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Intermolecular Redox-Neutral Carboamination of C−C Multiple Bonds Initiated by Transition-Metal-Catalyzed C−H Activation

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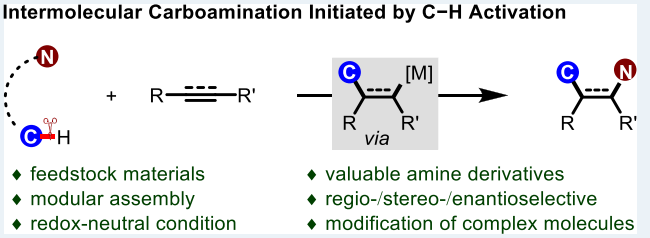
ABSTRACT: Carboamination of readily available feedstock-like alkenes, alkynes, and allenes has proven to be an efficient and powerful tool for the synthesis of diverse and valuable amine derivatives of relevance to medicinal chemistry, biochemistry, and material science. Among these developed carboamination methodologies, the direct use of the C−H activation strategy to leverage the carboamination process is particularly attractive due to the ubiquity of such bonds in organic molecules. In this review, we provide an overview of the development of intermolecular carboamination across C−C π-bonds initiated by C−H activation in a redox-neutral and nonannulative manner, with an emphasis on synthetic and mechanistic aspects. In principle, this review summarized these reactions with a key feature of involving an initial C−H metalation followed by an intermolecular migratory insertion into π-bonds and terminated by an electrophilic amination quenching, and thus, it is ordered by the sources of C- and N-based functionalities and further divided by π-compounds.



KEYWORDS: *carboamination, C−H activation, transition-metal catalysis, alkenes and alkynes, amine derivatives*

1. INTRODUCTION

Unsaturated hydrocarbons, such as alkenes, alkynes, and allenes, are readily available feedstock-like synthons that are engaged in diverse organic transformations. Difunctionalization of these substrates by adding two functional groups across C−C multiple bonds has emerged as an efficient and powerful strategy for the rapid buildup of molecular complexity.[1−11] Among them, the synchronous introduction of both C- and N-based functionalities (carboamination) toward these π-bonds is of particular interest, since it could provide expedient and modular entry to structurally diverse amine derivatives of close relevance to bioorganic,[12] agrochemical,[13] and medicinal chemistry[14] as well as material sciences.[15]

The established carboamination reactions often fall into three categories. Initial studies on this process focused on aza-Diels−Alder reactions by taking advantage of imines as electron-poor dienophiles or conjugated imines as electron-deficient azadienes.[16,17] These pericyclic reactions have found many applications in total synthesis but are limited to the synthesis of cyclic products. Alternatively, the radical-based reactions are also popular and efficient, but the involvement of free radical intermediates renders the stereoselective control of the reaction rather difficult (Scheme 1, right).[18,19] In contrast, the ionic-type manifolds are usually capable of participating in stereocontrol reaction manners.[20−22] Consequently, a series of advances involving the combinations of nitrogen nucleophiles and carbon electrophiles has emerged to furnish either *anti*- or *syn*-carboamination of different π-compounds via a key stereo-determining aminometalation step (Scheme 1, upper left).[23,24] This strategy, however, is restricted to the amine source with one or more electron-withdrawing groups on the nitrogen atom, due to the poisoning of the metal center by overcoordination. To address this limitation, an umpolung[25] amination strategy[26−30] with N−LG (LG = leaving group)-type electrophilic amination reagents has recently been introduced and its combination with a suitable nucleophilic carbon source would also allow for carboamination of C−C multiple bonds. For instance, organometallic reagents (C−m) undergo facile transmetalation and succeeding *syn*-specific migratory insertion into π-bonds.[31−35] Upon electrophilic amination, *syn*-carboamination products are obtained. Considering that many organometallic reactants are sensitive to moisture and air and often originate from aromatic or aliphatic hydrocarbons through the intermediacy of organic halides, the direct use of C−H substrates as an alternative carbon nucleophile would arguably be the most desirable method for this transformation (Scheme 1, lower left).

However, C−H bonds are relatively inert, rendering their catalytic cleavage more challenging. Moreover, the specific selectivity needs to be addressed during the reaction process.

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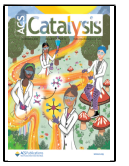

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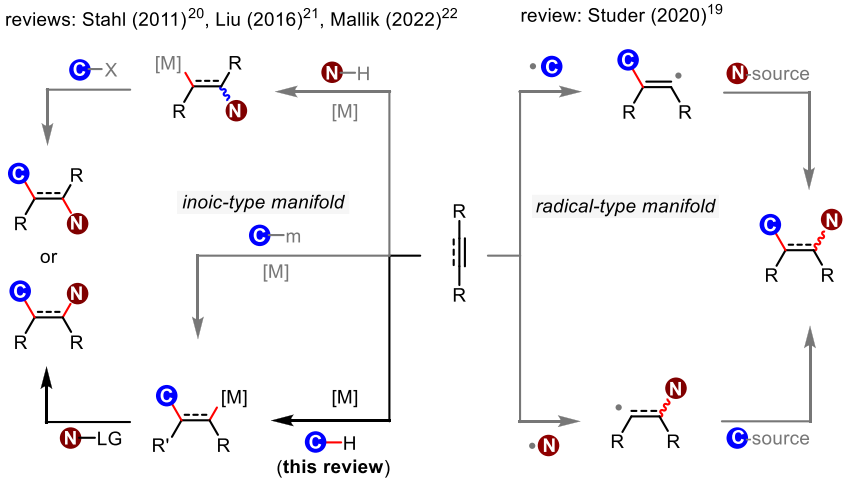
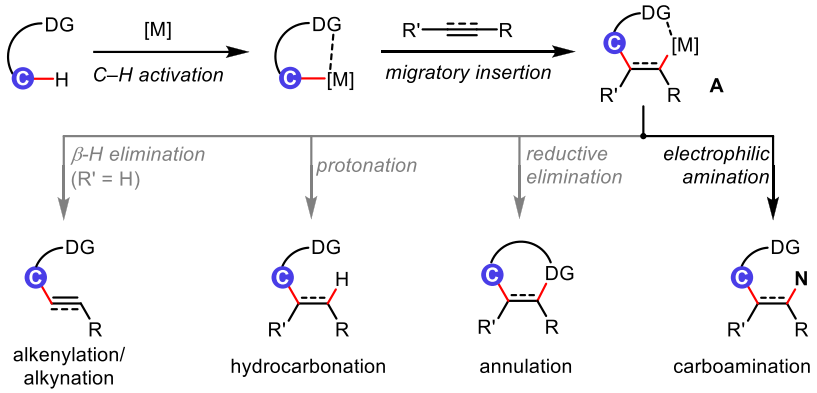
Scheme 1. Representative Reaction Modes for Intermolecular Carboamination toward C−C Multiple Bonds



Scheme 2. Potential Pathways of Transition-Metal-Catalyzed C−H Coupling with C−C Multiple Bonds



The electronic and steric nature occasionally defines a specific C−H bond activation.[36] In most cases, the position of bond activation is controlled by a coordinating group, which increases the reactivity of a certain C−H bond, thereby controlling the selectivity.[37−52] The organometallic intermediate, generated *in situ* by this way, undergoes a similar migratory insertion into the π-bonds to form the metallacycle intermediate **A** (Scheme 2). To ensure a carboamination event, this species should be stable enough to proceed with further electrophilic amination and meanwhile must suppress several potential pathways: e.g., β-H elimination, protodemetalation, and direct reductive elimination.

Such C−H activation mediated by the carboamination strategy allows C−H substrates acting as both carbon and amination sources to maximize the atom economy of the process. They can usually proceed under simple, mild, and redox-neutral conditions with good functional group tolerance. Most importantly, it has been proven to be predictable and feasible for the control of the diastereoselectivity and the enantioselectivity of the reaction, which empowers this synthetic strategy to prepare valuable chiral compounds.

Hence, this review summarizes the achievements of intermolecular carboamination of C−C multiple bonds initiated by organometallic C−H activation in a nonannulative manner, with an emphasis on synthetic and mechanistic aspects. These reactions involve an initial C−H metalation followed by an intermolecular migratory insertion into π-bonds and terminated by an electrophilic amination quenching. For intermolecular annulative carboamination reactions which deliver a heterocyclic product, the reader is directed to these well-documented reviews.[53−55] This review is ordered by the sources of C- and N-based functionalities and further divided by π-compounds.

2. DIVERSIFIED CARBOAMINATION OF π-COMPOUNDS WITH *N*-PHENOXY AMIDES

Due to the presence of a cleavable −ONHR moiety, *N*-phenoxy amides have been well-developed as versatile oxidizing directing groups (ODGs) in diverse Rh^{III}-, Ru^{II}-, Ir^{III}-, Pd^{II}-, and Co^{III}-catalyzed C−H functionalization reactions.[56,57] A series of π-compounds including alkynes, alkenes, and allenes have been proven to be suitable coupling partners (CPs) to fulfill C−H functionalization, among which the amide fragment could serve as an internal N-source to realize the carboamination of a π-bond in a redox-neutral manner.

2.1. Alkynes. In 2013, Lu, Liu, et al. introduced an elegant intermolecular carboamination of alkynes by taking advantage of Rh^{III}-catalyzed C−H activation of *N*-phenoxyacetamides (Scheme 3).[58] This process was enabled by the novel versatile group −ONHAc, which synergistically acted as the directing group, the internal oxidant, and the electrophilic amination source, thus leading to the *o*-hydroxyphenyl substituted enamide products under mild and redox-neutral conditions. The established method was widely applicable to biaryl and aryl alkyl disubstituted alkynes, as well as propiolates and ynamides. An investigation of the solvent effect revealed that the use of MeOH and ethylene glycol was crucial for the carboamination

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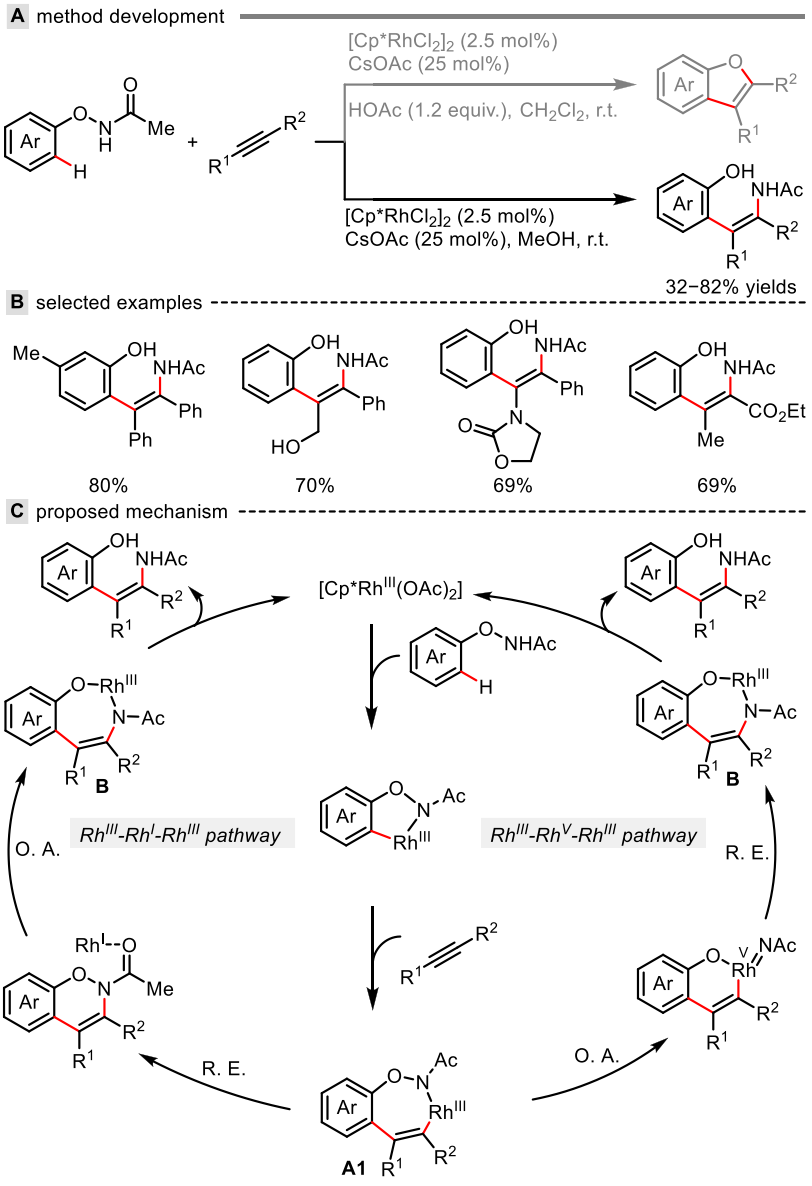
Scheme 3. Rh^{III}-Catalyzed 1,2-Carboamination of Alkynes with *N*-Phenoxyacetamides



event, whereas ^{t}BuOH, CH_2Cl_2, and toluene favored the benzofuran formation with the departure of the acetamido group (Scheme 3A). Meanwhile, the cost-effective Cp^*Co^{III} (Cp^* = 1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl) catalytic system turned out to be comparably efficient for this carboamination process, albeit limited to propiolates.[59]

Two distinct mechanistic pathways for the Rh^{III}-catalyzed carboamination reaction are illustrated in Scheme 3C. A Rh^{III}−Rh^{I}−Rh^{III} catalytic cycle was proposed in the pioneering work by Lu, Liu, et al., which commences with ONHAc-directed C−H activation and alkyne insertion into the C−Rh bond to form the seven-membered rhodacycle intermediate **A1**. This species might be stabilized by forming an 18-electron complex through the weak coordination of the solvent, such as methanol, which thereby facilitates reductive elimination (RE) to give a ligated Cp^*Rh^{I} complex. Subsequent oxidative addition (OA) into the O−N bond forms the isomeric seven-membered rhodacycle species **B**, which undergoes protonolysis with HOAc to release the enamide product and regenerate the active Cp^*Rh^{III} catalyst. Alternatively, Wu, Houk, et al.[60] figured out that a Rh^{III}−Rh^{V}−Rh^{III} catalytic pathway was much more favorable on the basis of detailed computational studies, in which the O−N bond cleavage with ring contraction proceeds to deliver a Rh^{V}-nitrenoid intermediate, which allows more facile C−N bond reductive elimination. In addition, density functional theory (DFT) calculations suggested that the dramatic solvent effect on tuning the reaction chemoselectivity probably resulted from the polarity instead of the ligand role. It is worth noting that most of the follow-up research work gave solid support to the intermediacy of the Rh^{V}-nitrenoid species.[61]

By virtue of the well-designed chiral cyclopentadienyl (Cp^X)-coordinated Rh^{III} catalyst,[62−64] recently Li and co-workers have achieved an asymmetric carboamination reaction using bulky 1-alkynylnaphthalenes as the versatile coupling partners (Scheme 4).[65] By using *N*-phenoxy amides as both C- and N-sources, a series of C−C axially chiral enamides, which would not otherwise be accessible, were obtained with good enantioselectivities and yields. The synthetic utilization of this protocol was further demonstrated by triflation of the free OH handle in the enamide product, followed by a Pd-catalyzed intramolecular

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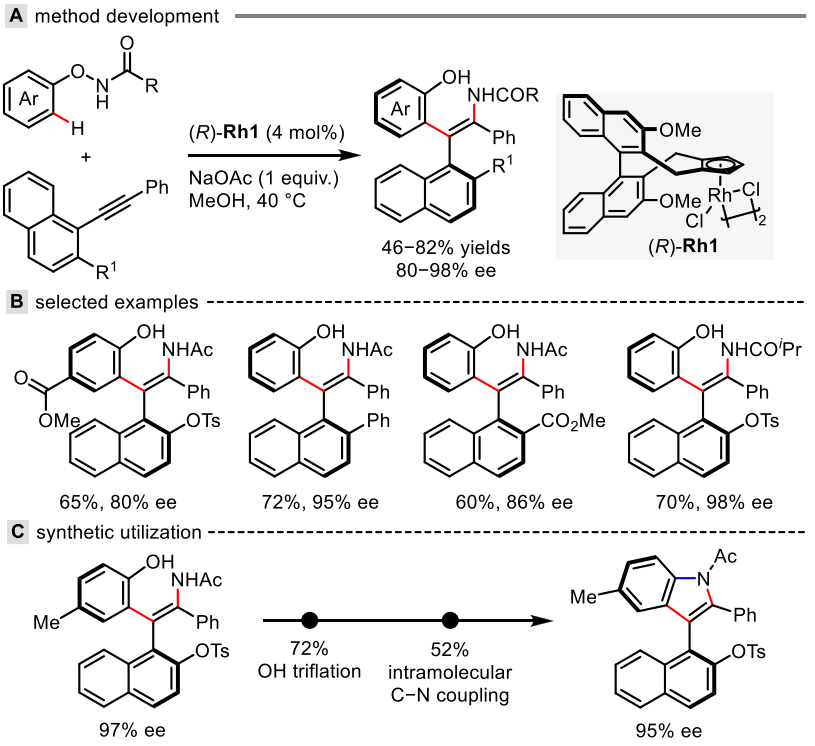
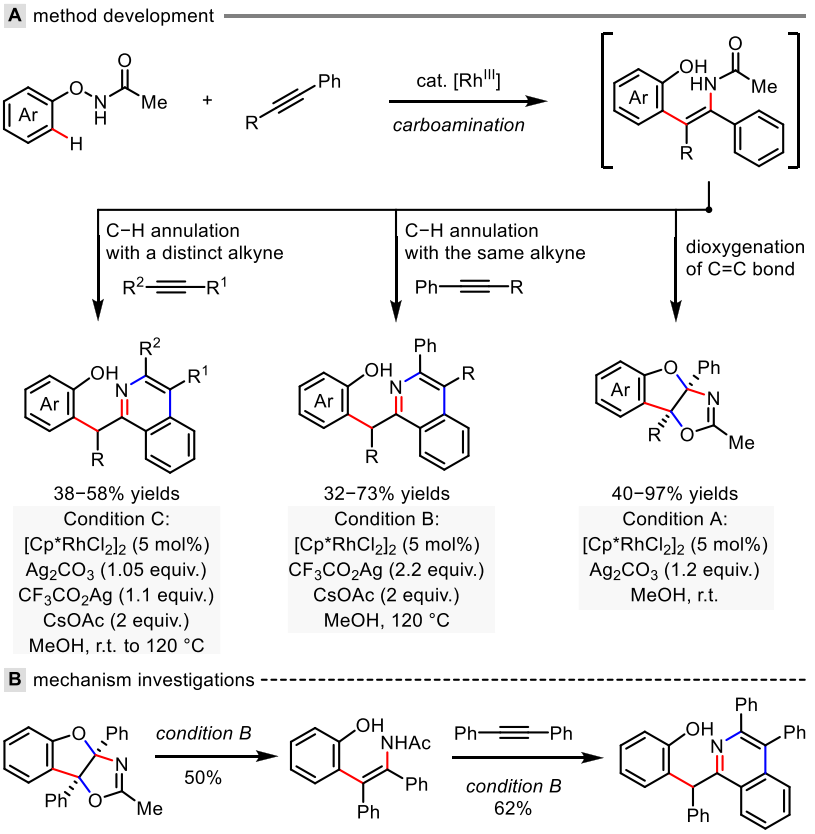
Scheme 4. $Cp^{X}Rh^{III}$-Catalyzed Enantioselective 1,2-Carboamination of 1-Alkynylnaphthalenes with *N*-Phenoxy Amides



Scheme 5. Rh^{III}-Catalyzed 1,2-Carboamination/Cyclization Sequences



amination to deliver a chiral indole without erosion of enantioselectivity.

In addition to the OH group, the presence of versatile amide moieties and C−C double bonds in the enamide products also enriched further diverse transformations to increase the molecular complexity. In this regard, Zhao, Huang, et al. disclosed a series of tandem reactions of *N*-phenoxyacetamides with alkynes involving the enamide species as the key

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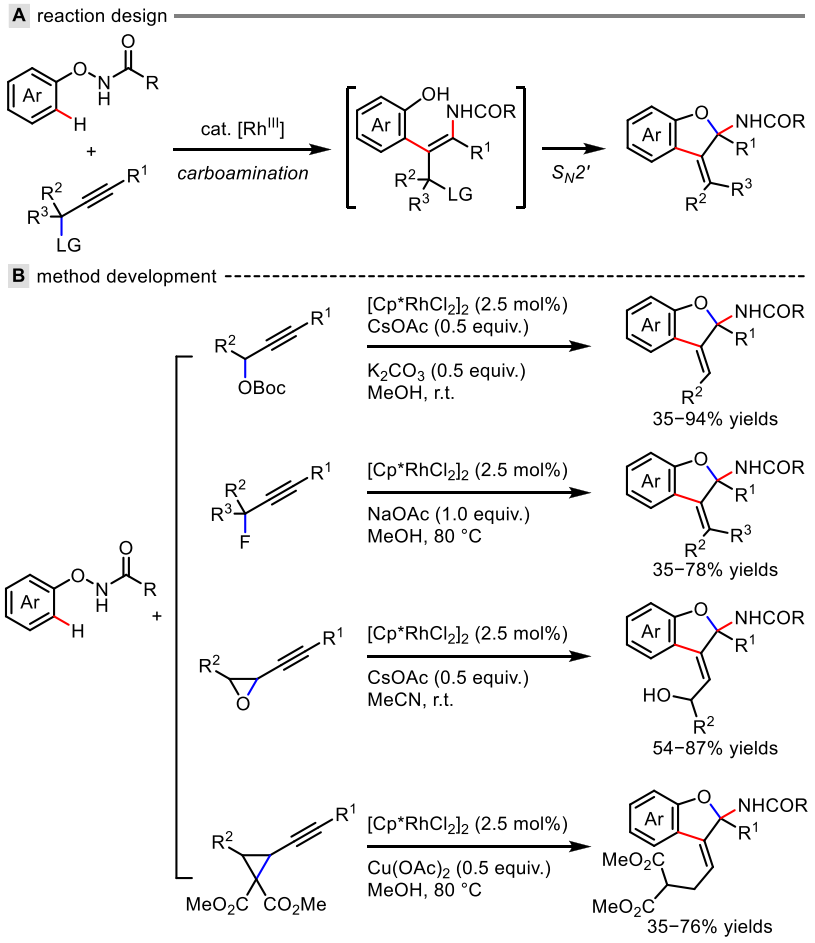
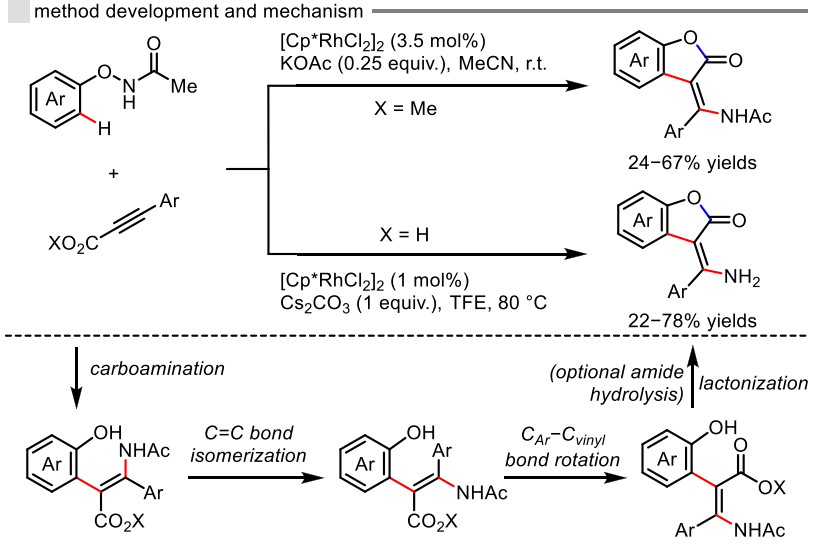
Scheme 6. Rh^{III}-Catalyzed 1,2-Carboamination/S_N2'-Type Substitution Sequences



Scheme 7. Rh^{III}-Catalyzed 1,2-Carboamination Followed by Intramolecular Lactonization



intermediates.[66] As shown in Scheme 5, the addition of Ag_2CO_3 as an oxidant promoted an extra intramolecular oxidation course of olefins, thus leading to dihydrobenzofuro[2,3-*d*]oxazoles in good yields (condition A). Additionally, the nascent amide unit could serve as a directing group to assist the second C−H [4 + 2] annulation with another molecule of either the same or a distinct alkyne in the presence of CF_3CO_2Ag at the evaluated temperature (conditions B/C). Interestingly, the tricyclic compound resulting from condition A could also be converted back into the enamide under condition B, which was capable of undergoing *ex situ* amide-directed C−H annulation to give highly functionalized isoquinolines (Scheme 5B). These stepwise transformations validated the involvement of the active enamide intermediates.

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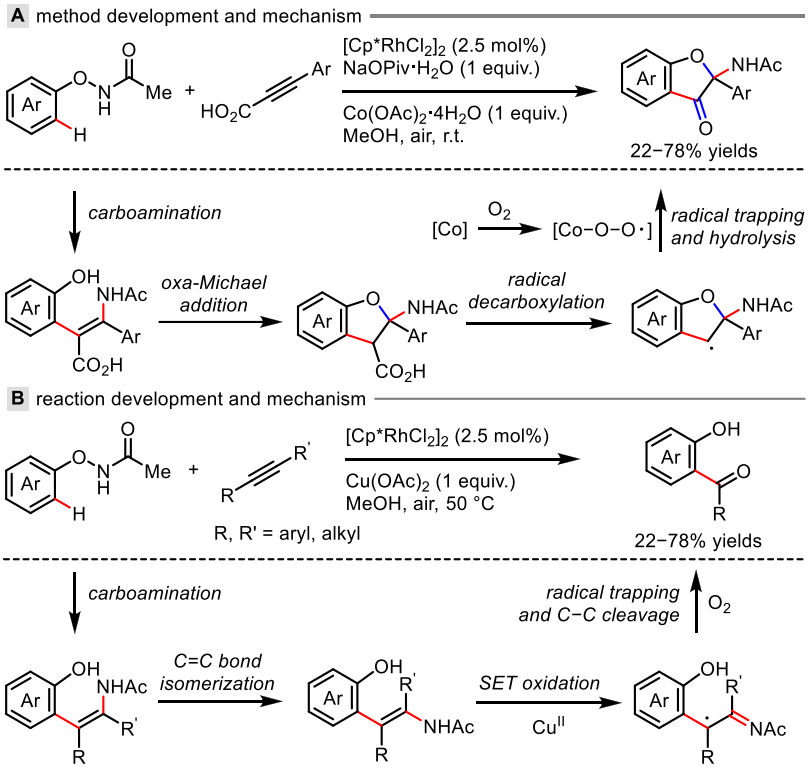
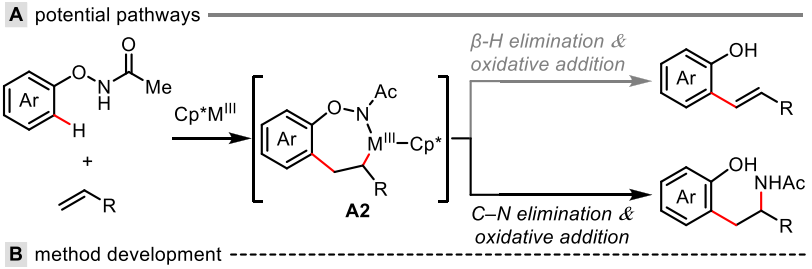
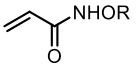
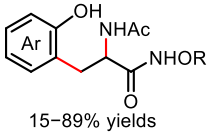
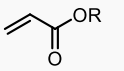
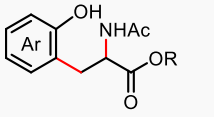
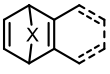
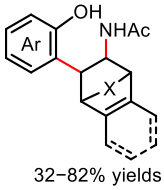
Scheme 8. Rh^{III}-Catalyzed 1,2-Carboamination Followed by Radical Aerobic Oxygenation



Scheme 9. Cp^*M^{III}-Catalyzed 1,2-Carboamination of Alkenes with *N*-Phenoxyacetamides



olefin CPs	reaction conditions	carboamination product
	$[Cp^*RhCl_2]_2$ (2.5 mol%) K_3PO_4 (0.5 equiv.), 4Å MS, MeCN, r.t.	 15–89% yields
	$Cp^*Co(CO)I_2$ (10 mol%) $AgSbF_6$ (20 mol%), CsOAc (0.25 equiv.) K_3PO_4 (0.5 equiv.), 3Å MS, TFE, 40 °C	 30–88% yields
 X = CH_2, O, NBoc	$Cp^*Co(CO)I_2$ (10 mol%) $AgSbF_6$ (20 mol%), KOAc (0.5 equiv.) K_3PO_4 (0.5 equiv.), TFE, 40 °C	 32–82% yields

When a suitable leaving group was preinstalled at the propargylic position, an S_N2'-type substitution could be expected due to the good nucleophilic ability of the phenol unit in the enamide intermediate (Scheme 6). This hypothesis was first realized by Lu, Liu, et al. employing *tert*-butyl carbonate (OBoc) as a leaving group for the synthesis of 3-alkylidene dihydrobenzofuran derivatives.[67] Such a protocol was applicable to both primary and secondary propargylic carbonates but failed with the tertiary series due to the steric hindrance. This limitation could be overcome by using the fluoride as an

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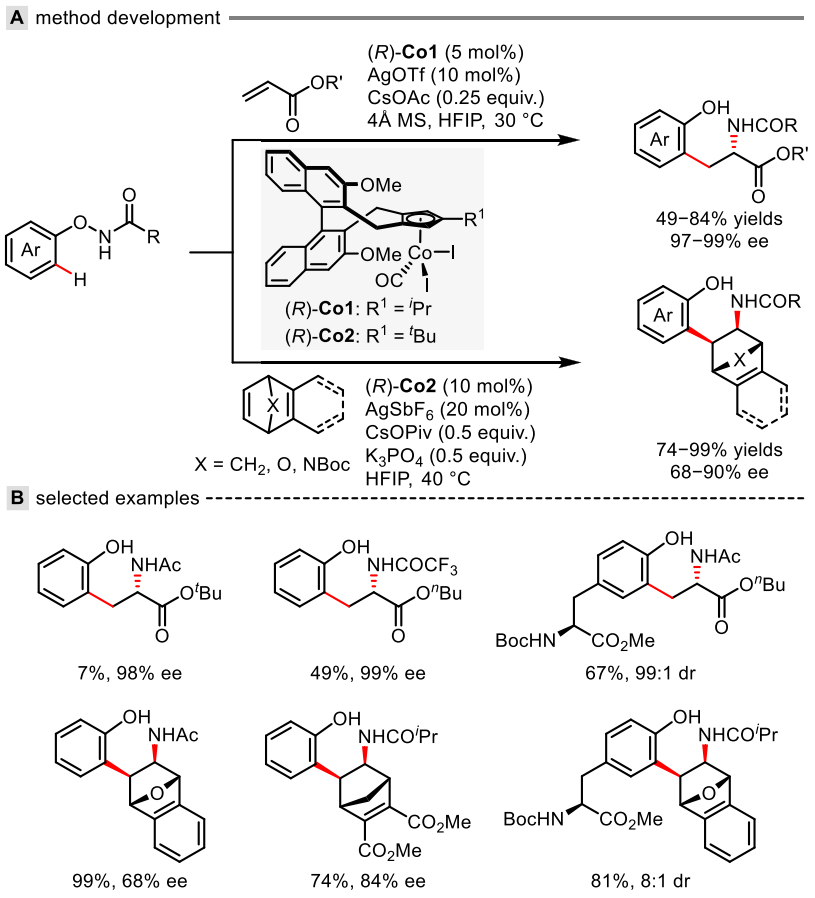
Scheme 10. $Cp^{X}Co^{III}$-Catalyzed Enantioselective 1,2-Carboamination of Alkenes with *N*-Phenoxy Amides



alternative leaving group, in which the [H···F] bonding-assisted intramolecular S_N2'-type substitution process might be involved by utilizing the fluorine atom as a feasible leaving group with less steric hindrance.[68] In addition, the introduction of an epoxide[69] or cyclopropane[70] at the propargylic position enabled similar intramolecular S_N2' ring-opening processes, thus illustrating the good compatibility of this strategy in constructing relative skeletons. Of note, these conversions all favored the stereoselective formation of an (*E*)-exocyclic C−C double bond.

In 2018, Zhang, Xia, et al. revealed a Rh^{III}-catalyzed tandem coupling reaction of 3-arylpropiolates with *N*-phenoxyacetamides (Scheme 7).[71] Complementary to the Cp^*Co^{III} counterpart,[59] this reaction addressed an opposite regioselective carboamination across the C−C triple bond with 2-hydroxyphenyl tethered to the initial 2-position of propiolates. DFT calculations revealed that the intramolecular N−H···O type hydrogen bond promotes the isomerization of a C−C double bond and rotation of a C−C single bond through enamine−imine tautomerism. Finally, an intramolecular transesterification course occurs to afford benzofuran-2(3*H*)-ones bearing an exocyclic enamino motif with exclusive *Z* selectivity. Interestingly, switching to 3-arylpropiolic acids as coupling partners gave rise to a similar backbone but with a free NH_2 group derived from the final hydrolysis of the amido group.[72]

In contrast, the use of $Co(OAc)_2{\cdot}4H_2O$ as an additive allowed an intramolecular oxa-Michael addition of the incipient enamides, followed by radical decarboxylative oxygenation with molecular oxygen to yield isomeric benzofuran-3(2*H*)-ones (Scheme 8A).[73] Replacing the cobalt salt with $Cu(OAc)_2$ caused an additional aerobic radical cleavage of the C═C bond in the enamides. Alternatively, it provided *ortho*-acylated phenols as the final products (Scheme 8B).[74]

2.2. Alkenes. Compared to the alkyne substrates, the initial C−H activation of *N*-phenoxy amides followed by facile alkene insertion would afford the similar seven-membered metallacycle intermediate **A2**. In contrast to the $C(sp^2)$−M bond formed through alkyne insertion, the $C(sp^3)$−M species is usually prone to undergo a *β*-H elimination process. Indeed, Lu et al. disclosed the feasible C−H olefination of *N*-phenoxyacetamides with acrylates or styrenes under rhodium catalysis, leading to the formation of diverse *ortho*-alkenyl phenol derivatives (Scheme 9A, top).[75] To achieve the desired carboamination process, such competitive *β*-H elimination must be suppressed, and the alternative C−N bond reductive elimination from either an Rh^{III} or Rh^{V} intermediate should be accelerated (Scheme 9A, bottom).

To address this issue, several strategies have been developed for the targeted alkene carboamination. In 2016, Liu et al. envisioned that the introduction of a chelating group in the olefin substrate might ensure the metal center of **A2** to be coordinatively saturated, thus shifting the elementary step of *β*-H elimination into C−N bond reductive elimination. For this reason, they utilized *N*-alkoxyacrylamides as the coupling partners and found that the commonly used Cp^*Rh^{III} catalytic system was sufficient to unleash the desired amido group transfer *en route* to *o*-tyrosine derivatives (Scheme 9B, top).[76] Control experiments verified the key role of the N−H bond rather than the *N*-alkoxy group in acrylamide for the overall carboamination event. Complementary to the Cp^*Rh^{III} counterpart, the Cp^*Co^{III} catalyst often requires no coordina-

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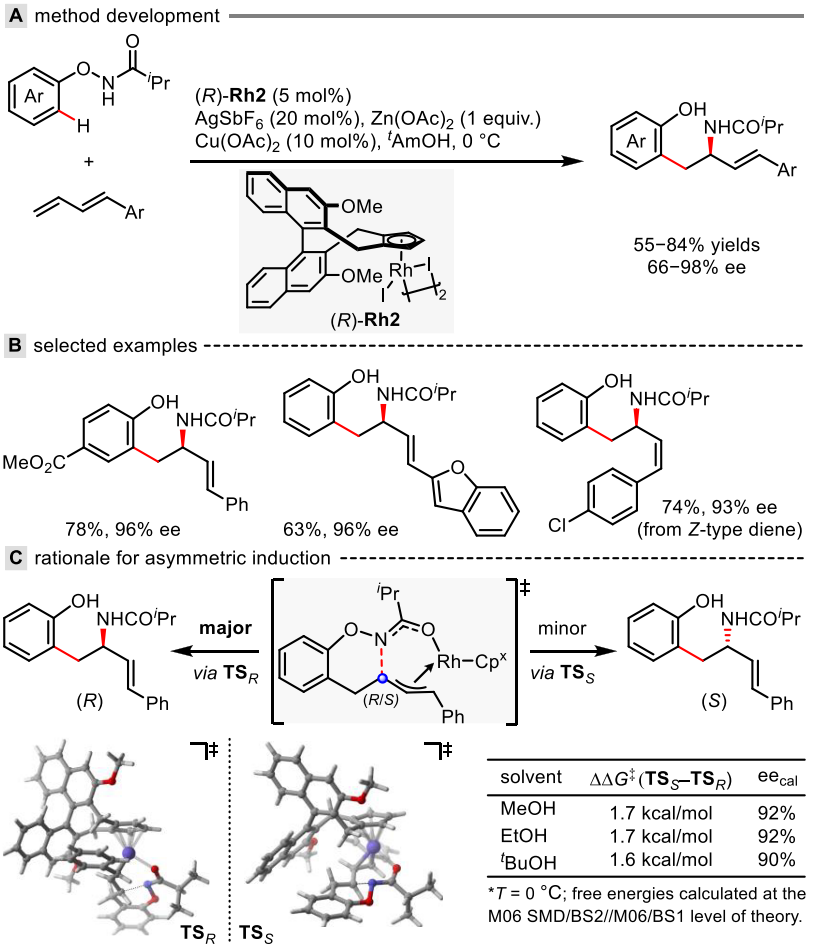
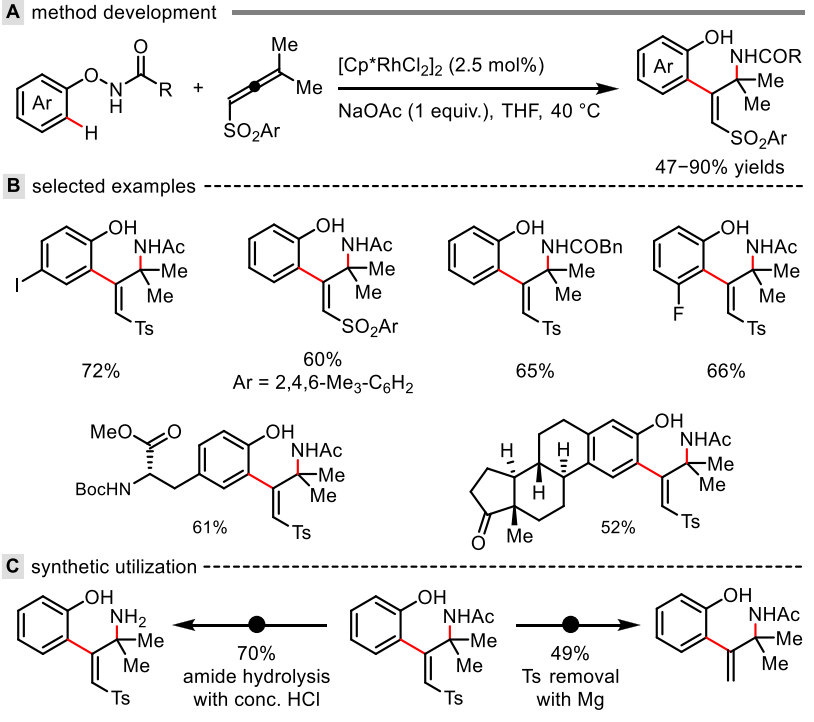
Scheme 11. $Cp^{X}Rh^{III}$-Catalyzed Enantioselective 1,2-Carboamination of 1,3-Dienes with *N*-Phenoxy Amides



Scheme 12. Rh^{III}-Catalyzed Carboamination of Sulfonyl Allenes with *N*-Phenoxy Amides



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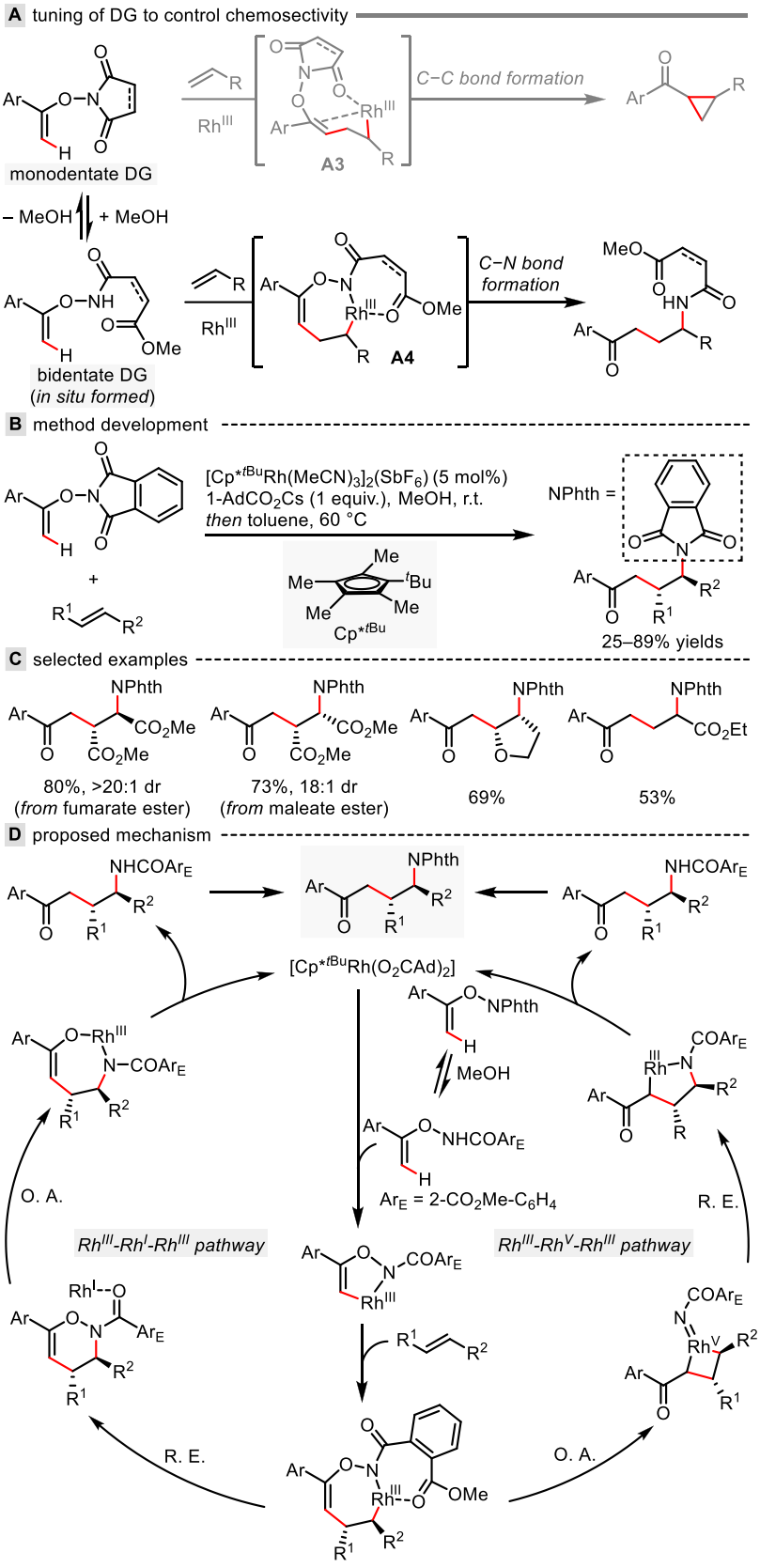
Scheme 13. Rh^{III}-Catalyzed 1,2-Carboamination of Alkenes with *N*-Enoxyphthalimides



tive saturation for the C(sp^3)–M center and inherently favors C–N bond reductive elimination over β-H elimination. The first example came from the Glorius group, who described a Co^{III}-catalyzed carboamination of simple acrylates with *N*-phenoxyacetamides for the direct synthesis of unnatural amino acid derivatives (Scheme 9B, middle),[77] rather than the Heck-type

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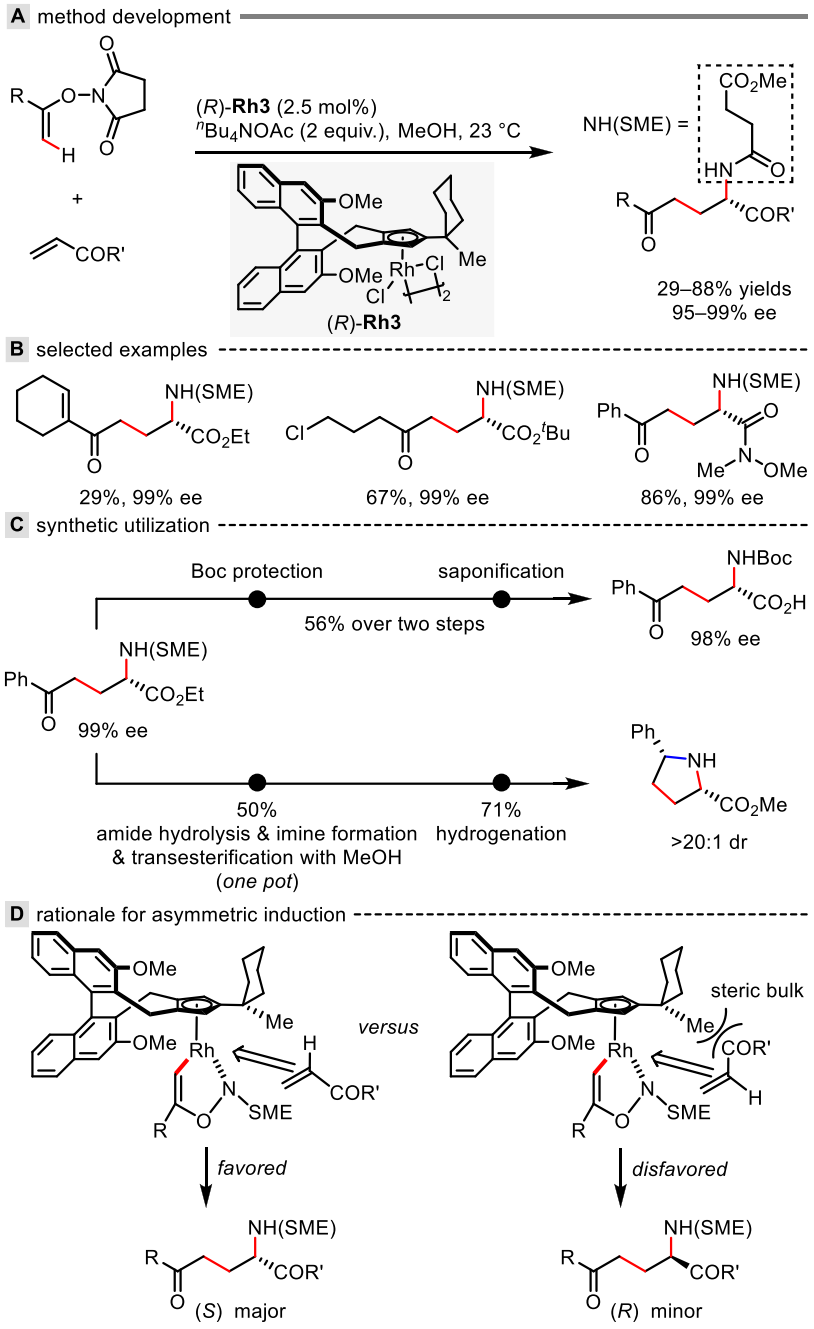
Scheme 14. Cp^XRh^{III}-Catalyzed Enantioselective 1,2-Carboamination of Acrylates with *N*-Enoxysuccinimides



product under rhodium catalysis observed by the Lu group. This cobalt system was further extended to stereoselective carboamination of bicyclic alkenes (Scheme 9B, bottom).[59]

Inspired by the prevalent chiral Cp^XRh^{III}-catalyzed asymmetric C−H functionalization reactions, several analogous chiral Cp^XCo^{III} catalysts were also rationally designed by the Cramer group and enabled asymmetric alkene carboamination with *N*-phenoxy amides as bifunctional reactants (Scheme 10).[78] They also revealed that a substituent on the cyclopentadienyl moiety was crucial for the enantioselective control. Based on these, acrylates and bicyclic alkenes were converted to attractive enantioenriched isotyrosine derivatives as well as elaborated amino-substituted bicyclic scaffolds with excellent enantioselectivity.

Despite the well-established carboamination of alkenes, the intermolecular carboamination reactions of conjugated dienes and allenes are still in their infancy. The C- and N-based functionalities could be typically incorporated into either 1,2- or 1,*n*-positions—such extra regioselectivity clearly increases the complexity. Very recently, Yi, Zhou, et al. established the first regioselective and enantioselective 1,2-carboamination of 1,3-dienes under chiral Cp^XRh^{III} catalysis for the synthesis of chiral allylic amine derivatives (Scheme 11).[79] The bulk of the amido group in the *N*-phenoxy amide substrates had a dramatic effect on the reactivity and enantioinduction, with isopropyl being the optimal substituent. Of note, both *Z*- and *E*-type 1,3-dienes were compatible to give the related chiral allylic amines with retention of the configuration. A combined experimental and computational study supports an unusual Rh^{III}−Rh^{I}−Rh^{III} catalytic

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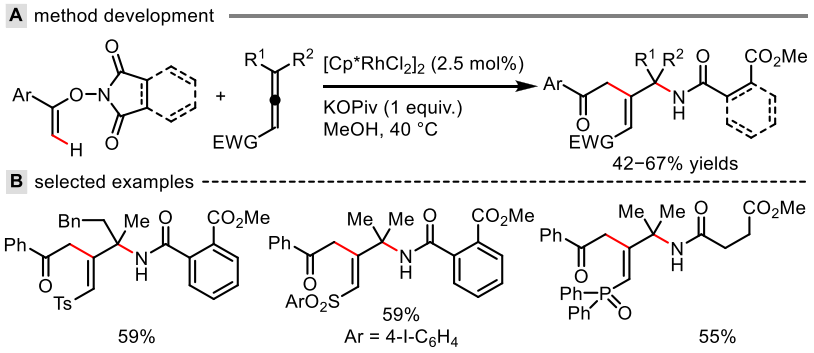
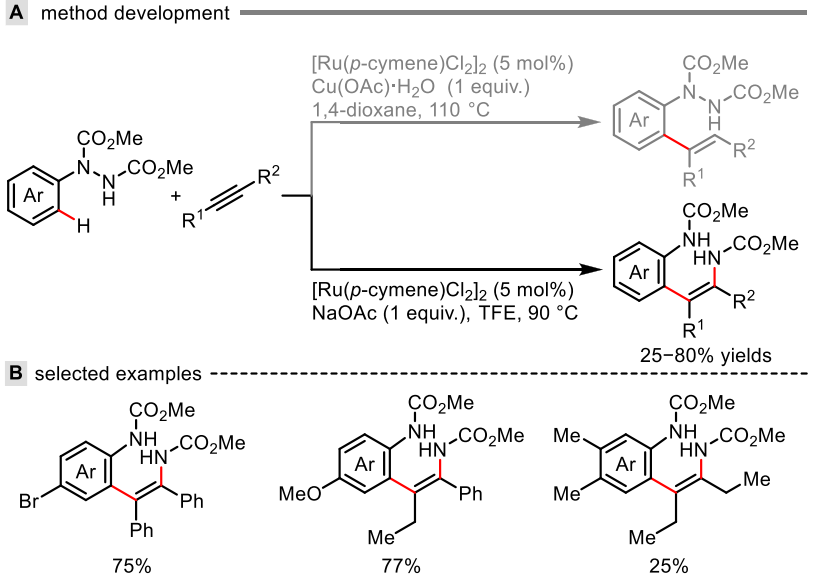
Scheme 15. Rh^{III}-Catalyzed Carboamination of Sulfonyl and Phosphinyl Allenes with *N*-Enoxy Imides



Scheme 16. Ru^{II}-Catalyzed 1,2-Carboamination of Alkynes with Arylhydrazine-1,2-dicarboxylates



pathway. Here, the presence of an additional C═C bond inherently favors the facile generation of an η^3-allylic Rh species prior to β-H elimination, which then undergoes a stereo-determining amide transfer through intramolecular nucleophilic substitution of imine to the π-allylrhodium moiety. The enantioselectivity was rationalized by comparing the energy differences between the two transition states $\mathbf{TS}_R$ and $\mathbf{TS}_S$ with respect to related enantiomers in several alcoholic solvents (Scheme 11C). The results indicated that the Gibbs free energy of $\mathbf{TS}_S$ is consistently higher than that of $\mathbf{TS}_R$ by about 1.7 kcal/mol, corresponding to good calculated ee values (up to 92% ee), which was well in line with the experimental observation that *R*-selective products were obtained with good enantioselectivity.

The same group later disclosed a Rh-catalyzed regio- and stereospecific carboamination of sulfonyl allenes with *N*-phenoxy amides (Scheme 12).[80] This protocol represented a straightforward approach for the construction of highly functionalized allylamine derivatives with the presence of an α-quaternary carbon center and could be facilely employed for the late-stage C−H modification of complex natural products and bioactive molecules. Divergent transformations of the allylamine products, such as hydrolysis of the amide moiety into free NH_2 and reductive desulfonylation, further demonstrated its profound synthetic potential.

3. *N*-ENOXY IMIDES AS BOTH C−H SUBSTRATES AND AMINATION SOURCES

In a search for versatile C−H substrates and N-sources for carboamination transformations, *N*-enoxy imides have attracted continuous interest from synthetic chemists.[81−86] In 2014, Rovis and colleagues disclosed that *N*-enoxyphthalimides underwent an Rh^{III}-catalyzed C−H activation and coupled with electron-deficient alkenes to afford the intriguing cyclopropane adducts (Scheme 13A).[86] The mechanism has been proposed to involve the formation of intermediate **A3** resulting from alkene carborhodation, wherein the rhodium center ligates the enol alkene fragment due to coordinative unsaturation and thus experiences an additional migratory insertion to form the C−C bond in the cyclopropane product.

Inspired by these advances, the authors envisioned that a bidentate directing group might enable the rhodium center to be coordinatively saturated, thus probably switching the reaction path from cyclopropanation to carboamination via a direct C−N bond reductive elimination. Based on this hypothesis, the same group later achieved a Rh^{III}-catalyzed *syn*-carboamination of alkenes using *N*-enoxyphthalimides as both the C- and N-sources (Scheme 13B,C).[87] The choice of methanol as the reaction solvent was decisive, which enabled *in situ* ring opening of the phthalimide fragment to form a phthalimide-derived amido ester as a transient bidentate directing group. In addition, further ligand modification revealed that a beneficial effect on

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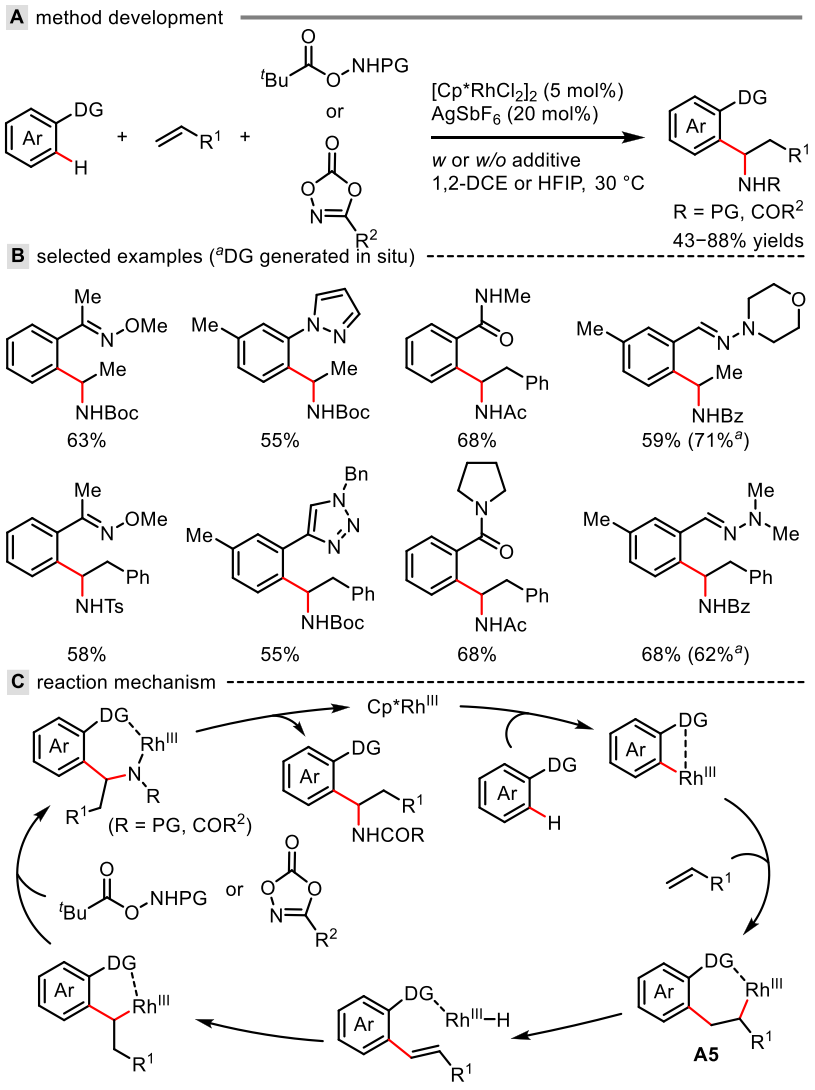
Scheme 17. $Cp^{X}Rh^{III}$-Catalyzed 1,1-Carboamination of Alkenes with Aromatic C−H Substrates and Electrophilic Aminating Agents



the reactivity and chemoselectivity was posed by increasing the steric hindrance of the cyclopentadienyl ligand, with *tert*-butyltetramethylcyclopentadienyl (Cp^{*tBu}) being optimal. Of note, the specific *syn*-selectivity of the reaction was verified by the stereochemical outcome of the parallel coupling with fumarate and maleate esters. Mechanistically, a Rh^{III}−Rh^{I}−Rh^{III} catalytic cycle was proposed by Rovis et al., in which the C−N bond reductive elimination followed by an oxidative addition process might be involved. An alternative Rh^{III}−Rh^{V}−Rh^{III} mechanism involving a Rh^{V}-nitrenoid intermediate was also assumed by Chen, Liu, et al. on the basis of a computational analysis (Scheme 13D).[88]

The asymmetric variant was recently achieved by Cramer and co-workers, who developed an enantioselective $Cp^{X}Rh^{III}$-catalyzed intermolecular carboamination of acrylates through vinylic C−H activation of *N*-enoxysuccinimides for the synthesis of chiral α-amino esters (Scheme 14).[89] Notably, related *N*-enoxyphthalimide derivatives failed to deliver the carboamination products. A tailored bulky trisubstituted chiral Cp^{X} ligand was also found to be essential to ensure the carboamination pathway as well as high levels of enantioselectivity. The observed enantioselectivity could be rationalized by the steric bulk between the methyl cyclohexyl moiety and the olefinic ester group, which resulted in the orientation to give the selective *S*-products.

In addition, allene carboamination was also investigated. In the context of carboamination of sulfonyl allenes with *N*-phenoxy amides (Scheme 12),[80] the Rh-catalyzed procedure also extended the use of both *N*-enoxyphthalimides and *N*-enoxysuccinimides as bifunctional reactants to carboaminate the allene moiety (Scheme 15).

4. ARYLHYDRAZINES AS BOTH C−H SUBSTRATES AND AMINATION SOURCES

In contrast to the above bifunctional substrates used for the transfer of nitrogen and carbon portions via the fission of the O−N bond, a similar N−N bond cleavage strategy for selective carboamination of π-compounds remains elusive. The sole example came from the Reddy group, in which they utilized arylhydrazine-1,2-dicarboxylates as the bifunctional reagents for carboamination of internal alkynes for the synthesis of enecarbamates (Scheme 16).[90] This reaction was exclusively enabled by a Ru^{II} catalytic system instead of the above $Cp^{*}M^{III}$ catalysis, and the proposed mechanism involved a Ru^{II}−Ru^{0}−

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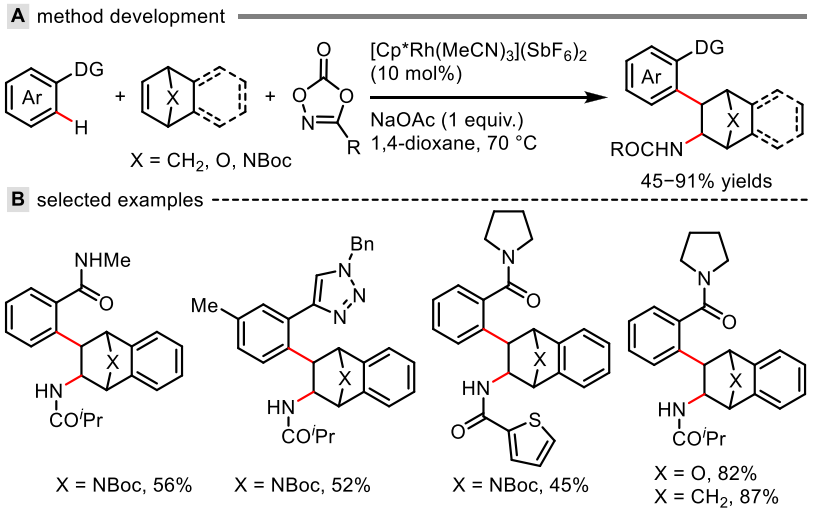
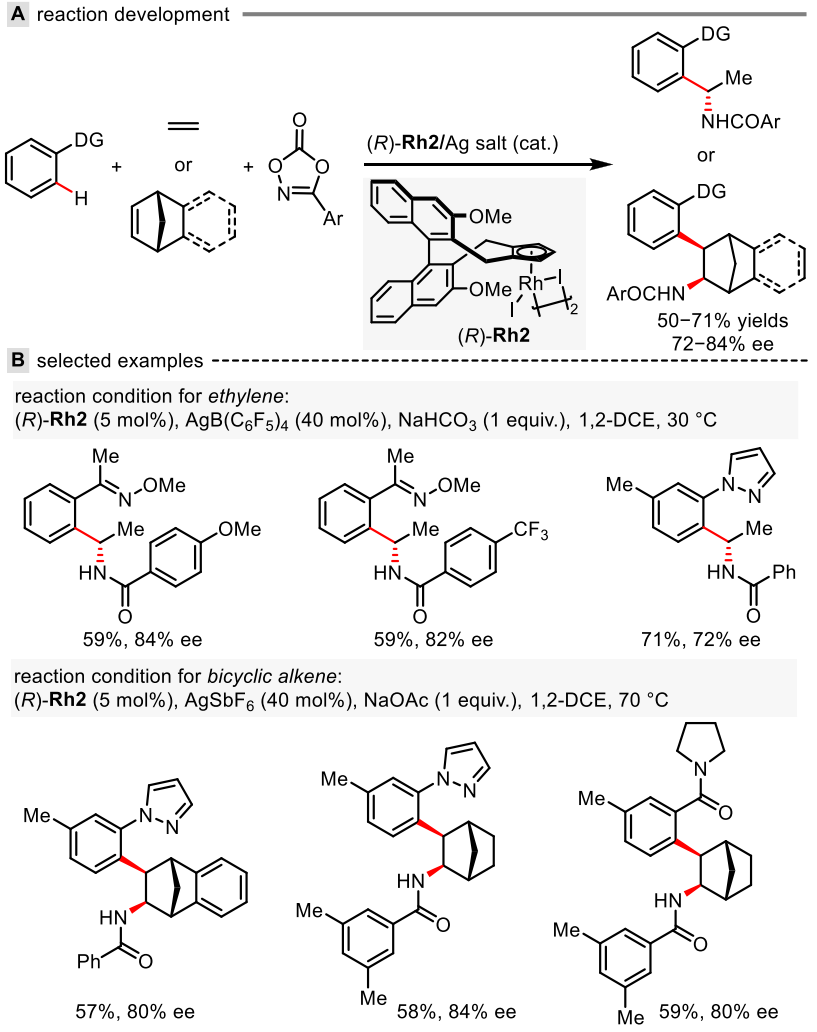
Scheme 18. Rh^{III}-Catalyzed 1,2-Carboamination of Bicyclic Alkenes of Aromatic C−H Substrates and Dioxazolones



Scheme 19. $Cp^{X}Rh^{III}$-Catalyzed Enantioselective Carboamination of Ethylene and Bicyclic Alkenes with Aromatic C−H Substrates and Dioxazolones



Ru^{II} catalytic pathway. A relatively higher reaction temperature was required to ensure moderate efficiency for this transformation, which was probably due to the lower reduction potential of the N−N bond than an O−N bond. Of note, the choice of trifluoroethanol as the reaction medium seems crucial to facilitate the C−N bond reductive elimination, thus suppressing the direct protonolysis process to form a hydroarylated product.

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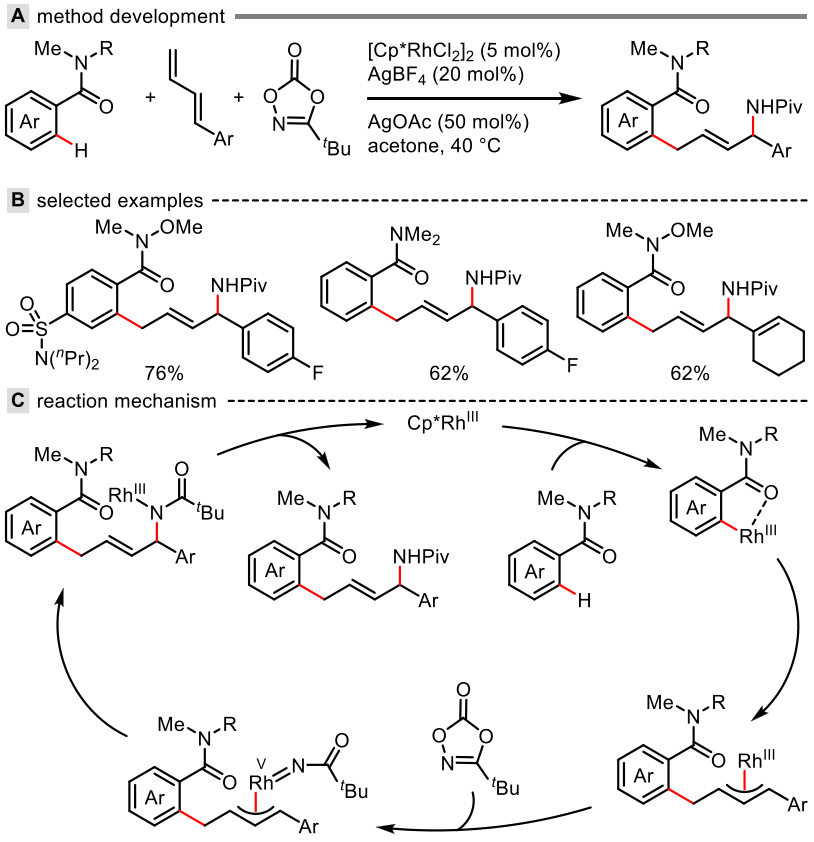
Scheme 20. $Cp^{X}Rh^{III}$-Catalyzed 1,4-Carboamination of 1,3-Dienes with Weinreb Amides and Dioxazolones



5. CONJUGATIVE COUPLING WITH DISCRETE C−H SUBSTRATES AND AMINATION SOURCES

The aforementioned two-component carboamination strategy uses a bifunctional reactant to serve as both C- and N-resources for difunctionalization of C−C π-compounds, but it often suffers from limited substrate accessibility and structural diversity. In contrast, the use of an exogenic aminating reagent would provide an alternative, three-component carboamination strategy of C−C π-bonds, thus enriching the reaction complexity and the substrate diversity to a certain extent.[91] In 2019, Ellman et al. reported an interesting Cp*Rh^{III}-catalyzed 1,1-addition of C−H bonds and aminating agents to terminal alkenes for the construction of diverse benzylamine derivatives (Scheme 17).[92] The robustness of the reaction was demonstrated by varying all three inputs to obtain a broad range of α-branched benzylamine products. Both *O*-acyl hydroxamic acids and dioxazolones *could* serve as electrophilic aminating sources to prepare carbamate- and toluenesulfonyl (Ts)-protected benzylamines, as well as alkyl and aryl amide derivatives, respectively. Remarkably, the protocol was widely applicable to styrenes, acrylates, and unactivated olefins, even including the bulk chemical feedstocks ethylene and propylene. Moreover, this transformation was amenable to different C−H bond substrates with commonly encountered directing groups, such as pyridine, pyrimidine, triazole, pyrazole, oxime, amide, and hydrazone. The *in situ* generated hydrazone substrates from related aromatic aldehydes and hydrazines also resulted in good reactivity, thus enabling a one-pot, four-component carboamination process with comparable efficiency.[93] Mechanistically, this unexpected 1,1-alkene addition could be rationalized by the β-H elimination of rhodacycle intermediate **A5** resulting from alkene carborhodation, followed by M−H reinsertion and terminated by an intermolecular electrophilic amination step (Scheme 17C).

Subsequently, the three-component carboamination strategy has been successfully extended to couple with bicyclic alkene partners, leading to the formation of the 1,2-addition products (Scheme 18).[94] In addition, the asymmetric variants of both 1,1-[92] and 1,2-carboamination[94] reactions have been achieved by virtue of the chiral $Cp^{X}Rh^{III}$ catalytic system, albeit with relatively moderate enantioselectivity (Scheme 19). Taken together, these advances not only provided a straightforward and high-efficiency route for the assembly of such skeletons in a stereoselective manner but also illustrated their profound synthetic potential for future application.

In comparison with alkenes, carboaminations of conjugated dienes could be conceivably more complicated by an additional regiocontrol. For instance, Glorius et al. achieved the intriguing Rh^{III}-catalyzed highly selective 1,4-carboamination of 1,3-dienes with Weinreb amides and dioxazolones (Scheme 20).[95] Their results showed that the use of a sterically demanding *tert*-butyl dioxazolone was essential for realizing the 1,4-selectivity, which was further confirmed by the experimental observation that an alternative 1,2-carboamination product was formed by switching *tert*-butyl dioxazolone to the less bulky methyl dioxazolone. A η^3 π-allyl rhodium species was proposed to be involved in the catalytic cycle, which proceeded by a steric-hindrance-controlled 1,4-selective C−N bond reductive elimination to furnish the desired products (Scheme 20C).

Despite the precedented two-component 1,2-carboamination of dienes, Li et al. recently reported a three-component chiral $Cp^{X}Rh^{III}$-catalyzed regiospecific and enantioselective 1,2-carboamination of dienes with amides, in which dioxazolones

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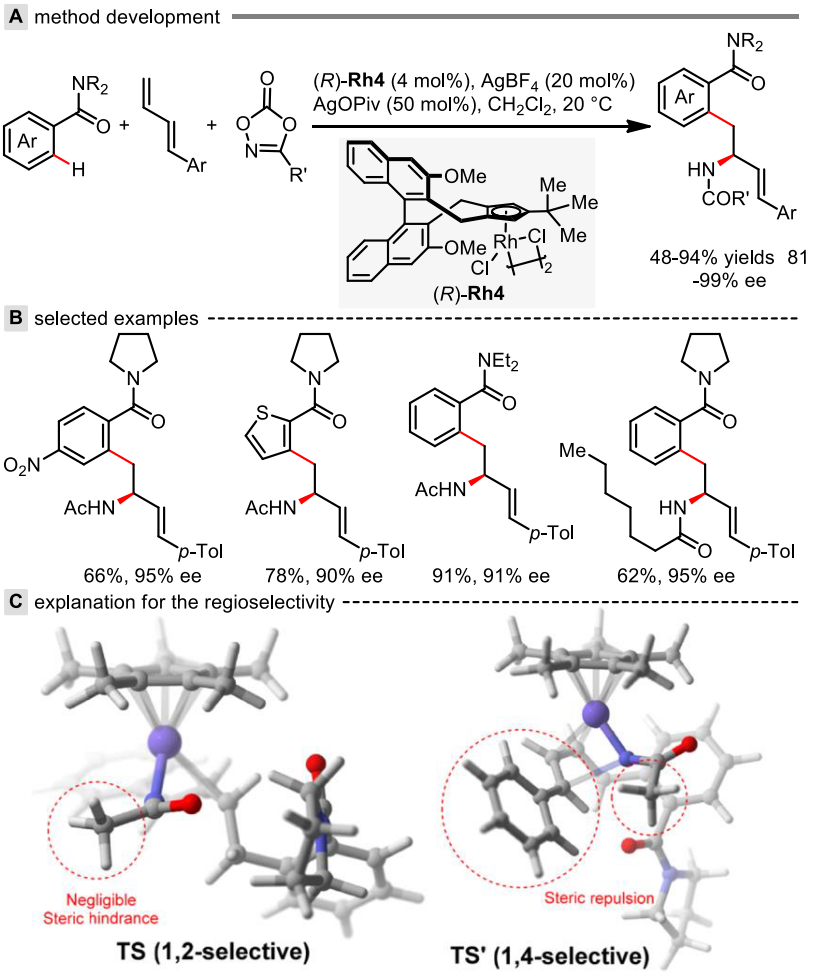
Scheme 21. Cp^XRh^{III}-Catalyzed Enantioselective 1,2-Carboamination of 1,3-Dienes with Aromatic Amides and Dioxazolones



were employed as versatile aminating reagents (Scheme 21).[96] The contrast of this protocol with the aforementioned 1,4-carboamination of dienes from the Glorius group, similar catalytic systems and substrates were engaged but resulted in distinct 1,2-/1,4-selective carboamination. Further DFT calculations were carried out to account for this difference, and the results revealed that the steric effect between the arene (directing group) and the aminating reagent played a crucial role in determining the regioselectivity (Scheme 21C).

Compared to the above three-component carboamination of alkene or diene substrates, such a strategy remains less developed for alkynes. This was probably due to the easier protonolysis in comparison to further electrophilic amination of a vinyl metal species generated via alkyne insertion. In contrast, the aryne chemistry has evolved as a powerful platform for vicinal difunctionalization of aromatic rings.[97] The *in situ* generated arynes are extremely reactive electron-deficient intermediates, which facilely undergo the nucleophilic addition process, followed by trapping with an electrophilic partner to give difunctionalized products. Based on this understanding, Xiao, Chen, et al. realized a Cu-catalyzed three-component carboamination of benzynes with C−H substrates and *O*-benzoylhydroxylamines (Scheme 22).[98] In the reaction, the benzyne species could be generated from a mild fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates. Moreover, further investigation found that terminal alkynes and benzoxazoles were able to be used as versatile C−H bond activation substrates. Taken together, this protocol represented an efficient carboamination of benzynes and provided modular access to *o*-alkynylanilines or *o*-benzoxazolyl anilines which were otherwise difficult to prepare.

6. CONCLUSION AND OUTLOOK

Intermolecular carboamination across C−C multiple bonds has emerged as an efficient and powerful tool for the synthesis of diverse and valuable amine derivatives. This review has summarized the recent development of organometallic C−H activation mediated by redox-neutral and nonannulative carboamination reactions. Mechanistically, these reactions commence with a C−H metalation, followed by an intermolecular migratory insertion into C−C π-bonds and terminated by an electrophilic aminating trapping.

Despite significant advances made in this reaction type, it is still far from synthetic maturity and remains to face new challenges in several aspects. (1) A deeper insight into the detailed mechanism is required, especially for the elementary electrophilic aminating step determining whether a higher-valent metal center is involved or not. (2) Most established carboamination reactions are enabled by elaborately designed Cp^XM^{III} catalysts—hence the development of a simple, abundant, and inexpensive catalytic system, e.g., based on the first-row transition metals, is highly desirable. (3) All the studies reviewed here originated from an organometallic C(sp^2)−H cleavage, and related C(sp^3)−H activation initiated variants are

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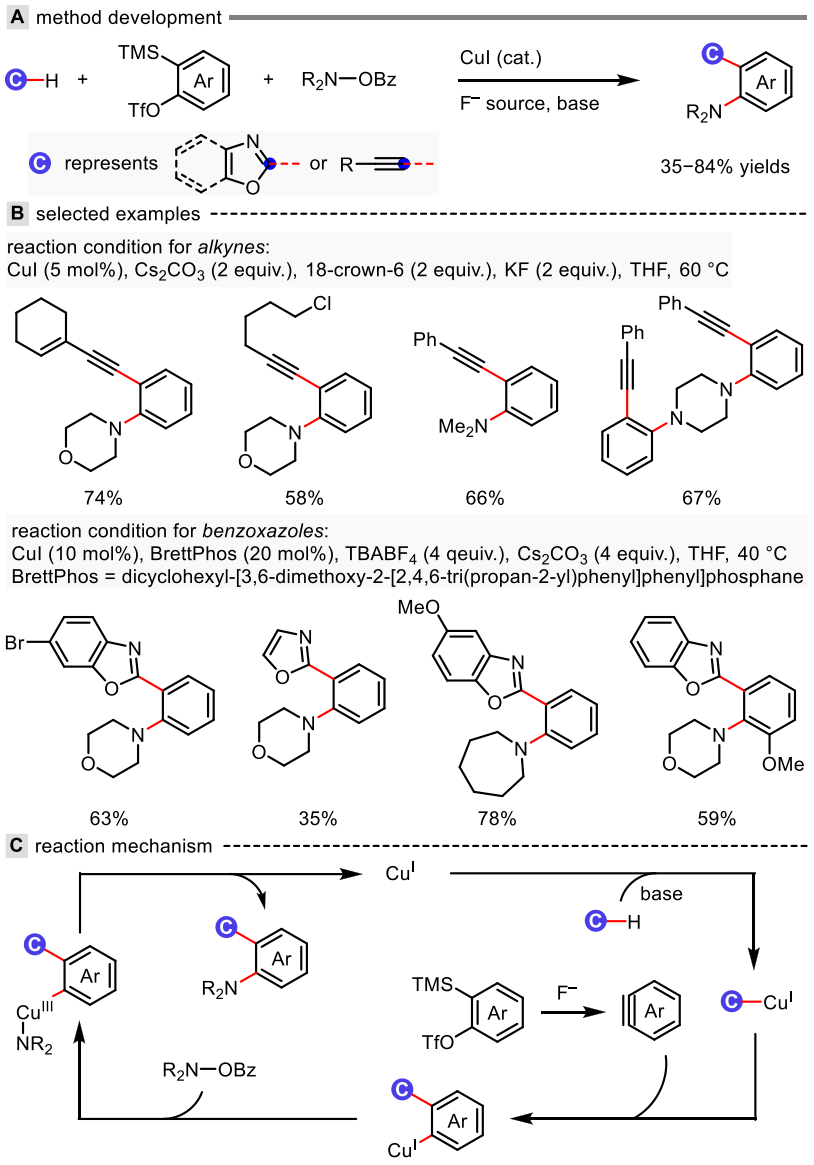
Scheme 22. Cu^{I}-Catalyzed 1,2-Carboamination of Benzynes with Terminal Alkynes/Benzoxazoles and *O*-Benzoylhydroxylamines



still unexplored. (4) Although a handful of asymmetric carboamination approaches have been developed, most of their enantioselectivities are still needed to be improved further.

Overall, intermolecular nonannulative carboamination represents an exciting and rapidly growing research field, which would bring many opportunities for method and catalyst developments, mechanistic investigations, and synthetic applications. We believe that this timely review will attract great enthusiasm of chemists over the coming years.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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