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# A General Method to Diverse Cinnolines and Cinnolinium Salts

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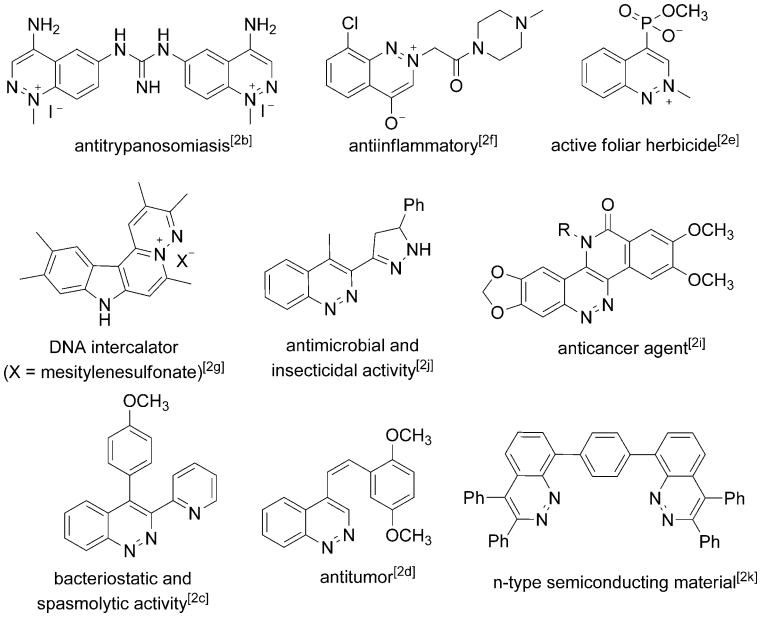
Cinnolines and cinnolinium salts represent pharmaceutically and biologically important structures with anticancer, antimicrobial, antiinflammatory, antiparasitic, trypanocidal, and foliar herbicide activities as well as structural motifs with optical and luminescent characteristics (Scheme 1).[1,2]




Scheme 1. Selected pharmaceutically and biologically active molecules and photoelectric materials with the cinnoline or cinnolinium structural motif.

However, accessible and efficient synthetic methods for these privileged structures are surprisingly under-represented. Traditional strategies for the preparation of cinnolines usually suffer from limited substrate scope and nontrivial multistep reaction sequences (Scheme 2, route A).[3]

Very recently, two significant contributions were made for the synthesis of cinnolines independently by Willis and Ge.[4] Willis et al. disclosed a two-step reaction sequence for the synthesis of cinnolines through the copper-catalyzed annulation of 2-(2-bromoalkenyl)aryl bromide with diethyl-1,2-hydrazinedicarboxylate and subsequent aromatization (Scheme 2, route B).[4a] Ge et al. developed the copper-catalyzed intramolecular dehydrogenative cyclization of *N*-methyl-*N*-phenylhydrazones to give cinnolines through sequential C($sp^3$)–H oxidation, cyclization, and aromatization (Scheme 2, route C).[4b] However, both of these catalytic methods were not yet extended to the preparation of cinnolinium salts. Compared with cinnolines, the synthesis of cinnolinium salts is less developed. Traditionally, 2-alkylcinnolinium salts could be synthesized by alkylation of the corresponding cinnolines, which frequently leads to a mixture of 1- and 2-alkylcinnolinium salts.[5] However, 2-arylcinnolinium salts cannot be obtained by direct N-arylation of cinnolines.[6] To the best of our knowledge, there is still no transition-metal-catalyzed version describing the formation of cinnolinium salts. In particular, none of the previously reported routes have a singularly high capacity for the synthesis of both cinnolines and cinnolinium salts. Undoubtedly, the development of a general and efficient route to both cinnolines and cinnolinium salts with easily tunable substitution patterns is highly warranted to enable a set of diverse scaffolds.

In recent years, it has become increasingly important to construct various heterocycles by transition-metal-catalyzed (including Pd, Rh, Ru, etc.) *ortho*-directed C–H bond activation and subsequent functionalization to the directing groups.[7–9] By using different types of imines as the directing group, Fagnou, Chiba, and Cheng et al. have independently developed versatile $Rh^{III}$-catalyzed chelation-assisted C–H bond activation strategies to synthesize isoquinolines[8k,p]

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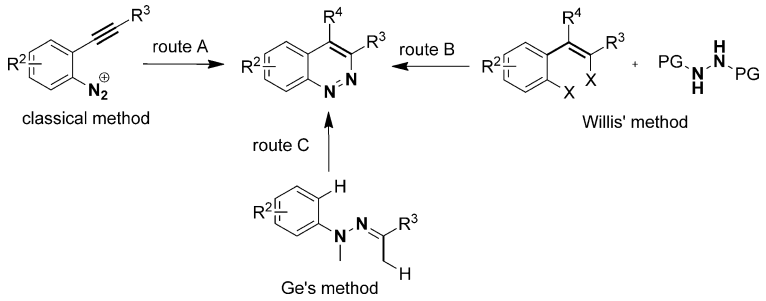
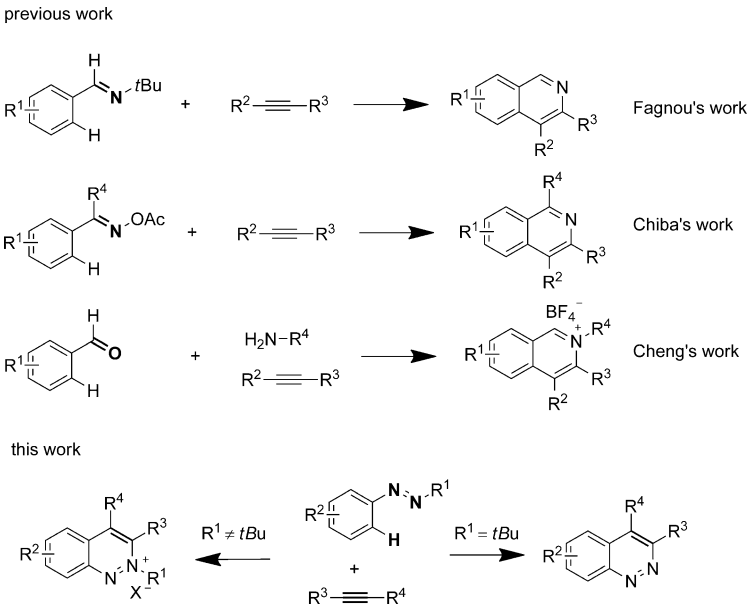



Scheme 2. Existing routes for the formation of cinnolines. PG = protecting group.




Scheme 3. $Rh^{III}$-catalyzed C–H bond activation strategy to isoquinolines, isoquinolinium salts, cinnolines, and cinnolinium salts.

and isoquinolinium salts[8t] (Scheme 3). However, the utility of this concept for the synthesis of cinnolines and cinnolinium salts has not yet been documented. Along the same lines, we envisioned that we could develop a general route to diverse cinnolines and cinnolinium salts with complete control of the substituent pattern through the rhodium(III)-catalyzed oxidative C–H activation/cyclization of azo compounds with various alkynes (Scheme 3).

Our initial investigation focused on the coupling of azobenzene (**1a**) with diphenylacetylene (**2a**; for screening of reaction conditions, see Table S1 in the Supporting Information). The cinnolinium salt **3a** was obtained in 98% isolated yield in the presence of $[RhCl_2(Cp^*)]_2$ ($Cp^* = C_5Me_5$) (2.0 mol%), $AgBF_4$ (1.0 equiv), and $Cu(OAc)_2$ (1.0 equiv) in *tert*-amyl alcohol at 110°C for 3 h (see Table S1, entry 4 in the Supporting Information). The structure of **3a** was confirmed to contain a cinnolinium cation and a tetrafluoroborate anion by single-crystal X-ray analysis (Figure 1).[10] Considering the high cost of the silver source, we envisioned whether the amount of $AgBF_4$ could be reduced to the substoichiometric level. Subsequently, we were pleased to find that 10 mol% of $Ag_2CO_3$ in combination with $NaBF_4$ (2.0 equiv) as the counteranion could afford **3a** in 96% yield by using $Cu(OAc)_2$ (2.0 equiv) as the oxidant (Table 1 and Table S1, entry 11 in the Supporting Information).

The counteranions are critical for regulating the properties of quaternary ammonium salts, such as melting point, density, viscosity, solubility, fluorescence characteristics, and electroconductivity.[11] Thus, it stimulated us to develop a concise route to the cinnolinium salts with different counteranions. Gratifyingly, the coupling of azobenzene (**1a**) with diphenylacetylene (**2a**) could smoothly give the cinnolinium salts **3** with diverse counteranions, such as $BF_4^-$, $NO_3^-$, $NTf_2^-$, $SbF_6^-$, and $OTf^-$ through an extra addition of stoichiometric alkali metal salts with different anions (Table 1). Notably, the nitrate salt **3b** has excellent water solubility, which may offer a precondition for the application in biological systems.

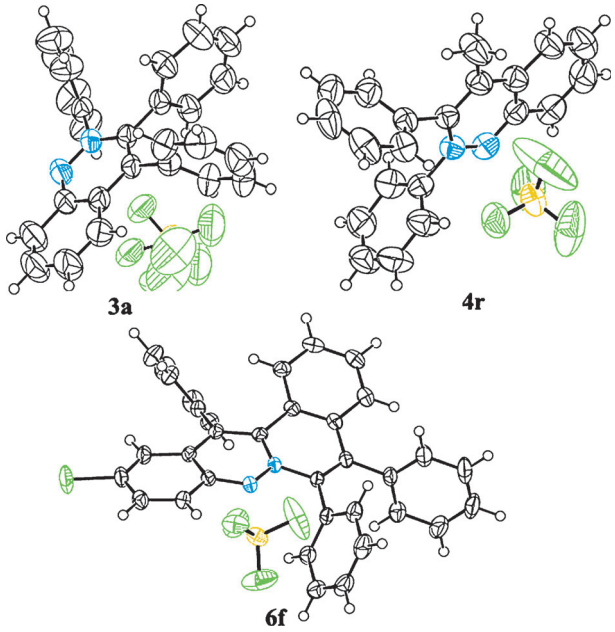
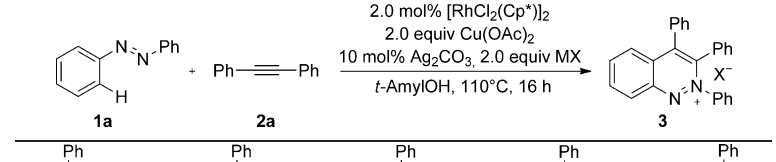
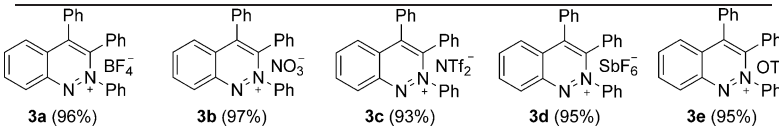



Figure 1. ORTEP diagrams of **3a**, **4r**, and **6f**. Thermal ellipsoids are shown at the 50% probability level.

Table 1. Preparation of the cinnolinium salts **3** with different counteranions.[a]



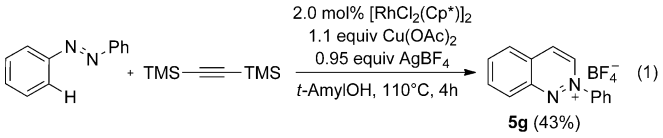

[a] MX: $NaBF_4$, $NaNO_3$, $LiNTf_2$, $NaSbF_6$, or NaOTf. Tf = trifluoromethanesulfonyl, *t*-AmylOH = *tert*-amyl alcohol.

Subsequently, we examined the scope of internal alkynes and azo compounds in the oxidative cross-coupling/cyclization. Overall, we were pleased with the generality of this method. As shown in Table 2, various azo compounds and internal alkynes proceeded smoothly to afford the desired cinnolinium salts in satisfactory yields. For example, the reactions occurred preferentially at the more sterically accessible position when a *meta*-substituent was attached to the phenyl ring of the azo compounds (Table 2, **4a**). The aryl group was installed at the 3-position of the cinnolinium salts when an unsymmetrical alkyl aryl alkyne was employed (Table 2, **4r** and **4s**). The structure of **4r** was confirmed by an X-ray analysis of single crystals (Figure 1).[10] The synthesis of unsymmetrical 3,4-bis(aliphatic)-substituted cinnolinium salts is a challenging task. It is important to stress that the reaction of an enyne with an azobenzene exclusively yielded the 3-alkenyl cinnolinium regioisomer under the optimized reaction conditions (Table 2, **4u**), which could offer an opportunity to unsymmetrical 3,4-bis(aliphatic)-substituted cinnolinium salts through a simple hydrogenation. In particular, this method was remarkably compatible with a variety of important functional groups such as halogens, hydroxyl, ester, acetyl, nitrile, and methoxy groups, which could be subjected to further synthetic transformations (Table 2, **4b–h, 4j–m, 4p**, and **4t**).

One of the commonly encountered limitations of the existing rhodium-catalyzed oxidative synthesis of N-heterocycles is the difficulty to incorporate terminal alkynes. As a result, it is challenging to construct monosubstituted heterocycles. Fortunately, the terminal alkynes, such as phenylacetylene, could undergo this type of oxidative cross-coupling/cyclization with azo compounds to give the monosubstituted cinnolinium salts **5** while the solvent was changed to dichloroethane (DCE) and the reaction time was prolonged to 20 h in the presence of stoichiometric $AgBF_4$. As shown in Table 3, both alkyl and aryl-substituted terminal alkynes gave the desired cinnolinium salts in yields of 75–83%. In addition, the regioselectivity of insertion was highly predictable with the terminal end located at the 4-position of cinnolinium salts.

To our delight, our synthetic strategy could be applied to the synthesis of 3,4-unsubstituted 2-arylcinnolinium salts by the reaction of azobenzene with 1,2-bis(trimethylsilyl)-ethyne, which underwent a sequential C–H activation, cyclization, and desilylation [Eq. (1)]. The previous research demonstrated that the reaction failed when bis(trimethylsilyl)acetylene was reacted with the cyclopalladated azobenzene complexes.[6]

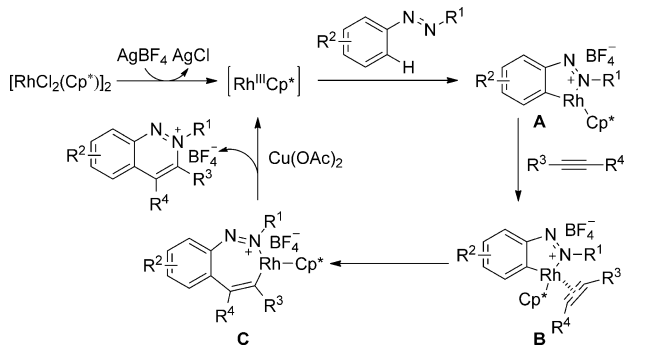
To further establish the validity of the methodology, we tried to synthesize neutral cinnolines. After extensive efforts we found that treatment of *N-tert*-butyl-aryldiazene with the dialkyl-substituted alkyne gave 3,4-dialkyl-substituted cinnolines (Table 4, **6a–d**). However, surprisingly we found that *N-tert*-butyl-aryldiazene could not give the desired neutral cinnolines when diaryl alkynes were




employed as the substrate. Instead, the sequential C–H activation/cyclization/C–H activation/cyclization cascade occurred to afford a variety of 5,6,13-trisubstituted isoquinolino-[2,1-*b*]cinnolinium tetrafluoroborates (Table 4, **6e–g**), which were confirmed by an X-ray analysis of single crystals of **6f** (Figure 1).[10] These novel polycyclic cinnolinium salts would find potential applications in materials science.

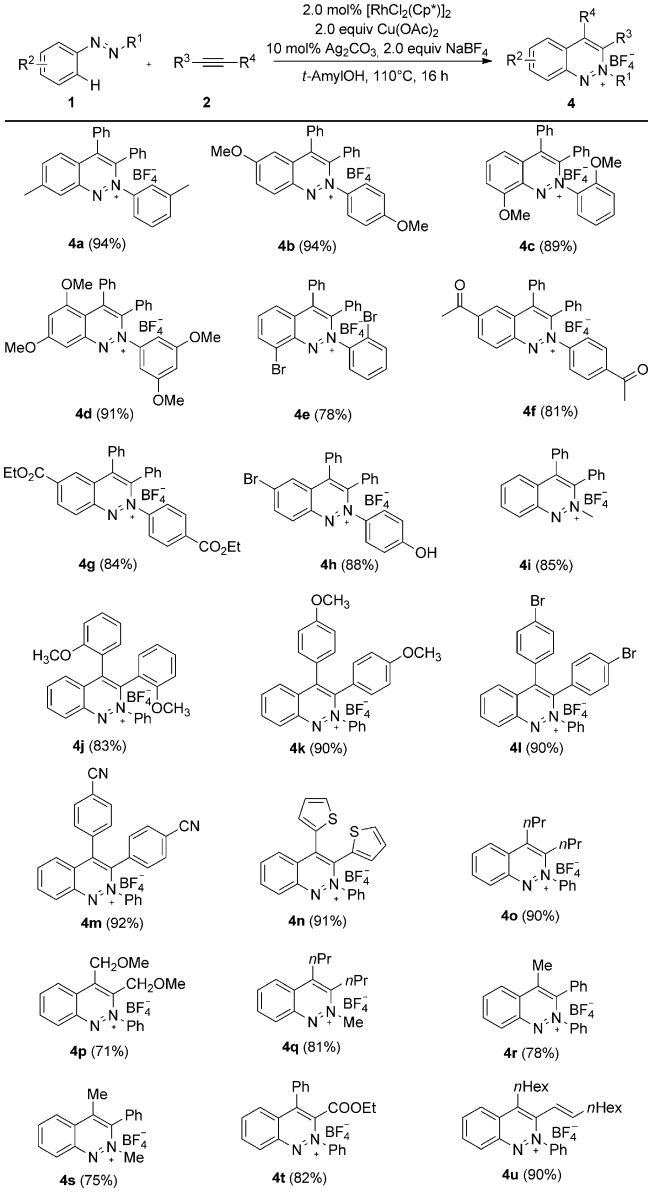
To afford the structurally diverse neutral cinnolines, we tried to remove the alkyl group from 2-alkyl cinnolinium salts. Upon treatment of the 2-methyl cinnolinium salt **4i** in pyridine at 140 °C, the corresponding 3,4-diphenyl cinnoline **7a** was obtained in 96% yield (Table 5). According to this method, we obtained various cinnolines including 3,4-diaryl-substituted, 3-aryl-4-alkyl-substituted, and monosubstituted cinnolines, which constituted an unprecedented route to neutral cinnolines with diverse substituent patterns incorporated and demonstrates the high-throughput of the methodology.

Although a more detailed investigation of the reaction mechanism is currently underway, we proposed a plausible catalytic cycle illustrated in Scheme 4.[8] The catalytic process was initiated through removal of chloride from $[RhCl_2(Cp^*)]_2$ with $AgBF_4$ to form the active $Rh^{III}$ species, followed by coordination with an azo compound to generate




Scheme 4. Proposed mechanism for the $Rh^{III}$-catalyzed synthesis of cinnolinium salts.

Table 2. Scope of internal alkynes and azo compounds in the oxidative cross-coupling/cyclization.[a]




[a] Reactions were carried out by using $[RhCl_2(Cp^*)]_2$ (2.0 mol%), $Cu(OAc)_2$ (2.0 equiv), $Ag_2CO_3$ (10 mol%), $NaBF_4$ (2.0 equiv), azo compound (0.30 mmol), and internal alkyne (0.25 mmol) in *t*-AmylOH (1.5 mL) at 110 °C for 16 h.

Table 3. Reactions of azo compounds with terminal alkynes.

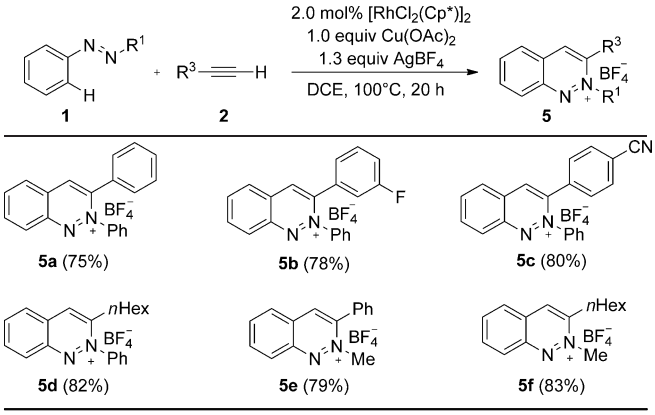
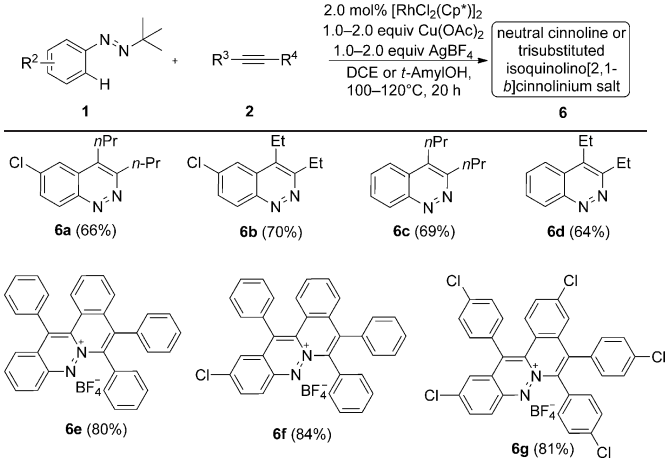
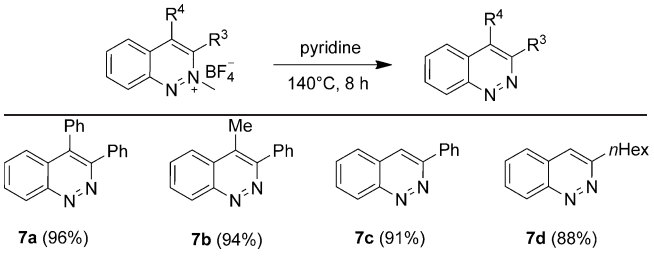



Table 4. Preparation of neutral cinnolines and polycyclic cinnolinium salts by starting from *N*-*tert*-butyl-aryldiazene.[a]




[a] For the detailed reaction conditions, see the Supporting Information.

Table 5. Demethylation of 2-methyl cinnolinium salts to diverse cinnolines.




the five-membered rhodacycle intermediate **A** through an *ortho*-directed C–H bond activation. Subsequently, the seven-membered rhodacycle intermediate **C** was formed through regioselective insertion of an alkyne into the rhodium–carbon bond of the intermediate **B**. $C(sp^2)$–$N(sp^2)$ bond reductive elimination of **C** gave the cinnolinium salt and $Rh^I$ species, which was oxidized by $Cu(OAc)_2$ to regenerate the $Rh^{III}$ species.

In summary, we have developed a highly efficient and general method to create both cinnoline and cinnolinium frameworks through the rhodium(III)-catalyzed oxidative C–H activation/cyclization of azo compounds with alkynes, which exhibits an unprecedented capacity to install versatile functional groups at various positions of the cinnoline ring. The catalytic protocol can be extended to synthesize polycyclic cinnolinium salts through twice *ortho*-directed C–H activation and cyclization. In this work, we have overcome a series of barriers: 1) the obstacle for establishing the catalytic cycle due to the high stability and general unreactivity of the cyclometalated azobenzene complexes,[6] 2) the installa-

tion of a facile leaving group as one N-substitutent of azo compounds to afford the neutral cinnolines, 3) the regioselectivity control including the activation of aryl C–H bonds and the insertion of unsymmetrical alkynes, 4) the hindrance of insertion of terminal alkynes, and 5) the competitive reaction from the rhodium-catalyzed addition of alkynes with azo compounds to form l-(arylamino)indoles.[12] However, the current methodology also suffers from some limitations. For example, these azobenzene derivatives are not always straightforward to prepare. In particular, some alkyl-substituted azobenzene derivatives need to be prepared by diazonium intermediates.[13] Additional applications of this methodology to the synthesis of biologically active molecules as well as luminescent materials and investigations into the detailed mechanisms are in progress.

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**Keywords:** catalysis · cinnolines · cinnolinium salts · heterocycles · rhodium

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[10] CCDC-894757 (**3a**), CCDC-895040 (**4r**), and CCDC-895037 (**6f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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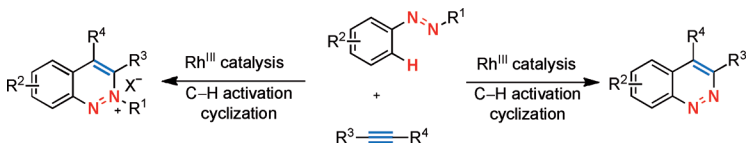


**Rhodium catalysis**: A highly efficient and general method has been established to prepare cinnolines, cinnolinium salts, and polycyclic cinnolinium salts through the rhodium(III)-catalyzed oxidative C–H activation/cyclization of azo compounds with alkynes (see scheme). Key features of this methodology include the unprecedented capacity to create both cinnoline and cinnolinium frameworks.

**Heterocycles**