RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2022, **12**, 5847

1,2-Difunctionalizations of alkynes entailing concomitant C–C and C–N bond-forming carboamination reactions

Santosh Kumar Nanda * and Rosy Mallik

Vicinal carboamination of alkynes is a highly reliable and efficient practical strategy for the quick preparation of valuable and diverse amine derivatives starting from simple synthons. The last decade has witnessed numerous practical methods employing transition-metal-based/metal-free carboamination approaches using alkynes for the synthesis of these N-bearing entities. Driven by the renaissance of transition metal catalysis, intermolecular and intramolecular carboamination of alkynes comprising concomitant C–N and C–C bond formation has been studied extensively. In contrast to metal catalysis, though analogous metal-free approaches have been relatively less explored in the literature, they serve as alternatives to these expensive approaches. Despite this significant progress, reviews documenting such examples are sporadic; as a result, most reports of this type remained scattered throughout the literature, thereby hampering further developments in this escalating field. In this review, different conceptual approaches will be discussed and examples from the literature will be presented. Further, the reader will get insight into the mechanisms of different transformations.

Received 3rd September 2021
Accepted 30th January 2022

DOI: 10.1039/d1ra06633a

rsc.li/rsc-advances

1. Introduction

Carbon–carbon multiple bonds are essential and versatile synthons that engage in diverse organic transformations. Difunctionalization of carbon–carbon multiple bonds by constructing two different vicinal chemical bonds is an invincible strategy and has attracted significant attention from the synthetic community in the last decade. In this context, carboamination of alkenes, alkynes, and allenes has provided a straightforward route for the synthesis of functionalized amines and their congener heterocycles.[1–12]

Carboamination of alkynes has come to the forefront as a method of choice for the synthesis of an avenue of N-bearing

Department of Chemistry, School of Applied Science, Centurion University of Technology and Management Paralakhemundi, Odisha-761211, India. E-mail: sknanda@cutm.ac.in

Dr Santosh K. Nanda was born in Jajpur, Odisha, India in 1987. He received his M.Sc. degree from Utkal University (2011). He obtained his PhD from the Indian Institute of Technology, Bombay in 2018, working with Professor Santosh J. Gharpure, and subsequently he became a postdoctoral fellow. Then he joined the Department of Chemistry, CUTM-Odisha as an assistant professor. Recently, he has been working as a postdoctoral fellow at the Department of Chemistry, University of Texas at San Antonio, USA. His research is focused on developing methods for the stereoselective synthesis of various functionalized heterocycles employing the cascade functionalization of alkynes.

Dr Rosy Mallik was born in Bhadrak, Odisha, India in 1979. She received her M.Sc. degree from Berhampur University (2001). She obtained her PhD from the National Chemical Laboratory, Pune, Maharashtra, India. Dr Mallik has post-doctoral research experience at The Central University, Hyderabad, India and the University of Jyväskylä, Finland. She joined the Department of Chemistry, CUTM-Odisha as an assistant professor in 2019. Her research is focused on organic synthesis, natural product synthesis, and organo-catalysis.

aromatic heterocycles and has attracted significant attention from the synthetic community.

The other arguable advantage of this protocol may be the quick access to a synthetically useful and celebrated intermediate, *i.e.* enamine (Fig. 1). To showcase the proficiency of this method, various strategies have been developed in the literature. In this context, the contribution of transition metal catalysis has been exceptional and has delivered an enormous number of protocols for the expedient synthesis of N-bearing scaffolds. On the other hand, corresponding metal-free approaches have also been documented in the literature for the synthesis of variously substituted N-heterocycles. Unlike the gathering together of various reports on the carboamination of alkenes in the literature as reviews, the analogous compilation of literature on carboamination of alkynes is scant.

In the present review, an overview of developments on the diastereoselective as well as the enantioselective carboamination of alkynes is given, with specific attention to the mechanism for each transformation in detail. The review contains sections in which the reactions are categorized under various headings depending upon the operative reaction mechanism. The first such section will describe the developments in carboamination of alkynes using transition metal-catalyzed oxidative addition to fragments consisting of both carbon and nitrogen source. The second section will elaborate the reactions based upon metal-catalyzed C–H activation. The third section will enlighten upon reports of carboamination triggered by cycloaddition reactions. The fourth section will demonstrate carboamination of benzynes. The fifth section will tell us about the intramolecular carboamination approach towards the synthesis of complex aza-cycles. The final section will elaborate on methods utilizing electrocatalysis in carboamination reactions and metal-free carboamination reactions.

2. Carboamination of alkynes

2.1 Transition metal-catalyzed carboamination

Transition metals have shown promising reactivity in the difunctionalization of alkynes. In this context, carboamination of alkynes has been studied extensively for the synthesis of N-bearing aromatic heterocycles. Several strategies involving transition metal-catalyzed C–H bond functionalization, cycloaddition, difunctionalization of benzyne, and intramolecular carboamination have been studied. Furthermore, corresponding metal-free approaches have also been reported. This section will provide a concise idea about the recent developments.

2.1.1 Oxidative addition-triggered carboamination. In this domain, Ni-catalyzed decarbonylative carboamination reaction of phthalimides to alkynes was studied by Kurahashi and co-workers for the synthesis of isoquinolones (Scheme 1).[13] Reaction of phthalimides **1** and alkynes **2** with 10 mol% $Ni(cod)_2$ and 40 mol% PMe_3 resulted in various isoquinolones **3** in good to excellent yield. When the substrate scope was studied, it was found that the presence of electron-withdrawing substituents on the *N*-aryl ring gave better yields in comparison with phenyl or aryl rings bearing electron-donating groups. Further, unsymmetrical alkynes led to a mixture of regio-isomers. The formation of the product can be explained as follows. Nickelacycles **Int-A** was formed by oxidative addition, which upon decarbonylation gave **Int-A1**. The **Int-A1** furnished **Int-A2** *via* carbo-nickelation with alkynes. Finally, reductive elimination led to the formation of **3**.

On similar lines, Matsubara and co-workers have reported a Ni-catalyzed decarboxylative carboamination strategy for the facile synthesis of 4-quinolones (Scheme 2).[14] Reaction of *N*-arylisatoic anhydrides **4** with alkynes **2** in the presence of 5 mol% $Ni(cod)_2$ and 5 mol% PCy_3 afforded the corresponding 4-quinolones **5** in good yield. Interestingly, both aliphatic and aromatic symmetrical alkynes resulted in the formation of the desired quinolone. In the case of unsymmetrical alkynes, a mixture of regio-isomers was formed. The regio-isomeric ratio was dictated by the bulkiness of the substituent attached to the alkynes. The effect of bulkiness was so pronounced that the presence of *tert*-butyl and TMS groups led to the exclusive formation of a single product with the less bulky group near to the nitrogen atom. The reaction followed a similar path to arrive at **5** through **Int-B** to **Int-B2**.

Similarly, a Ni-catalyzed decarbonylative–decarboxylative carboamination cascade was reported by Matsubara and co-workers for the facile synthesis of indoles (Scheme 3).[15] Reaction of isatoic anhydrides **6** with alkynes **2** in the presence of 5 mol% $Ni(cod)_2$, 20 mol% PMe_2Ph, and 10 mol% of the additive MAD (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)) furnished the corresponding indole

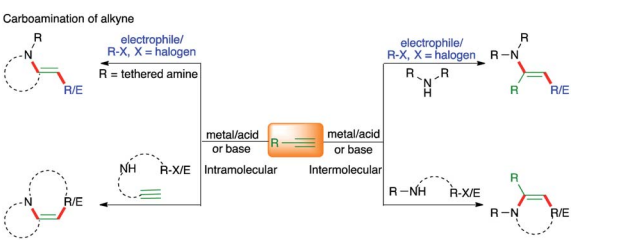
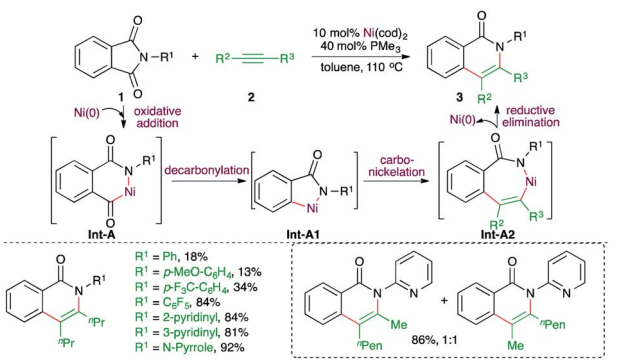
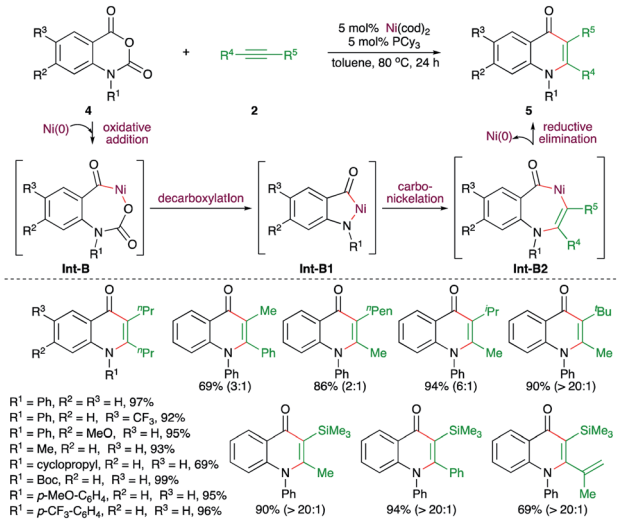


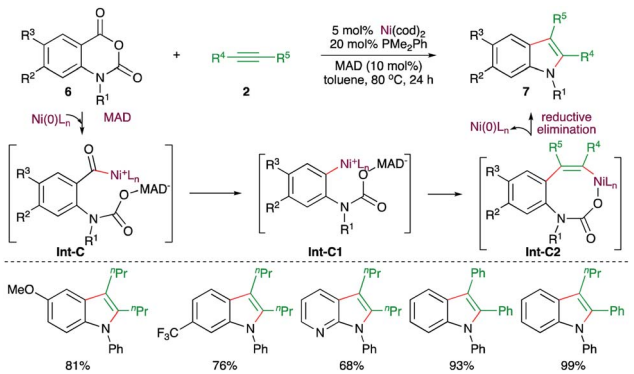
Fig. 1 Different possible paths for the carboamination of alkynes under metal/metal-free conditions.



Scheme 1 Decarbonylative carboamination reaction of phthalimides with alkynes.



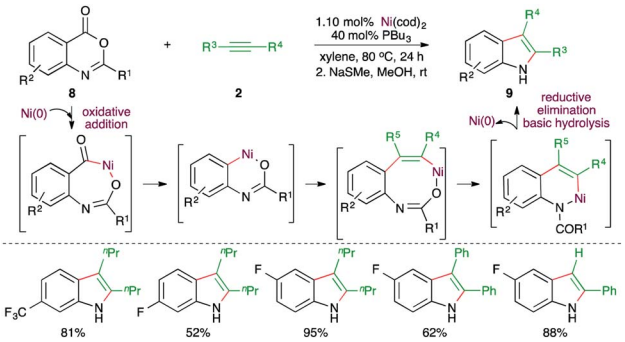
Scheme 2 Decarboxylative carboamination reaction of phthalimides with alkynes.



Scheme 3 Decarbonylative–decarboxylative carboamination cascade.

derivatives **7** in good yield. The suggested mechanism revealed that the use of MAD is responsible for the formation of **7** not **5** (see Scheme 7) as it chose a different reaction pathway. Thus, in the presence of MAD, **Int-C** was formed, which upon decarbonylation gave **Int-C1**. The **Int-C1** performed carbo-nickelation with alkynes to generate **Int-C2**. The **Int-C2** then underwent decarboxylation and reductive elimination of nickel to give indoles. The entire different path may be attributed to temporary coordination of bulky DMAD to the carbamate inhibiting the decarboxylation prior to decarbonylation.

Further, Matsubara and co-workers have also reported a Ni-catalyzed decarbonylative-acyl migration–amide hydrolysis carboamination cascade for the expedient synthesis of variously substituted indoles from readily available anthranilic acid derivatives (Scheme 4).[16] Reaction of anthranilic acid derivatives **8** with alkynes **2** in the presence of 10 mol% $Ni(cod)_2$ and 40 mol% PPr_3 furnished the corresponding indoles **9** in good to excellent yield. Initially, the N-protected amide was obtained along with some unprotected indole. Thus, after the reaction, basic hydrolysis was carried out to get rid of the protecting



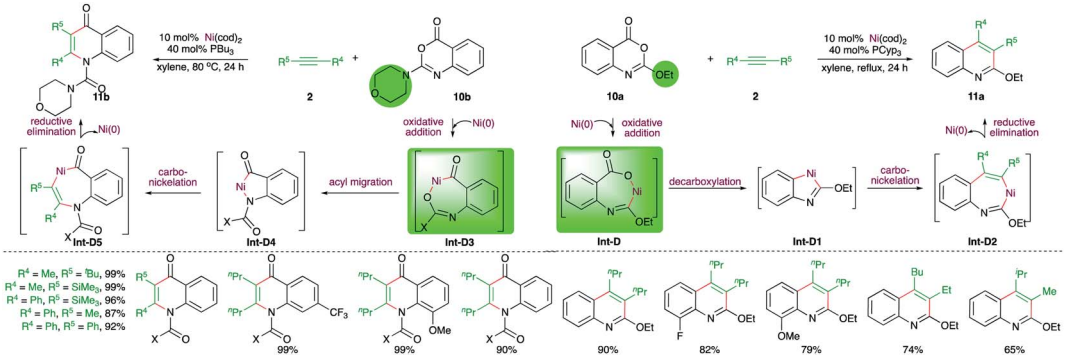
Scheme 4 Decarbonylative–acyl migration–carboamination–amide hydrolysis cascade.

group. Variously substituted indoles were synthesized from different alkynes. However, regio-isomeric mixtures were obtained in the case of unsymmetrical alkynes.

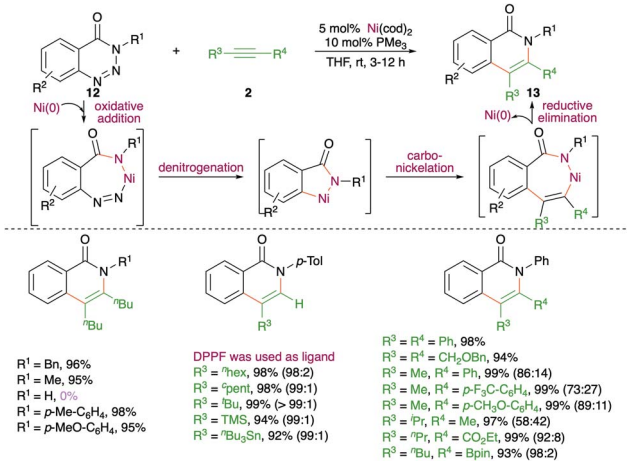
Matsubara and co-workers have also reported an elegant method describing the effect of protecting groups on the Ni-catalyzed intermolecular carboamination reactions. It was observed that benzoxazinones **10a** with alkoxide protecting group (R^1 = alkoxide) upon reaction with alkynes in the presence of 10 mol% $Ni(cod)_2$ gave 2-alkoxyquinolines **11a**, whereas the presence of amine as the protecting group in **10b** (R^1 = amine) led to the formation of quinolones **11b** under the same reaction conditions (Scheme 5).[17] The different outcome could be explained depending upon the operative mechanism. In the case of alkoxide-tethered benzoxazinones **10a**, the initial oxidative addition takes place at the vinylic C–O bond guided by the offered temporary coordination from the oxygen atom to generate **Int-D**, which upon decarboxylation gives metallacycle **Int-D1**. **Int-D1** upon subsequent carbo-nickelation and reductive elimination furnishes **11a** *via* **Int-D2**. On the other hand, when the protecting group is bigger, like ^{t}Bu or *N*-morpholinyl, the temporary coordination factor is overruled by steric prohibition of the oxidative addition at the vinylic C–O bond. Thus, the oxidative addition occurs at the carbonylic C–O bond to give **Int-D3**, which upon acyl migration furnishes **Int-D4**. The **Int-D4** upon carbo-nickelation and reductive elimination affords quinolones **11b** *via* **Int-D5**.

A nickel-catalyzed domino denitrogenative-carboamination strategy was developed by Murakami and co-workers for the synthesis of isoquinolones (Scheme 6).[18] Reaction of benzotriazin-4(3*H*)-ones **12** with alkynes **2** in presence of nickel(0)/phosphine catalyst gave corresponding isoquinolones **13** in good yield. Both internal and terminal alkynes were engaged in the reaction. However, in the case of unsymmetrical alkynes and terminal alkynes, a mixture of regio-isomers was obtained and the ratio was found to be a function of steric factors. The bulkier the substituent, the higher is the selectivity.

2.1.2 C–H insertion-triggered carboamination. During the invention of these elegant methods, another strategy became very popular for the synthesis of these N-bearing heterocycles. The strategy relied upon the directing group-assisted/free formation of metallacycle *via* insertion at C–H bonds. The



Scheme 5 Ni-catalyzed protecting group-dependent divergent synthesis of N-heterocycles.



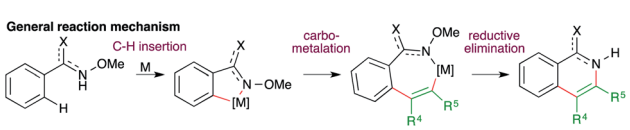
Scheme 6 Denitrogenative carboamination cascade.

metallacycle then participated in a carbometalation process with alkynes to generate a new metallacycle. Finally, reductive elimination of metal led to the formation of N-bearing heterocycles (Scheme 7).

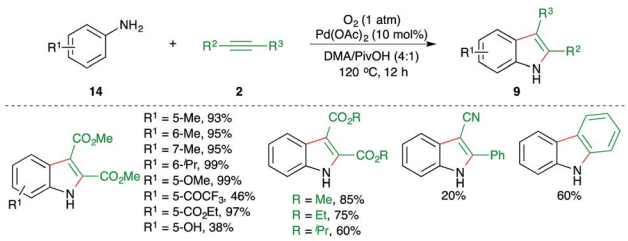
Jiao and co-workers have reported a practical synthesis of indole using Pd-catalyzed carboamination of alkynes with anilines (Scheme 8).[19]

The reaction of anilines **14** with electron-deficient alkynes **2** in the presence of 10 mol% $Pd(OAc)_2$ and molecular oxygen as oxidant gave variously substituted indoles **9** in good to excellent yield. The reaction has an excellent scope and functional group compatibility. The reaction only worked in the case of electron-deficient alkynes.

On similar lines, Huang and co-workers have used palladium instead of ruthenium to effect the carboamination cascade. The



Scheme 7 Mechanism for the carboamination of alkynes involving C–H functionalization.

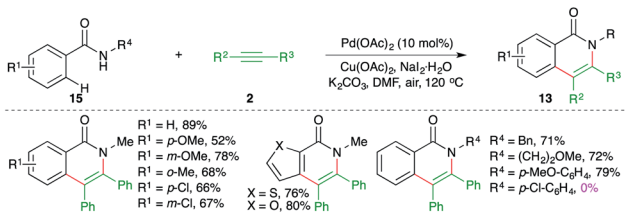


Scheme 8 Carboamination of alkynes with anilines.

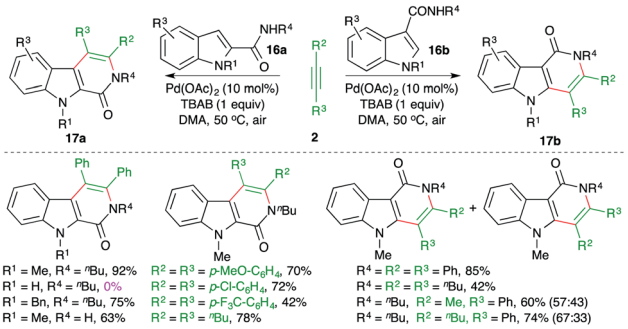
reaction of *N*-alkyl/aryl benzamides **15** with alkynes **2** in the presence of 10 mol% $Pd(OAc)_2$ and 2 equivalents of copper acetate as oxidant delivered the corresponding *N*-aryl/alkyl iso-isoquinolones **13** in good yield (Scheme 9).[20] The reaction demonstrated excellent scope for aryl amides. However, a limited number of alkynes were used in the transformations. Further, in the case of unsymmetrical alkynes, a mixture of regio-isomers was obtained and the regioselectivity was governed by the bulkiness of the group present on nitrogen as aryl groups led to the exclusive formation of one regio-isomer. It should be noted that *N*-aryls and halogen-substituted aryls failed to give the product.

Jiao and co-workers have reported a Pd-catalyzed intermolecular carboamination method for the rapid synthesis of β- and γ-carbolinones from the corresponding indole-tethered amides and alkynes in air (Scheme 10).[21] The treatment of amides **16a,b** with alkynes **2** in the presence of 10 mol% $Pd(OAc)_2$ gave the respective carbolines **17a,b** in good yield.

The reaction worked well for aliphatic and aromatic alkynes. However, in the case of unsymmetrical alkynes, a mixture of



Scheme 9 Carboamination of alkynes with aryl amides.



Scheme 10 Carboamination of alkynes with indole-tethered amides.

regio-isomers was obtained. Unfortunately, free indoles (R^4 = H) did not participate in the reaction.

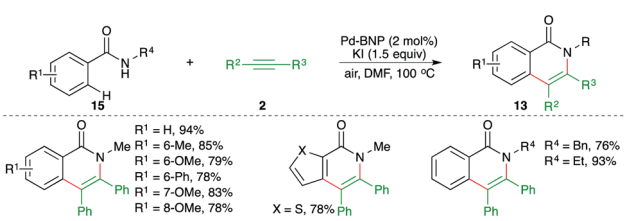
A binaphthyl-stabilized palladium nanoparticle (Pd-BNP)-catalyzed intermolecular carboamination of alkynes was reported by Sekar and co-workers for the facile synthesis of various isoquinolones in good yield. The Pd-BNP was easily recovered and could be reused four times without loss in activity. The reaction of amides **15** with alkynes **2** in the presence of 4 mol% Pd-BNP gave the corresponding isoquinolones **13** in good yield (Scheme 11).[22] Aromatic internal alkynes were found to be the suitable substrate for coupling rather than aliphatic alkynes.

A combined catalytic system consisting of palladium and ytterbium triflate catalyst for the carboamination reaction of 2-alkenyl anilines **18** with propargylic esters **19** was studied by Zeng and co-workers for the facile synthesis of benzo[*b*]azepine derivatives **20** (Scheme 12).[23] Although the reaction had an excellent scope, terminal alkynes could not form the desired benzo[*b*]azepines under the optimized conditions.

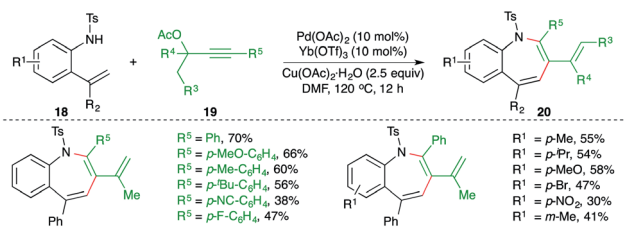
On similar lines, Li and co-workers have studied Rh-catalyzed carboamination reaction of alkynes **2** with 2-pyridienyl anilines **21** for the synthesis of pyridine-tethered indoles **22** (Scheme 13).[24] Here pyridine acted as the directing group. The method is limited to only symmetrical alkynes.

A Rh-catalyzed intermolecular carboamination of aryl imines with alkynes delivered the corresponding isoquinolines, as reported by Fagnou and co-workers. The reaction of imines **24** with alkynes **2** in the presence of 2.5 mol% $[Cp^*Rh(MeCN)_3][SbF_6]_2$ formed substituted isoquinolines **25** in good to excellent yield (Scheme 14).[25]

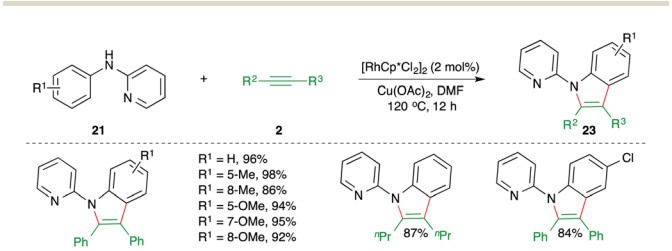
Similar to the previous reports, Chiba and co-workers reported a method describing the synthesis of isoquinolines to form corresponding oximes or isoxazoles (Scheme 15).[26] The method involved treatment of oximes or isoxazoles **27a,b** with alkynes **2** in the presence of 2.5 mol% $[Cp^*RhCl_2]_2$ to furnish isoquinolines **26a,b** in good yield. The reaction worked well for



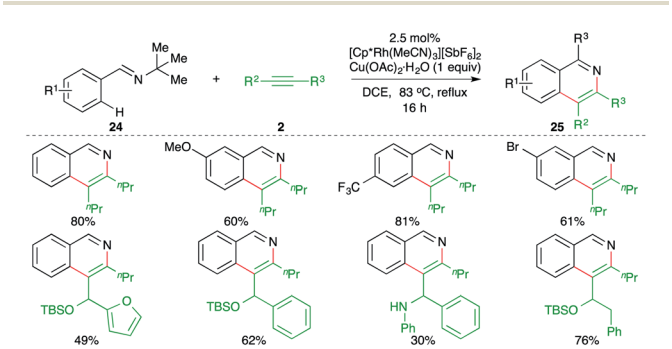
Scheme 11 Carboamination of alkynes with amides for the synthesis of isoquinolones.



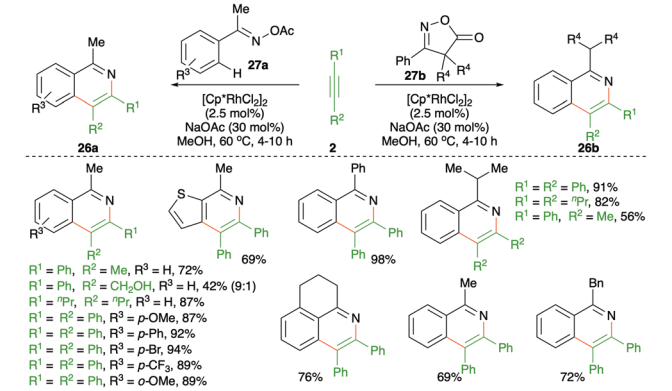
Scheme 12 Carboamination of alkynes with *o*-alkenyl anilines.



Scheme 13 Directing group-assisted carboamination of alkynes with anilines.



Scheme 14 Carboamination of alkynes with imines.



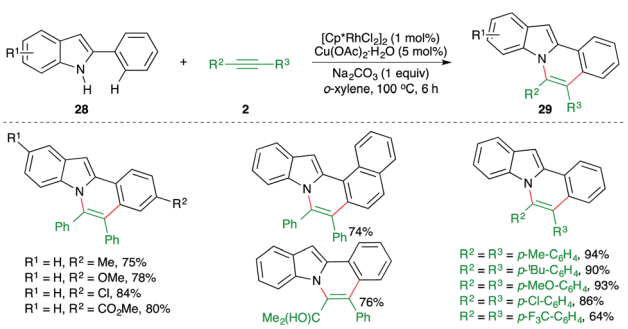
Scheme 15 Carboamination of alkynes with imines and oxazoles.

both aliphatic and aromatic alkynes. However, unsymmetrical alkynes produced a mixture of regio-isomeric products.

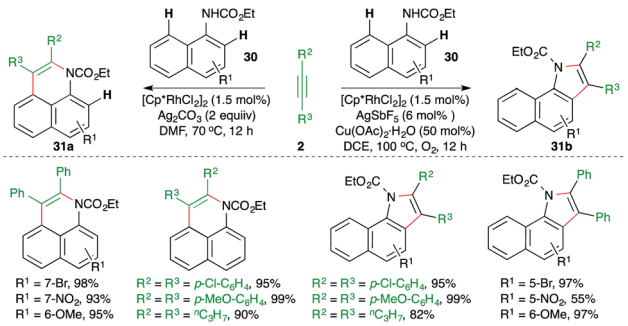
The intermolecular carboamination strategy has also been applied for the construction of highly promising *N*-fused indole motifs. The reaction of 2-arylindoles **28** with various alkynes **2** in the presence of 1 mol% $[Cp^*RhCl_2]_2$ and copper acetate as oxidant furnished the required *N*-fused indoles **29** in good yield (Scheme 16).[27]

A diverse Rh-catalyzed approach for the construction of benzoquinolines and benzoindoles from naphthyl carbamates through the engagement of a carboamination strategy was elaborated by Jin and co-workers (Scheme 17).[28] The method consisted of reaction of naphthyl carbamates **30** with alkynes **2** in the presence of a Rh-catalyst to generate different N-heterocycles **31a,b**. The formation of the different products was dictated by the additive. The use of copper additive made neutral rhodium into cationic rhodium, which governed the *ortho* C–H activation and led to the formation of benzoindoles **31b**. On the other hand, additives like silver accelerated the *peri* C–H activation to furnish benzoquinolines **31a**.

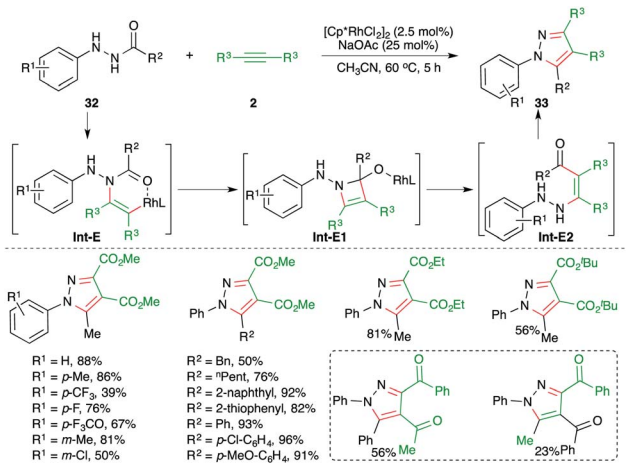
An Rh-catalyzed intermolecular carboamination–cyclization cascade was achieved by Liu and co-workers for the quick synthesis of pyrazole derivatives. The reaction of *N*-acyl hydrazines **32** with electron-deficient alkynes **2** in the presence of 2.5 mol% $[Cp^*RhCl_2]_2$ gave the corresponding pyrazole derivatives **33** in good yield (Scheme 18).[29] Various alkynes were used in the transformation to obtain the corresponding pyrazoles in good yield. However, alkynones gave a mixture of products and the minor one was formed *via* condensation with the keto group



Scheme 16 Carboamination of alkynes with 2-aryl indoles.



Scheme 17 Carboamination of alkynes with naphthyl carbamates.

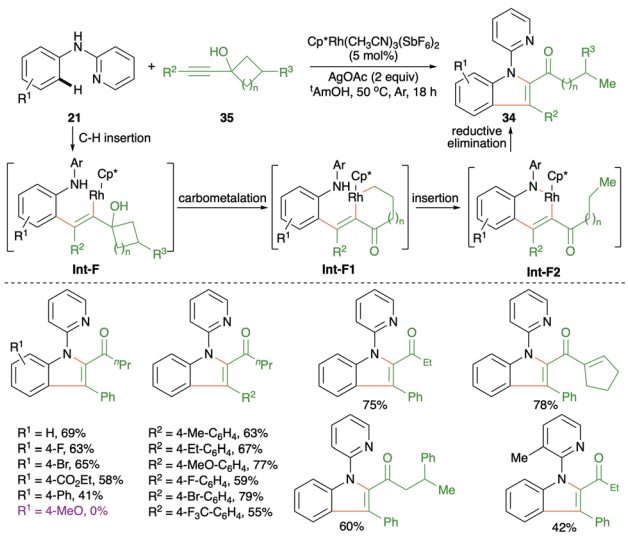


Scheme 18 Carboamination of alkynes with hydrazines.

of the alkynes. The reaction mechanism involved hydroamination of alkynes through Rh-activation of alkynes to generate rhodacycles **Int-E**, which upon subsequent intramolecular cyclization led to the formation of **Int-E1**. The **Int-E1** underwent C–N bond cleavage to give the carboamination adducts **Int-E2**. Finally, intramolecular condensation furnished the desired pyrazoles.

Carboamination of alkynes has emerged as a powerful tool for the synthesis of various enamines. Further, these types of cascades are being used frequently in the literature to synthesize heteroaromatic entities. In this direction, Zeng *et al.* have reported the synthesis of 2,3-disubstituted indoles **34** from internal alkynols **35** and directing group-tethered aniline derivatives **21** by using an Rh-catalyzed intermolecular carboamination strategy (Scheme 19).[30]

The cascade involved Rh-catalyzed addition at the *ortho* C–H bond in alkynes to generate rhodacycles **Int-F1**, which upon nucleophilic attack by nitrogen onto rhodium furnished **Int-F2**.



Scheme 19 Carboamination of alkynes with anilines.

Finally, reductive elimination of rhodium from **Int-F2** furnished 2,3-disubstituted indoles **34**. In general, it was observed that alkynols with electron-donating substituents on the aryl ring failed to give the desired indole derivatives.

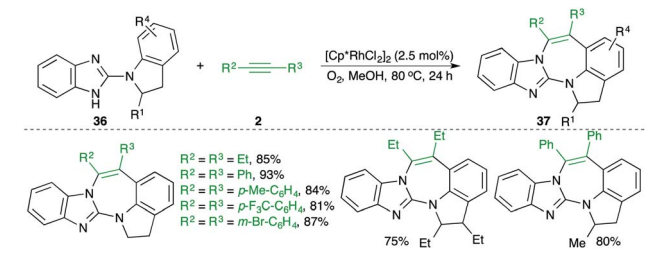
A Rh-catalyzed carboamination reaction of arylguanidines **36** and alkynes **2** for the quick synthesis of 1,3-benzodiazepines **37** was studied by Saá and co-workers (Scheme 20).[31] In general, it was observed that use of molecular oxygen as oxidant was accompanied by better yields in comparison with the traditional oxidants like silver. Both aromatic and aliphatic alkynes were used in the reaction.

A multicomponent approach using Ru-catalyzed intermolecular carboamination of alkynes was outlined by Cheng and co-workers for the expedient synthesis of isoquinolium salts. The method involved the reaction of aldehydes **38** with amines **39** and alkynes **2** in the presence of 2 mol% $[RuCl_2(p\text{-cymene})]_2$ and 10 mol% $AgBF_4$ to give the corresponding isoquinolium salts **40** in good yield (Scheme 21).[32] The reaction mechanism involves condensation of amines **38** with aldehydes **39** to generate imines **Int-G**, which upon subsequent C–H insertion, carbometalation to alkenes and reductive elimination furnish isoquinolium salts **40**.

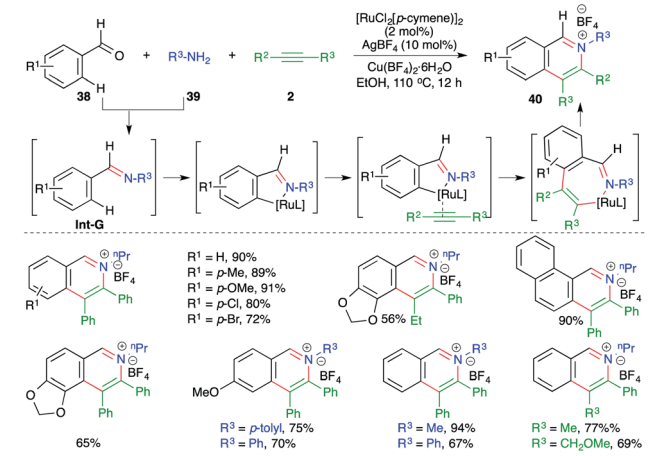
A directing group-free, Ru-catalyzed carboamination approach was demonstrated by Urriolabeitia and co-workers for the quick synthesis of isoquinolines. The reaction involved treatment of benzyl amine derivatives **41** with alkynes **2** in the presence of 10 mol% $[RuCl_2(p\text{-cymene})]_2$ and gave the corresponding isoquinolines **25** in good yield. Further, the method was also applied to the synthesis of benzoisoquinolines, thieno[3,2-*c*]pyridines, and fused heteroaryl[2,3-*c*]pyridines (Scheme 22).[33]

Ru-catalyzed carboamination reaction of 1*H*-pyrazole-tethered arenes was elaborated by Ackermann and co-workers for the facile synthesis of substituted 1*H*-pyrazole derivatives (Scheme 23).[34] The method involved treatment of arenes **42** with alkynes **2** in the presence of 5 mol% $[RuCl_2(p\text{-cymene})]_2$ to give the desired pyrazoles **43** in good yield. Intriguingly, in the case of unsymmetrical alkynes, the developed method exhibited excellent regioselectivity, leading to the exclusive formation of a single regio-isomer.

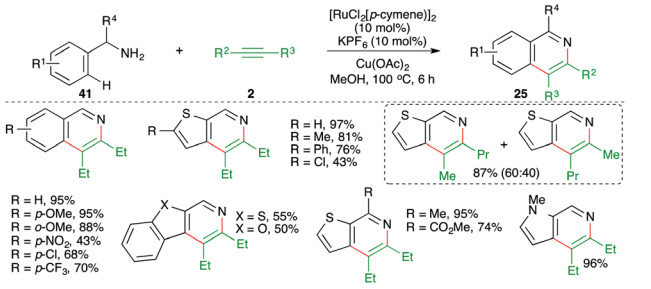
In addition to the above report, Ackermann and co-workers have also studied extensively this type of Ru-catalyzed intermolecular carboamination of various aryl amides with alkynes for the synthesis of an avenue of N-heterocycles. The aryl amides **44a** upon reaction with alkynes **2** in the presence of 5 mol% Ru-catalyst gave the corresponding isoquinolones **13a** in good yield. Various isoquinolones were synthesized successfully using both symmetrical as well as unsymmetrical alkynes. It is pertinent to mention that, in the case of unsymmetrical alkynes, excellent regioselectivity was observed, leading to the formation of a single regio-isomer. On similar lines, they have also reported synthesis of variously substituted indoles **13b** using the Ru-catalyzed intermolecular carboamination of alkynes **2** with directing-group-tethered anilines **13b** (Scheme 24). Further, they extended their strategy for the synthesis of isoquinolones **13a** and N-fused indoles **13c** from the corresponding hydroxamic acids **44c** and indole-tethered arenes **44d**.



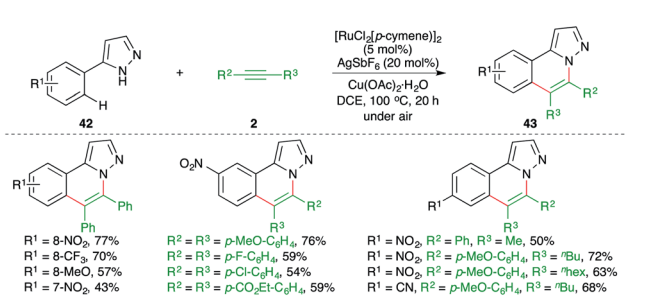
Scheme 20 Carboamination of alkynes with arylguanidines.



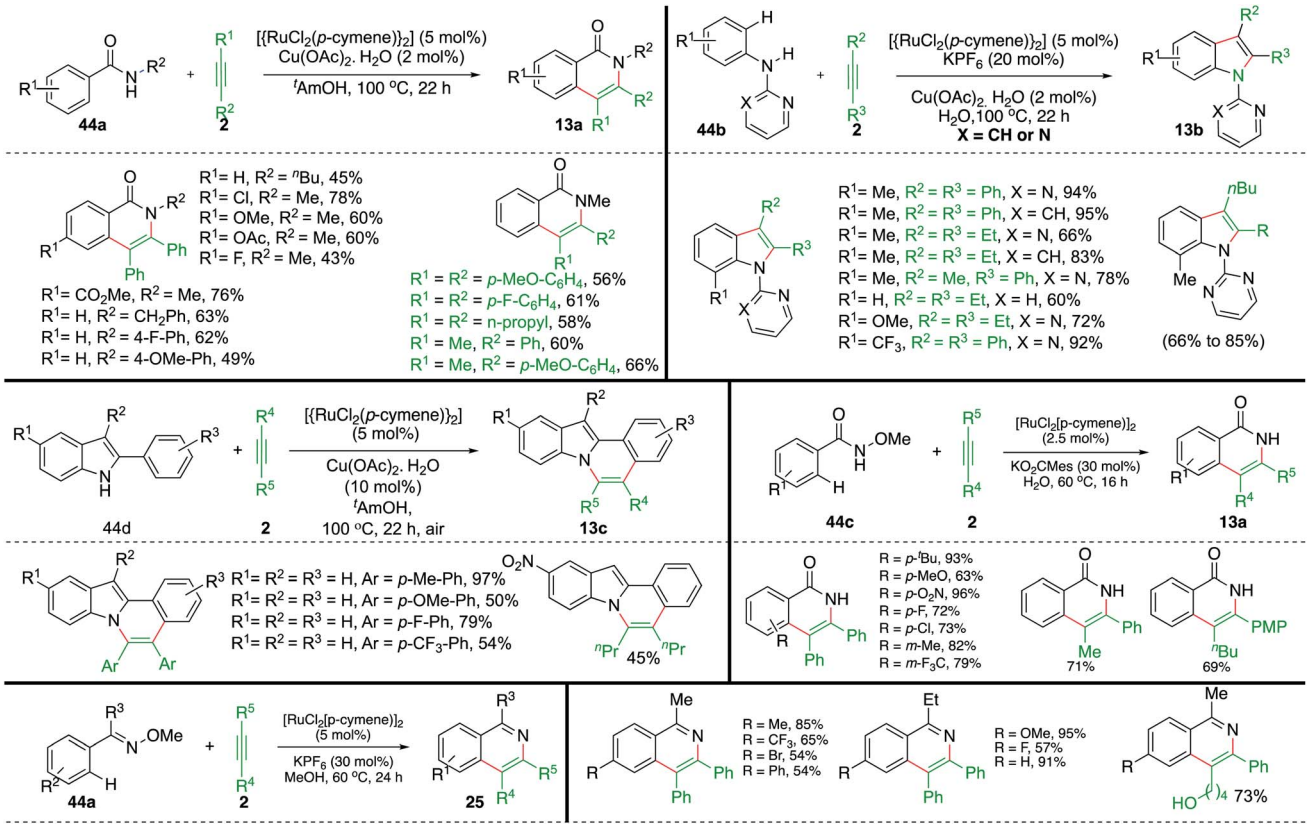
Scheme 21 A three-component carboamination approach.



Scheme 22 Carboamination of alkynes with benzyl amines.



Scheme 23 Carboamination of alkynes with pyrazole-tethered arenes.

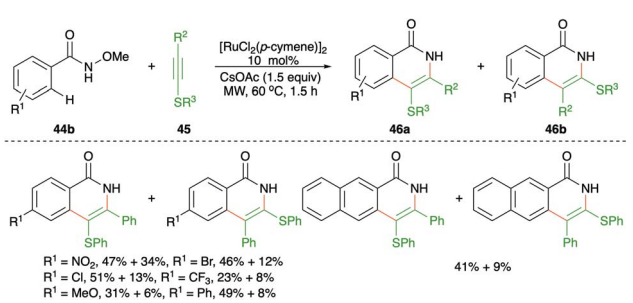


Scheme 24 Carboamination of alkynes with aryl oximes and aryl amides.

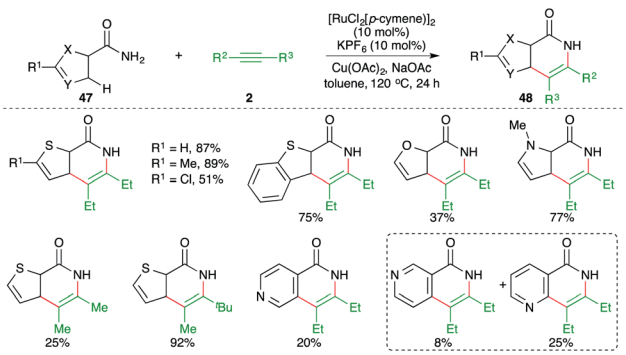
Variously substituted N-heterocycles were successfully synthesized in good yield and with excellent regioselectivity using both symmetrical as well as unsymmetrical alkynes. In this context, Ackermann's group and Jeganmohan *et al.* studied synthesis of isoquinolines **25** from corresponding oximes **44a** using Ru-catalysis.[35–39]

On similar lines, Yao and co-workers have used aryl/alkyl(phenylethynyl)sulfanes instead of simple alkynes for the synthesis of *S*-tethered isoquinolones. The approach involved the reaction of *N*-methoxy aryl amides **44b** with aryl/alkyl(phenylethynyl)sulfanes **45** in the presence of 10 mol% $[RuCl_2(p\text{-cymene})]_2$ to afford a mixture of *S*-tethered isoquinolones **46b** in good yield (Scheme 25).[40] Although this was the first report on the reaction of these types of alkynes, they were unable to produce exclusively a single regioisomer.

Reactions involving C–H activation of free amides are difficult as mostly the C–H activation requires directing group assistance for the C–H insertion of metal. However, methods describing directing group-free C–H activations have been documented in the literature. In this direction, Urriolabeitia and co-workers have reported a carboamination reaction of directing group-less heteroarene-tethered amides **47** with alkynes **2** in the presence of a Ru-catalyst to give the corresponding heteroarene-fused quinolones **48** in good yield (Scheme 26).[41] The reaction worked well for 5-membered



Scheme 25 Carboamination of alkynes with aryl oximes.



Scheme 26 Carboamination of alkynes with aryl amides.

heteroarene-fused (thiophene) amides, whereas in the case of 6-membered heteroarenes, poor yields of the corresponding quinolones were obtained. Further, in cases where there were two potential sites of C–H insertion, a mixture of products was obtained. Interestingly, in the case of unsymmetrical alkynes, only one product was obtained.

Regioselective C–H functionalization of chromene-3-carboxamides was described by Swamy and co-workers using a Ru-catalyzed intermolecular carboamination reaction (Scheme 27).[42] The method involved the reaction of chromene-3-carboxamides **49** with alkynes **2** in the presence of 5 mol% $[RuCl_2(p\text{-cymene})]_2$ to furnish pyridinones **50a** in good yield *via* the selective functionalization of the benzylic C–H bond. However, use of excess alkynes led to the formation of vinyl-substitute pyridinones **50b** through double C–H activation. Interestingly, in the case of unsymmetrical alkynes, *i.e.*, aliphatic–aromatic alkynes, a single regio-isomer was formed. In contrast, alkynes having different aryl substituents led to a mixture of regio-isomers.

Chatani and co-workers have reported a chelation-assisted strategy for the synthesis of quinolones by using Ni-catalyzed carboamination (Scheme 28).[43]

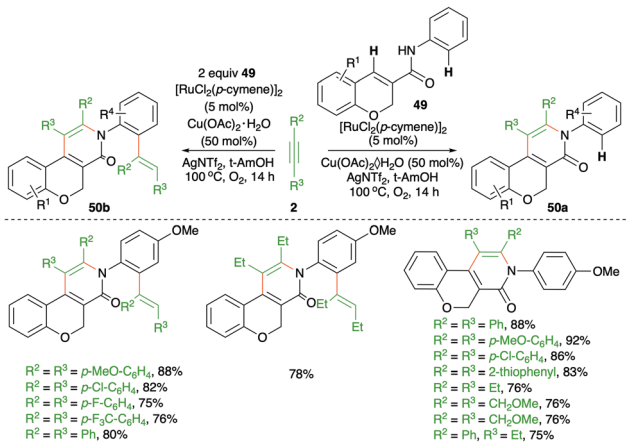
The method involved treatment of directing group *i.e.*, pyridine-tethered benzamides **44** with alkynes **2** in the presence of 5 mol% $Ni(cod)_2$ to form the corresponding isoquinolones **13** in good yield. The reaction has a very broad scope with excellent functional group tolerance. Further, both aliphatic as well as aromatic internal alkynes were used in the transformation. Intriguingly in the case of unsymmetrical alkynes, excellent regioselectivity was observed; the ratios are given in parentheses in Scheme 28.

Ni-catalyzed carboamination reaction involving tandem C–F and N–H bond activation was elaborated by Chatani and co-workers for the facile synthesis of isoquinolones (Scheme 29).[44] The reaction of *o*-fluoro aryl amides **51** with alkynes **2** in the presence of $Ni(cod)_2$ gave the corresponding isoquinolones **25** in good yield. Although the reaction had a very broad scope, it was limited to internal alkynes only. Further, in the case of unsymmetrical alkynes, a mixture of regio-isomers was obtained.

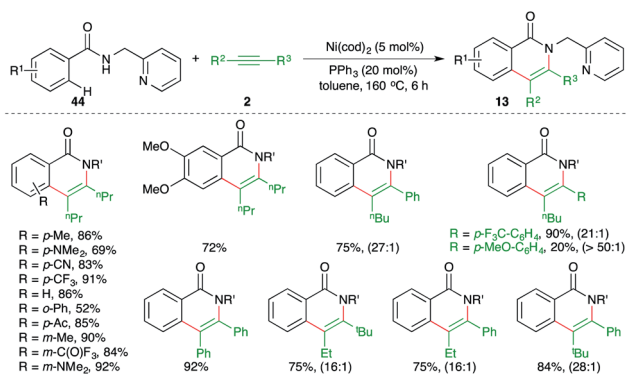
Jeganmohan *et al.* studied the feasibility of similar carboamination approaches with different metals and they found that other than Rh-metal, cobalt could drive the cascade. The reaction of *N*-aryl oximes **44b** with alkynes **2** in the presence of $[CoCp^*(CO)I_2]$ gave the corresponding isoquinolones **13** in good yield (Scheme 30).[45]

On similar lines, a Co-catalyzed directing group-assisted intermolecular carboamination of alkynes was studied by Daugulis and co-workers for the synthesis of isoquinolones (Scheme 31).[46] The reaction of 8-amino quinoline-tethered aryl amides **44b** with alkynes **2** in presence of 20 mol% $Co(OAc)_2$ gave the corresponding isoquinolones **13b** in good yield. Both internal, as well as terminal, alkynes were employed in the reaction to furnish the desired product in good yield.

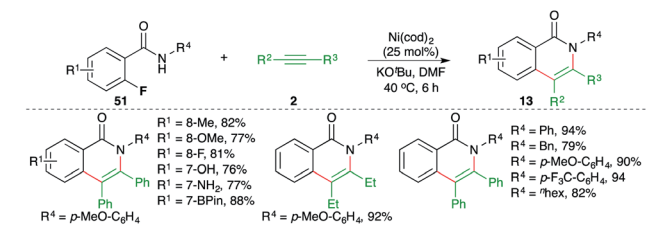
A cobalt-catalyzed directing group-assisted carboamination strategy was described by Yang and co-workers for the



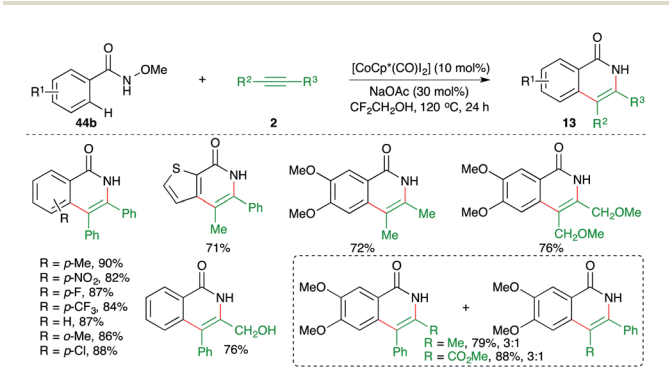
Scheme 27 Carboamination of alkynes with aryl amides.



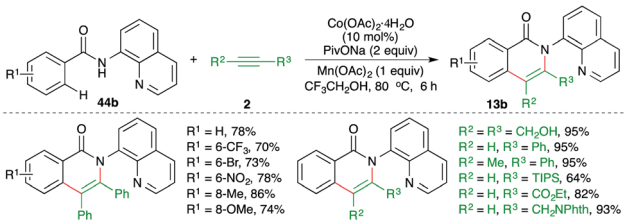
Scheme 28 Carboamination of alkynes with aryl amides.



Scheme 29 Carboamination of alkynes with *o*-fluoro aryl amides.



Scheme 30 Carboamination of alkynes with aryl amides.

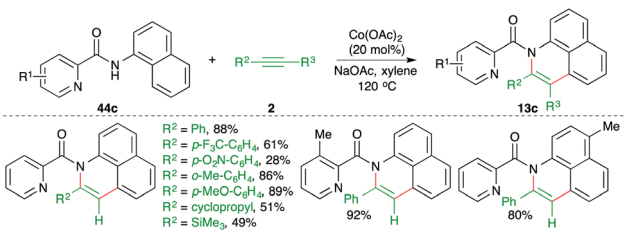


Scheme 31 Carboamination of alkynes with directing group-tethered aryl amides.

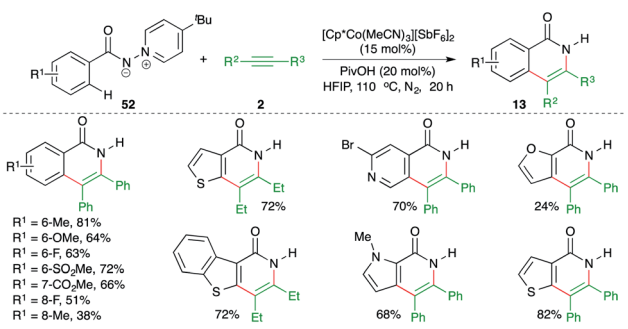
construction of benzoquinolines (Scheme 32).[47] The reaction of picolinamides **44c** with alkynes **2** in the presence of 20 mol% cobalt acetate delivered the corresponding benzoquinolines **13c** in good yield. Both internal alkynes and terminal alkynes were used in the transformation. Aryl alkynes with electron-withdrawing groups on the aryl ring gave a lesser yield.

Ylide, as a directing group for the assisted C–H activation is not so common in the literature despite the fact that it is of equal capability in comparison with the bidentate auxiliaries. In this context, Daugulis and co-workers have reported an *N*-iminopyridinium ylide-directed, cobalt-catalyzed carboamination reaction of aryl amides **52** with alkynes **2** for the synthesis of isoquinolones **13** in good yield (Scheme 33).[48] Interestingly, the directing group was removed in the same pot.

Fluoroalkylated alkynes have also been used in the carboamination process involving C–H activation. Konno and co-workers have studied a cobalt-catalyzed carboamination reaction of directing group-tethered aryl amides **44b** with fluoroalkylated alkynes **53** to give the corresponding isoquinolones



Scheme 32 Carboamination of alkynes with directing group-tethered aryl amides.

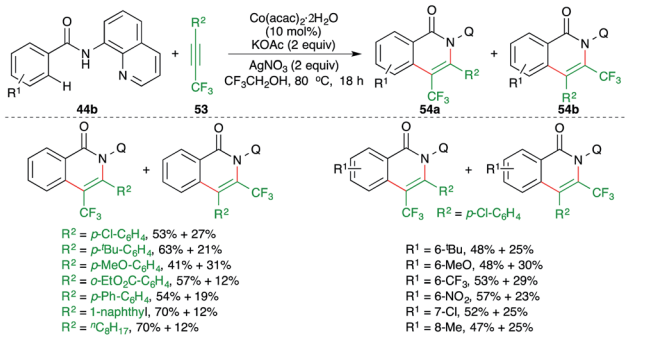


Scheme 33 Carboamination of alkynes with ylide-tethered aryl amides.

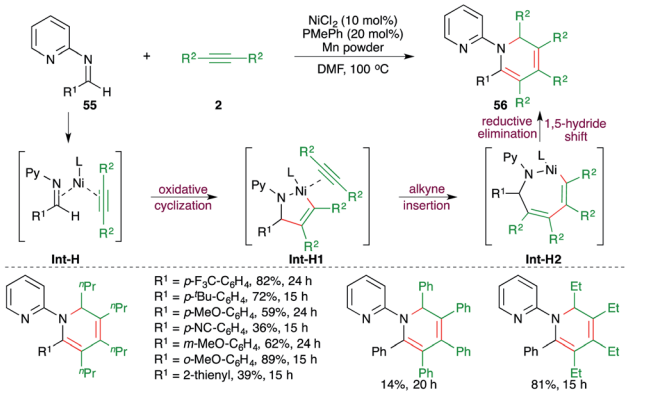
54a,b in good yield (Scheme 34).[49] Although the method gave rapid access to the fluorinated isoquinolones, a mixture of regio-isomers was obtained in all cases. Furthermore, the reaction only worked with 8-quinolinyl-masked amides.

2.1.3 Carboamination triggered by cycloaddition. Ni-catalyzed [2 + 2 + 2] cycloaddition or iterative carboamination of imines **55** with alkynes **2** has been reported by Yoshikai and co-workers for the facile synthesis of substituted dihydropyridiene derivatives **56** in good yield (Scheme 35).[50] In general, it was observed that aliphatic alkynes offered a better yield of the desired product in comparison with aromatic alkynes. The reaction mechanism involves oxidative cyclization to form **Int-H1**, which upon alkyne insertion leads to the formation of **Int-H2**. Finally, a reductive elimination–1,5-hydride shift cascade furnishes **56**.

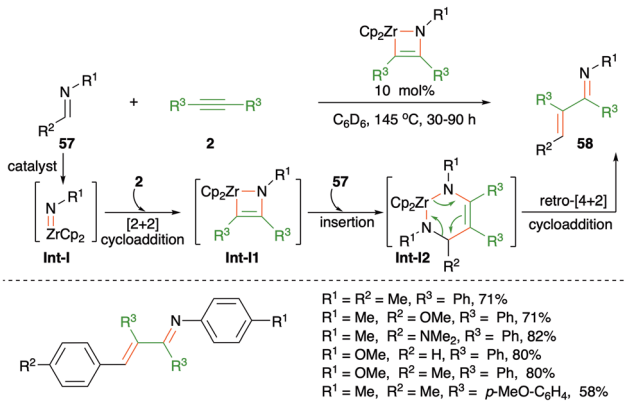
The use of imidozirconium complexes as catalyst has provided a vital solution to many organometallic problems such as hydroamination of alkynes or of allenes. In this direction, Bergmann and co-workers have reported imidozirconium complex-catalyzed carboamination of alkynes **2** with imines **57** for the generation of α,β-unsaturated imines, *i.e.* enimines, **58** in good yield (Scheme 36).[51] The formation of product can be explained through **Int-I-I2** *via* cascade [2 + 2] cycloaddition, insertion/carbozirconation, and retro [4 + 2] cycloaddition process, respectively.



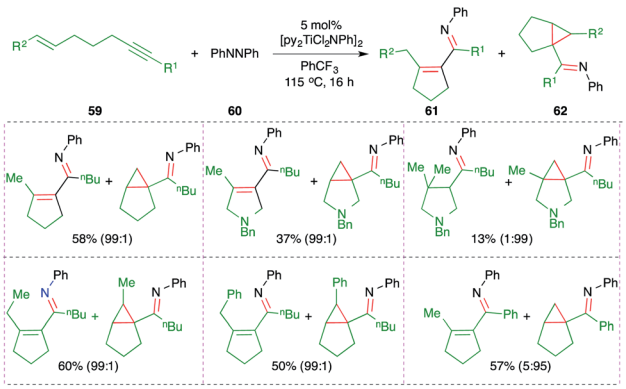
Scheme 34 Carboamination of fluoroalkylated-alkynes with directing group-tethered aryl amides.



Scheme 35 Ni-catalyzed carboamination of alkynes with imines for the synthesis of dihydropyridines.



Scheme 36 Synthesis of azadienes using the Zr-catalyzed carboamination of alkynes.



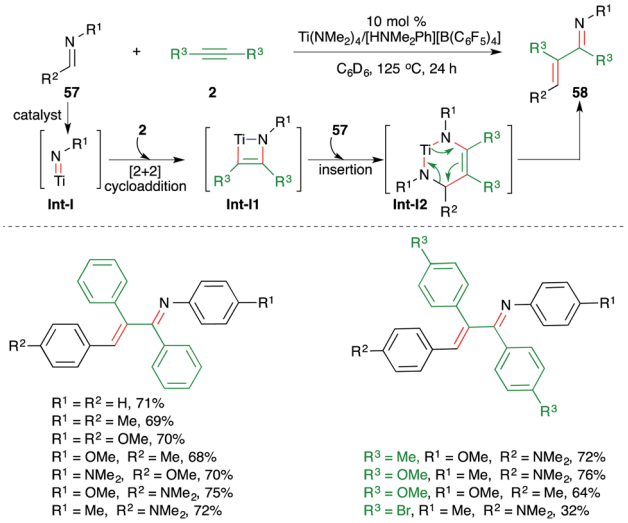
Scheme 38 Synthesis of cyclic azadienes using the Ti-catalyzed carboamination of alkynes.

On similar lines, a catalytic carboamination process of alkynes using a $Ti(NMe_2)_4/[HNMe_2Ph][B(C_6F_5)_4]$ combined catalytic system was studied by Mindiola and co-workers for the facile synthesis of enimines **58** from corresponding alkynes **2** and imines **57** (Scheme 37).[52] Although the reaction gave direct access to various enimines, it was limited to symmetrical alkynes, aromatic alkynes, and imines from aromatic aldehydes.

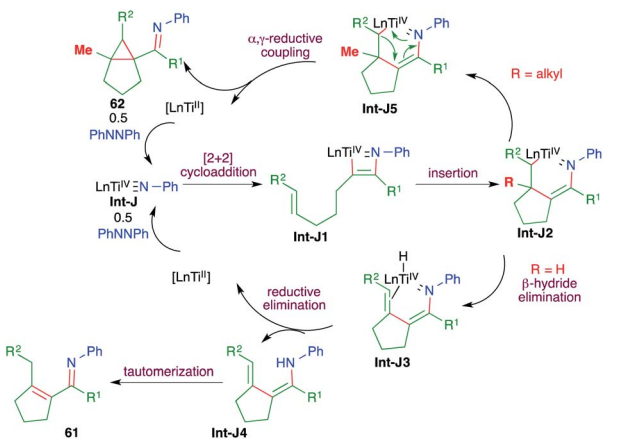
A titanium-catalyzed intermolecular carboamination reaction of alkynes **59** with hydrazines **60** for the synthesis of enimines **61** or imine-tethered cyclopropanes **62** was studied by Tonks and co-workers (Scheme 38).[53] Treatment of alkene-tethered alkynes with diazine in the presence of 5 mol% $[py_2TiCl_2NPh]_2$ gave the corresponding enamine- or imine-tethered cyclopropanes in good yield.

The reaction mechanism involves the initial formation of **Int-J** by the combination of hydrazine **60** and $[py_2TiCl_2NPh]_2$. The **Int-J** upon [2 + 2] cycloaddition reaction with alkynes **59** generates **Int-J1**. The **Int-J1** gives a Ti-incorporated 6-membered cyclic transition state **Int-J2** *via* intramolecular insertion. Interestingly, if R = H in **Int-J2**, then β-hydride elimination takes place to give **Int-J3**. Finally, reductive elimination of titanium from **Int-J3** gives enamines **Int-J4**, which upon subsequent tautomerization lead to the formation of enimines **61**. On the other hand, if R = alkyl in **Int-J2**, then instead of β-hydride elimination α,γ-reductive coupling takes place to give cyclopropane **62** *via* **Int-J5** (Scheme 39).

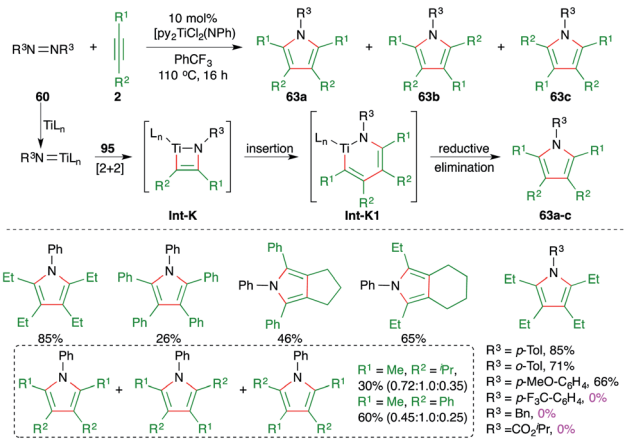
Furthermore, Tonks and co-workers have also developed a novel three-component oxidative C–N bond formation reaction with titanium catalyst. The reaction involved [2 + 2 + 1] cyclization reaction of various alkynes **2** and diazenes **60** to furnish the respective polysubstituted pyrroles **63a–c** in good yield (Scheme 40).[54] The reaction was proposed to proceed *via* a Ti(II)/Ti(IV) redox cycle where an azatitanacyclobutene intermediate **Int-K** is formed from the [2 + 2] addition of one equivalent of alkynes and titanium imido complex $(py)_3TiCl_2(NR)$. Another equivalent of alkynes undergoes insertion into the **Int-K**, forming an azatitanacyclohexadiene **Int-K1**, followed by reductive elimination to give the pyrroles **63a–c**. In general, the reaction worked well with less hindered alkynes. Further, in the case of unsymmetrical alkynes, a mixture of regio-isomers was obtained. It was also observed that aryl diazines with electron-withdrawing substituents could not deliver the required product.



Scheme 37 Synthesis of azadienes using the Ti-catalyzed carboamination of alkynes.



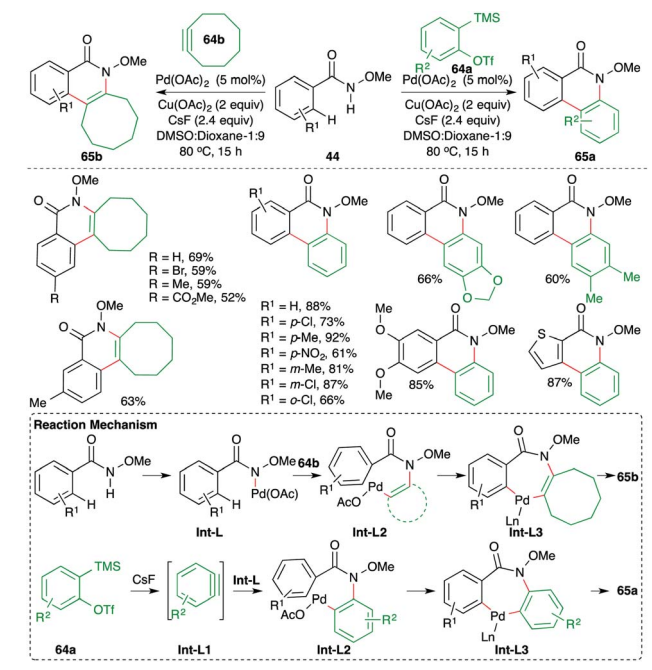
Scheme 39 Reaction mechanism for obtaining **61** and **62**.



Scheme 40 Synthesis of pyrroles using the Ti-catalyzed carboamination of alkynes.

2.1.4 Carboamination of benzynes. Benzynes are very synthetically useful intermediates and in a true sense, they have shown the capacity of difunctionalization of carbon–carbon multiple bonds. Although they are very unstable, their *in situ* generation and cascade reactivity have provided a new route to a suite of really interesting building blocks. In this domain, carboamination of benzyne has also been reported.

A Pd-catalyzed intermolecular carboamination of arynes strategy was developed by Xu and co-workers for rapid access to highly functionalized N-heterocycles (Scheme 41).[55] The method involved the reaction of aryl-tethered *N*-methoxy amides **44** with 2-(trimethylsilyl)aryl triflates **64a** and strained alkynes **64b** in the presence of 5 mol% $Pd(OAc)_2$ to give the corresponding N-heterocycles **65a,b**, respectively, in good yield. Both electron-rich and electron-poor amides participated equally in the reaction, leading to the formation of the desired N-heterocycles. The reaction proceeds through the formation of **Int-L** *via* N–H insertion, which on amino-palladation with alkynes **64b** or benzynes **Int-L1** (generated *in situ* from **64a**) gives **Int-L2**. **Int-L2** upon C–H activation generates palladacycles **Int-L3**. Finally, reductive elimination of palladium from **Int-L3** leads to the formation of **65a,b**.



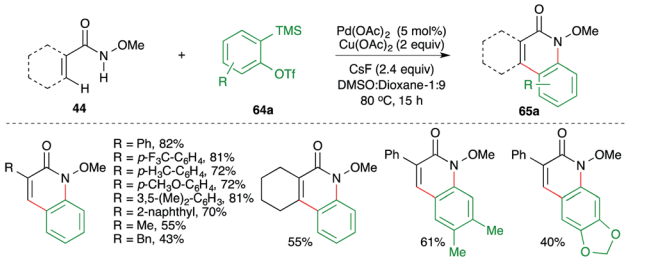
Scheme 41 Carboamination of benzynes with amides.

On similar lines, Tonks and co-workers have also reported such a cascade for the synthesis of isoquinolones starting from a comparatively difficult precursor for C–H activation, *i.e.* non-tethered *N*-methoxy amides (Scheme 42).[56]

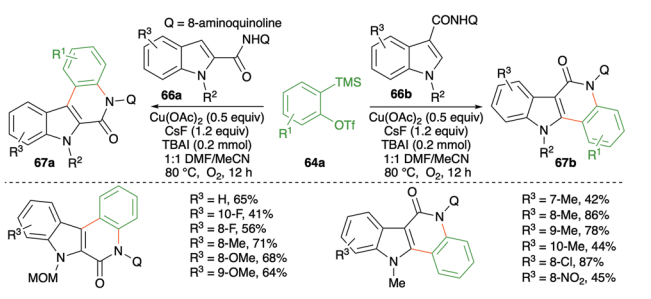
The method involved treatment of *N*-methoxy amides **44** with 2-(trimethylsilyl)aryl triflates **64a** in the presence of CsF and $Pd(OAc)_2$ to give isoquinolones **65a**. The method has a very good scope along with good functional group tolerance.

Similarly, instead of aryl amides, the reactivity of indole-tethered amides in this direction was explored by Zhang and co-workers. Reaction of indolyl amides **66a,b** with aryne precursor **64a** in the presence of $Cu(OAc)_2$ (0.5 equiv.), CsF (0.24 mmol), and TBAI (0.2 mmol) furnished the corresponding indolo[3,2-*c*]quinolones **67a** and indolo[2,3-*c*]quinolones **67b**, respectively (Scheme 43).[57] In general, it was observed that *N*-alkyl indoles, *N*-MOM, were suitable partners for coupling, whereas *N*-Cbz-protected indoles failed to give the desired product. Further, the yield was found to be dependent more upon steric factors than electronic factors as 5-substituted indoles gave a lower yield of the requisite adducts.

A copper-catalyzed carboamination of *in situ*-generated benzyne was studied by Xiao and co-workers for the facile synthesis of substituted aniline and *o*-benzoxazolyl aniline derivatives (Scheme 44).[58]



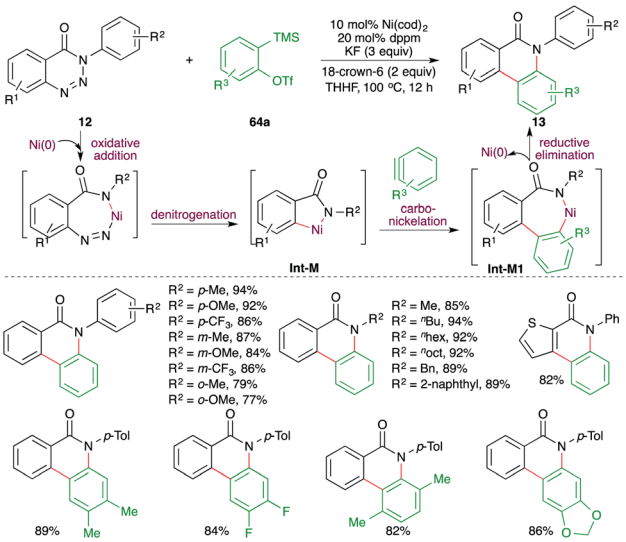
Scheme 42 Synthesis of *N*-methoxy isoquinolones using the carboamination of benzynes.



Scheme 43 Synthesis of indole-fused isoquinolones using the carboamination of benzynes.

The reaction of various 2-(trimethylsilyl)phenyl trifluoromethanesulfonates **64a** with terminal alkynes **2a** and *o*-benzoylhydroxylamines **68** in the presence of 5 mol% CuI and KF resulted in the formation of *o*-alkynyl anilines **69a** in good yield. The reaction exhibited excellent functional group tolerance and variously substituted anilines were prepared. Aromatic and aliphatic alkynes participated equally well to form the corresponding *o*-alkynyl anilines in good yield. Further, the method was successfully extended towards the replacement of terminal alkynes **2a** with benzoxazoles **70** for the synthesis of the corresponding *o*-benzoxazolyl aniline derivatives **69b**. However, in this case the reaction conditions had to be adjusted to get the desired products: 20 mol% of Brettphos was used as additive and $TBABF_4$ was used instead of KF. The reaction mechanism involved the initial formation of benzyne followed by carboamination reaction.

A Ni-catalyzed denitrogenative cascade annulation method for the synthesis of phenanthridinone scaffolds was demonstrated by Cheng and co-workers (Scheme 45).[59] The report involved treatment of benzotriazin-4-(3*H*)-ones **12** with 2-(trimethylsilyl)aryl triflates **64a** in the presence of 10 mol% $Ni(cod)_2$, 20 mol% dppm, and 3 equiv. of KF as the fluoride source to generate the corresponding phenanthridinone scaffolds **13** in good yield. The reaction involves fluoride-promoted formation of benzynes, which upon carbo-nickelation reaction with **Int-M** furnish nickelacycles **Int-M1**. The **Int-M1** follows a reductive elimination path to give **13**. The reaction has a very broad substrate scope indeed.

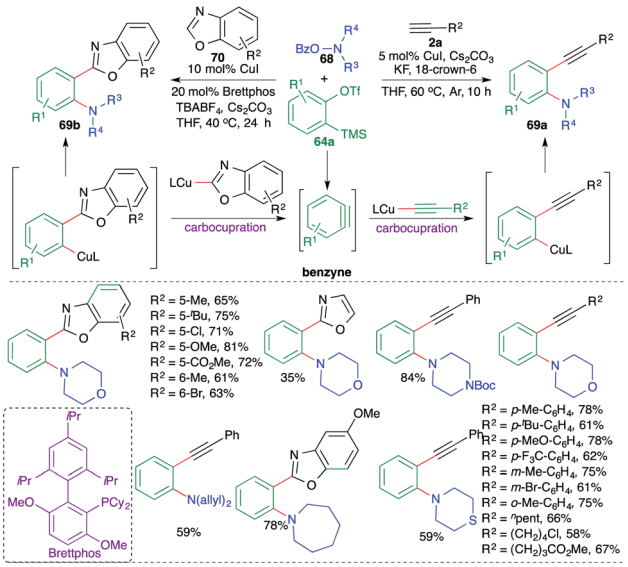


Scheme 45 Denitrogenative carboamination cascade of benzynes.

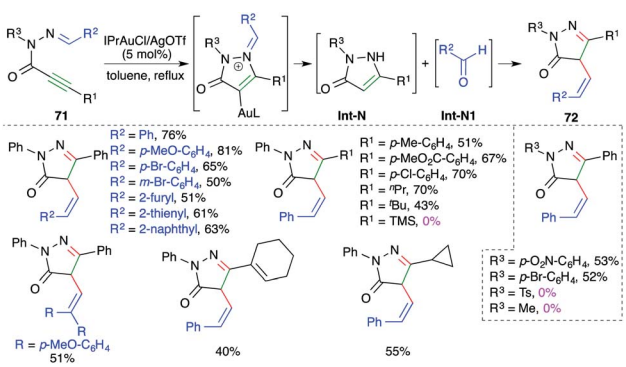
3. Intramolecular carboamination

N-Propioloyl hydrazones were found to be suitable precursors for the intramolecular carboamination of alkynes, as described by Zhan and co-workers, for the quick synthesis of 4-arylidene pyrazolones. The reaction of alkynones **71** with 5 mol% IPrAuCl and AgOTf delivered the corresponding cyclic derivatives **72** in good yield *via* tandem amination and [1,3]-shift (Scheme 46).[60] The reaction worked well with aliphatic as well as aromatic alkynes, except TMS-alkynes. Further, in general it was observed that tosyl/aliphatic amides (R^3 = TMS, alkyl) did not furnish the required products. The formation of the product is explained as follows. Gold catalyzes the intramolecular amination followed by hydrolysis to give enamines **Int-N** and aldehydes **Int-N1**. Finally, **Int-N** and **Int-N1** condense together to give **72**.

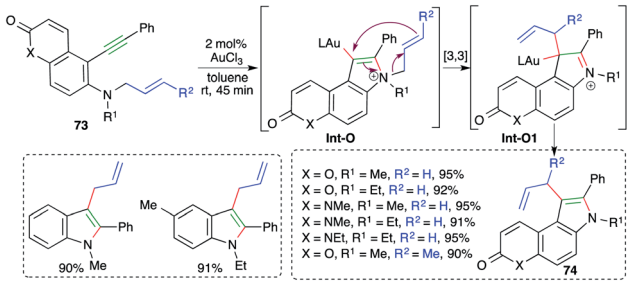
On similar lines, a gold-catalyzed intramolecular carboamination of alkynes was designed by Majumdar and co-workers for the synthesis of functionalized indoles **73** from corresponding *o*-alkynyl-*N*-allyl anilines **74** (Scheme 47).[61] Interestingly, it was also applied for the synthesis of indoles. However, the reaction had a limited scope for alkynes. The proposed reaction mechanism involves gold-catalyzed intramolecular amination to give iminium ions **Int-O**, which upon further [3,3]-sigmatropic shift give **Int-O1**. Finally, deauration furnishes **74**.



Scheme 44 Synthesis of *o*-alkynyl anilines using the carboamination of benzynes.



Scheme 46 Synthesis of pyrazolidin-3-ones using intramolecular carboamination.



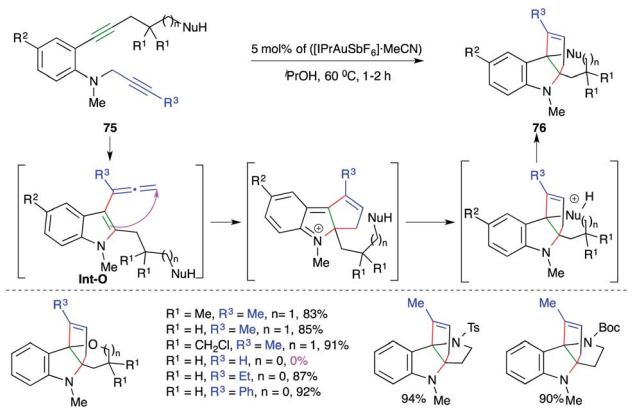
Scheme 47 Synthesis of 3-allylated indoles using intramolecular carboamination.

A gold-catalyzed carboamination cascade was elaborated by Ohno and co-workers for the synthesis of complex N-heterocycles.

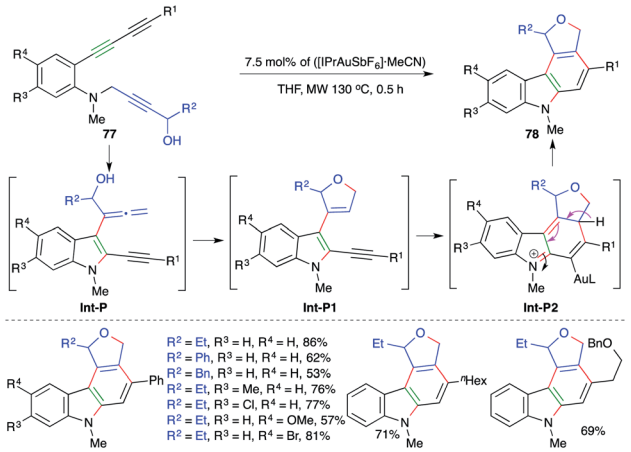
The cascade involved the reaction of *N*-propargyl *o*-alkynyl anilines **75** with 5 mol% ([IPrAuSbF$_6$]·MeCN) to give the corresponding N-heterocycles **76** in excellent yield (Scheme 48).[62] The carboamination cascade involved intramolecular carboamination to generate allene **Int-O** (as labelled in Scheme 48), which upon subsequent intramolecular cyclization afforded the desired adducts. The reaction had a broad scope. However, in the case of terminal alkynes, the reaction did not work.

Similar to the above report, Ohno and co-workers have also extended their strategy to a differently designed substrate **77** for the expedient synthesis of cyclic ether/amine-fused carbazoles **78** (Scheme 49).[63] Various carbazoles were synthesized in good yield. Both internal and terminal alkynes (R^1 = aryl/alkyl) were employed in the reaction. However, the corresponding terminal alkynes were not used in the transformation. The formation of the product occurs through initial amination and [3,3]-shift to give allenes **Int-P**. The **Int-P** upon 5-*endo-trig* cyclization gives **Int-P1**. Finally, 6-π electrocyclic ring closure of **Int-P1** gives **Int-P2**, which after aromatization affords **78**.

Carbazoles find themselves in a much specially focused area of organic synthesis as a result of their intriguing electrical, optical, and pharmacological properties, and as a result several strategies involving decorative synthesis upon indole have been



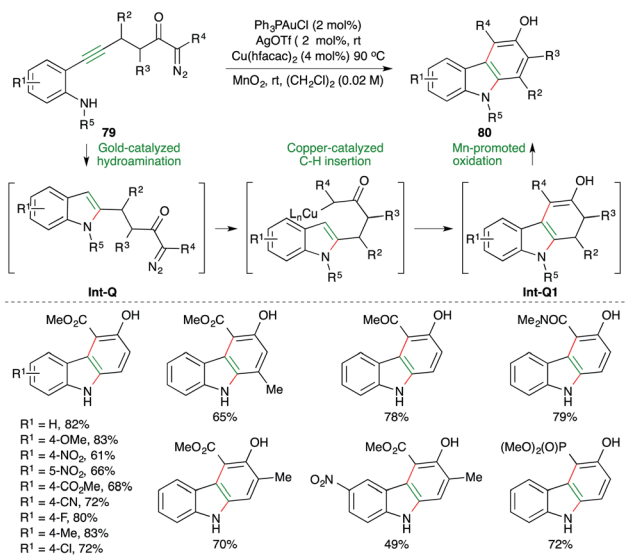
Scheme 48 A carboamination–Friedel-Crafts alkylation–intramolecular cyclization cascade.



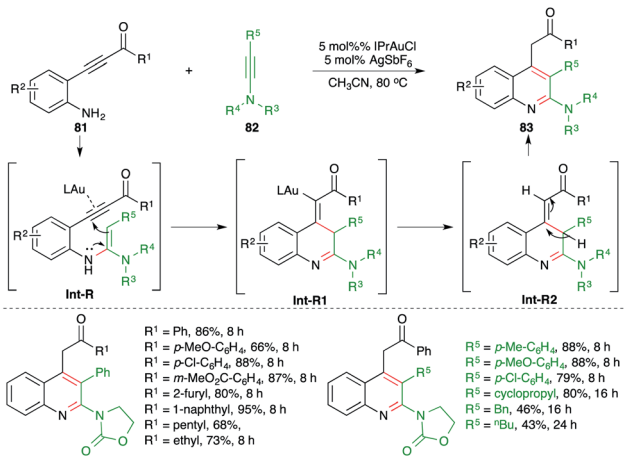
Scheme 49 A carboamination–hydroalkoxylation–intramolecular cyclization cascade.

reported. A gold-catalyzed carboamination reaction of alkynes for the synthesis of carbazoles has been reported by Park and co-workers. The reaction of diazo-tethered *o*-alkynyl anilines **79** with 2 mol% Ph$_3$PAuCl and 2 mol% AgOTf, along with 4 mol% Cu(hfacac)$_2$, furnished corresponding carbazoles **80** in good to excellent yield (Scheme 50).[64] The reaction involves initial gold-catalyzed hydroamination reaction to form **Int-Q**, which upon subsequent copper-catalyzed C–H insertion gives **Int-Q1**. The **Int-Q1** upon Mn-promoted oxidation leads to the formation of the desired carbazoles **80**.

A gold-catalyzed carboamination cascade was studied by Arcadi and co-workers for the synthesis of 2-amino quinoline derivatives (Scheme 51).[65] The reaction of *o*-alkynyl anilines **81** with ynamides **82** in the presence of 5 mol% IPrAuCl gave the corresponding 2-amino quinolines **83** in good yield. The reaction exhibited excellent scope and functional group compatibility. A range of ynamides were used in the reaction. The



Scheme 50 Hydroamination–C–H insertion cascade.

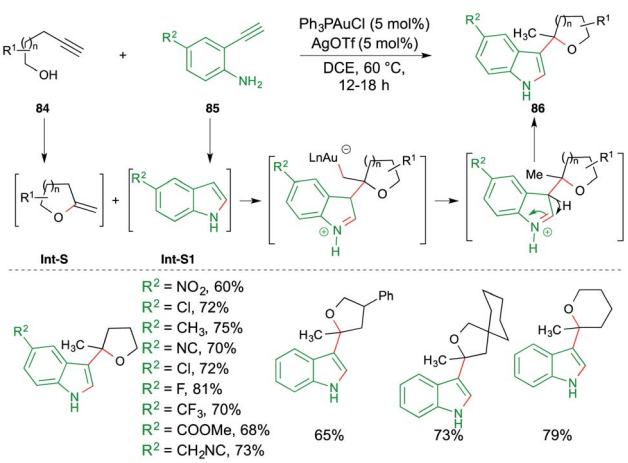


Scheme 51 Synthesis of 2-amino quinolines using the carboamination of ynamides.

formation of the product can be explained as follows. Au-catalyzed intermolecular hydroamination furnishes enamines **Int-R**, which upon a subsequent intramolecular 5-*exo-dig* cyclization–protonation sequence afford **Int-R2** *via* **Int-R1**. Finally, proto-deauration of **Int-R2** leads to the formation of 2-aminoquinolines.

A carboamination reaction of terminal alkynols **84** and *o*-alkynyl anilines **85** was reported by Patil *et al.* for the rapid synthesis of variously C-3-substituted indoles **86.** The reaction involved treatment of **84** with **85** in the presence of Ph_3PAuCl (5 mol%) and AgOTf (5 mol%). The proposed mechanism consists of a tandem hydroalkoxylation–hydroamination–Friedel-Crafts alkylation cascade. Alkynols **84** and anilines **85** upon 5/6-*exo-dig* hydroalkoxylation and 5-*endo-dig* hydroamination give exocyclic enol ethers **Int-S** and indoles **Int-S1**, respectively. The indoles **Int-S1** upon further Friedel–Crafts alkylation with **Int-S** furnish the required substituted indoles **86** in good yield (Scheme 52).[66]

A Pt-catalyzed intramolecular carboamination reaction was reported by Yamamoto and co-workers for the facile synthesis of

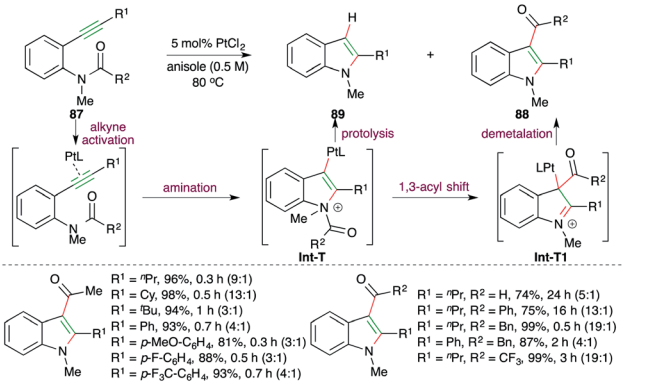


Scheme 52 Hydroalkoxylation–carboamination cascade.

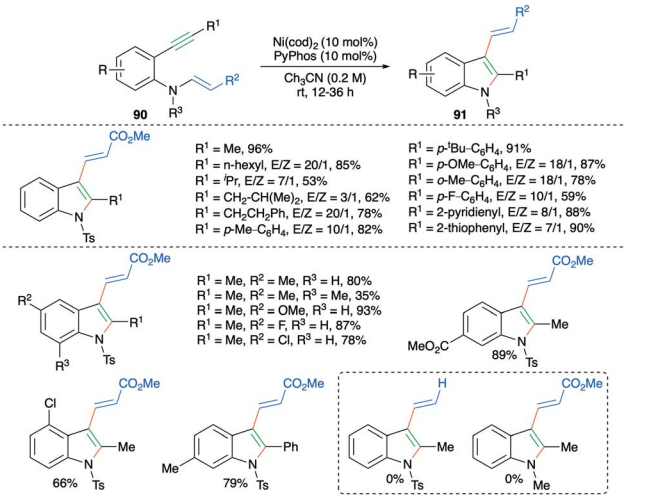
indoles (Scheme 53).[67] Reaction of *o*-alkynyl amides **87** with 1.5 mol% $PtCl_2$ delivered the required 3-acyl indoles **88** as the major product along with indoles **89** as the minor product. The protocol involves Pt-catalyzed intramolecular amination of alkyne to generate Pt-tethered iminium ion **Int-T**, which upon subsequent 1,3-acyl migration affords **Int-T1**. Finally, proteolysis of **Int-T1** furnishes the required indoles.

Nickel-catalyzed *trans*-carboamination of internal alkynes was studied by Cho and co-workers for the facile synthesis of highly substituted indole motifs (Scheme 54).[68] Reaction of various 2-alkynyl anilino acrylates **90** with 10 mol% each of $Ni(cod)_2$ and PyPhos furnished the required indoles **91.** Various indole derivatives were synthesized with good to excellent yield. It was observed that aromatic enamines (R^2 = Ph) afforded the corresponding indoles in better yield and with better diastereoselectivity in comparison with aliphatic enamines (R^2 = Ph).

The reaction mechanism involves oxidative cyclization of 90 to give nickelacycles **Int-U**, which upon C–N bond cleavage afford **Int-U1**. The **Int-U1** upon charge redistribution leads to the formation of **Int-U2. Int-U2** upon N–Ni bond formation gives



Scheme 53 Carboamination accompanied by acyl migration.



Scheme 54 Synthesis of 3-allyl indoles using intramolecular carboamination.

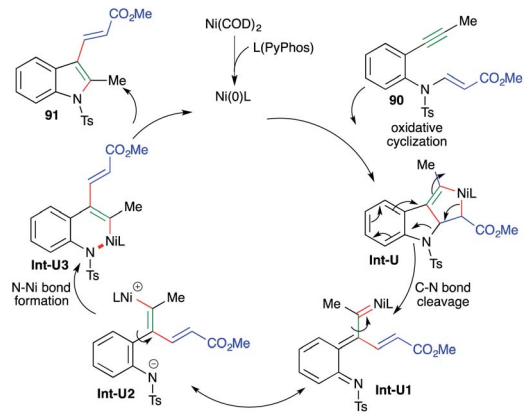
Int-U3. Finally, reductive elimination of nickel furnishes the desired indole derivatives **91** (Scheme 55).

Werz *et al.* reported an elegant cascade consisting of intramolecular *anti*-carbopalladation–amination, *i.e.* carboamination for the diastereoselective synthesis of tetrasubstituted enamines and pyrroles (Scheme 56).[69] They chose propargyl amine-tethered bromobenzenes 92 as suitable precursors, which upon treatment with $PdCl_2(PhCN)_2$ (5 mol%), [$^tBu_3PH$][BF_4] (10 mol%) and 5 equivalents of K_3PO_4 as the base, afforded tetrasubstituted amines **93** as the sole product in excellent yield. On the other hand, the use of 5 mol% $Pd(dba)_2$ and 5 equivalents of Et_3N as the base delivered pyrroles 94 as the sole product. Although various aliphatic alkynes and terminal alkynes were tried in the reaction to synthesize enamines/pyrroles, it was limited to aryl alkynes.

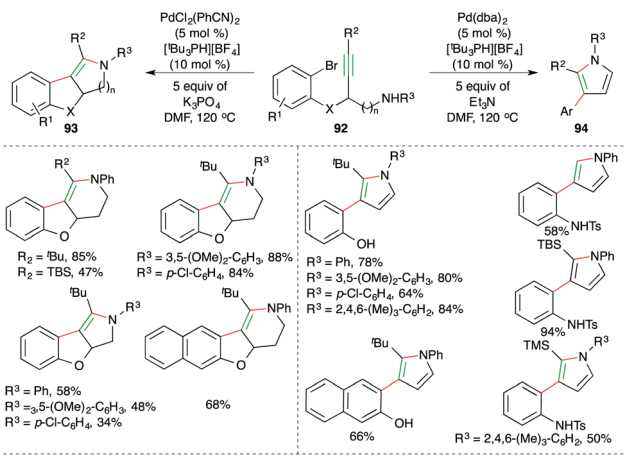
The reaction mechanism can be explained in two ways as follows.

In both pathways the initial step is oxidative addition of palladium to aryl bromide to give **Int-V**. After oxidative addition, in pathway-I, metal activates the alkynes and triggers the hydroamination step to form **Int-V1**, which upon subsequent reductive elimination furnishes enamines **93**. The enamines upon elimination of phenol give pyrroles **94**. In pathway-II, *syn*-carbopalladation occurs after the oxidative addition to give palladacycles **Int-V2**. The palladacycles then rotate to give *anti*-carbopalladation adducts **Int-V3**. The **Int-V3** then undergo a second oxidative addition to furnish **Int-V4**, which upon reductive elimination give enamines 93 (Scheme 57).

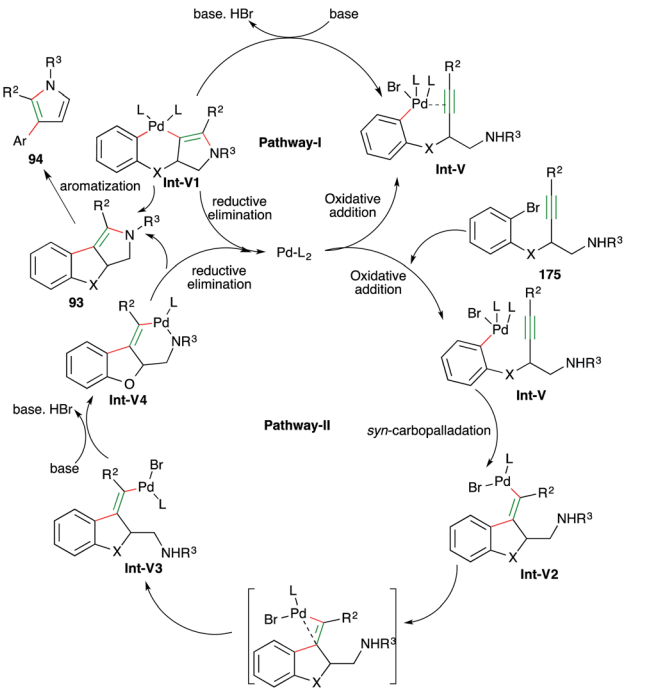
A Pd-catalyzed carboamination cascade was described by Wu and co-workers for the facile synthesis of cyclic amine-fused-2-amino quinoline motifs (Scheme 58).[70] The reaction of *o*-alkynyl anilines **95** with isocyanates **96** in the presence of 10 mol% $Pd(PPh_3)_4$ gave corresponding cyclic amine-fused-2-amino quinoline motifs **97** in good yield. The reaction mechanism involves initial *trans*-aminopalladation of **95** to generate enamines **Int-W**, which upon migratory insertion give **Int-W1**.



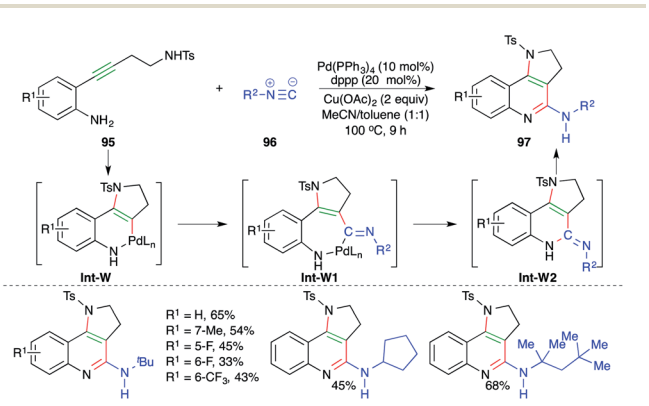
Scheme 55 Reaction mechanism for the generation of 91.



Scheme 56 Pd-catalyzed *trans*-carboamination.



Scheme 57 Reaction mechanism for obtaining 93 and 94.



Scheme 58 Synthesis of cyclic amine-fused quinolines using a carboamination approach.

Finally, **Int-W1** upon reductive metalation and isomerization furnishes **97** *via* **Int-W2**.

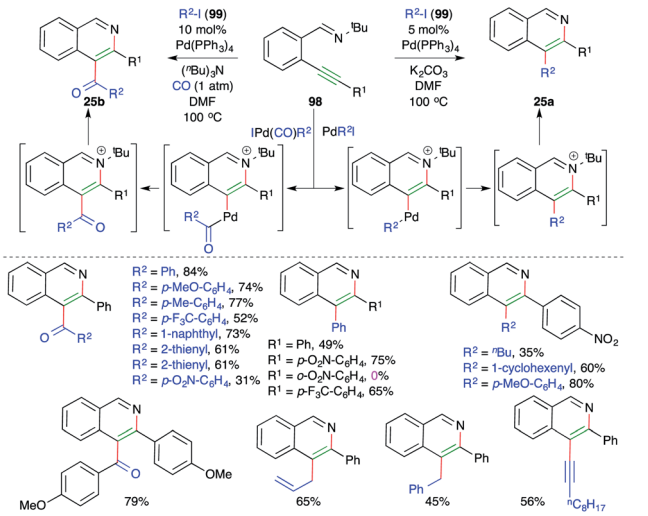
Activation of alkynes by alkylated/arylated/vinylated–Pd complex has emerged as an invincible technique for the concomitant construction of C–C and C–N/O/S bonds. In this context, Larock and co-workers have reported intermolecular carboamination for the synthesis of 3-arylated and 3-acylated isoquinolines. The reaction of alkyne-tethered imines **98** with aryl/vinyl/allyl/alkynyl iodides **99** in the presence of 5 mol% $Pd(PPh_3)_4$ gave the corresponding 3-substituted isoquinolines **25a**. On other hand, when CO was added to the reaction medium, the corresponding 3-acylated isoquinolines **25b** were obtained (Scheme 59).[71,72]

Similarly, a Pd-catalyzed intermolecular carboamination cascade involving intramolecular amination of alkylated Pd-complex-activated alkynes was studied by Yao and co-workers for the quick assembly of 2,3-dialkylated isoquinolines. The reaction of *O*-allylated iodo phenols **100** with *o*-alkynyl aryl imines **101** in the presence of 5 mol% $Pd(PPh_3)_4$ gave the corresponding isoquinolines **102** in good yield (Scheme 60).[73] The reaction has a very broad scope. Only internal alkynes were used; aryl alkynes gave better yields in comparison with aliphatic alkynes. The formation of the product can be explained as follows. The iodo phenol **101** gives alkylated-Pd complexes **Int-X** *via* intramolecular Heck cyclization, which in turn activate alkynes and to give **Int-X1** through 6-*endo-dig* amination. The **Int-X1** upon reductive elimination give **Int-X2**, which upon subsequent dealkylation give **102**. Furthermore, the reaction did not work in the case of electron-deficient alkynes.

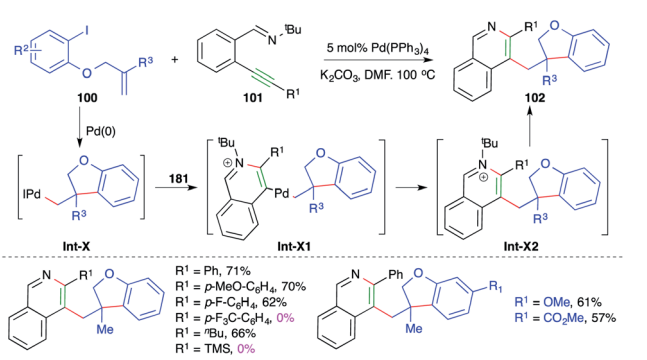
On the lines of the previous report, a strategy with the same basis was studied by Lin and co-workers for the synthesis of bisindolyl methanes. The reaction of *o*-iodo/bromo aryl amides **103** with *o*-alkynyl amines **104** in the presence of 5 mol% $Pd(PPh_3)_4$ gave the corresponding bisindolyl methanes **105** in good yield (Scheme 61).[74] The reaction offered rapid access to variously substituted bisindole moieties. Further, both internal and terminal/TMS-alkynes reacted in the desired manner with a little bit of discrepancy as terminal alkynes afforded the desired bisindoles in lesser yield. Despite the excellent functional group compatibility, free amides did not furnish the desired bisindoles.

Pd-catalyzed carboamination reaction using arenediazonium tetrafluoroborates as the carbon surrogate was explained in 2010 by Cacchi and co-workers. The reaction of *o*-alkynyltrifluoroacetanilides **106** with amines **107** in the presence of $Pd(PPh_3)_4$ and TBAI gave the corresponding indoles **108** in good yield (Scheme 62).[75]

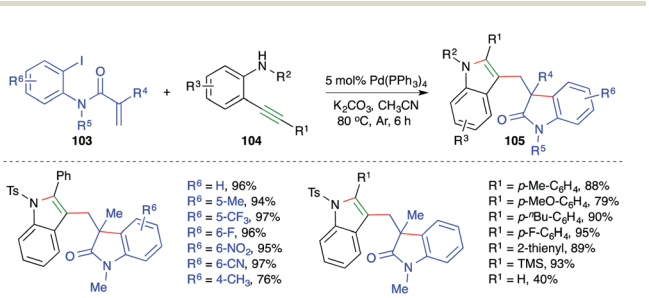
Nitrogen-doped polycyclic aromatic hydrocarbons (PAHs) are useful motifs because of their application in the fields of optoelectronics, light-emitting diodes, supercapacitors, and bioimaging. They were recently employed as efficient DNA intercalators as well. In this direction, Patil and co-workers have reported a cascade consisting of intramolecular carboamination of alkynes using Cu-catalysis. Further, the divergent



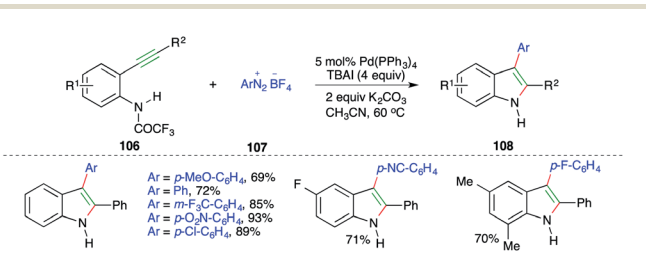
Scheme 59 Synthesis of 3-acyl/aryl isoquinolines using a carboamination approach.



Scheme 60 Tandem Heck reaction–carboamination approach.



Scheme 61 Tandem Heck reaction–carboamination approach.



Scheme 62 Use of arenediazonium tetrafluoroborates as carbon surrogates in carboamination.

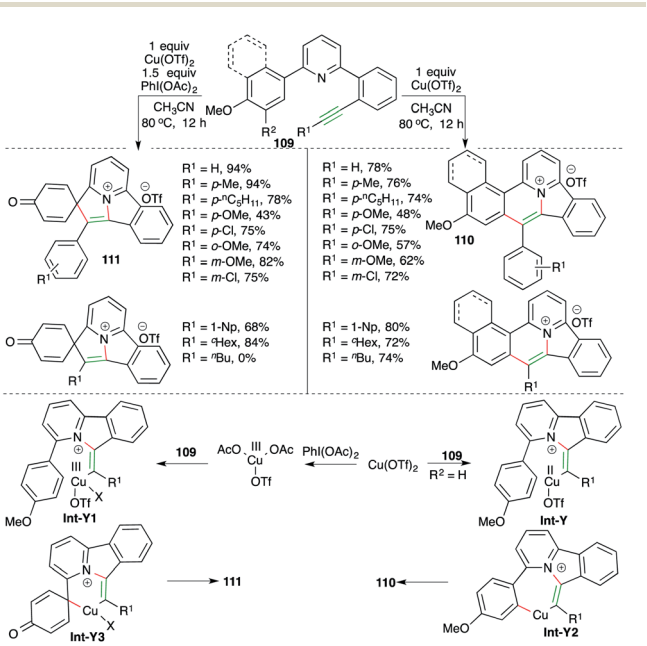
outcome of the current method could manifold its synthetic utility. The reaction of various alkyne-tethered pyridines **109** with $Cu(OTf)_2$ gave corresponding PAHs **110** in good yield. Interestingly, the use of oxidant $PhI(OAc)_2$ as an additive offered a completely different product **111** (Scheme 63).[76] The reaction offered access to variously substituted PAHs. Interestingly, aliphatic alkynes did not produce the desired **111**, but **110** was obtained in good yield. The detailed reaction mechanism is explained as follows. Alkynes **109** upon treatment with copper triflate give **Int-Y** or **Int-Y1**. **Int-Y** upon C–H insertion furnishes **Int-Y2**, whereas **Int-Y1** gives **Int-Y3** *via ipso*-substitution. Finally, **Int-Y2** and **Int-Y3** give the desired PAHs **110** and **111** through reductive elimination.

Cossy and co-workers have studied Rh-catalyzed intramolecular carboamination reaction of cyclobutene-tethered carboxamides **112** for the quick synthesis of cyclobuta[*c*] pyridones and -pyridines **113** (Scheme 64).[77] The reaction worked well for internal as well as terminal alkynes. Furthermore, aliphatic, aromatic, and TMS-alkynes were also employed in the reaction to synthesize corresponding N-heterocycles. To manifold the synthetic utility, some complex N-heterocycles were also synthesized using the developed method.

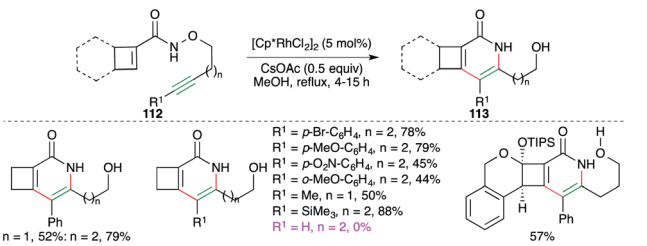
Rhenium-catalyzed carboamination of *o*-alkynyl *N*-homoallyl anilines 114 for the expedient synthesis of various 3-allyl indoles 115 was studied by Zi and co-workers (Scheme 65).[78] It is not the first time they had synthesized such reported scaffolds, but here they could successfully replace the use of precious metals such as Pd, Pt, and Rh with rhenium (Re). Various 3-allyl indoles were synthesized using the developed method. Moreover, they have also used this method for the synthesis of 3-allylated furans. The proposed mechanism suggested that the formation of 3-allylated indoles takes place *via* initial rhenium activation of the alkynes by Re playing the role of a π-acid, followed by a charge-accelerated [3,3]-sigmatropic rearrangement.

4. Metalla-electrocatalyzed carboamination

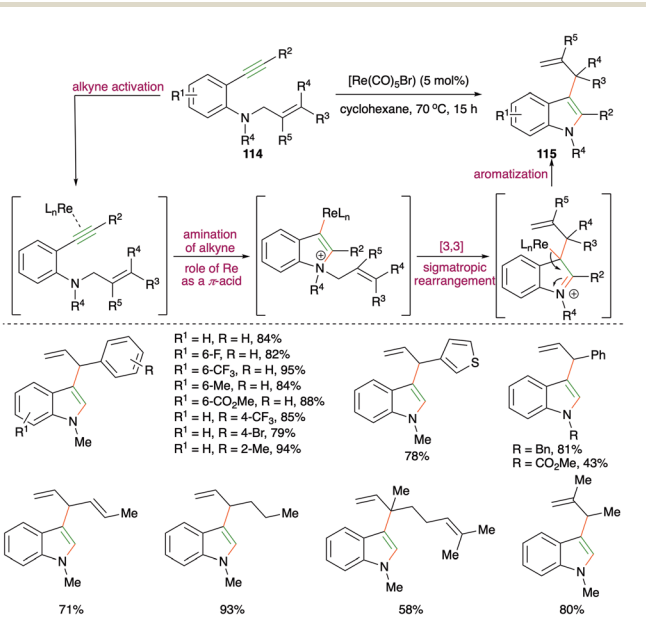
Indubitably, transition metal-catalyzed carboamination of alkynes has solved many long-standing problems and has offered a plethora of strategies for the synthesis of various N-bearing scaffolds and their congeners. Although it has drastically reduced the catalyst loading, the stochiometric use of co-oxidants varying from transition metals to hypervalent iodine has brought some non-negotiable limitations in terms of generation of a considerable amount of byproducts. To overcome these deficiencies, the synthetic community has chosen electrolysis. Arguably, metalla-electrocatalyzed carboaminations have solved the stochiometric use of co-oxidants and have delivered many elegant methods. A recent account describing developments in this context was documented in 2019 by Ackermann.[79] We wish to include the preceding developments in this review to position the efficacy of the current strategy in this field.



Scheme 63 Intramolecular carboamination reaction for the synthesis of carbazoles.



Scheme 64 Tandem carboamination and N–O bond cleavage.



Scheme 65 Rhenium-catalyzed intramolecular carboamination.

An electrochemically enabled, Ru-catalyzed bis-carboamination of aryl amides was developed by Tang and co-workers for the synthesis of polycyclic isoquinolone motifs. The method included the reaction of aryl amides **15** with alkynes **2** in an electrolytic cell in the presence of 5 mol% $[RuCl_2(p\text{-cymene})]_2$ to give the corresponding isoquinolones **116** in good yield. The key feature of the reaction was the observed regioselectivity in the case of unsymmetrical alkynes (Scheme 66).[80]

Ackermann and co-workers have reported carboamination of alkenyl imidazoles **117** with various alkynes **2** using an operationally simple undivided cell setup equipped with a GF (graphite felt) anode and a Pt cathode and 5 mol% $[RuCl_2(p\text{-cymene})]_2$ as the metal catalyst for the synthesis of N-heterocycles **118** (Scheme 67).[81] The isolated aza–ruthenium complex and its crystal structure revealed formation of a ruthenacycle through the C–H insertion, which after carboruthenation of alkynes and reductive metalation led to the formation of the desired adducts.

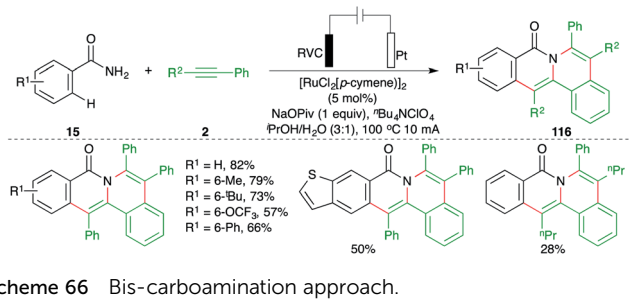
On similar lines, a Co-catalyzed electrochemical carboamination reaction of directing group-tethered (quinolin-8-yl) aryl sulfonamides was elaborated by Lei and co-workers. The developed method involved treatment of aryl amides **119** with alkynes **2** in an electrochemical cell containing 5 mol% cobalt salt to give the corresponding sultams **120** in good yield (Scheme 68).[82] Only terminal alkynes were used extensively as internal alkynes led to the formation of a mixture of regio-isomers.

5. Transition-metal-free carboamination

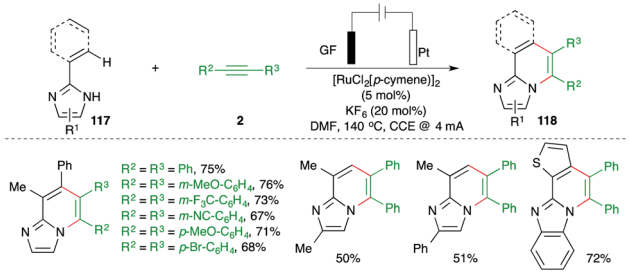
Undoubtably, *o*-quinone methide has been used extensively as the diene partner for the synthesis of oxygen-bearing heterocycles. In contrast, its nitrogen congener, *o*-aza-quinone methide, is comparatively much less studied.[83] In this domain, methods describing intermolecular [4 + 2] cycloaddition of *o*-aza-quinone methide with alkynes have been studied for the synthesis of quinolines. In this direction, Verma and co-workers have reported a metal-free base-promoted intermolecular carboamination strategy for the synthesis of variously substituted quinolines (Scheme 69).[84] The method involved treatment of *o*-amino benzyl alcohols **121** with internal alkynes **2** in the presence of 1 equiv. of a base such as KOH to furnish quinolines **122** in good yield. The reaction involved the base-promoted generation of *o-aza* quinone methides **Int-Z** from **121**, which upon subsequent intermolecular carboamination reaction with alkynes **2** furnished dihydroquinolines **Int-Z1**. Finally, autoxidation of **Int-Z1** delivered variously substituted quinolines. Although reactions have employed aromatic alkynes ($R^2 = R^3$ = aryl) or aromatic aliphatic alkynes (R^2 = alkyl, R^3 = aryl), aliphatic alkynes ($R^2 = R^3$ = alkyl) did not furnish the required quinolines.

In continuation of their study on the synthesis of quinolines, they also reported reaction of *o*-amino benzyl alcohols **121** with terminal alkynes **2a** in the presence of 1 equiv. of a base such as KOH to furnish the requisite 3-substituted quinolines **122a** in good yield (Scheme 70).[85]

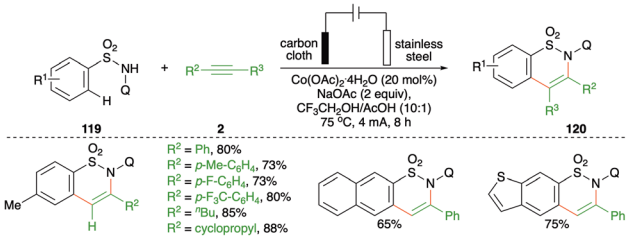
On similar lines, Niggemann and Stopka have studied metal-free, acid-promoted intermolecular carboamination of alkynes for the quick synthesis of variously substituted quinolines. The reaction of *o*-azido benzyl alcohols **123** with alkynes **2** in the presence of 1.5 equiv. of pTSA and 10 mol% triflimide furnished the requisite quinolines **124** in good yield (Scheme 71).[86] The reaction has excellent substrate scope. Most types of alkynes



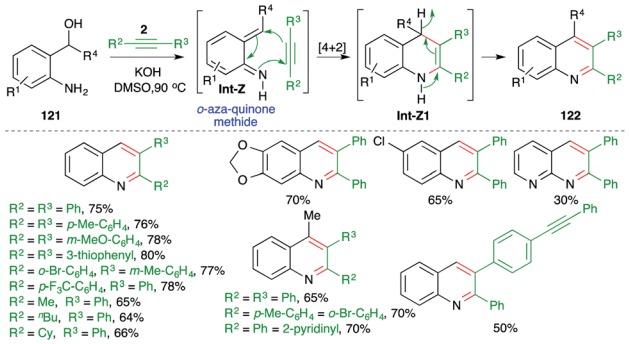
Scheme 66 Bis-carboamination approach.



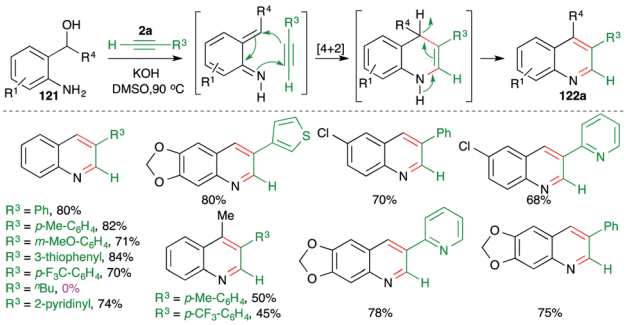
Scheme 67 Ru-catalyzed carboamination in an undivided cell.



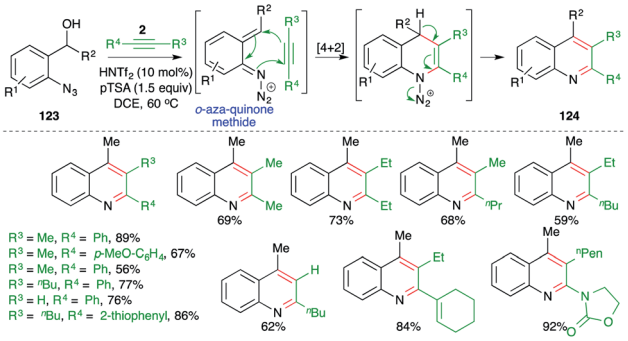
Scheme 68 Co-catalyzed carboamination in an undivided cell.



Scheme 69 Base-promoted carboamination of alkynes.



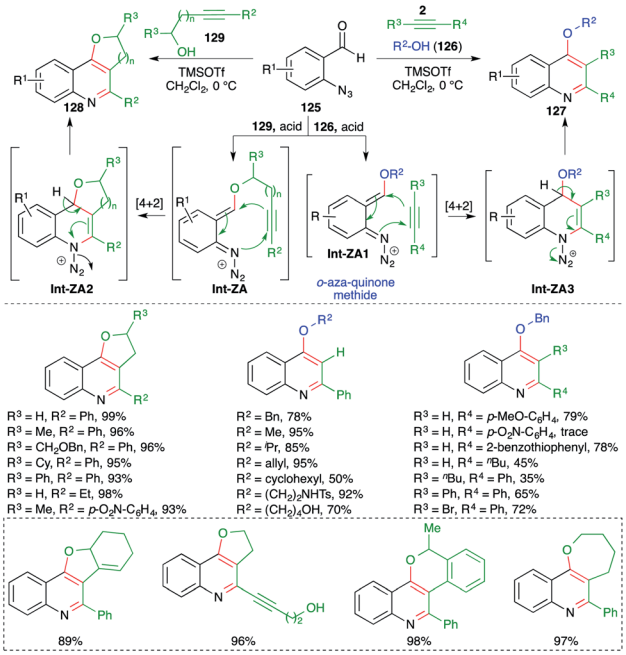
Scheme 70 Base-promoted carboamination of alkynes.



Scheme 71 Synthesis of quinoline using a metal-free carboamination approach.

participated in the reaction, leading to the formation of corresponding quinoline derivatives. As well as classical alkynes, enynes and ynamides were also used to synthesize their respective quinolines.

In contrast to the attention devoted towards quinoline, synthesis of its congeners such as 4-alkoxy quinolines as well as cyclic ether-fused quinolines has been less explored. In this context, Gharpure and co-workers reported a metal-free Lewis acid-promoted multicomponent carboamination cascade for the synthesis of these motifs. The method included the reaction of *o*-azido benzaldehydes **125** with alkynes **2** and alcohol **126** in the presence of TMSOTf as Lewis acid to generate 4-alkoxy quinoline **127** in excellent yield. The developed method has a very broad substrate scope with excellent functional group tolerance. Almost all types of alkynes participated to give the corresponding 4-alkoxy quinolines, except electron-deficient alkynes *i.e.* aryl alkynes with an electron-withdrawing group on the aromatic ring (Scheme 72).[87] Further, the method was also applied in the synthesis of cyclic ether-fused quinolines **128** from the corresponding alkynols **129** and *o*-azido benzaldehydes **125**. The formation of desired quinolines can be explained as follows. The reaction of *o*-azido benzaldehydes **125** with alcohol **129, 126** generated *o-aza* quinone methide **Int-ZA-ZA1** through acid-mediated condensation. The **Int-ZA-ZA1** then underwent inter- or intramolecular carboamination reaction *i.e.* a formal [4 + 2] cycloaddition reaction leading to the formation of dihydroquinoline **Int-ZA2-ZA3**, which upon concomitant

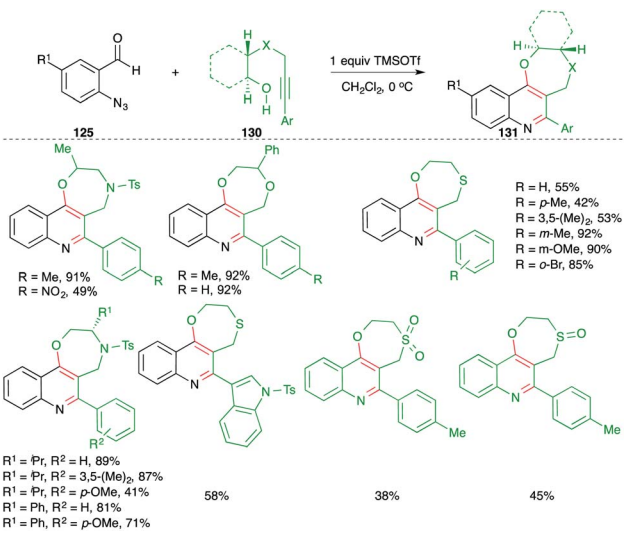


Scheme 72 Synthesis of 4-alkoxy quinoline using a metal-free carboamination approach.

elimination of H and N_2 afforded desired quinolines **128** and **127**, respectively.

On similar lines, they also applied the developed strategy for the synthesis of 1,4-heterocycle-fused quinoline motifs **130** from hetero-atom tethered alkynols **131** (Scheme 73).[88] Various enantiopure 1,4-oxazepino-quinolines were synthesized in good yield from the corresponding amino acid-derived alkynols. Further, *O*/*S*-tethered alkynols were employed in the reaction to synthesize dioxepino/oxathiepino-quinolines.

On similar lines, 4-methoxy quinolines **132** were synthesized under metal-free conditions from the intermolecular



Scheme 73 Synthesis of cyclic ether-fused quinoline using a metal-free carboamination approach.

carboamination of aryl isocyanates **133** with alkynes **2** and MeOTf **134** (Scheme 74).[89] Various aryl isocyanates and alkynes were employed in the reaction to give the corresponding quinolines. However, the reaction is limited to only aryl alkynes, and in the case of unsymmetrical alkynes, a mixture of separable regio-isomers was obtained. The proposed reaction mechanism involved the initial generation of carbocation **Int-ZB** from **133** and methyl triflate, which upon intermolecular trapping with alkyne led to the formation of a new vinyl cation **Int-ZB1**. The **Int-ZB1** upon intramolecular amination gave **Int-ZB2**, which upon ring opening furnished **Int-ZB3**. Finally, intra-molecular Friedel–Crafts alkylation afforded **132**.

An elegant approach describing metal-free, intermolecular carboamination reaction of alkynols **135** with cyclic aminals **136** was described by Frontier and co-workers for the stereoselective synthesis of cyclic ether-fused cyclic enamines **137** (Scheme 75).[90]

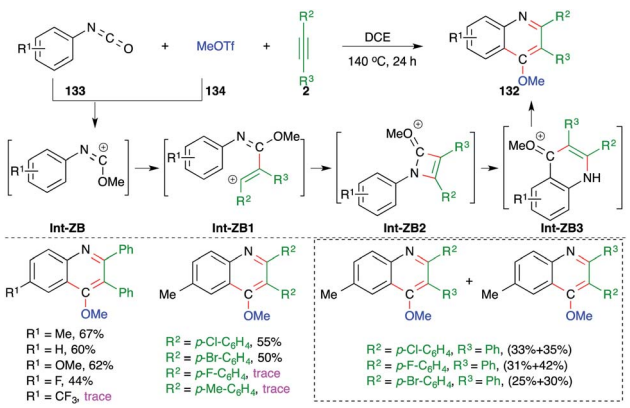
The suggested reaction mechanism involves formation of aminals **Int-ZC** through the coupling of alkynols **135** with aminals **136** *via* iminium ion trapping. The aminals **Int-ZC** give oxonium ions **Int-ZC1** and vinyl cations **Int-ZC2**, respectively, through a ring-opening-alkyne trapping cascade. Finally, **Int-ZC2** upon intramolecular amination leads to the formation of **137**. Various bicyclic heterocycles were prepared in good yield and with good diastereoselectivity.

An iminium ion-driven intermolecular carboamination strategy was depicted by Wong *et al.* for the facile synthesis of amino indenes **140a** and 3-amino indanones **140b** (Scheme 76).[91] The method involved reaction of *o*-alkynyl benzaldehyde derivatives **138** with secondary amines **139** in acetonitrile to give **140a** as the sole product through direct filtration of crude mass. Further, silica gel column chromatography of the crude reaction mixture gave **140b** through hydrolysis of **140a**. The reaction involves the initial formation of aminal **Int-ZD**, which upon intramolecular cyloisomerization leads to the formation of **140a**. Finally, quick passage of **140a** furnishes 3-amino indanones **140b** in good yield. The reaction has an excellent substrate scope and good functional group tolerance. However, the reaction is limited to terminal alkynes only.

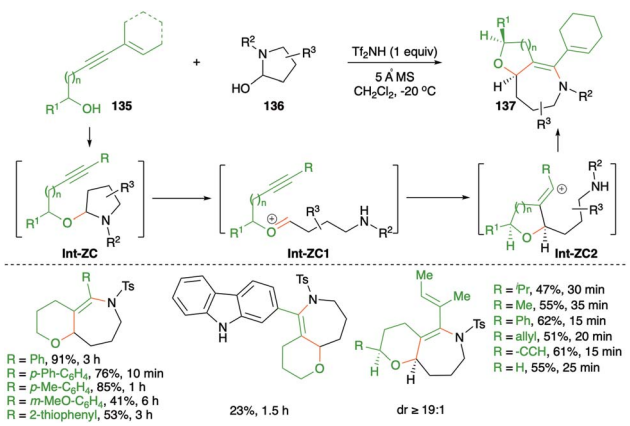
A metal-free base-promoted intermolecular carboamination reaction of amides **141** with *o*-bromoaryl ketones **142** was exemplified by Ma and co-workers for the rapid construction of 4-quinoline moieties **143** (Scheme 77).[92] Potassium carbonate was used as base in DMF as solvent. The reaction has indeed a very wide substrate scope. The carboamination involved a base-promoted *aza*-Michael addition–Smiles rearrangement–SO_2-extrusion–intramolecular aromatic nucleophilic substitution cascade to arrive at the desired quinolones. The method also worked well in the case of aliphatic alkynones (R^4 = methyl).

On similar lines, a green approach was developed by Cheng and co-workers for the synthesis of 4-quinolones. They used similar precursors (fluorides instead of bromides) to arrive at 4-quinolones through the use of Cs_2CO_3 in air instead of K_2CO_3 under nitrogen atmosphere (Scheme 78).[93] Further, the method has a very wide substrate scope. However, only a small number of examples were accomplished using aliphatic alkynones.

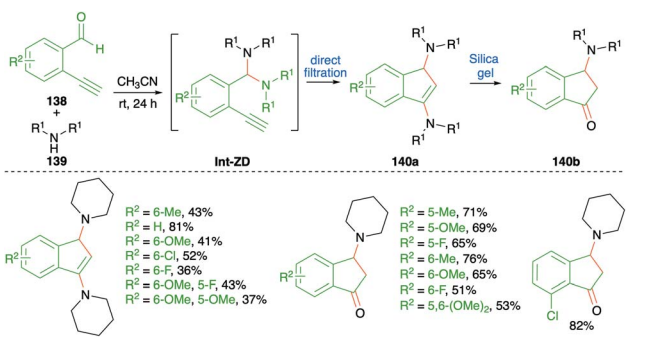
A metal-free intermolecular carboamination approach was reported by Larock and co-workers for the facile synthesis of *o*-acyl anilines (Scheme 79).[94] Reaction of *N*-aryltrifluoroacetamides **144** with 2-(trimethylsilyl)aryl triflates **64a** in the presence of CsF gave *o*-acyl anilines **145** in good yield. The fluoride accelerates the formation of benzyne, which upon either [2 + 2] cycloaddition with imine or step-wise nucleophilic



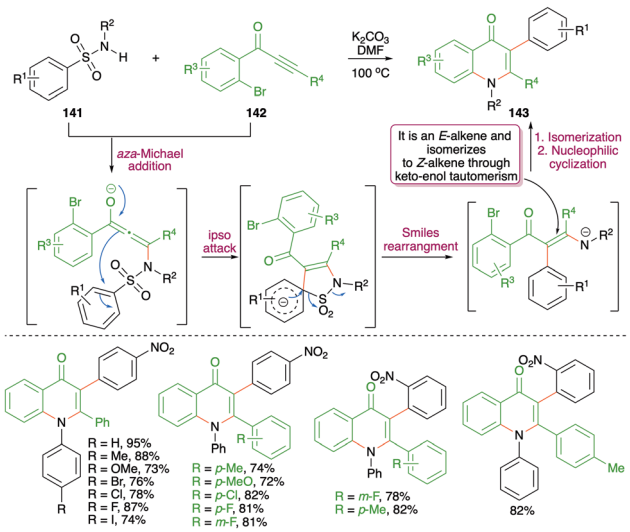
Scheme 74 Synthesis of 4-methoxy quinoline using a metal-free carboamination approach.



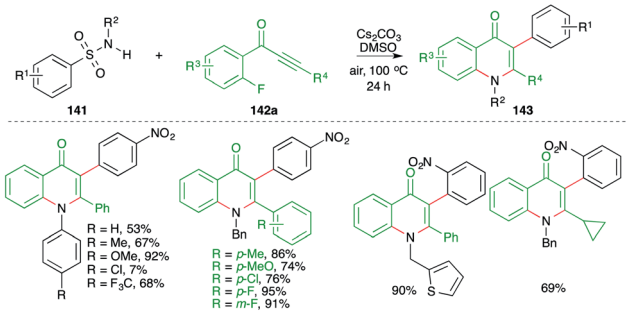
Scheme 75 Synthesis of bicyclic heterocycles using a metal-free carboamination approach.



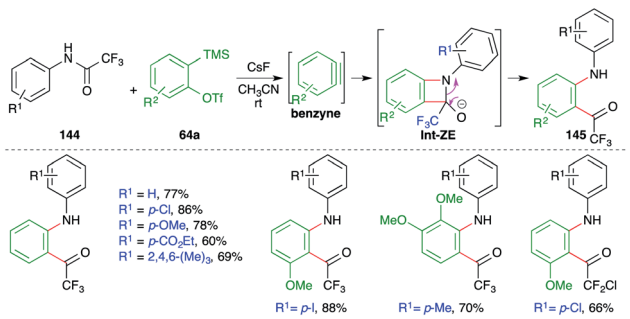
Scheme 76 Synthesis of indanones using a metal-free carboamination approach.



Scheme 77 Metal-free *aza*-Michael addition–Smiles rearrangement sequence.



Scheme 78 Synthesis of quinolones using a carboamination reaction.



Scheme 79 Metal-free carboamination of benzynes.

attack forms oxetane derivatives **Int-ZE**. The **Int-ZE** upon ring-opening and protonation leads to the formation of *o*-acyl anilines.

6. Summary and outlook

In this review, different strategies to conduct the intermolecular/intramolecular carboamination of alkynes leading to the synthesis of various chemically interesting scaffolds have been discussed. In this context, events utilizing both metal and metal-free conditions were covered.

Further, the carboamination of alkynes offered an array of excellent approaches for the synthesis of nitrogen-bearing aromatic heterocycles. These developed methods were studied under both metal and metal-free conditions. In particular, the metal-catalyzed transformations were broadly classified into two categories. In category 1, the key step of the transformation was either metal-catalyzed decarbonylation or decarboxylation or denitrogenation, and this was followed by an alkyne insertion–reductive elimination sequence. In category 2, the reactions were driven by directing group-assisted/free C–H bond functionalization leading to the formation of a metallacycle, which, upon alkyne insertion and reductive elimination, offered access to N-bearing aromatic entities. Further, metal-catalyzed cycloaddition reactions were also used in the carboamination reactions. On the other hand, the corresponding metal-free approaches have offered some excellent paths towards the synthesis of N-bearing complex entities.

Although significant progress has been achieved in the field of the carboamination of alkynes, still there is room for practical developments. Most of the developed strategies rely upon the use of costly transition metals, leaving a blank space for corresponding metal-free approaches. Further, methods utilizing the metal-based as well as metal-free carboamination of alkynes have led to the documentation of some excellent protocols for the rapid synthesis of N-bearing aromatic heterocycles. However, the use of alkynes was found to be limited and in most of the cases, an excess of alkynes was also used. One more key understudied area is that, in the case of unsymmetrical alkynes, a mixture of regio-isomers was obtained. Although Ackermann's group have solved this problem to a major extent, further development of methods using unsymmetrical alkynes leading to the formation of single regio-isomers is highly desirable. In order to avoid the use of costly metals, various groups across the globe have invented a unique strategy, *i.e.*, metalla-electrocatalyzed carboamination. Although it has solved cost-effectiveness problems, the regioselectivity issue still persists. Though the above functionalization has offered some really good access to unsaturated heterocycles, methods for the synthesis of the corresponding saturated heterocycles are scarce in the literature, despite the presence of these heterocycles in a wide range of bioactive natural products. Thus, a unified effort to tackle these issues is exceedingly required so that these methods can be applied in the synthesis of various natural products and pharmacophores.

Apart from the above-mentioned deficiencies, one of the most important concerns is the use of terminal alkynes in the carboamination reactions. The formation of metal salts with alkynes having acidic hydrogen may be one cause of the unsuitability in this type of reaction. However, in some cases they have been used but found to be unsatisfactory. Thus, a general and concise approach supporting the use of terminal alkynes is desirable.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge Centurion University of Technology and Management, Odisha, India for support and facilities.

Notes and references

1 Z. J. Garlets, D. R. White and J. P. Wolfe, *Asian J. Org. Chem.*, 2017, **6**, 636–653.
2 J. P. Wolfe, *European J. Org. Chem.*, 2007, 571–582.
3 J. P. Wolfe, *Synlett*, 2008, 2913–2937.
4 X. Wu, S. Wu and C. Zhu, *Tetrahedron Lett.*, 2018, **59**, 1328–1336.
5 H. Jiang and A. Studer, *Chem. Soc. Rev.*, 2020, **49**, 1790–1811.
6 G. Broggini, T. Borelli, S. Giofré and A. Mazza, *Synth*, 2017, **49**, 2803–2818.
7 G. J. P. Perry, T. Jia and D. J. Procter, *ACS Catal.*, 2020, **10**, 1485–1499.
8 S. R. Chemler, *J. Organomet. Chem.*, 2011, **696**, 150–158.
9 R. K. Dhungana, S. Kc, P. Basnet and R. Giri, *Chem. Rec.*, 2018, **18**, 1314–1340.
10 M. P. Plesniak, H.-M. Huang and D. J. Procter, *Nat. Rev. Chem.*, 2017, **1**, 1–16.
11 Z. Liu, Y. Gao, T. Zeng and K. M. Engle, *Isr. J. Chem.*, 2020, **60**, 219–229.
12 D. J. Mindiola, *Comments Inorg. Chem.*, 2008, **29**, 73–92.
13 Y. Kajita, S. Matsubara and T. Kurahashi, *J. Am. Chem. Soc.*, 2008, **130**, 6058–6059.
14 Y. Yoshino, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2009, **131**, 7494–7495.
15 K. Nakai, T. Kurahashi and S. Matsubara, *Chem. Lett.*, 2013, **42**, 1238–1240.
16 N. Maizuru, T. Inami, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2011, **13**, 1206–1209.
17 N. Maizuru, T. Inami, T. Kurahashi and S. Matsubara, *Chem. Lett.*, 2011, **40**, 375–377.
18 T. Miura, M. Yamauchi and M. Murakami, *Org. Lett.*, 2008, **10**, 3085–3088.
19 N. Jiao, Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding and Y. Cui, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572–4576.
20 N. Zhang, B. Li, H. Zhong and J. Huang, *Org. Biomol. Chem.*, 2012, **10**, 9429–9439.
21 Z. Shi, Y. Cui and N. Jiao, *Org. Lett.*, 2010, **12**, 2908–2911.
22 N. Sharma, R. Saha, N. Parveen and G. Sekar, *Adv. Synth. Catal.*, 2017, **359**, 1947–1958.
23 H. Qiao, S. Zhang, K. Li, Z. Cao and F. Zeng, *J. Org. Chem.*, 2019, **84**, 10843–10851.
24 J. Chen, G. Song, C. Pan and X. Li, *Org. Lett.*, 2010, **12**, 5426–5429.
25 N. Guimond and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 12050–12051.
26 P. C. Too, Y. F. Wang and S. Chiba, *Org. Lett.*, 2010, **12**, 5688–5691.
27 K. Morimoto, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 2068–2071.
28 X. Zhang, W. Si, M. Bao, N. Asao, Y. Yamamoto and T. Jin, *Org. Lett.*, 2014, **16**, 4830–4833.
29 D. Y. Li, X. F. Mao, H. J. Chen, G. R. Chen and P. N. Liu, *Org. Lett.*, 2014, **16**, 3476–3479.
30 X. Hu, X. Chen, Y. Zhu, Y. Deng, H. Zeng, H. Jiang and W. Zeng, *Org. Lett.*, 2017, **19**, 3474–3477.
31 N. Martínez-Yáñez, J. Suárez, A. Cajaraville, J. A. Varela and C. Saá, *Org. Lett.*, 2019, **21**, 1779–1783.
32 K. Parthasarathy, N. Senthilkumar, J. Jayakumar and C. H. Cheng, *Org. Lett.*, 2012, **14**, 3478–3481.
33 P. Villuendas and E. P. Urriolabeitia, *J. Org. Chem.*, 2013, **78**, 5254–5263.
34 W. Ma, K. Graczyk and L. Ackermann, *Org. Lett.*, 2012, **14**, 6318–6321.
35 L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379–6382.
36 L. Ackermann, L. Wang and A. V. Lygin, *Chem. Sci.*, 2012, **3**, 177–180.
37 L. Ackermann and A. V. Lygin, *Org. Lett.*, 2012, **14**, 764–767.
38 C. Kornhaaß, J. Li and L. Ackermann, *J. Org. Chem.*, 2012, **77**, 9190–9198.
39 R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 3032–3035.
40 S. Sarathkumar, V. Kavala and C. F. Yao, *Asian J. Org. Chem.*, 2019, **8**, 1830–1833.
41 S. Ruiz, C. Carrera, P. Villuendas and E. P. Urriolabeitia, *Org. Biomol. Chem.*, 2017, **15**, 8904–8913.
42 R. N. P. Tulichala, M. Shankar and K. C. K. Swamy, *J. Org. Chem.*, 2017, **82**, 5068–5079.
43 H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952–14955.
44 I. Nohira, S. Liu, R. Bai, Y. Lan and N. Chatani, *J. Am. Chem. Soc.*, 2020, **142**, 17306–17311.
45 G. Sivakumar, A. Vijeta and M. Jeganmohan, *Chem. –Eur. J.*, 2016, **22**, 5899–5903.
46 L. Grigorjeva and O. Daugulis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10209–10212.
47 Y. Yao, Q. Lin, W. Yang, W. Yang, F. Gu, W. Guo and D. Yang, *Chem. –Eur. J.*, 2020, **26**, 5607–5610.
48 S. H. Kwak and O. Daugulis, *Chem. Commun.*, 2020, **56**, 11070–11073.
49 S. I. of K. Paper, Aldenderfer, Mark S., Craig, Nathan M., Speak. Robert Jeff, Popelka-Filcoff, Rachel S., 1997, 2, 1–5.
50 L. Adak, W. C. Chan and N. Yoshikai, *Chem. – An Asian J.*, 2011, **6**, 359–362.
51 R. T. Ruck, R. L. Zuckerman, S. W. Krska and R. G. Bergman, *Angew. Chem., Int. Ed.*, 2004, **43**, 5372–5374.
52 H. Aneetha, F. Basuli, J. Bollinger, J. C. Huffman and D. J. Mindiola, *Organometallics*, 2006, **25**(10), 2402–2404.
53 Z. W. Davis-Gilbert, L. J. Yao and I. A. Tonks, *J. Am. Chem. Soc.*, 2016, **138**, 14570–14573.
54 Z. W. Gilbert, R. J. Hue and I. A. Tonks, *Nat. Chem.*, 2016, **8**, 63–68.
55 X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu and C. H. Tung, *Org. Lett.*, 2014, **16**, 5354–5357.

56 W. Wang, X. Peng, X. Qin, X. Zhao, C. Ma, C. H. Tung and Z. Xu, *J. Org. Chem.*, 2015, **80**, 2835–2841.
57 T. Y. Zhang, C. Liu, C. Chen, J. X. Liu, H. Y. Xiang, W. Jiang, T. M. Ding and S. Y. Zhang, *Org. Lett.*, 2018, **20**, 220–223.
58 S. L. Niu, J. Hu, K. He, Y. C. Chen and Q. Xiao, *Org. Lett.*, 2019, **21**, 4250–4254.
59 V. H. Thorat, N. S. Upadhyay, M. Murakami and C. H. Cheng, *Adv. Synth. Catal.*, 2018, **360**, 284–289.
60 Z. C. Ding, H. T. Tang, R. H. Li, L. C. Ju and Z. P. Zhan, *J. Org. Chem.*, 2015, **80**, 9307–9313.
61 K. C. Majumdar, S. Hazra and B. Roy, *Tetrahedron Lett.*, 2011, **52**, 6697–6701.
62 Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Angew. Chem., Int. Ed.*, 2015, **54**, 7862–7866.
63 M. Taguchi, Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2015, **17**, 6250–6253.
64 S. Choi, V. Srinivasulu, S. Ha and C. M. Park, *Chem. Commun.*, 2017, **53**, 3481–3484.
65 N. D. Rode, A. Arcadi, A. Di Nicola, F. Marinelli and V. Michelet, *Org. Lett.*, 2018, **20**, 5103–5106.
66 N. T. Patil, V. Singh, A. Konala and A. K. Mutyala, *Tetrahedron Lett.*, 2010, **51**, 1493–1496.
67 T. Shimada, I. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 10546–10547.
68 S. D. Tambe, N. Iqbal and E. J. Cho, *Org. Lett.*, 2020, **22**, 8550–8554.
69 T. Schitter, S. Stammwitz, P. G. Jones and D. B. Werz, *Org. Lett.*, 2019, **21**, 9415–9419.
70 F. Paquin, J. Rivnay, A. Salleo, N. Stingelin and C. Silva, *J. Mater. Chem. C*, 2015, **3**, 10715–10722.
71 G. Dai and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7042–7047.
72 G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920–928.
73 T. Yao, T. Liu and C. Zhang, *Chem. Commun.*, 2017, **53**, 2386–2389.
74 K. Yuan, L. Liu, J. Chen, S. Guo, H. Yao and A. Lin, *Org. Lett.*, 2018, **20**, 3477–3481.
75 S. Cacchi, G. Fabrizi, A. Goggiamani, A. Perboni, A. Sferrazza and P. Stabile, *Org. Lett.*, 2010, **12**, 3279–3281.
76 A. C. Shaikh, S. Banerjee, R. D. Mule, S. Bera and N. T. Patil, *J. Org. Chem.*, 2019, **84**, 4120–4130.
77 T. J. Saiegh, H. Chédotal, C. Meyer and J. Cossy, *Org. Lett.*, 2019, **21**, 8364–8368.
78 M. G. Rong, T. Z. Qin and W. Zi, *Org. Lett.*, 2019, **21**, 5421–5425.
79 L. Ackermann, *Acc. Chem. Res.*, 2020, **53**, 84–104.
80 Z. Q. Wang, C. Hou, Y. F. Zhong, Y. X. Lu, Z. Y. Mo, Y. M. Pan and H. T. Tang, *Org. Lett.*, 2019, **21**, 9841–9845.
81 L. Yang, R. Steinbock, A. Scheremetjew, R. Kuniyil, L. H. Finger, A. M. Messinis and L. Ackermann, *Angew. Chem., Int. Ed.*, 2020, **59**, 11130–11135.
82 Y. Cao, Y. Yuan, Y. Lin, X. Jiang, Y. Weng, T. Wang, F. Bu, L. Zeng and A. Lei, *Green Chem.*, 2020, **22**, 1548–1552.
83 B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926–7953.
84 R. K. Saunthwal, M. Patel and A. K. Verma, *Org. Lett.*, 2016, **18**, 2200–2203.
85 R. K. Saunthwal, M. Patel and A. K. Verma, *J. Org. Chem.*, 2016, **81**, 6563–6572.
86 T. Stopka and M. Niggemann, *Chem. Commun.*, 2016, **52**, 5761–5764.
87 S. J. Gharpure, S. K. Nanda, P. A. Adate and Y. G. Shelke, *J. Org. Chem.*, 2017, **82**, 2067–2080.
88 S. J. Gharpure, S. K. Nanda and D. J. Fartade, *Adv. Synth. Catal.*, 2021, **363**, 2562–2567.
89 Y. Liu, X. Zhang and C. Xi, *Tetrahedron Lett.*, 2018, **59**, 2440–2442.
90 S. Abdul-Rashed, G. Alachouzos, W. W. Brennessel and A. J. Frontier, *Org. Lett.*, 2020, **22**, 4350–4354.
91 J. F. Cui, R. Tang, B. Yang, N. C. H. Lai, J. J. Jiang, J. R. Deng and M. K. Wong, *Adv. Synth. Catal.*, 2019, **361**, 569–577.
92 C. Xie, D. Yang, X. Wang and C. Ma, *J. Org. Chem.*, 2020, **85**, 14937–14944.
93 J. Liu, D. Ba, W. Lv, Y. Chen, Z. Zhao and G. Cheng, *Adv. Synth. Catal.*, 2020, **362**, 213–223.
94 Z. Liu and R. C. Larock, *J. Am. Chem. Soc.*, 2005, **127**, 13112–13113.