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Rh(III)-Catalyzed Three-Component *Syn*-Carboamination of Alkenes Using Arylboronic Acids and Dioxazolones

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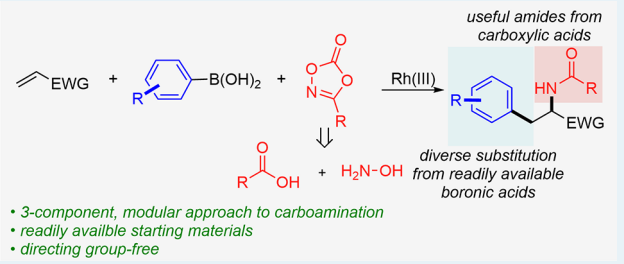
ABSTRACT: Herein, we report a Rh(III)-catalyzed three-component carboamination of alkenes from readily available aryl boronic acids as a carbon source and dioxazolones as nitrogen electrophiles. This protocol provides facile access to valuable amine products including α-amino acid derivatives in good yield and regioselectivity without the need for a directing functionality. A series of experiments suggest a mechanism in which the Rh(III) catalyst undergoes transmetalation with the aryl boronic acid, followed by turnover limiting alkene migratory insertion into the Rh(III)-aryl bond. Subsequently, fast Rh-nitrene formation provides the *syn*-carboamination product selectively after reductive elimination and proto-demetalation. Importantly, the protocol provides three-component coupling products in preference to a variety of two-component undesired byproducts.



KEYWORDS: *carboamination, Rh(III) catalysis, α-amino acid synthesis, alkene difunctionalization, directing group-free*

The simultaneous installation of two functional groups across the ubiquitous alkene double bond in a stereoselective manner is a powerful transformation in organic synthesis[1] and provides an efficient way of rapidly increasing molecular complexity from readily available starting materials. Among various potential difunctionalizations, the carboamination of alkenes offers direct access to valuable and pharmaceutically important amine products by forming both C−C and C−N bonds in a single step.[2] A handful of powerful annulations,[3] or intramolecular carboaminations,[4] have been developed, which are currently limited to the synthesis of cyclic products.

In 2015, we described a Rh(III)-catalyzed stereospecific, *syn*-carboamination of activated alkenes using *N*-enoxyphthalimide as both carbon and nitrogen source of the reaction to furnish acyclic amine products (Scheme 1a).[5] Subsequently, Glorius reported the carboamination of acrylates initiated by Cp*Co(III)-catalyzed Csp^2−H activation of *N*-phenoxyamides (Scheme 1b),[6] followed more recently by Cramer's demonstration of an asymmetric version of this reaction.[7] Recently, Ellman reported the synthesis of α-branched amine through the Rh(III)-catalyzed three-component 1,1-carboamination of terminal alkenes that also was initiated by directing-group-assisted C−H activation (Scheme 1c).[8]

Other significant contributions toward the linear carboamination of alkenes have been made utilizing Pd or Ni catalysis with olefins bearing covalently linked aminoquinoline directing groups,[9] as well as through single electron pathways involving nitrogen or carbon centered radicals.[2b,10]

Despite recent progress in the field, the current state-of-the-art in carboamination involves additional steps to install and remove the often-undesired directing functionality, an inherent loss in stereocontrol imparted through open shell intermediates, or synthetically taxing substrates that limit the chemical space available to their practical application.

In searching for a more general solution to this problem, we became interested in developing an intermolecular three-component carboamination that uses readily accessible carbon and nitrogen sources. Such a modular approach would enable the rapid synthesis of a diverse library of functionalized amine products by simply switching coupling partners. As a reaction design to achieve this goal (Scheme 1d), we envisioned that a carbon nucleophile coordinates to Cp*Rh(III) complex after transmetalation or ligand displacement then undergoes highly regioselective migratory insertion with activated alkenes in the absence of directing group. Subsequent reaction with nitrene precursors forms Rh-nitrene intermediates which will undergo reductive elimination to form a C−N bond and deliver desired carboamination products.

The challenge is that there are several undesired side product pathways as the reaction becomes a multicomponent system. For example, after transmetalation, it can undergo dimerization of carbon source or direct C−N coupling if subsequent alkene migratory insertion is slow. Also, after

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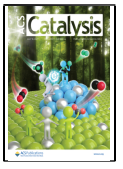
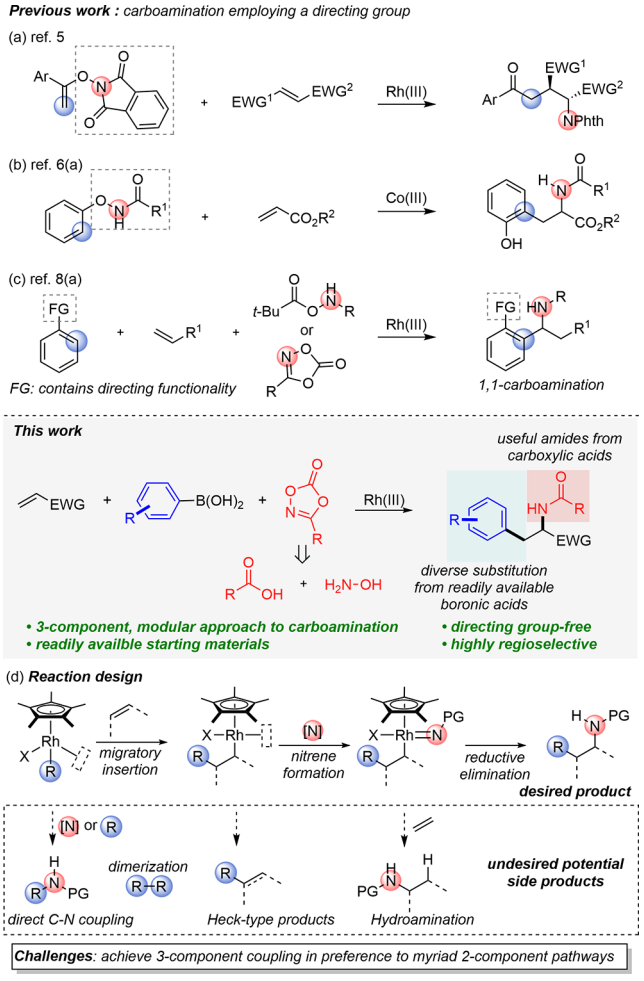


Scheme 1. Intermolecular Carboamination of Alkenes

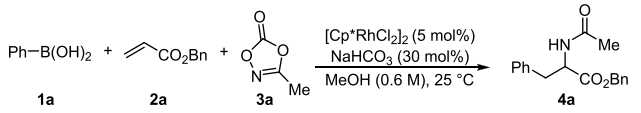


migratory insertion of Rh-carbon bond into the alkenes, undesired β-hydride elimination or protodemetalation will result in Heck-type and hydroarylation products. Last, hydroamination side product also can be formed if the nitrogen source of the reaction directly reacts with the alkene coupling partner.

With this hypothesis in mind, we initiated a systematic investigation of carbon nucleophiles such as organoboron and organostannanes, with nitrene precursors such as azides, hydroxamates, and dioxazolones, under various reaction conditions. An initial hit was identified when we combined phenylboronic acid (**1a**), benzyl acrylate (**2a**), and 3-methyl-1,4,2-dioxazol-5-one (**3a**) with $[Cp^*RhCl_2]_2$ as a catalyst in methanol at room temperature delivering the desired carboamination product (**4a**) in 8% yield, with the mass balance consisting of Heck-type, hydroamination, and direct C−N coupling products. Inspired by a large library of commercially available boronic acids and readily accessible dioxazolones that can be easily prepared from carboxylic acids,[11] we decided to optimize the reaction and gratifyingly, achieved a 77% yield of the desired carboamination product (**4a**) (Table 1, entry 1; see the Supporting Information for details).

Other nitrene precursors[12] that are frequently used for amination chemistry with Cp* group 9 catalysis are completely ineffective for this chemistry. In the cases of Ts-N_3, Ts-NH-OPiv, 5,5-dimethyl-1,4,2-dioxazole, and 1,4,2-dioxazol-5-thi-

Table 1. Reaction Optimization[a]



1a 2a 3a 4a

entry	deviation from standard conditions	yield of **4a**[b] (%)
1	none	77 (68)[c]
2	other nitrene precursors instead of **3a**	–
3	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ instead of $[Cp^*RhCl_2]_2$	–
4	$[Rh(COD)_2Cl]_2$ instead of $[Cp^*RhCl_2]_2$	–
5	NaOAc instead of $NaHCO_3$	5
6	60 °C instead of 25 °C	42
7	**1a** (2 equiv)/ **2a** (1 equiv)/ **3a** (1 equiv)	64
8	1 mmol scale with 2.5 mol % $[Cp^*RhCl_2]_2$	78 (69)[c]

[a]Reactions were conducted on a 0.1 mmol scale using **1a** (2.5 equiv), **2a** (3.0 equiv), and **3a** (1 equiv). [b]Determined by analysis of ^{1}H NMR of the unpurified reaction mixture. [c]Isolated yield.

one, no conversion of starting materials is observed. When *N*-(pivaloyloxy)amides are used as the nitrogen source of the reaction, direct C−N coupling product was observed as major side product and *N*-(tetrafluorophenoxy)amides give Heck-type and hydroarylation side products in high yield. (entry 2; see Table S1 in the Supporting Information for details). Also, the choice of the catalyst is important since cationic Rh(III) catalysts such as $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (entry 3) or an in-situ-generated cationic Rh(III) complex does not lead to the desired product. Several Rh(I) catalysts such as $[Rh(COD)_2Cl]_2$ (entry 4) that are commonly used for conjugate addition chemistry with arylboronic acids[13] or other Cp* group 9 catalysts such as $[Cp^*CoCl_2]_2$ or $[Cp^*IrCl_2]_2$ failed to deliver the carboamination products.

Screening of base additives shows that bicarbonate, carbonate, or fluoride generally gives a higher reaction yield, compared to acetates, and $NaHCO_3$ was selected as the optimal additive. When acetates are used as additive (entry 5), the reaction yield is significantly decreased, and Heck-type product becomes major product of the reaction in low yield. One possible explanation is that acetates act as bidentate ligand and prevent coordination of dioxazolone. The reaction proceeds smoothly at room temperature and has a tendency to give a lower yield at a higher temperature, as shown with the 42% yield obtained when the reaction was conducted at 60 °C (entry 6). When both alkene (**2a**) and dioxazolone (**3a**) are used as the limiting reagent of the reaction, the reaction gives synthetically useful a 64% yield (entry 7), and a 77% yield was achieved when **1a** (2.5 equiv), **2a** (3 equiv), and **3a** (1 equiv) was used for the reaction (See Table S4 in the Supporting Information for details). Lastly, the reaction can be performed on a 1.0 mmol scale with 2.5 mol % catalyst loading without loss of the product (entry 8).

Having optimized the reaction conditions, we next sought to explore the scope of the transformation (Scheme 2). The reaction with aryl boronic acids containing a variety of functional groups at the para position of phenyl ring proceeds smoothly, delivering products with -CF_3 (**4b**), −F (**4c**), −Br (**4d**), −OMe (**4e**), hydroxy (**4f**), silyl ether (**4g**), alkene (**4h**), alkyl (**4i**), nitrile (**4j**), and aldehyde (**4k**) functional groups in good yield. Aryl boronic acids with a substituent in the meta position (**4l**), having multiple substituents (**4o**, **4p**), naphthyl boronic acid (**4q**), and 3,4-methylenedioxyphenylboronic acid

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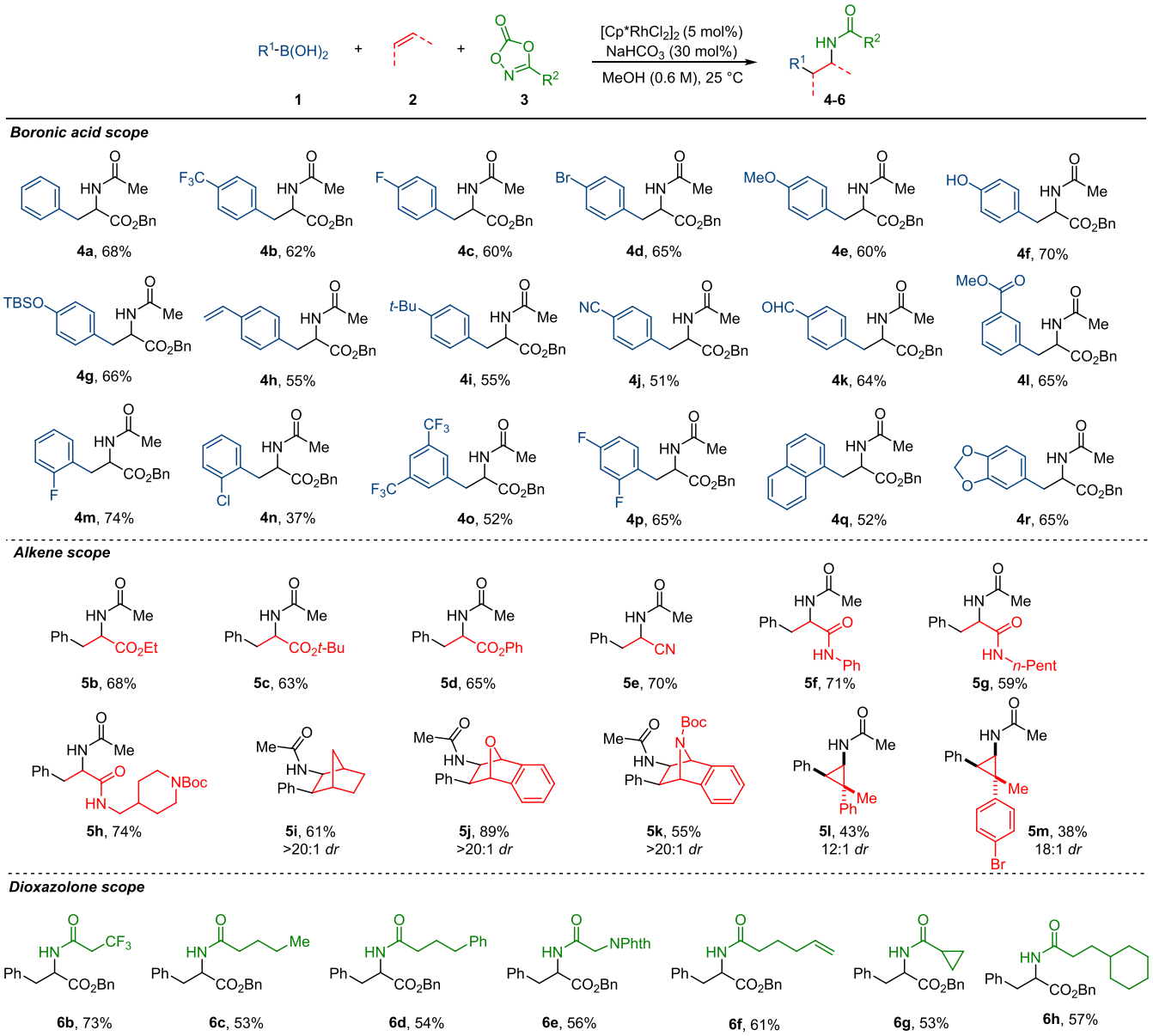
Scheme 2. Substrate Scope[a]



[a]Reactions were conducted on a 0.1 mmol scale using **1** (2.5 equiv), **2** (3.0 equiv), and **3** (1.0 equiv). Yields of isolated products after purification by chromatography are reported.

(**4r**) also work well in this reaction. In the case of vinyl boronic acids such as 1-penten-1-ylboronic acid or alkyl boronic acids, the reactions are unsuccessful. (See the Supporting Information for limitations).

For alkene substrate scope, the reaction with monosubstituted acrylates gives corresponding phenylalanine derivatives (**5b**−**5d**) in good yield. Acrylonitrile (**2e**) also works well in this reaction, providing a potential for further functional group derivatization. Secondary acrylamides are also good alkene coupling partners, delivering carboamination products (**5f**−**5h**) containing two amide bonds. The reaction with bridged bicyclic alkenes such as norbornene (**2i**), oxabenzonorbornadiene (**2j**), and aza-benzonorbornadiene (**2k**) gives *syn*-carboamination products (**5i**−**5k**) in good yield and diastereoselectivity. In the case of the reactions with cyclopropenes (**2l**−**2m**), the reaction occurs cis to the methyl group, presumably because of a smaller steric demand during the alkene migratory insertion step, giving cyclopropyl amine products (**5l**−**5m**) in high diastereoselectivity.

Internal electron-deficient alkenes such as ethyl crotonate, ethyl cinnamate, or cyclopentenone and less-strained cyclic alkenes such as cyclohexene or 3,4-dihydropyran do not lead to the product formation and direct *N*-phenylation (**9**) products are observed as a major side product of the reaction in high yield presumably due to the slow alkene migratory insertion (see Supporting Information for details).

Lastly, a variety of functional groups can be installed at the amide side chain using dioxazolones with different substituents at the 3 position (**3b**-**3h**) prepared from corresponding carboxylic acids. The reactions with dioxazolone **3d** or **3f** containing allylic or benzylic C−H bonds give the carboamination products selectively (**6d**, **6f**). These are noteworthy as they have been used for intramolecular C−H amination chemistry.[14] The carboamination occurs intermolecularly in

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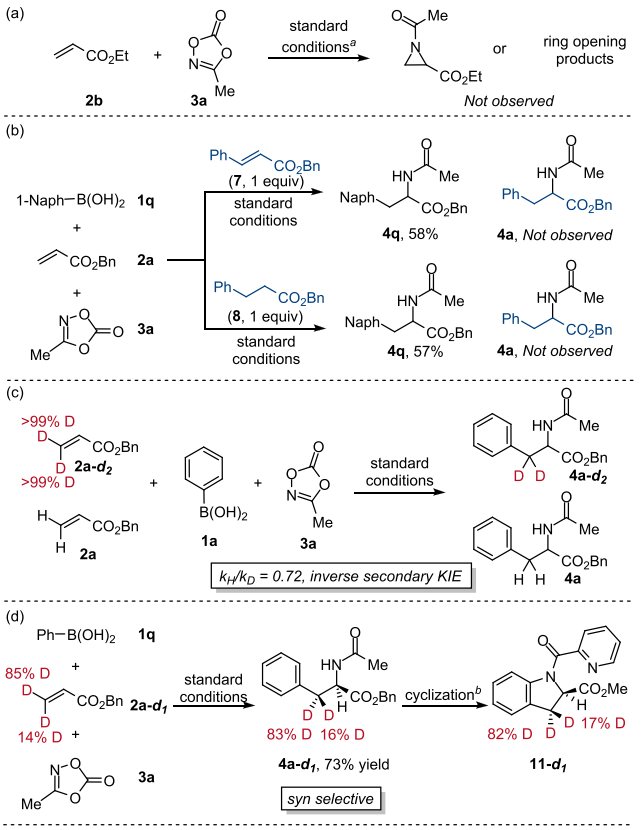
preference to an intramolecular C−H insertion suggesting a mechanistic dichotomy with Chang's Ir-based system.

We next designed a series of experiments to interrogate the mechanism of the reaction. First, we conducted the reaction under standard conditions, but without phenylboronic acid (Scheme 3a). As a result, neither *N*-acyl aziridine nor aziridine

Scheme 3. Mechanistic Investigation



[a]Standard conditions: $[Cp^*RhCl_2]_2$ (5 mol %), $NaHCO_3$ (30 mol %), MeOH (0.6 M), dioxazolone (1 equiv), arylboronic acid (2.5 equiv), alkene (3 equiv), 25 °C. [b](1) 6 M HCl; (2) $SOCl_2$, MeOH; (3) picolinic acid, EDCI, HOBt, DCM; and (4) $Pd(OAc)_2$, $PhI(OAc)_2$, DCM.

ring-opening products[15] are observed after the reaction. This strongly indicates that the Rh(III)-catalyzed alkene aziridination and subsequent ring-opening with phenylboronic acid is unlikely as the mechanism of the reaction. During the optimization study, we observed Heck-type (**7**) and hydroarylation products (**8**) as side products of the reaction, presumably formed through β-hydride elimination and protodemetalation after the alkene migratory insertion.

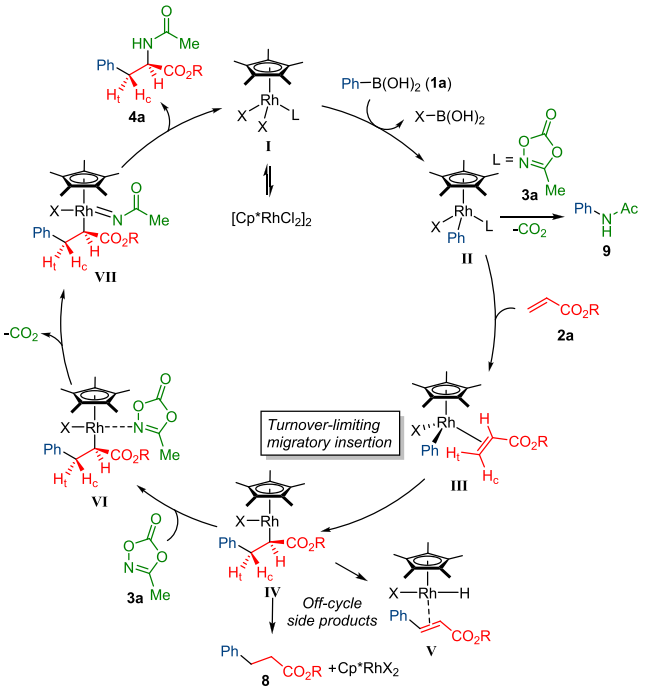
To determine whether these side products give the desired carboamination product (**4**), both benzyl cinnamate (**7**) and benzyl 3-phenylpropanoate (**8**) were subjected to the reaction using 1-naphthyl boronic acid (**2q**) as the carbon source of the reaction (Scheme 3b). While both reactions give the desired product (**4q**) from 1-naphthyl boronic acid (**2q**) in good yield, carboamination products (**4a**) from these side products (**7** or **8**) are not observed. These experiments suggest that **7** and **8** are off-cycle side products that do not re-enter the catalytic cycle. In addition, monitoring the reaction progress with ^1H NMR indicates that the reaction with dioxazolone that leads to product formation is faster than β-hydride elimination at the beginning of the reaction. The amount of β-hydride elimination product increases after consumption of limiting dioxazolone (**3a**) (see the Supporting Information for details).

In order to determine the turnover limiting step of the reaction, we investigated the alkene migratory insertion step with benzyl acrylate (**2a**) and deuterated benzyl acrylate (**2a**−**2d$_2$**). The inverse secondary kinetic isotope effect (KIE) value of 0.72, measured from the intermolecular competition experiment (Scheme 3c), or 0.55, which was calculated by comparing the initial rate of two separate reactions, one with benzyl acrylate (**2a**) and one with deuterated benzyl acrylate (**2a-d$_2$**) (see Supporting Information for details) suggest sp^2 to sp^3 hybridization change occurs during the turnover limiting step of the reaction (Scheme 3c).[16]

In order to determine the relative stereochemistry of the product, we conducted the reaction with monodeuterated benzyl acrylate (**2a-d$_1$**, 85:14 E/Z) (Scheme 3d). Interestingly, the reaction gives the product (**4a-d$_1$**) containing almost identical deuterium incorporation with starting alkene (**2a-d$_1$**) which suggests the carboamination is highly diastereoselective. The product was cyclized by Pd-catalyzed intramolecular C−H amidation,[17] which confirmed *syn*-carboamination of the alkene.

Based on these experiments, we propose the following mechanism for the reaction (Scheme 4). First, the active

Scheme 4. Proposed Mechanism



monomeric Rh complex **I** undergoes transmetalation with phenylboronic acid (**1a**) to give Rh-phenyl complex **II**. Next, turnover limiting migratory insertion into the Rh-aryl bond forms Rh(III) intermediate **IV**. Subsequently, dioxazolone (**3a**) coordinates to the electron-rich alkyl Rh(III) complex **IV**, followed by Rh(V)-nitrene formation with the exclusion of CO_2. The desired *syn*-carboamination product (**4a**) is formed after reductive elimination and proto-demetalation with the regeneration of active Rh catalyst **I**.

In summary, we have developed Rh(III)-catalyzed three-component regioselective *syn*-carboamination of alkenes. The

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reaction shows a broad scope with a variety of commercially available arylboronic acids and dioxazolones easily prepared from carboxylic acids. Mechanistic investigations suggest alkene migratory insertion to be the turnover limiting step supported by secondary KIE. In addition, deuterium labeling experiments provide experimental evidence for stereoselective *syn*-carboamination process. This method provides a rapid access to valuable amines including non-natural α-amino acids from abundant alkenes with good regioselectivity and high diastereoselectivity with internal cyclic alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02406.

Experimental procedures, detailed optimization table, characterization, copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

Cp* pentamethylcyclopentadienyl

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