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Three-Component Regioselective Carboamidation of 1,3-Enynes via Rhodium(III)-Catalyzed C-H Activation

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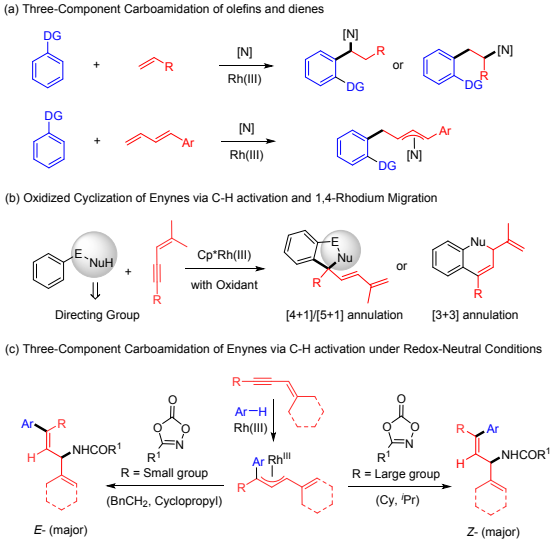
Rhodium-catalyzed regio- and stereoselective three-component carboamidation of 1,3-enynes has been realized using indoles and dioxazolones as the functionalizing reagents. The reaction proceeded via C-H activation, alkyne insertion, and formal 1,4-rhodium migration to give Rh(III) allyl intermediates that undergo regioselective electrophilic amination. A wide range of multi-substituted skipped 1,4-dienes have been constructed in good yields and excellent stereoselectivity. The stereoselectivity is under substrate control. 1,3-Enynes bearing a relatively bulky alkyne terminus reacted with *Z*-selectivity. In contrast, a sterically less hindered alkyne terminus tends to predominantly give the *E*-configured skipped diene.

Multicomponent reactions allowed the rapid assembly of three or more reagents to construct value-added complex structures from simple precursors in one shot. The presence of multiple functional groups in the products also offers useful handles and enhances the molecular complexity toward applications.[1] With the development of metal-catalyzed C-H functionalization,[2] unactivated C-H bonds in arenes serve as a convenient and abundant carbon source that reacts with two different coupling partners for the synthesis of an enormous range of products.[3] In this context, three-component carboamination reactions provide a highly efficient strategy to create C-C and C-N bonds in a single step.[4] In 2019, Ellman elegantly reported Rh(III)-catalyzed 1,1-carboamination of terminal alkenes using dioxazalone as the amidating reagent.[5] Subsequently, Ellman[6] and Rovis[7] independently reported 1,2-carboamination of bridged bicyclic alkenes or acrylates. Recently, Glorius reported 1,4-carboamidation of conjugated dienes,[8] and our group realized the related enantioselective version with the complementary 1,2-regioselectivity.[9] Despite the progress, the coupling partner of three-component carboamination reactions have been limited to alkenes and conjugated dienes, and the regioselectivity has also been quite limited.[10] Given the abundance of unsaturated reagents, it is necessary to explore reagents other than olefins and dienes. The employment of other multifunctional unsaturated coupling reagents should enhance the reaction patterns, the structural complexity of the products, and utility of the multifunctional products.



Scheme 1. Carboamination of Olefins or Enynes via C-H Activation

In this context, the Lam group introduced 1,3-enynes as versatile reactants in Rh(III)-catalyzed C-H bond activation-annulation reactions.[11] These reactions were proposed to occur via a key step of alkenyl-to-allyl 1,4-rhodium migration, resulting in formation of reactive π-allyl intermediates, and subsequent interactions with the nucleophilic directing group afforded the [3 + 3], [4 + 1], or [5+1] annulation with

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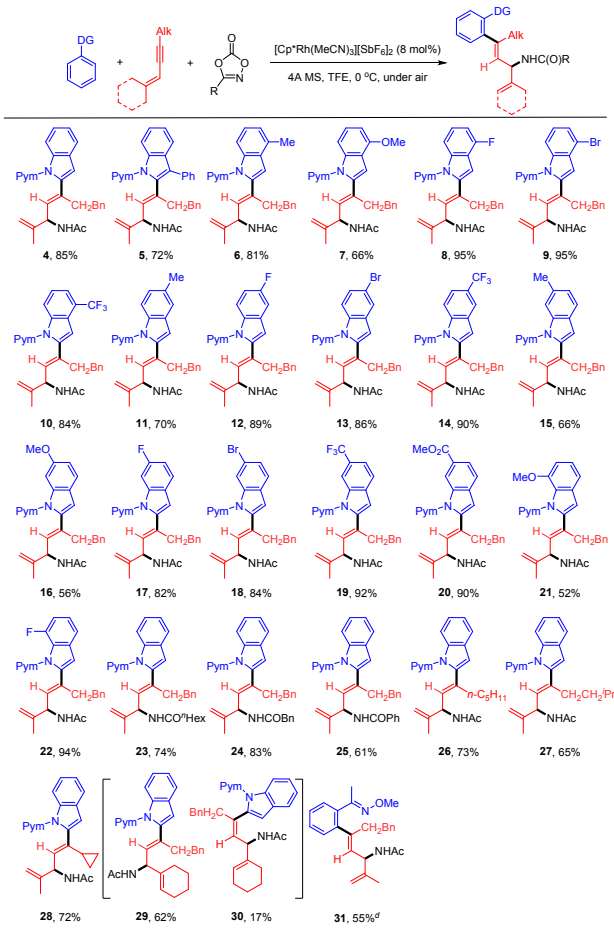
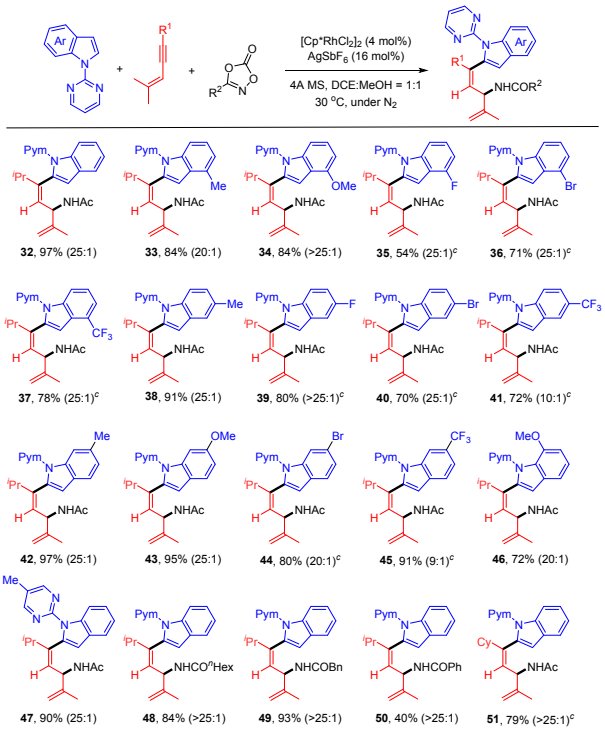
concomitant formation of C-C and C-N bonds.[12] In 2020 during the development of the asymmetric version of this system,[13] our group further explored the mechanism of the allyl formation and proposed an alternative mechanism based experimental and computational studies.[12b] Despite the systematic development, the reaction pattern is limited to two-component annulation, where stoichiometric amounts of oxidant were required in order to re-oxidize the Rh(I) species back to the Rh(III) to complete the catalytic cycle.[14] We reasoned that the key rhodium η^3-allyl species generated from the interactions between the Rh-aryl bond and the 1,3-enyne could be trapped by an electrophilic amidating reagent under redox-neutral conditions.[15] However, the reaction may be complicated by regioselectivity of the allyl amidation because two eta-3 allyl species can be possible. In addition, the stereoselectivity issue may add to the complexity. Herein, we report Rh(III)-catalyzed three-component carboamination reaction between indoles, 1,3-enynes, and dioxazolones with high *E*/*Z* selectivity and high regioselectivity.



Scheme 2. Three-component carboamidation for the synthesis of *E*-products. [a]Reaction Conditions: Arene (0.2 mmol), 1,3-enynes (0.3 mmol), amidating reagents (0.24 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (8 mol%), and 4 Å M.S. (100 mg) in TFE (2 mL) at 0 °C for 12 h without exclusion of air or moisture. [b]Isolated yield; *E*/*Z* ratio >25:1 unless otherwise mentioned. [c]The ratio of *E*/*Z*. [d]At 15 °C for 24 h.

We initiated our investigation by identifying the reaction conditions with *N*-pyrimidylindole **1a**, 1,3-enyne **2a**, and methyldioxazolone **3a** as the model substrates (ESI, Table S1). To our delight, we observed the desired carboamidation product **4** in moderate yield and with > 25:1 *E*/*Z* ratio in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ and 4 Å M.S. in HFIP at 30 °C for 12 h without exclusion of air or moisture (entry 1). The *E* configuration of the product **4** was determined by X-ray crystallography (CCDC 2239434). Switching the catalyst to $[Cp^*RhCl_2]_2/AgSbF_6$ or $[Cp^*Rh(OAc)_2]$ only gave lower yields (entries 2-3). Screening of solvents revealed that TFE was the best choice, which afforded the desired product in 65% yield (entries 4-8). In contrast, poor stereoselectivity was obtained when a halogenated solvent was used. To our delight, the yield was increased to 88% when the reaction temperature was lowered to 0 °C without elongation of the reaction time (entries 9-10)

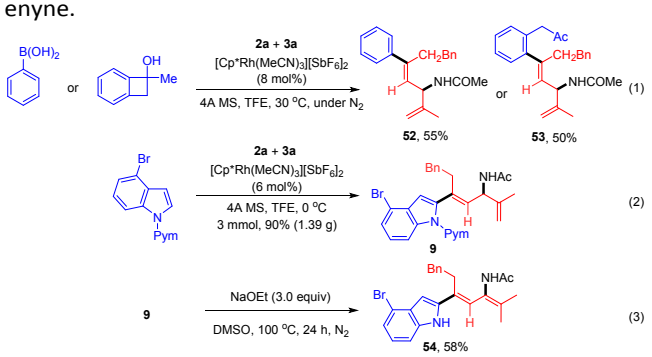


Scheme 3. Three-component carboamidation for the synthesis of Z-products. [a]Reaction Conditions: Indoles (0.2 mmol), 1,3-enynes (0.3 mmol), amidating reagents (0.24 mol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), and 4 Å M.S. (100 mg) in DCE/MeOH = 1:1 (2 mL) at 30 °C for 12 h under N_2. [b]Isolated yield (*Z*/*E* ratio in parentheses). [c]DCE/2-Methyl-2-butanol = 1:1.

Under the optimized reaction conditions, the scope and limitation of this three-component carboamidation reaction were examined (Scheme 2). As anticipated, *N*-pyrimidinylindoles bearing electron-donating, -withdrawing and halogen groups at the C4/C5/C6/C7 positions were all tolerated and reacted to give the corresponding products in 52-95% yields and with perfect *E*-selectivity (**6**-**22**). When 3-phenyl substituted indole was employed, the reaction afforded product **5** in 72% yield, which indicated that the reaction efficiency was insensitive to the steric effect. Next, a broad scope of the other two coupling partners has also been established. *n*-Hexyl, benzyl, and phenyl substituted dioxazolones all worked smoothly to furnish the carboamidation products in moderate to good yields (**23**-**25**).

1,3-Enynes with less bulky alkyl or cycloalkyl terminus reacted smoothly to yield the corresponding products in 65-73% yields (**26**-**28**). In all these cases, the carboamidation product was exclusively *E*-configured. In contrast, two stereoisomeric products (*E* and *Z* configuration, **29** and **30**) were isolated in 62% and 17% yield, respectively, for cyclic olefin substituted 1,3-enyne, indicative of the stereoelectronic effect of the alkyne. In addition, the arene has also been extended to an oxime ether, accessing the product in acceptable yield in the same selectivity (**31**).

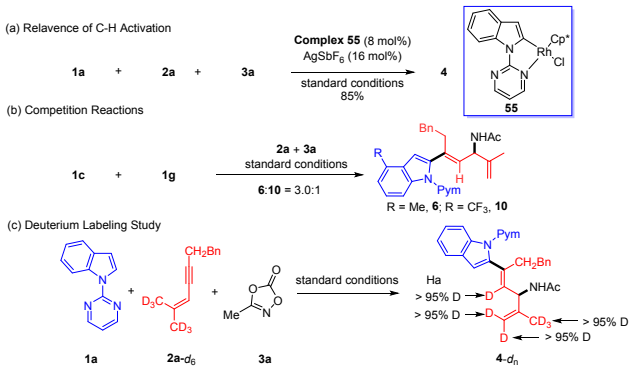
To better define the scope of the enyne substrate, we further examined those with a relatively bulky alkyne terminus. Delightfully, the *Z*-configured product **32** was obtained in excellent yield and selectivity after quite extensive optimization studies using the alkyne with a large ^{i}Pr terminus. The scope of the carboamidation reaction in this selectivity was then explored (Scheme 3). *N*-pyrimidinylindoles containing electron-donating groups (Me, OMe), -withdrawing groups (CF_3), as well as halogen substituents (F, Br) at the C4/C5/C6 positions all coupled effectively, and the products were isolated in 54-97% yields and with 9:1 to > 25:1 *Z*-selectivity (**32**-**45**). The reaction also tolerated a 7-methoxyl-substituted indole substrate, and the product **46** was isolated in 72% yield. Introduction of a Me group into the pyrimidyl ring was also tolerated, affording the corresponding product in high yield (**47**). Replacement of the Me group in the dioxazolone by other alkyl or aryl groups such as n-hexyl, benzyl or phenyl group also afforded the product in 40-93% yields (**48**-**50**) and in excellent selectivity. In addition, cyclohexyl-substituted 1,3-enyne could also be employed, and the product **51** was isolated in 79% yield. The *Z* configuration of product **51** was confirmed by X-ray crystallography (CCDC 2239432). In contrast, no reaction occurred for an aryl-linked enyne.



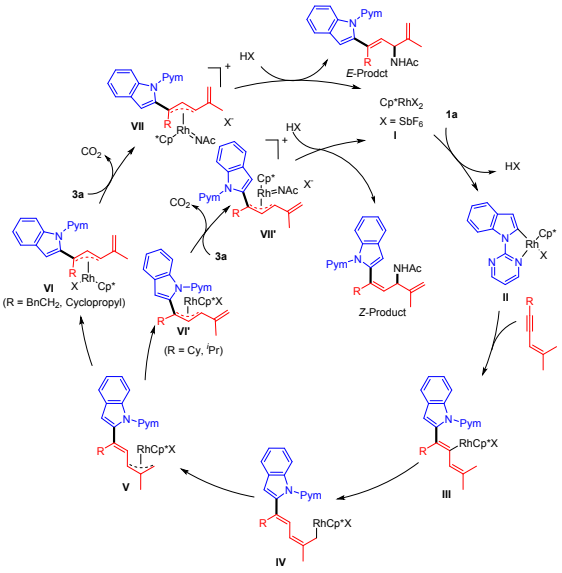
Scheme 4. Scale-Up and Derivatization Reactions.

Additional experiments have been conducted to further explore the scope of this three-component carboamination reaction. The carbon-based nucleophile has been extended to phenylboronic acid and 7-methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol, which reacted to give the corresponding reactive organorhodium intermediate via transmetalation or β-carbon elimination, affording the products **52** and **53** in moderate yields (eq 1). These results indicated that the directing group in the arene is no longer necessary. To demonstrate the synthetic utility of this protocol, a scale-up (3 mmol) synthesis of product **9** was performed, which proceeded smoothly to give **9** in 90% isolated yield under reduced catalyst loading (eq 2). Synthetic application has been also briefly explored. The treatment of **9** with NaOEt afforded 1,3-diene **54** in 58% yield with removal of the directing group (eq 3).

To interrogate the mechanism of this coupling system, several experiments have been conducted (Scheme 5). The carboamination product **4** was isolated in 85% yield when using rhodacyclic complex **55** as a catalyst precursor under otherwise the same conditions. This observation suggests that the reaction follows a C-H activation pathway. Next, competition experiments using an equimolar mixture of electronically differentiated indoles (4-Me and 4-CF_3) revealed that electron-rich substrate is kinetically favored. Furthermore, the reaction of **1a** with the hexadeuterated 1,3-enyne [D]$_6$-**2a** was conducted. Significant levels of deuteration (>95% D) were observed at the alkenyl and the original methyl positions, and essentially no deuterium scrambling was detected in the product. This seems to suggest irreversible 1,4-Rh migration and the previously proposed δ-elimination pathway is probably not relevant.[12b]



Scheme 5. Mechanistic Studies.



Scheme 6. Proposed Catalytic Cycle.

Based on the experimental results and previous related mechanistic proposals,[11-12] a plausible catalytic cycle is outlined in Scheme 6. C-H activation of indole **1a** gives a five-membered rhodacycle **II**. Subsequently, coordination of the 1,3-enyne and

regioselective migratory insertion of Rh-C(aryl) delivers a rhodium alkenyl intermediate **III**, which is proposed to undergo 1,4-Rh(III) migration to generate the intermediate **IV**. Allyl-to-allyl rearrangement of **V** generates a π-allyl rhodium(III) specie **VI** or **VI'**, and the stereochemistry of the allyl ligand is largely dictated by steric effect of the R group in the 1,3-enyne such that minimized repulsions between the rhodium and the indole ring or the R group is experienced. This π-allylrhodium intermediate then undergoes ligation of the dioxazolone, followed by decarboxylation to give a reactive Rh(V) allyl nitrene species **VII** or **VII'**. Then C-N reductive elimination from this intermediate and protodemetalation releases *E* or *Z*-configured products and closes the catalytic cycle.

In conclusion, we have developed a Rh(III)-catalyzed stereoselective three-component carboamination reaction between indoles, 1,3-enynes, and dioxazolones, providing a new approach to access multi-substituted 1,4-dienes in a redox-neutral fashion. The stereoselectivity is under substrate control. Large 1,3-enynes with a large alkyne terminus (Cy, ^{i}Pr) tend to give *Z*-configured products, whereas small steric group at this position ($BnCH_2$, cyclopropyl) reacted predominantly with the *E*-selectivity. The reaction pathway likely involves the Rh(III)-catalyzed C-H activation, alkyne insertion, 1,4-Rh(III) migration, allyl-to-allyl rearrangement, and subsequent electrophilic amidation. Further studies on the three-component difunctionalization reaction of other unsaturated coupling partner are currently underway in our laboratories.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest to declare.

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