free –OH for insertion between the 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 very good 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 functionalisation. 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. 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 functionalisation.



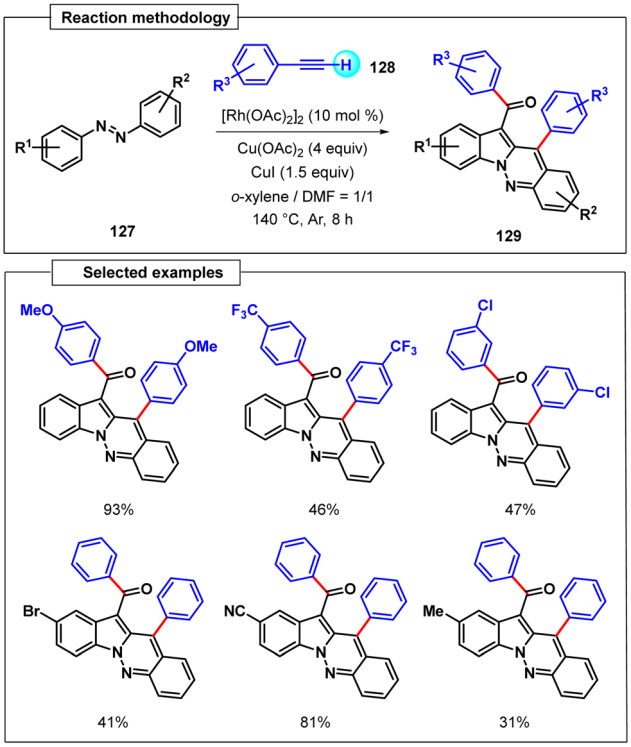
Scheme 42 Iridium-catalysed annulation of benzocyclobutenol with alkynes.



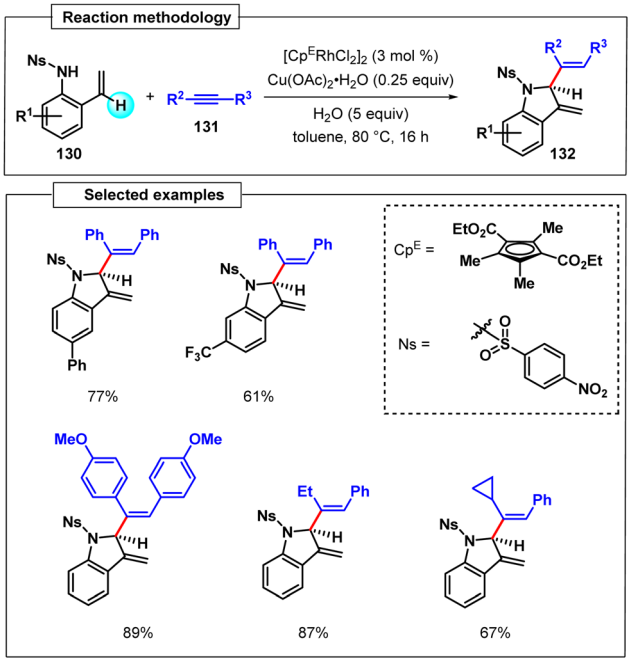
Scheme 43 Rhodium-catalysed formal C–O insertion reaction for the synthesis of indol-3-ol skeletons.

Furthermore, 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 unsymmetrical 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 the 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 effects.

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. Unsymmetrical 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. Furthermore, in 2020, Lin *et al.* reported a novel method for selective trans-exo arylative cyclization of 1,6-enynes **134a**. The reaction was carried out in the presence of an Rh-catalyst and *N*-heterocyclic directing

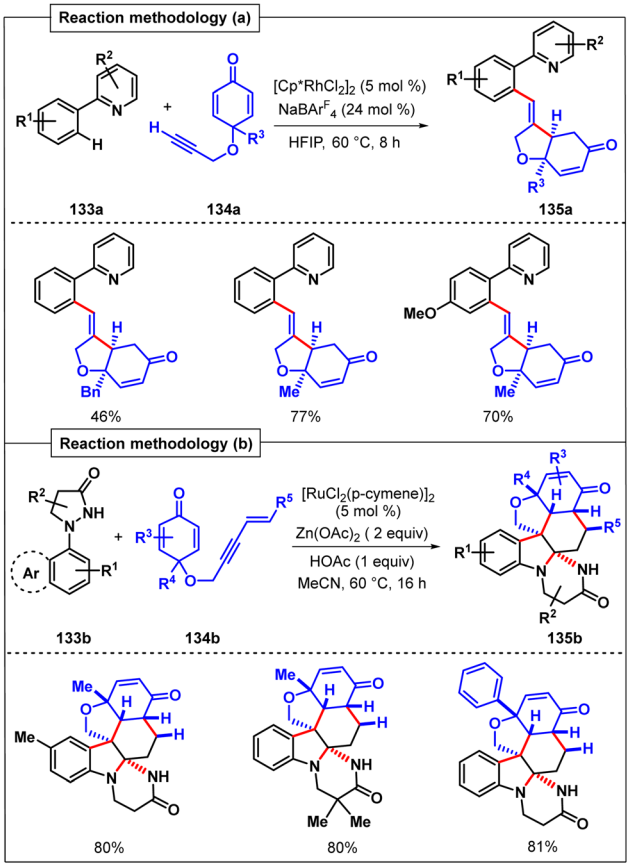


Scheme 44 Rhodium-catalysed cascade annulation of azobenzenes with terminal alkynes.



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

group **133a** (Scheme 46a).[57a] Enynes containing sterically crowded aryl groups as R^3-substituents showed lower yields than those containing less crowded aliphatic groups.

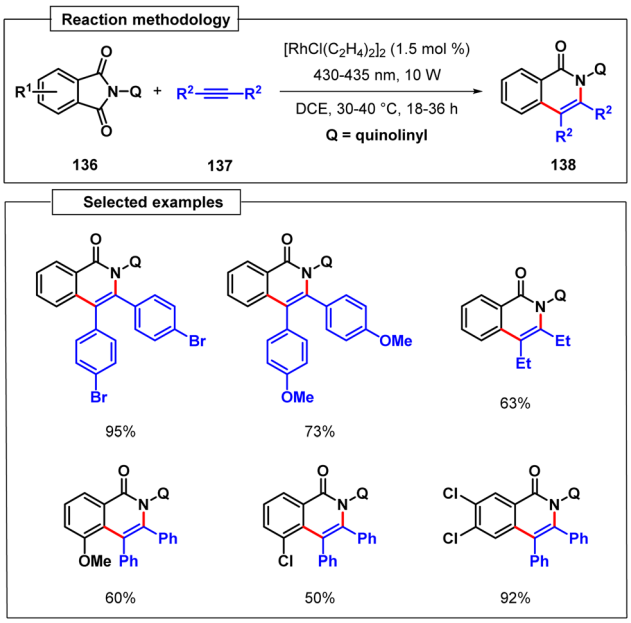


Scheme 46 Rhodium and ruthenium-catalysed cyclization of alkyne-tethered cyclohexadienones.

Remarkably, enynes bearing sensitive groups such as bromo- could also be tolerated in good yields.

Next, the scope of the 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. Furthermore, Li *et al.* have utilized alkyne-tethered cyclohexadienones **134b** as the reacting partner for the synthesis of hexacyclic indolines **135b** (Scheme 46b).[57b] This cascade cyclisation goes through ruthenium-catalysed C–H bond activation of phenidones **133b** followed by [4+2] cyclisation. This method gives easy access to natural polycyclic indoline alkaloids in a highly diastereoselective manner. 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.

Recently, Chen *et al.* reported an Rh-catalysed 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



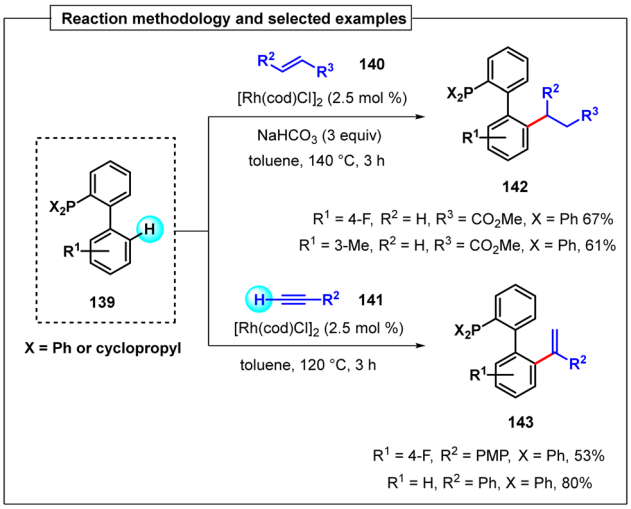
Scheme 47 Rhodium-catalysed decarbonylative coupling of imides with alkynes.

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.

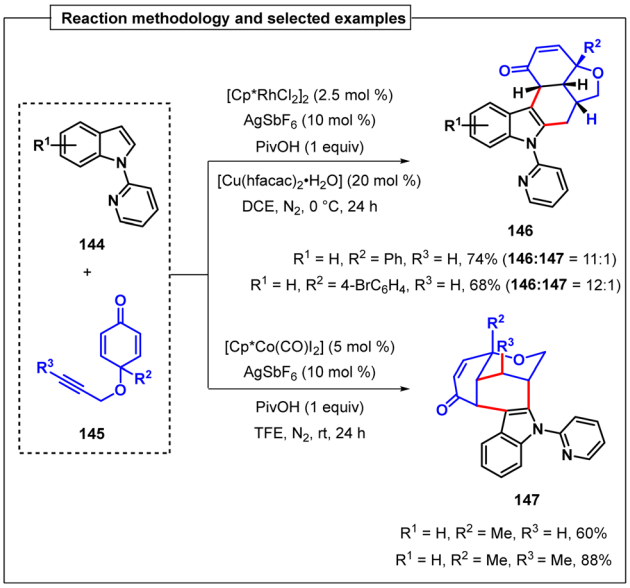
Furthermore, Shi *et al.* reported the synthesis of biarylphosphines **142** and **143** *via* direct hydroarylation of alkenes **140** and alkynes **141** with tertiary phosphines **139** (Scheme 48).[59] The first method corresponds to di-substituted alkylated products. Various substitution patterns 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 the 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.

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 a cobalt catalyst was employed. The products obtained in each case were [6,5]-fused cycles **146** and bridged [3,3,1]-cycles **147**, respectively. 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. A *para*-bromo substituted phenyl ring gave a slightly better result than an unsubstituted phenyl ring. In the cobalt-catalysed reaction, most of the reactions were carried out using enynes bearing electron-donating groups, out of which two examples are shown in Scheme 49.

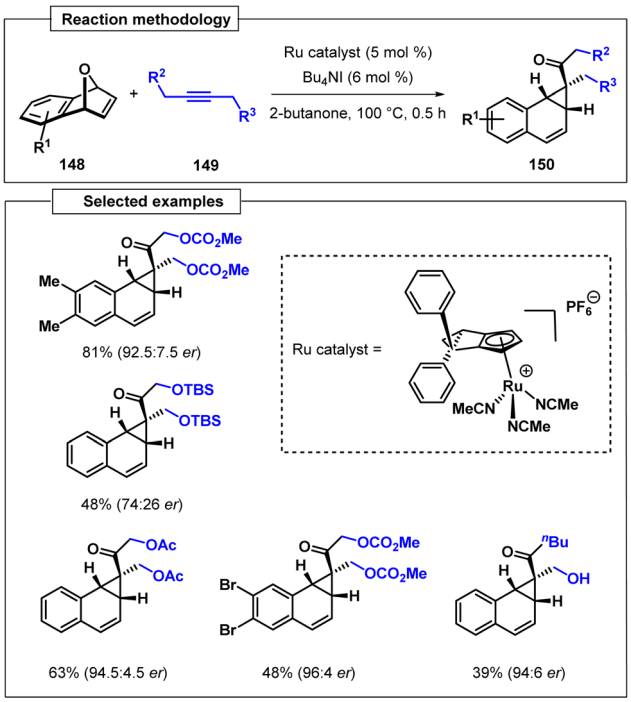
In 2019, Cramer *et al.* described the synthesis of benzonorcaradienes **150** from oxabenzonorbornadienes **148** and alkynes **149** (Scheme 50).[61] The reaction scope was studied by varying the substitution patterns on the substrate. Oxabenzonorbornadiene with two methyl groups reacted very efficiently, giving the desired product in high yield. Subsequently, the substrate containing two bromo- groups showed excellent enantioselectivity, although it 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



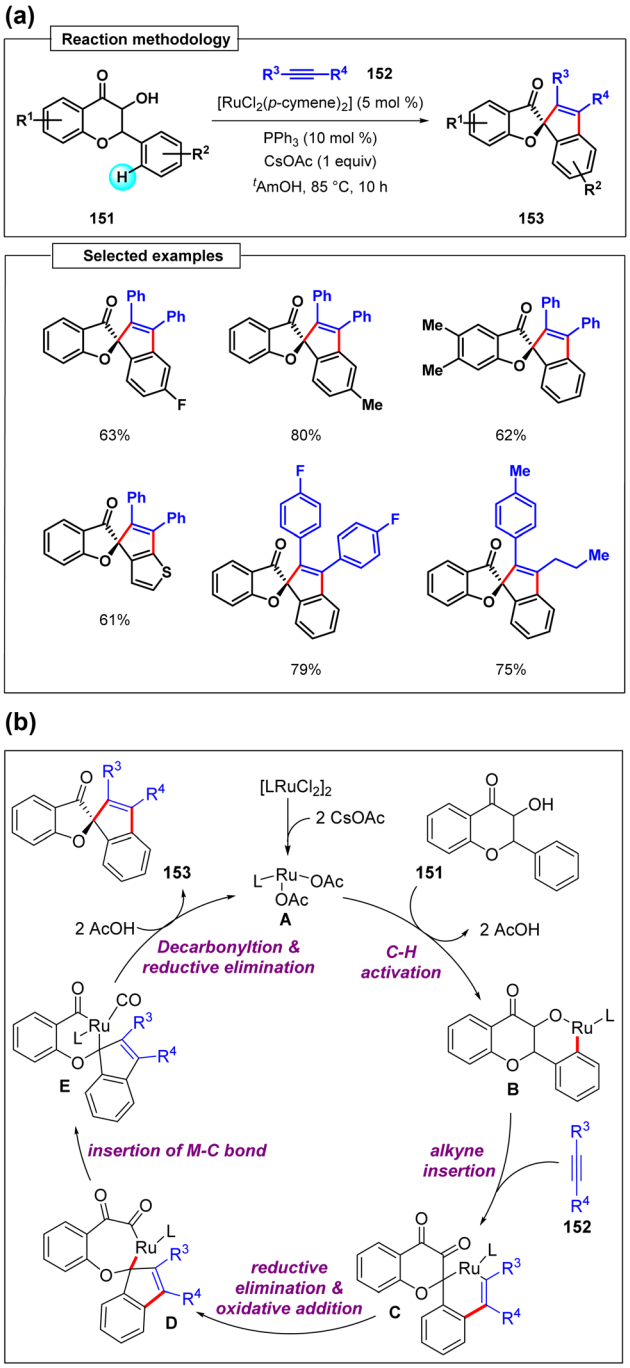
Scheme 48 Rhodium-catalysed hydroarylation of alkenes and alkynes.



Scheme 49 Rhodium and cobalt-catalysed alkyne insertion into indoles.



Scheme 50 Ruthenium-catalysed coupling of oxabenzonorbornadienes with alkynes.

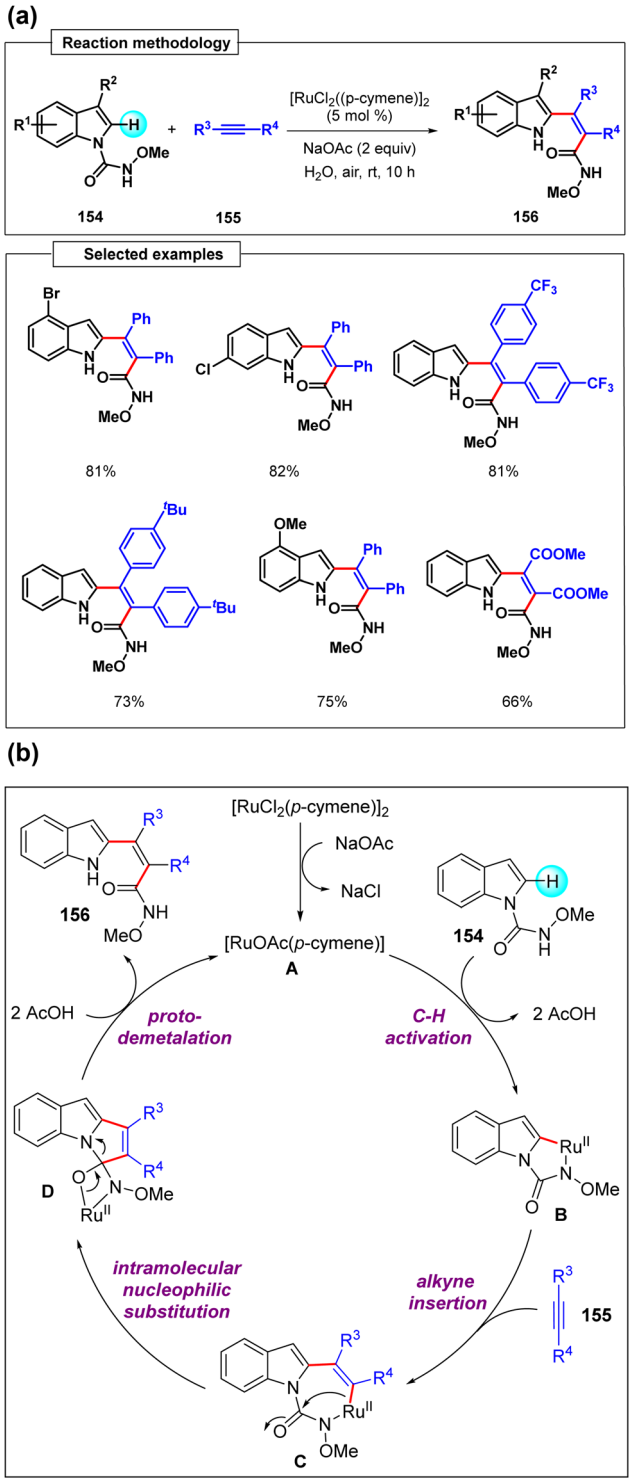


Scheme 51 (a) Ruthenium-catalysed synthesis of spirobenzofuranones. (b) Catalytic cycle for ruthenium-catalysed synthesis of spirobenzofuranones.

corresponding products in moderate to good yields. Apart from these, the reactivity of various unsymmetrical alkynes was also tested, all of which showed high enantioselectivities.

Furthermore, 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 substitutions at the R^2-position were tolerable; however, electron-donating groups showed better reactivity. Similarly, substituents of different electronic nature at the R^1-position successfully gave the desired products in good yields. Notably, substitution with a heterocycle at the R^2-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 conditions. 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. Furthermore, 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 the M–C bond gives intermediate **C**. Further reductive elimination followed by oxidation of the metal-catalyst leads to the formation of species **D**. Then, the further insertion of the 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.

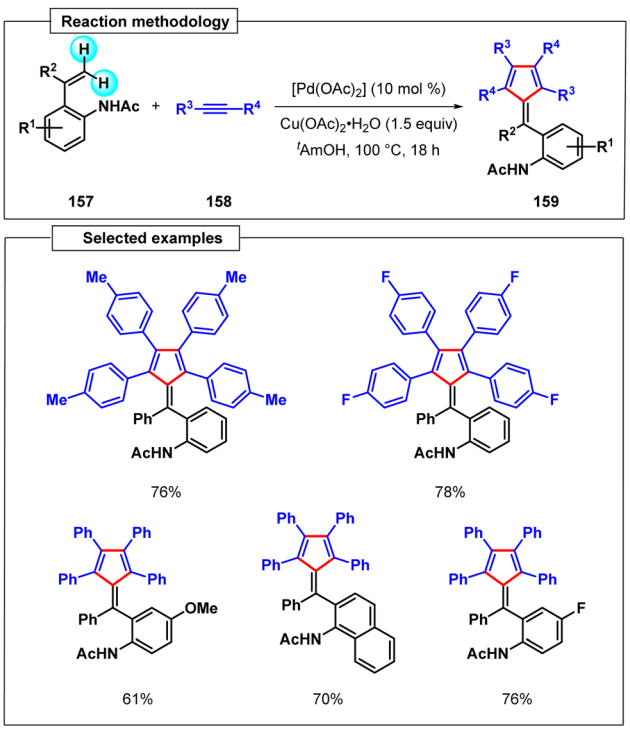
Recently, Zhang *et al.* have reported a method to synthesize tetrasubstituted alkenes **156** *via* olefination of indoles **154** and alkynes **155** (Scheme 52a).[63] The amide directing group attached at the nitrogen atom of the indole moiety promotes this Ru-catalysed transformation under aqueous conditions. Substrate scope studies revealed that indoles containing varied substitution patterns were amenable to the reaction conditions.



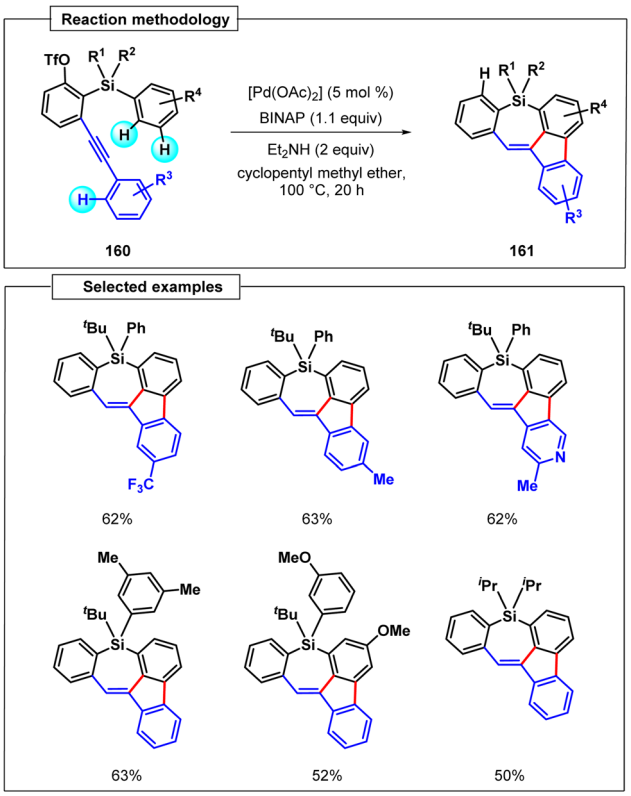
Scheme 52 (a) Ruthenium-catalysed olefination of indoles with alkynes. (b) Catalytic cycle for ruthenium-catalysed olefination of indoles *via* directing group migration.

For instance, 4-methoxy as well as 4-bromo-indoles were 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.

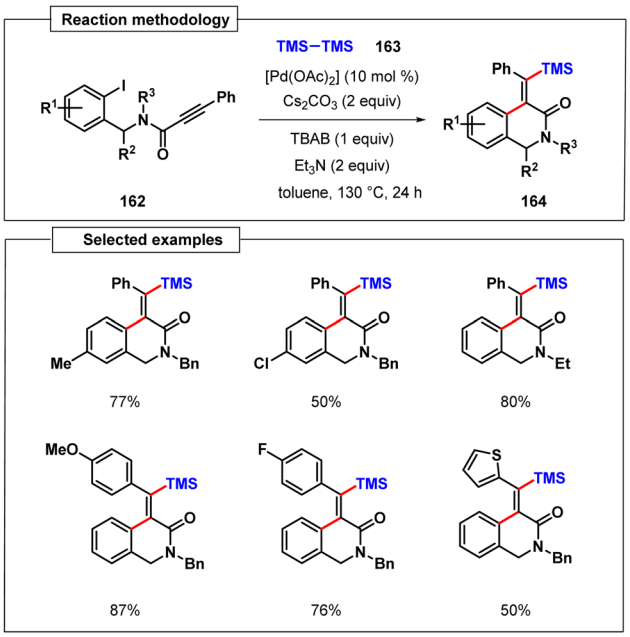
Next, the interesting mechanism of this olefination of indoles, going *via* directing-group migration, is discussed (Scheme 52b). First, sodium acetate initiates the ligand exchange with $[RuCl_2(p\text{-cymene})]_2$ to generate the active catalyst **A**. This active catalyst then coordinates with the indole **154** to generate a five-membered ruthenacycle **B** *via* a concerted metalation deprotonation pathway. Next, alkyne **155** insertion results in intermediate **C**, which then undergoes an intramolecular nucleophilic substitution to result in the formation of directing-group migrated intermediate **D**. Finally, protodemetalation yields the final product **156** along with the regeneration of active catalyst **A**. Notably, in 2020, Gogoi *et al.* demonstrated the first report on transition-metal catalysed 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 a 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-



Scheme 53 Palladium-catalysed double annulation of vinylic compounds.



Scheme 54 Palladium-catalysed *anti*-carbopalladation of alkynes.



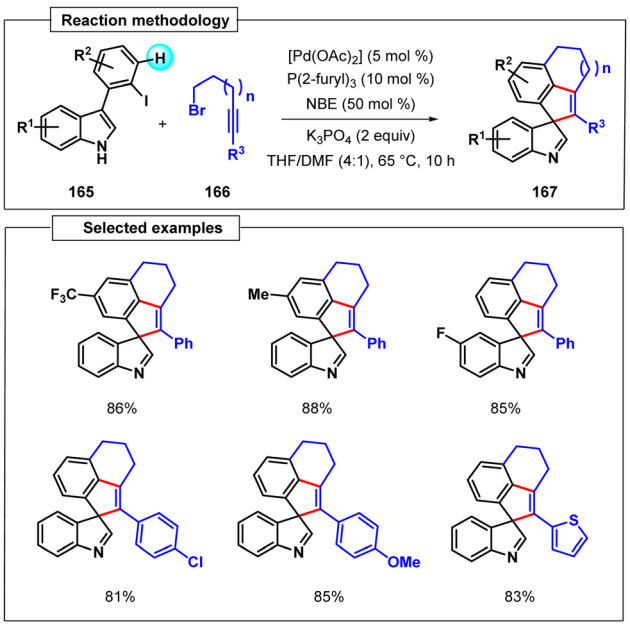
Scheme 55 Palladium-catalysed carbosillylation of alkynes to produce exocyclic vinylsilanes.

containing acetamide was identified as amenable and provided the corresponding product in a satisfactory amount.

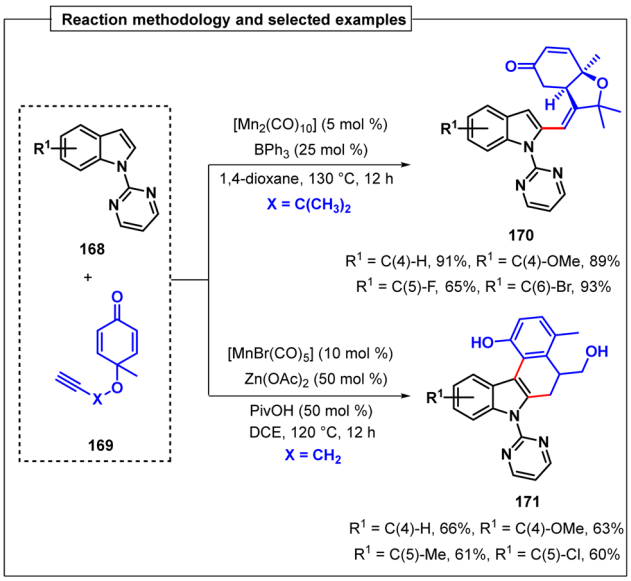
Shintani *et al.* reported an unforeseen method for synthesizing dibenzosilepins **161** from silyl-containing aryl triflates **160** (Scheme 54).[65] The reaction proceeded *via* 1,*n* migration of palladium followed by *anti*-carbopalladation of the attached alkyne moiety. The scope of this transformation 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. Furthermore, Zhang *et al.* have also demonstrated their work on palladium-catalysed *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 conditions. Substrates containing electron-rich groups proved to be more successful than their electron-withdrawing group-containing analogs. Alkyl substitution on the 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.

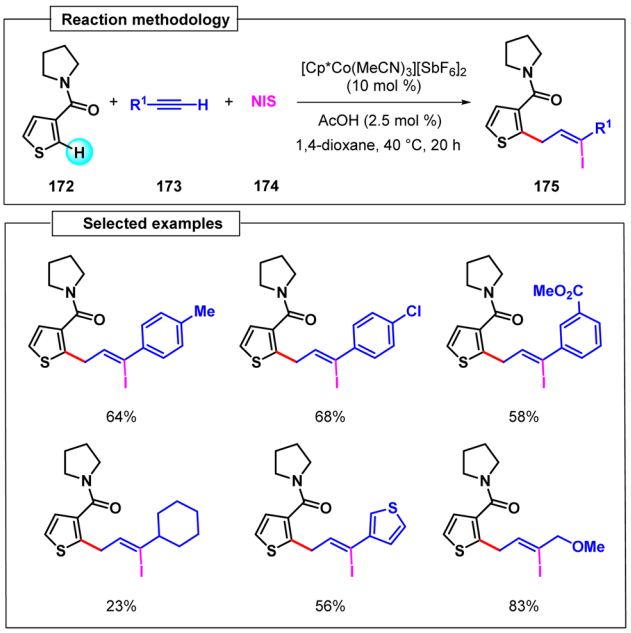
Also, Luan *et al.* described the synthesis of spiro-indolenin containing pentacyclic frameworks **167** *via* intermolecular domino annulation of biaryl indoles **165** with bromo-alkyl alkynes **166** (Scheme 56).[67] Overall, the authors observed good compatibility of a diverse range of substrates 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. All alkynes



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



Scheme 57 Manganese-catalysed C–H bond functionalization followed by cascade cyclization.



Scheme 58 Cobalt-catalysed a three-component addition reaction for the synthesis of alkenyl halides.

smoothly coupled with the substrate under the given conditions 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.

Xingwei Li *et al.* have reported the manganese-catalysed regioselective C(2)–H bond activation of indole **168** using alkyne-tethered cyclohexadienones **169** (Scheme 57).[68] In this protocol, varied transformations were obtained by switching the reaction conditions and reacting partner. Also, they have noticed the effective role of BPh_3 as an additive for alkenylation followed by cyclization. This method was found to be quite general towards various indole and alkyne derivatives.

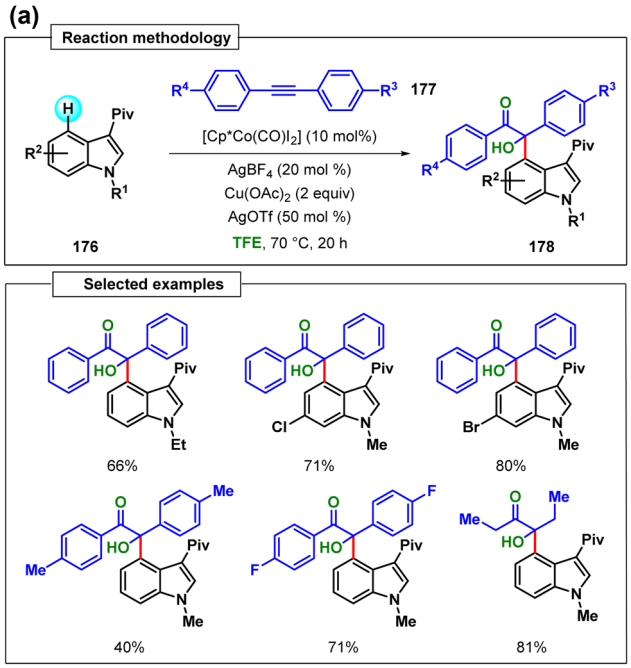
In 2017, Ellman *et al.* reported an unusual three-component addition reaction between pyrrolidin-1-yl(thiophen-3-yl)methanone **172** terminal alkynes **173** and halogenating agents **174** giving functionalised alkenyl halides **175** as the product (Scheme 58).[69] After optimizing the reaction conditions, the substrate scope was determined.

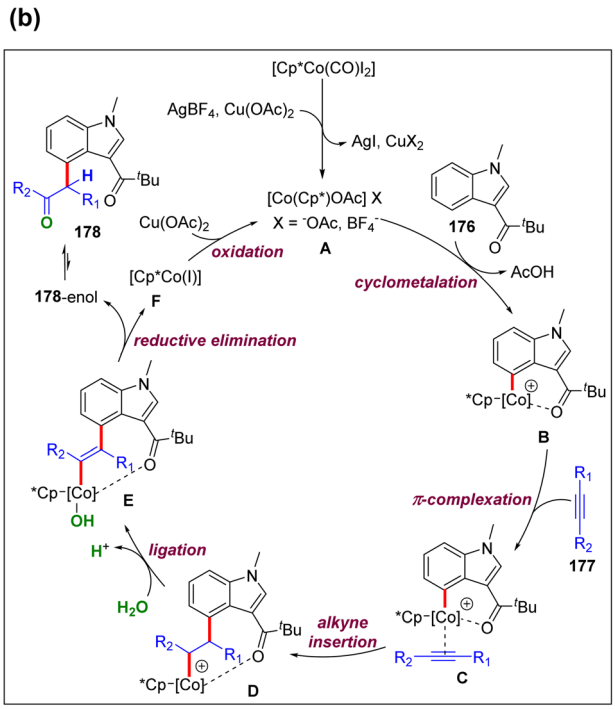
A broad range of alkyl and aryl terminal alkynes were compatible with the reaction conditions. Alkynes containing electronically distinct substituents such as *p*-tolyl and *p*-chlorophenyl gave comparable yield. *meta*-Carbonyl substituted alkynes were also tested, which provided the desired product in moderate yield. Apart from these, heterocycles such as 3-thienyl were also compatible and gave reasonable yields. Moreover, aliphatic alkynes containing a cyclohexyl ring and a methoxy group were identified as amenable, although the former alkyne displayed poor reactivity. Recently, another novel reactivity of alkynes has been observed by Ravikumar *et al.* They have disclosed the cobalt-catalysed regioselective C(4)–H functionalisation of indoles **176** with alkynes **177** for the formation of α-hydroxy ketones **178** (Scheme 59a).[70] This work was promoted by chelation of a pivaloyl directing group with the metal towards the 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.

The substrate scope of this reaction was studied after optimizing the conditions. The indoles containing halogens at the C-6 position were successfully converted to the desired products in good yields. In addition, various substitutions on nitrogen were 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.

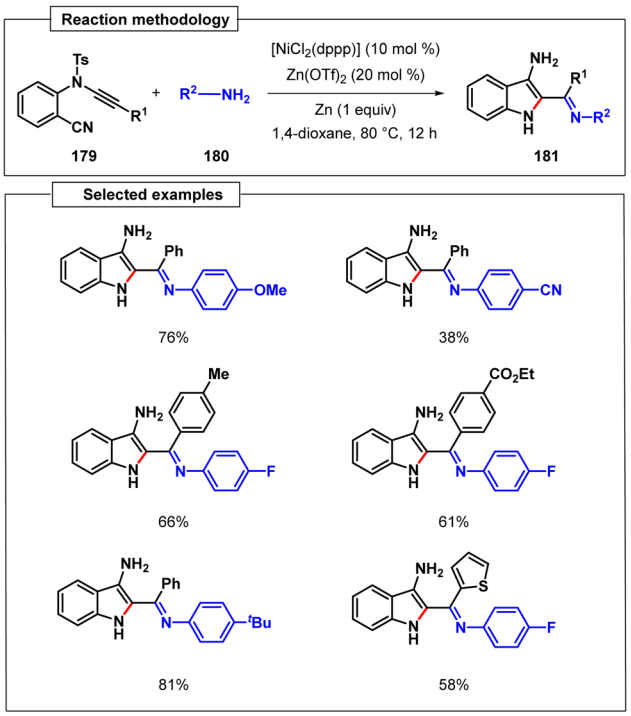
Moreover, aliphatic alkynes were also identified as amenable and gave the corresponding products in good yields. Notably, the unsaturated ketone has been obtained with an unsymmetrical alkyne with this protocol. The mechanism for regioselective indole C(4)–H functionalisation has been depicted in Scheme 59b. The active catalyst **A** is generated in the presence of silver salt and copper acetate, which affords the cyclometalated intermediate **B** after regio-selective C–H bond activation of 3-pivaloyl indole **176**. Then, alkyne **177** coordination followed by insertion gives species **D**. Furthermore, the ligation of species **D** forms intermediate **E**. Next, reductive elimination of intermediate **E** produces the desired product **178** 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 **181** *via* regio-selective cyclization of ynamide-nitriles **179** and amines **180** (Scheme 60).[71] The electron-donating substituents on the amine significantly increased its nucleophilicity, which elevated its reactivity. *para*-Substitution with an *N*,*N*-dimethyl





Scheme 59 (a) Cobalt-catalysed regioselective C(4)–H functionalisation of indoles. (b) Cobalt-catalysed regioselective C(4)–H functionalisation of indoles.

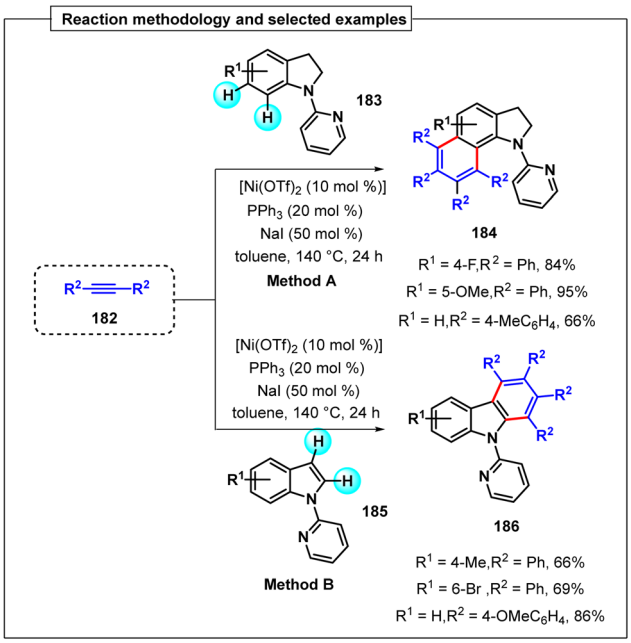


Scheme 60 Nickel-catalysed cyclization of ynamide-nitriles with amines.

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.

Furthermore, in 2021 Ravikumar *et al.* demonstrated the synthesis of poly-heterocyclic indoline **184** and bioactive carbazole motifs **186** *via* sequential C–H bond activation of indoline **183** and indole **185** using alkynes **182** (Scheme 61).[72] This selective functionalisation of indole, even in the presence of C7–H, makes this approach unique. The reaction conditions were 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 functionalisation 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.

As evident, the extent and variation of the reactivity of alkyne towards the M–C bond has no limits. Therefore, the use of alkyne as a coupling partner is constantly on the rise. As a result, new reactivities of alkyne are being uncovered, giving rise to unforeseen transformations. This will undoubtedly take the application of alkyne as a coupling partner in transition metal-catalyzed C–H activation to greater heights.



Scheme 61 Nickel-catalysed annulation of indole and indoline.

7. Conclusions and future prospects

Transition metal-catalysed C–H bond activation and functionalisation has become a 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 have been 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 a 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 has been limited. The reactivity of alkynes with low-valent transition metals such as Pd(0), Co(0/I), Fe(0), and Ni(0), as well as simple salts like $RhCl_2$, $RuCl_2$, and $CoBr_2$ 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 favourable possibility of β-hydride elimination. The enantioselective metal-catalysed C–H functionalisation 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 highlight review 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 highlight will inspire chemists to work on unexplored and less explored areas stated above in the near future.

Abbreviations

Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
TFE	Trifluoro-ethanol
DCE	1,2-Dichloroethane
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
AcOH	Acetic acid
THF	Tetrahy-drofuran
BHT	Butylated hydroxytoluene
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
OTf	Trifluoromethanesulfonate
PivOH	Pivalic acid
HOSA	Hydroxylamine-*O*-sulfonic acid
Et2O	Diethyl ether

Conflicts of interest

The authors declare no competing financial interest.

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