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Rhodium(III)-catalyzed diverse [4 + 1] annulation of arenes with 1,3-enynes *via* sp^3/sp^2 C–H activation and 1,4-rhodium migration†

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Nitrogen-rich heterocyclic compounds have a profound impact on human health. Despite the numerous synthetic methods, diversified, step-economic, and general synthesis of heterocycles remains limited. C–H bond functionalization catalyzed by rhodium(III) cyclopentadienyls has proven to be a powerful strategy in the synthesis of diversified heterocycles. Herein we describe rhodium(III)-catalyzed sp^2 and sp^3 C–H activation-oxidative annulations between aromatic substrates and 1,3-enynes, where alkenyl-to-allyl 1,4-rhodium(III) migration enabled the generation of electrophilic rhodium(III) π-allyls *via* remote C–H functionalization. Subsequent nucleophilic trapping of these species by various sp^2-hybridized N-nucleophiles delivered three classes (external salts, inner salts, and neutral azacycles) of five-membered azacycles bearing a tetrasubstituted saturated carbon center, as a result of [4 + 1] annulation with the alkyne being a one-carbon synthon. All the reactions proceeded under relatively mild conditions with broad substrate scope, high efficiency, and excellent regioselectivity. The synthetic applications of this protocol have also been demonstrated, and experimental studies have been performed to support the proposed mechanism.

Introduction

Nitrogen-containing heterocyclic compounds are prevalent in natural products and bioactive molecules. They are also found in a large number of drugs used to combat a broad range of diseases (Scheme 1a). Advances in transition-metal catalyzed C–H functionalization have significantly streamlined the synthesis of a plethora of heterocyclic molecules.[1] In many cases, the heteroatom directing group participated in the annulation reaction besides offering chelation assistance, which calls for sufficient interactions between the metal center and the directing group. In this context, C–H bond activation catalyzed by high valent Rh(III) complexes has stood out as a powerful strategy for step-economical construction of C–C bonds and has become one of the increasingly important strategies in organic syntheses.[2] In these systems, a large scope of directing groups can be accommodated to ensure high activity and selectivity of the C–H bond. In annulation reactions, development of mild and straightforward C–H activation processes assisted by a multifunctional directing group is especially attractive, allowing realization of molecular diversity and synthetic versatility.[3] On the other hand, alkynes are widely used as a typical unsaturated coupling partner in numerous annulation reactions, and in most cases they react as a two-carbon synthon.[4] To move beyond this limitation, the Lam group pioneered excellent work in oxidative coupling of arenes bearing a nucleophilic directing group and 1,3-enynes,[5,6] which occurred *via* 1,4-rhodium migration and Rh(III) allyl intermediates, leading to [*n* + 3] and [*n* + 1] annulation in most cases. Still, the [*n* + 1] type annulation with the alkyne being a C1 synthon is still rare,[5a,c] where the nucleophilic directing group has been limited to 1,3-dione, acidic OH groups, and imide groups, and the corresponding C(sp^3)–H activation has not been realized.

On the other hand, quaternary ammonium salts are versatile building blocks for a number of naturally occurring products and functional materials.[7]Although a number of methods for the synthesis of such ionic compounds are available, many are limited by the lack of generality, limited functional group tolerance, and lengthy synthetic procedures.[8] Recently, quaternary ammonium salts have been synthesized through sp^2 C–H activation of arenes and annulations with alkynes or diazo substrates in the presence of stoichiometric amounts of metal

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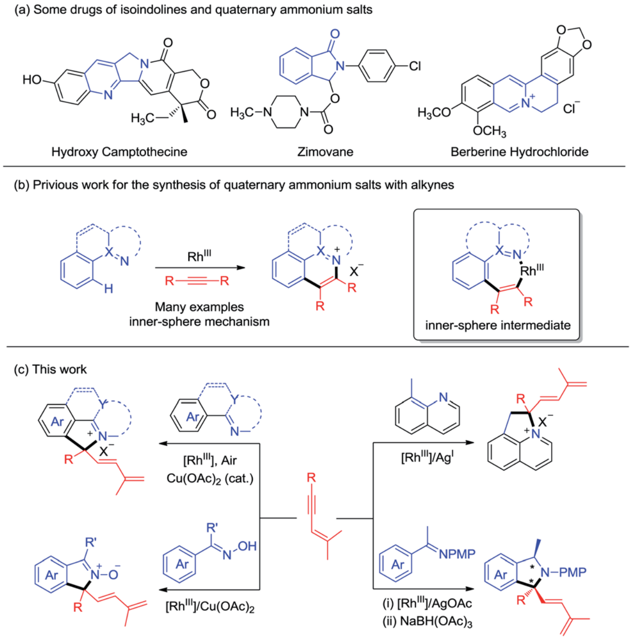
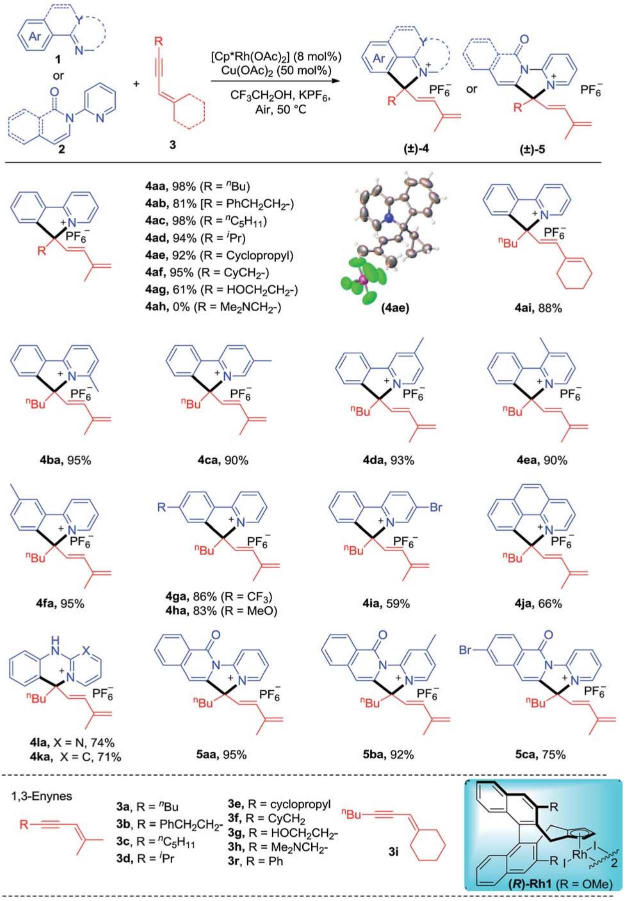


Scheme 1 Rh(III)-catalyzed oxidative annulation of 1,3-enynes or alkynes. (a) Some drugs with isoindoline or the quaternary ammonium motif. (b) Quaternary ammonium salts formed *via* coupling with alkynes. (c) Synthesis of diversified heterocycles bearing a quaternary carbon center *via* coupling of arenes and 1,3-enynes.



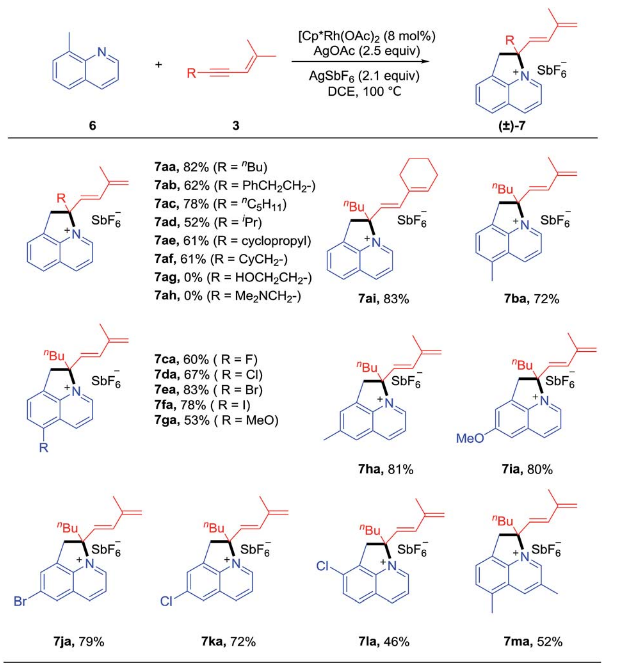
Scheme 2 Scope of the coupling of 2-phenylpyridines with 1,3-enynes. Reaction conditions: arene **1** or **2** (0.2 mmol), enyne **3** (0.22 mmol), [Cp*Rh(OAc)$_2$] (8 mol%), Cu(OAc)$_2$ (50 mol%), and KPF$_6$ (0.5 mmol) in CF$_3$CH$_2$OH (2.0 mL) under air, 50 °C, monitored by TLC, isolated yields. See general procedure A.

oxidants/additives, as has been pioneered by Cheng and others. While quaternary ammonium salts could be synthesized through the [*n* + 2] reaction with alkynes, the synthesis of quaternary ammonium salts[9] bearing a quaternary carbon center is limited because of the challenge of C(tertiary)–N reductive elimination,[4,10] an inner-sphere reaction pathway (Scheme 1b). However, it is challenging to construct a quaternary carbon center through an outer-sphere mechanism. Herein, we report diverse synthesis of four classes of nitrogen-containing heterocycles *via* C–H activation, 1,4-rhodium(III) migration, and allyl-to-allyl rearrangement. Importantly, quaternary ammonium salts can be readily accessed *via* Rh(III)-catalyzed sp^2 and sp^3 C–H functionalization with Cu(OAc)$_2$/air as the oxidant. Besides ionic products, zwitterionic and neutral N-containing heterocycles bearing a quaternary carbon can also be accessed when oximes and ketimines are employed as the arene source. All the coupling systems have been realized with high regio- and chemoselectivity (Scheme 1c).

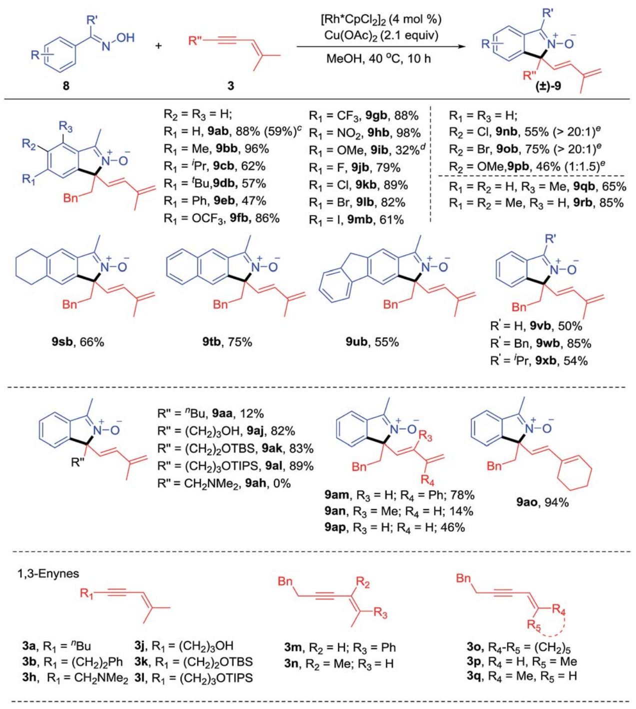
Results and discussion

We commenced our studies by exploring the reaction parameters of the coupling of 2-phenylpyridine (**1a**) and 1,3-enyne (**3a**, see ESI Table 1†). An excellent yield of quaternary ammonium salt **4aa** was obtained with Cp*Rh(OAc)$_2$ as a catalyst, Cu(II)/air as the oxidant, and KPF$_6$ as the anion source under mild conditions. With the optimized conditions in hand, we next investigated the scope and generality of this coupling system (Scheme 2). Various 1,3-enynes were tolerated (**4aa-4ai**, 61–98%), and the identity of product **4ae** has been confirmed by X-ray crystallography (CCDC 1861504†). However, 1,3-enyne **3h** containing an alkylamino moiety showed poor reactivity. The phenyl-substituted 1,3-enyne **3r** reacted with poor regio- and chemoselectivity, and the [4 + 2] annulation side product was isolated in 45% yield.[4m] 2-Phenylpyridines bearing Me, electron-donating, electron-withdrawing, and bromo groups were fully tolerated (**4ba-4ia**, 59–95%). We also investigated preliminarily the enantioselectivity of the reactions of **1a** and **3a** using chiral (R)-Rh1, and so far, only <5% of **4aa** was obtained under standard conditions. The reaction also worked well for benzo[*h*]quinoline, and the product **4ja** was isolated in 66% yield. The arene was not limited to 2-arylpyridines. Thus, the coupling for *N*-phenylpyrimidin-2-amine and *N*-phenylpyridin-2-amine afforded the ionic products **4la** and **4ka** in good yields, respectively. Moreover, several *N*-pyridylisoquinolones were also viable substrates, providing the desired products (**5aa-5ca**) in good to excellent yields (75–95%). In all cases, the well-explored [*n* + 2] annulation side products were not detected.

To better define the scope of this reaction system, we next extended the reaction system to 8-methylquinolines (Scheme 3). To our delight, the quaternary ammonium salt **7aa** was obtained in 82% yield *via* benzylic C–H activation, and AgOAc and



Scheme 3 Scope of the coupling of 8-methylquinolines with 1,3-enynes. Reaction conditions: **6** (0.2 mmol), **3** (0.3 mmol), [Cp*Rh(OAc)$_2$] (8 mol%), AgSbF$_6$ (0.2 mmol), AgOAc (0.3 mmol), DCE (2.0 mL), monitored by TLC, isolated yields. see general procedure B.

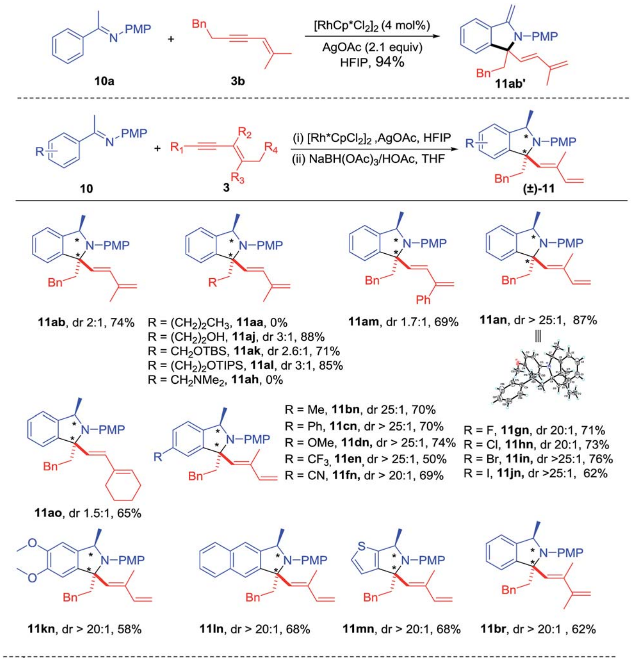


Scheme 4 Scope of the coupling of oximes with 1,3-enynes.[a,b] [a]Reaction conditions A: **8** (0.20 mmol), **3** (0.22 mmol), [Rh*CpCl$_2$]$_2$ (4.0 mol%), Cu(OAc)$_2$ (2.1 equiv.), MeOH (2 mL) at 40 °C under N$_2$ for 10 h. [b]Isolated yields. [c]Reaction was performed with 4 mmol of **8** at 2.5 mol% catalyst loading. [d]Isoquinoline **9ib′**, a [4 + 2] annulation product, was also isolated in 10% yield (see ESI†). [e]regioselectivity. See general procedure C.

AgSbF$_6$ were identified as the optimal oxidant and anion source (see ESI Table 2†). The scope of this sp^3 C–H coupling system was examined under the optimal conditions. The scope of the 1,3-enynes is reasonably broad (**7aa-7af**, 52–82%) although several heteroatom-functionalized enynes (**3g** and **3h**) were inactive. Various substituted 8-methylquinolines bearing methyl, halogen, and methoxy groups at the 5- and 6-positions all reacted with moderate to good yields (**7ba-7ka**, 53–83%). 7-Substituted and 3,5-disubstituted quinolines also reacted smoothly but with slightly lower yields (**7la-7ma**, 46–52%)

To our delight, the arene substrates of this [4 + 1] coupling reaction system could be smoothly extended to oximes (Scheme 4) and ketimines (Scheme 5, see ESI Table 3†).[11] The coupling of readily available ketoximes afforded zwitterionic isoindole 2-oxides. The generality of this system was examined for oximes with different substituents at the *para* position using enyne **3b** as a coupling reagent. Alkyl-substituted oximes gave good to excellent yields (57–96%, **9ab-9db**) while relatively lower efficiency (**9ib**) was found when an electron-donating group (OMe) was present. Furthermore, an isoquinoline **9ib′**, resulting from redox-neutral [4 + 2] annulation, was also detected as a by-product.[4g] Introduction of electron-withdrawing groups, such as –OCF$_3$ (**9fb**), –CF$_3$ (**9gb**), and –NO$_2$ (**9hb**) all resulted in high efficiency, indicative of tolerance of electronic effect. We next evaluated the compatibility of halogen groups, and **9jb-9mb** were delivered in good yields. Moreover, the reaction also proceeded smoothly when various *meta* substituents were present (**9nb-9pb**, 46–75%). High regioselectivity at the less hindered site was obtained for *meta* Cl- and Br-substituted oximes, while nearly equal amounts of two regioisomeric products were obtained for the *meta* MeO-substituent. Besides, introduction of *ortho* Me (**9qb**) was also tolerated. Doubly substituted arenes at the *meta* and *para* positions were also tolerated, providing products **9rb-9ub** in 55–85% yields. Other oximes **8v**, **8w** and **8x** also worked well to yield **9vb-9xb** in good yields (50–85%). The ketoxime (**8a**) was next evaluated in reaction with a range of 1,3-enynes. 1,3-Enynes with the *n*-butyl substituent at the alkyne terminus gave an inferior result (**9aa**, 12%), probably due to the poor reactivity of such substrates, while unprotected or silyl-protected alcohol substituents were tolerated, affording the N-oxide in high yields (**9aj-9al**, 82–89%). However, alkylamino-substituted 1,3-enyne **3h** showed poor reactivity. Variation of the group *trans* to the alkyne from phenyl (**3m**) to methyl (**3a**) was also successful. We also examined 1,3-enyne **3n** that contains a *trans* butenyl group, giving high *E* selectivity albeit with lower yield (**9an**, 14%). Furthermore, 1,3-enyne **3o** containing a cyclohexyl group was also an effective coupling partner with 94% yield (**9ao**). To confirm whether the allylic hydrogen atom *cis* to the alkyne is necessary, ketoxime **8a** was allowed to react with 1,3-enynes **3p** and **3q**. It was found that reaction with **3p** gave the [4 + 1] annulation product in 46% yield. However, no product was obtained when **3q** was employed as a coupling partner. Those results demonstrated that allylic hydrogen *cis* to the alkyne in the 1,3-enyne is crucial for this reaction, which is consistent with a 1,4-Rh migration pathway.

Extension of the oxime to ketimine substrate was next explored. We reasoned that the oxidative [4 + 1] annulation may



Scheme 5 Oxidative annulation of ketimines with 1,3-enynes and sequential hydrogenation. Reaction conditions: imine **10** (0.20 mmol), enyne **3** (0.22 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol%), AgOAc (2.1 equiv.), HFIP (2 mL) at 100 °C under N_2 for 10 h; $NaBH(OAc)_3$ (2.5 equiv.)/HOAc (20 equiv.) was sequentially added and was kept for 30 min at room temperature, followed by quenching with NaOH solution. Isolated yields. See general procedure D.

afford an iminium salt. However, using a ketimine of acetophenone in the presence of a base may lead to further deprotonation of the putative iminium species, generating an enamine that is probably not air-stable. Indeed, reaction of ketoimine **10a** and 1,3-enyne **3b** under streamlined conditions delivered **11ab**′ in excellent yield as an air-sensitive oil (see ESI Fig. 9†). To facilitate product isolation, intermediate **11ab**′ was hydrogenated using $NaBH(OAc)_3$,[12] which provided stable amine **11ab** in 74% total yield albeit with low diastereoselectivity (Scheme 5). Next, various 1,3-enynes were tested through this two-step process. It was found that 1,3-enynes terminated with an *n*-butyl or alkylamino group failed to react (**11aa and 11ah**), while several other 1,3-enynes coupled in good yields but with low diastereoselectivity (**11aj-11am**, **11ao**). Delightfully, the coupling with 1,3-enyne containing a *trans* butenyl group (**3n**) provided excellent diastereoselectivity and high yield (**11an**). Therefore, the introduction of a methyl substituent at the alkenyl carbon had a positive effect on the diastereoselectivity in the hydrogenation step. Meanwhile, the identity of **11an** was unambiguously confirmed by X-ray crystallography (CCDC 1457168†). Next, various electron-donating, electron-withdrawing, and halogen substituents at the *para* position of phenyl were examined by coupling with **3n**, from which >20 : 1 dr and moderate to good yields were obtained (**11bn-11jn**). In addition, the arene substrates have been extended to disubstituted and heteroaryl ketimines, leading to **11kn-11mn** in high diastereoselectivity and good yields. Besides, a trimethyl-substituted 1,3-enyne was also evaluated in the reaction with ketamine **10a**, affording **11br** with good yield and diastereoselectivity.

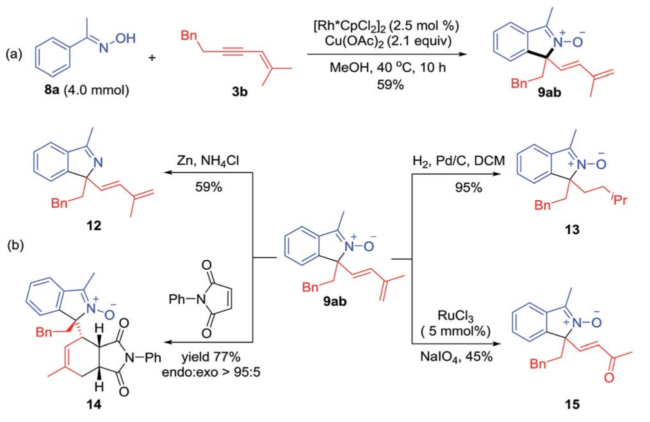
Synthetic applications

Several derivatization reactions of an N-oxide product **9ab** have been performed to briefly demonstrate the synthetic utility of the coupling system. First, a gram-scale synthesis of **9ab** has been realized in 59% yield under reduced catalyst loading (Scheme 6a). Reduction of **9ab** by Zn delivered the corresponding isoindole **12** in 59% yield (Scheme 6b). Furthermore, hydrogenation of conjugated diene using Pd/C as a catalyst gave **13** in 95% yield with retention of the N–O group (Scheme 6b). Diels–Alder reaction of 1,3-diene **9ab** and *N*-phenylmaleimide in toluene at 80 °C proceeded smoothly to give adduct **14** in 77% yield with >95 : 5 endo : exo selectivity. In addition, **9ab** underwent smooth oxidative cleavage when treated with $NaIO_4$ to deliver α,β-unsaturated ketone **15** in 45% yield (Scheme 6b).

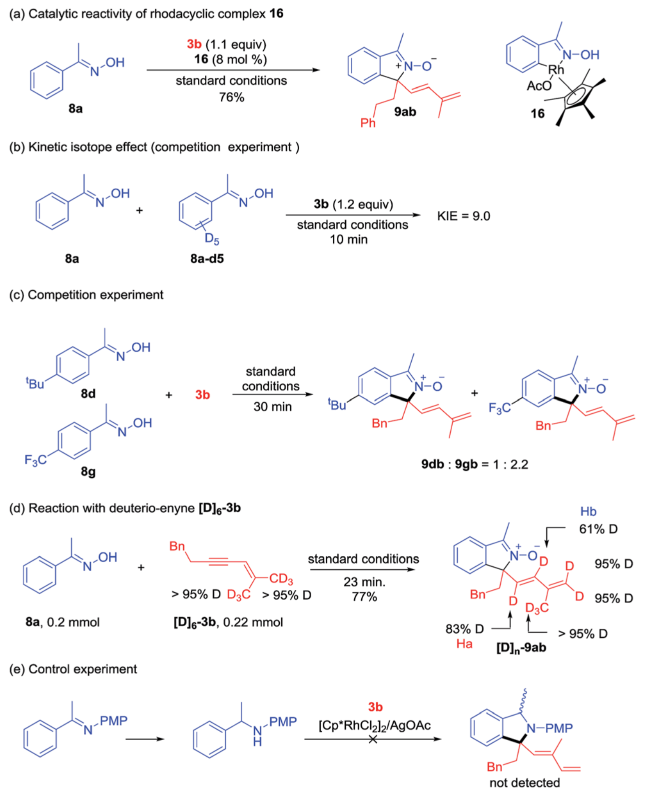
Mechanistic investigations

A series of experiments have been conducted to probe the reaction mechanism. Rhodacyclic complex **16** has been prepared from cyclometalation of oxime **8a**, and it proved to be an active catalyst for the coupling of **8a** and **3b** (Scheme 7a), indicating relevancy of C–H activation. A kinetic isotope effect (KIE) value of 9.0 was then obtained in the competitive coupling of **8a** and **8a**-d_5 with **3b** under the standard conditions at a low conversion (Scheme 7b). A large KIE value was also obtained in the competitive coupling between **6a** and **6a**-d_3 with **3a** (see ESI Fig. 5†). These results indicated that cleavage of the C–H bond is likely involved in the turnover-limiting step of all the above coupling systems. When an equimolar mixture of **8d** and **8g** was allowed to competitively couple with **3b**, products **8dn** and **8gb** were obtained in a 1 : 2.2 ratio, indicating that an electron-poor oxime reacted at a slightly higher rate (Scheme 7c).

To understand the 1,4-Rh migration process, a reaction of **8a** and hexadeuterated 1,3-enyne **3b**-d_6 was then conducted (Scheme 7d). Observation of partial deuteration (83% D) at the



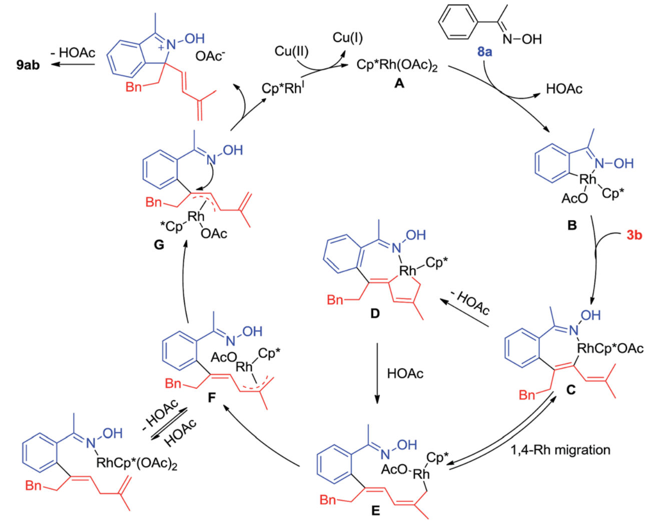
Scheme 6 Applications of the coupling reaction. (a) Reaction on a gram scale. (b) Derivations of a coupled product through chemoselective reduction, Diels–Alder reaction and oxidative cleavage.



Scheme 7 Mechanistic studies. (a) Catalytic reactivity of a rhodacyclic intermediate. (b) Kinetic isotope effect. (c) Competition experiment. (d) Reaction with deuterio-enyne [D]6-**3b**. (e) Control experiment.

alkenyl carbon close to the quaternary center and slight loss of deuterium at the alkene terminus positions (95% D) suggested relevancy of reversible 1,4-Rh migration and this migration may occur under acetate-assistance (H_a), and this result is consistent with those in Lam's work.[5,6] The partial deuteration (61% D) of H_b may suggest reversible protonolysis at the allylic position in our system (see ESI Fig. 10† for another proposed mechanism).[13] Interestingly, the total number of deuterium atoms in $[D]_n$-**9ab** is greater than that in **3b**, and this may result from additional H/D exchange with the $[D]_6$-**3b**. Additionally, a control experiment (Scheme 7e) revealed that an NH benzyl amine failed to react under similar conditions, indicating that the reaction had to be performed by a two-step process.

On the basis of mechanistic studies and previous reports,[14] a plausible catalytic cycle is proposed in Scheme 8 for the representative coupling of **8a** and **3b**. Starting from an active [Cp*Rh(OAc)$_2$] species (**A**), cyclorhodation of oxime **8a** gives a five-membered rhodacycle **B**. Coordination of the incoming 1,3-enyne **3b** and regioselective migratory insertion of Rh–C(aryl) afford a Rh(III) alkenyl intermediate **C**, and the regioselective insertion of this step is largely controlled by electronic effects of the biased alkyne.[4m] Subsequently, reversible 1,4-Rh(III) migration occurs under acetate-assisted concerted metalation–deprotonation to generate intermediate **D**, and subsequent protonolysis may produce **E**. Allyl-to-allyl rearrangement of **F** generates a π-allylrhodium species **G**, and nucleophilic attack of the directing group at π-allyl carbon provides the



Scheme 8 Proposed mechanism.

conjugate acid of the [4 + 1] annulation product, deprotonation of which delivers the final product **9ab**. In the case of 2-phenylpyridine and 8-methylquinoline, the resulting ionic product is stable enough for isolation. The Rh(I) intermediate generated from the nucleophilic attack is reoxidized by Cu(II)/O$_2$ to regenerate the active rhodium(III) species for the next catalytic cycle.

Conclusions

In summary, we have realized Rh(III)-catalyzed diversified oxidative annulation of 2-arylpyridines, 8-methylquinolines, oximes, and ketimines with 1,3-enynes through alkenyl-to-allyl 1,4-rhodium(III) migration. The C–N coupling/annulation occurred *via* the nucleophilic attack of the sp^2-hybridized N-nucleophiles. Various ionic, zwitterionic, and neutral N-containing five-membered azacycles bearing a quaternary carbon center have been efficiently synthesized. Mechanistic studies including KIE and competition experiments have been performed and supported the proposed mechanism. Further studies on the C–H activation of other arenes that highlight the unique role of 1,3-enynes are currently underway in our laboratories.

Conflicts of interest

The authors declare no competing financial interests.

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