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Rh-Catalyzed Reaction of Vinyl Azides with Isonitriles and Alkynes/Benzynes

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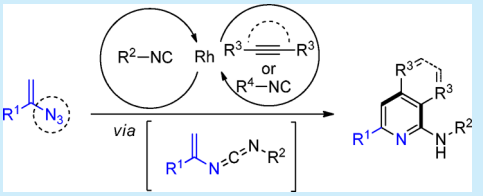
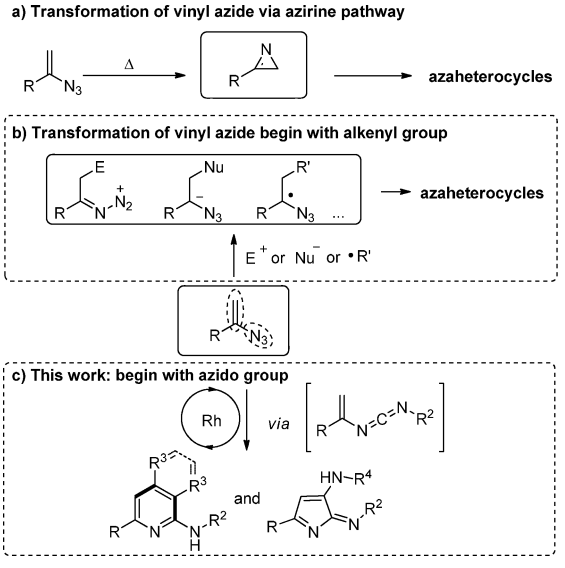
Supporting Information

ABSTRACT: In contrast to well-known transformations of vinyl azides via azirine intermediates or initiating at the alkene moiety, herein we report a Rh(I)-catalyzed coupling reaction of vinyl azides with isonitriles at the azide moiety to form active vinyl carbodiimide intermediates and following tandem cyclization with unsaturated compounds, such as alkynes and benzynes, to give different classes of azaheterocycles. Mechanistically, controlled experiments and DFT calculations disclose that Rh-nitrene is the vital species in the first coupling step, and the Rh(I) catalyst can also play an important role in the cyclization step of alkynes.



N-Containing heterocycles are important structural components in natural products, pharmaceuticals, and functional materials. The construction of azaheterocycles is a prominent field in organic synthesis.[1] As an efficient nitrogen source, the transformations of organic azides have been explored.[2] In particular, vinyl azides, which contain two distinct functional groups, have received considerable attention in the synthesis of different types of azaheterocycles.[3] The most common pathway of vinyl azide transformations proceeds through azirine intermediates (Scheme 1a).[4] Another pathway initiates at the alkene moiety of vinyl azides, which react with electrophiles/radicals/nucleophiles to generate the corresponding intermediates (Scheme 1b).[5] Although vinyl azides have shown multifaceted reactivities, transition-metal-catalyzed sequential reactions that initiate at the azido group are not common.[6] On the other hand, vinyl carbodiimides, which have two unsaturated functionalities, hold great potentials for constructing azaheterocycles. However, the lack of facile access to a vinyl carbodiimide intermediate and its instability in isolation and storage limit its application.[7] Herein, we report a Rh(I)-catalyzed coupling reaction of vinyl azides with isonitriles to form different substituted vinyl carbodiimide intermediates in a facile access and following tandem cyclization with unsaturated compounds, such as alkynes and benzynes, to give different classes of azaheterocycles, i.e., aminopyridine, isoquinoline, and pyrroleimine (Scheme 1c). Controlled experiments/DFT calculations reveal that Rh-nitrene is the vital species in the first coupling step, and Rh(I) catalyst also plays an important role in the cyclization of alkynes.

Scheme 1. Cyclization Pathway of Vinyl Azide



At the outset, (1-azidovinyl)benzene (**1a**) was used to react with *t*-BuNC (**2a**) under $[Rh(COD)Cl]_2$ catalyst, and then the addition of diethyl but-2-ynedioate (**3a**) could furnish aminopyridine (**5a**) in 44% yield (eq 1). To our delight, the isolation and characterization of the unstable vinyl carbodiimide intermediate (**4a**) was also achieved.

Based on the above result, the formation and isolation of active vinyl carbodiimide intermediates were studied (Scheme 2). In the presence of $[Rh(COD)Cl]_2$, the isolated yield of **4a** was 86%, and the NMR yield was up to 92%. The addition of the 2,2′-bpy ligand gave a similar 93% NMR yield. However,

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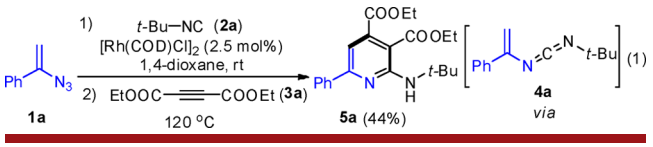
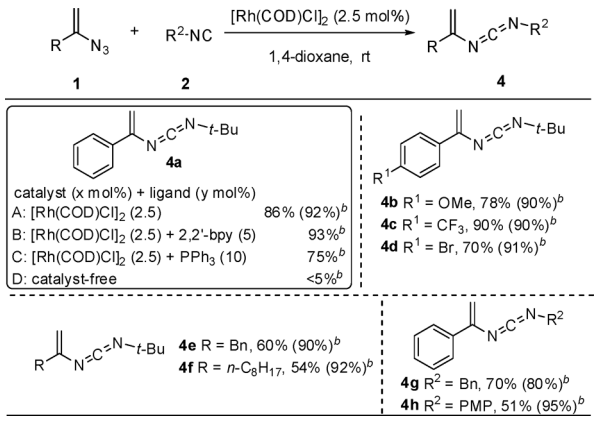


Scheme 2. Substrate Scope of Vinyl Azide with Isonitrile[a]



[a]Reaction conditions: **1** (0.30 mmol), **2** (0.30 mmol), [Rh(COD)Cl]$_2$ (2.5 mol %), 1,4-dioxane (2 mL), isolated yield, 2′-bpy = 2,2′-bipyridine. [b]NMR yield with mesitylene as the internal standard.

the addition of phosphine PPh_3 ligand decreased the NMR yield to 75%.[8] For different vinyl azides and isonitriles, NMR yields were all excellent (>80%), but some isolated yields were relatively low because of their instability. Aryl-substituted vinyl azides gave better isolated yields (**4a**−**4d**, 70−90%), whereas benzyl- and alkyl-substituted vinyl azides gave only 54% and 60% isolated yields (**4e**−**4f**). For different isonitriles, the desired vinyl carbodiimides were obtained in 51−86% isolated yields (**4a**, **4g**, 4**h**).

To gain insight into the mechanistic details of this reaction, several control experiments were carried out (Figure 1a). When **1a** was stirred under standard conditions, no 3-phenyl-2*H*-azirine was detected, and 95% of **1a** was recovered after 8 h. Then, 3-phenyl-2*H*-azirine was subjected to the reaction under the standard conditions, and no vinyl carbodiimide was detected, even when heated to 120 °C. Mixing 3-phenyl-2*H*-azirine with isonitrile and alkyne under the cyclization conditions also could not give the aminopyridine product. These results ruled out azirine as an intermediate in this coupling/cyclization reaction. Additionally, the vinyl carbodiimide product could not be accessed in the absence of Rh catalyst.

To further understand the mechanism, DFT calculations were performed by using Gaussian 09 programs.[9] 2-Azidoprop-1-ene, isocyanomethane, and chlorobis(ethylene)rhodium dimer were used as model substrates (Figure 1b). Rh(I) dimer catalyst dissociated to monomeric active catalyst and coordinated with isonitrile to form active intermediate **I**, which coordinated with vinyl azide to generate **II**. Complex **II** showed a Rh−N bond of 2.23 Å and a Rh−C bond of 1.89 Å, which revealed Rh(I) configuration. Species **II** released N_2 to produce nitrene intermediate **III**, which passed through an exergonic transition state **TS-1a** of 25.6 kcal/mol. Because the length of the N−Rh bond was 2.01 Å, it could be regarded as having a nitrene Rh−N bond character.[9a] The nitrene moiety of **III** subsequently coupled with the isonitrile to form the vinyl carbodiimide, which coordinated with the Rh center via **TS-2a**.

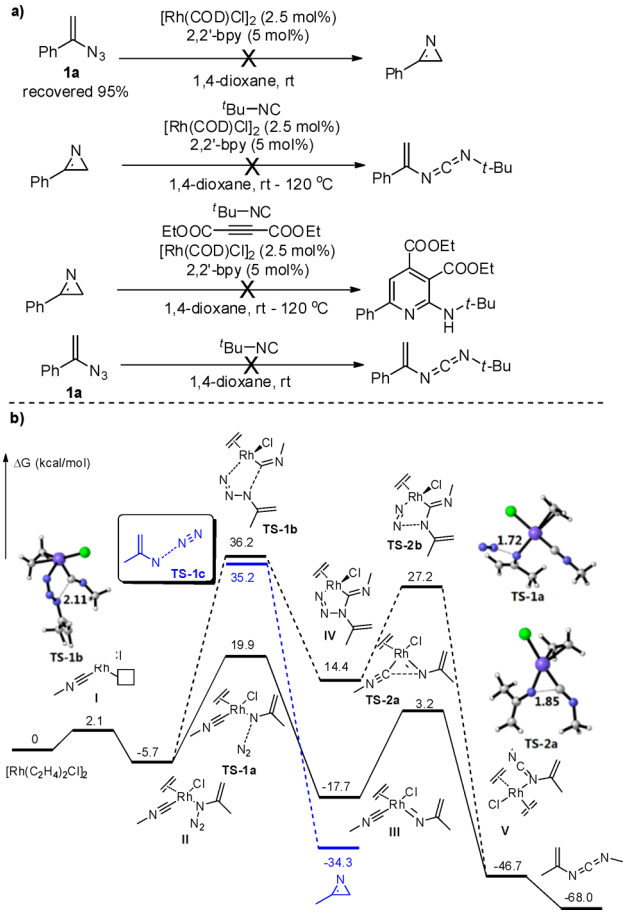


Figure 1. (a) Controlled experiments and (b) DFT calculation of the coupling step.

Finally, ligand exchange generated free vinyl carbodiimide with a sharp decline of Gibbs energy (ΔG = 21.3 kcal/mol). The transition state (**TS-1c**, ΔG = 35.2 kcal/mol) of azirine formation, which came from vinyl azide directly without Rh catalyst, was obviously unfavorable as compared to **TS-1a**. In addition, the coupling reaction of azide with CO that passed through a five-membered metallacycle intermediate has been reported,[10] so the reaction via a similar mechanism was also calculated. The five-membered intermediate **IV** was generated by an oxidant addition transition state **TS-1b** (ΔG = 41.9 kcal/mol), which had much higher Gibbs energy than **TS-1a**. In the structure of species **IV**, the Rh−N and Rh−C bonds were 1.99 and 2.00 Å, respectively. To produce intermediate **V**, complex **IV** needs to pass through another unfavorable **TS-2b** (ΔG = 12.8 kcal/mol). These results also supported that the coupling step should involve a Rh-nitrene intermediate.

After the inspection of vinyl carbodiimide's formation, which is unstable in isolation and storage, we further investigated the construction of azaheterocycles in a tandem process. Using 2.5 mol % [Rh(COD)Cl]$_2$/5 mol % 2,2′-bpy and adding NH_4Cl/$NaHCO_3$ in the second cyclization step, the reaction of vinyl azide (**1a**) with *t*-BuNC (**2a**) and alkyne (**3a**) gave aminopyridine **5a** with the best 71% isolated yield.[8] Based on this optimized condition, the substrate scope was studied (Scheme 3). The reaction showed good substrate generality: all steric hindrance, electron, and halogen variation of aromatic rings in the vinyl azides could be successfully introduced, providing the desired product in moderate to excellent yields

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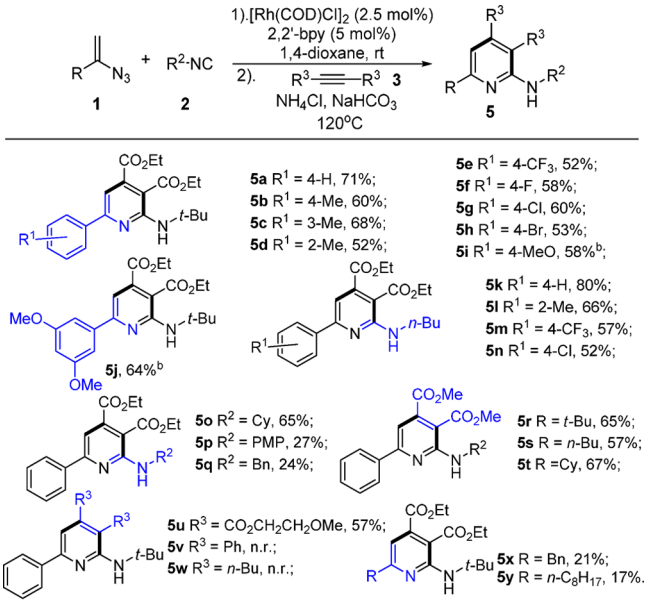
Scheme 3. Substrate Scope of Cyclization with Alkyne[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.15 mmol), **3** (0.30 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), 2,2′-bpy (5 mol %), NH_4Cl (0.15 mmol), $NaHCO_3$ (0.15 mmol), 1,4-dioxane (2 mL), isolated yield, n.r. = no reaction. [b]Reaction conditions: **1** (0.30 mmol), **2** (0.30 mmol), **3** (0.15 mmol).

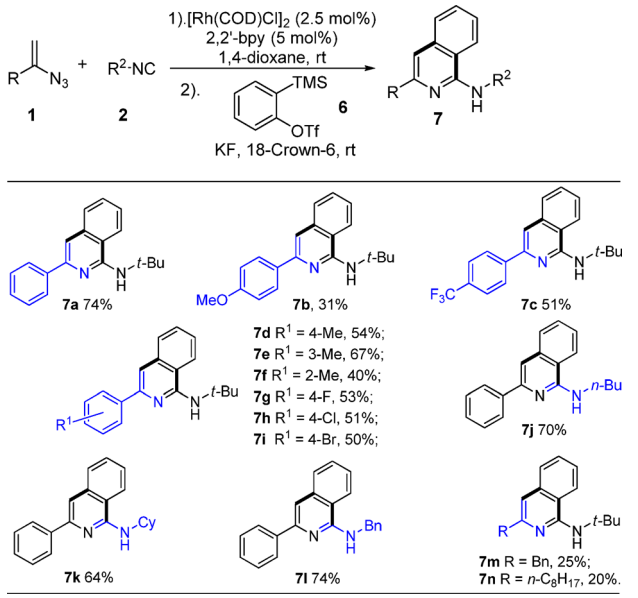
(**5a**−**5j**). Benzyl- and alkyl-substituted vinyl azides could also participate, albeit with relatively low yields (**5x**−**5y**). Investigation of different isonitriles revealed that all alkyl-, aryl-, and benzyl-substituted isonitriles reacted smoothly to furnish the corresponding products (**5o**−**5t**). In particular, *n*-BuNC showed better reactivity than *t*-BuNC, which provided up to 80% yield (**5k**−**5n**). When **3a** was replaced with other alkynes, the reaction was less efficient (**5r**−**5w**), and no reaction was observed when diphenyl acetylene or 5-decyne was used.

The tandem cyclization was further extended from alkynes to benzynes, which afforded aminoisoquinolines as the product.[8] As shown in Scheme 4, the aromatic ring of vinyl azide bearing an electron-withdrawing group gave a better result than that with an electron-donating group (**7b** vs **7c**). The methyl substituent on the different positions of the aromatic ring all gave moderate yields (**7g**−**7i**), and amino-isoquinolines from benzyl- and alkyl-substituted vinyl azides were obtained in 25% and 20% yields (**7m**−**7n**). In addition, alkyl- and benzyl-substituted isonitriles also furnished the desired products in good yields (**7j**−**7l**).

Other common cyclic building blocks were also employed to construct different azaheterocycles (Figure 2a). Aminopyridine **8** was obtained in 74% yield when vinyl carbodiimide reacted with an allene. Benzoquinone led to the formation of aminoisoquinoline-5,8-dione **9** in 65% yield.[11] The vinyl carbodiimide intermediate could also undergo α,α-insertion reaction with another isonitrile to produce pyrrole-2-imine **10** with 30% yield.

The functional groups of **5a** could also been transformed easily (Figure 2b): (1) The *t*-Bu group was cleaved to furnish **11** in 97% yield. (2) The ester groups were hydrolyzed to afford dicarboxylic acid **12** in 86% yield, which could be further converted to different salts or amides. (3) The ester groups

Scheme 4. Substrate Scope of Cyclization with Benzyne[a]



[a]Reaction conditions: **1** (0.30 mmol), **2** (0.30 mmol), **6** (0.15 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), 2,2′-bpy (5 mol %), KF (0.30 mmol), 18-crown-6 (0.30 mmol), 1,4-dioxane (2 mL), isolated yield.

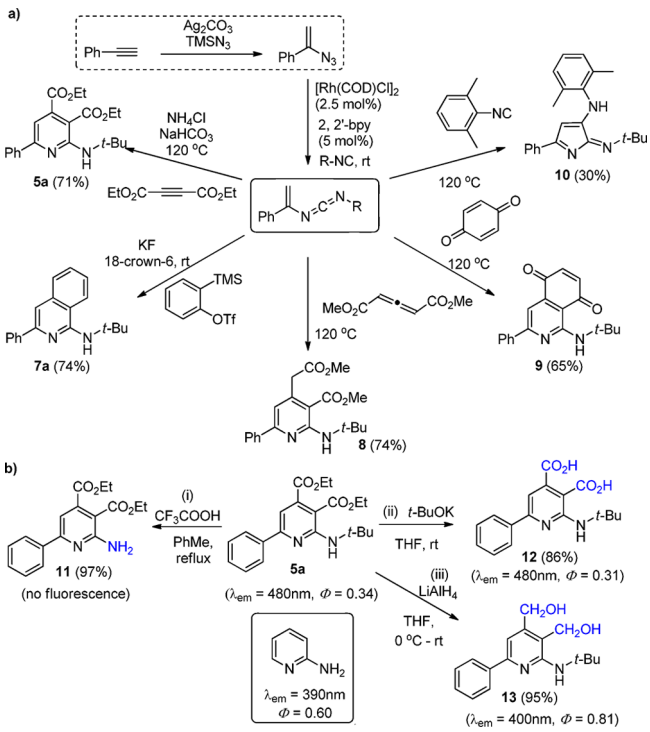


Figure 2. (a) Rh(I)-catalyzed tandem transformation of vinyl azide. (b) Functional group transformations of aminopyridine **5a**.

were reduced by $LiAlH_4$ to give diol **13** in 95% yield. Compared to the simple pyridine-2-amine (Φ = 0.6, λ_{em} < 380 nm), the above multisubstituted/conjugated aminopyridine derivatives exhibit either better quantum yield or more diverse maximum emission wavelength.[12] This preliminary fluorescence study further shows the potential utility of this new synthesis method.

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Taking aminopyridine, for example, the second cyclization step of the vinyl carbodiimide intermediate has two possible pathways, direct electrocyclization or Rh(I)-catalyzed oxidative cyclization/reductive elimination (Figure 3a). In the reaction

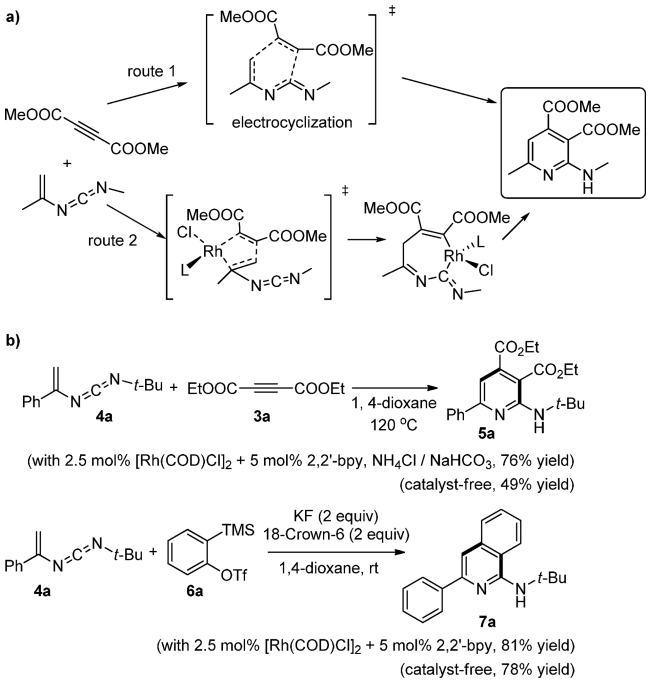

Figure 3. (a) Two possible pathways of the second cyclization step. (b) Controlled experiments.

of isolated vinyl carbodiimide intermediate **4a** with alkyne **3a**, the standard Rh(I)-catalyzed condition afforded **5a** in 76% yield, while the catalyst-free condition gave only 49% yield (Figure 3b). Further detailed controlled experiments and DFT calculations also suggested that the Rh(I)-catalyzed oxidative cyclization/reductive elimination mechanism was the dominant pathway. When alkyne was displaced by a more active benzyne, the effect of Rh catalyst became inapparent. The Rh(I)-catalyzed conditions and the catalyst-free conditions gave similar yields. For more details about the mechanism of study of the cyclization step, see the SI, Parts 6 and 7.

In summary, we developed a Rh(I)-catalyzed coupling reaction of vinyl azide with isonitrile to form vinyl carbodiimide, which is an efficient kind of azaheterocycle building block. We utilized this access to synthesize and characterize a series of vinyl carbodiimides, which could further undergo tandem cyclizations with alkynes, benzynes, allenes, and alkenes etc. to furnish different classes of azaheterocycles, i.e., aminopyridine, isoquinoline, and pyrroleimine, respectively. Controlled experiments and DFT calculations disclose that Rh-nitrene is the vital species in the first coupling step, and Rh(I) catalyst also plays an important role in the cyclization of alkynes. A preliminary fluorescence study of aminopyridine and its derivatives further reveals the potential utility of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03115.

Preparation of vinyl azide substrates, general procedure for Rh-catalyzed reaction of vinyl azides with isonitriles and alkynes/benzynes, examination of reaction conditions, general procedure for other azaheterocycles and aminopyridine derivatives, controlled experiments, additional DFT calculations of the cyclization, spectral data, and optimized structure and Gibbs energy of DFT calculation (PDF)

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Notes

The authors declare no competing financial interest.

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