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Annulation of Hydrazones and Alkynes via Rhodium(III)-Catalyzed Dual C−H Activation: Synthesis of Pyrrolopyridazines and Azolopyridazines

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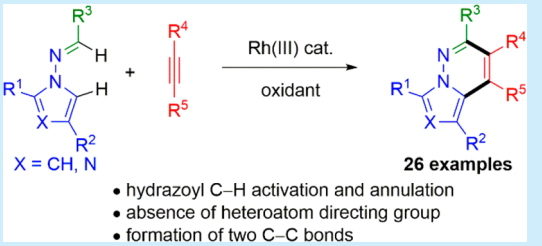
ABSTRACT: Hydrazones readily synthesized from *N*-aminopyrroles or *N*-aminoazoles and aldehydes undergo Rh(III)-catalyzed dual C−H activation and coupling with aryl- and alkyl-substituted alkynes to give pyrrolopyridazines or azolopyridazines, respectively. This transformation represents a rare example of hydrazoyl C−H activation and proceeds without heteroatom functionality to direct C−H activation. Hydrazones derived from aromatic, alkenyl, and aliphatic aldehydes were effective inputs, and tethering the alkyne to the hydrazone enabled annulations to more complex, tricyclic products.



Rhodium(III)-catalyzed imidoyl C−H functionalization provides a powerful approach for the rapid synthesis of diverse nitrogen heterocycles due to the straightforward preparation of the imine C−H bond substrates from readily available aldehydes and amines.[1] We have in particular focused on the synthesis of fused [5,6]-bicyclic nitrogen heterocycles with a ring junction nitrogen because these classes of heterocycles are found in a large number of drugs and clinical candidates.[2] This approach is exemplified by the synthesis of azolopyrimidines **2** by Rh(III)-catalyzed annulations of aldimines **1** with a variety of different coupling partners (Scheme 1A).[1a,c]

Satoh and Miura as well as Dong and Chen have reported innovative annulations of phenyl-substituted five-membered heteroaromatics and alkynes wherein two C−C bonds are formed by transition-metal-catalyzed dual C−H activation without the assistance of a proximal heteroatom directing group to afford polycyclic heteroarenes (Scheme 1B).[3] Other examples of dual C−H activation and coupling with alkynes to give heterocycles have subsequently been reported,[4] as exemplified by the conversion of *N*-arylpyridiniums **6** to polycyclic quinoliniums **7** (Scheme 1C).[5]

Inspired by the dual C−H activation annulation approach, we herein report annulations proceeding by dual C−H activation of hydrazones **8** followed by alkyne coupling for the rapid assembly of drug-relevant pyrrolopyridazines and azolopyridazines **9** (Scheme 1D).[6] This work contrasts with our previously reported annulations, which proceed by imidoyl C−H activation, in three significant ways: (1) no heteroatom is present to direct C−H activation, (2) the annulation proceeds by dual C−H activation with alkyne insertion to form two new C−C bonds, and (3) the reaction occurs by Rh(III)-catalyzed hydrazoyl C−H activation, which has rarely been explored.[7,8] The use of a commercially available and air-stable Rh(III) precatalyst and microwave heating allow for the rapid assembly of the heterocycle products from easily prepared hydrazones and readily available alkynes. Moreover, tethering the alkyne to the hydrazone enabled annulations to more complex, tricyclic products with a central pyridazine ring.

We began our investigation by identifying optimal conditions for coupling hydrazone **8a** and tolan (**4a**) (Table 1). Good yields were obtained using 5 mol % of $[Cp^*RhCl_2]_2$ as precatalyst and 2 equiv of $Cu(OAc)_2$ as the stoichiometric oxidant in dioxane (0.2 M) at 120 °C for 16 h (entry 1). Acid and base additives were tested, but neither pivalic acid nor sodium acetate improved the yield (entries 2 and 3). Dropping the loading of $[Cp^*RhCl_2]_2$ to 1 mol % resulted in a comparable yield (entry 4), which is advantageous for larger-scale reactions (vide infra). However, no product formed when either the Rh(III) catalyst or stoichiometric oxidant were removed (entries 5 and 6). When AgOAc was used as the stoichiometric oxidant in place of $Cu(OAc)_2$, a lower yield of **9aa** was obtained (entry 7), although a more modest drop in yield was observed when pivalic acid was also added (entry 8). Significantly, AgOAc and pivalic acid were necessary to obtain acceptable yields for annulations with unsymmetrical alkynes (vide infra and Table S1 in the Supporting Information). Decreasing the concentration to 0.1 M or increasing the concentration to 0.4 M did not have a dramatic effect on the yield (entries 9 and 10). The analogous group IX catalysts $[Cp^*IrCl_2]_2$ and $[Cp^*CoCl_2]_2$ were also evaluated but provided little to no desired product (entries 11 and 12).

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Scheme 1. Heterocycle Synthesis by C−H Activation

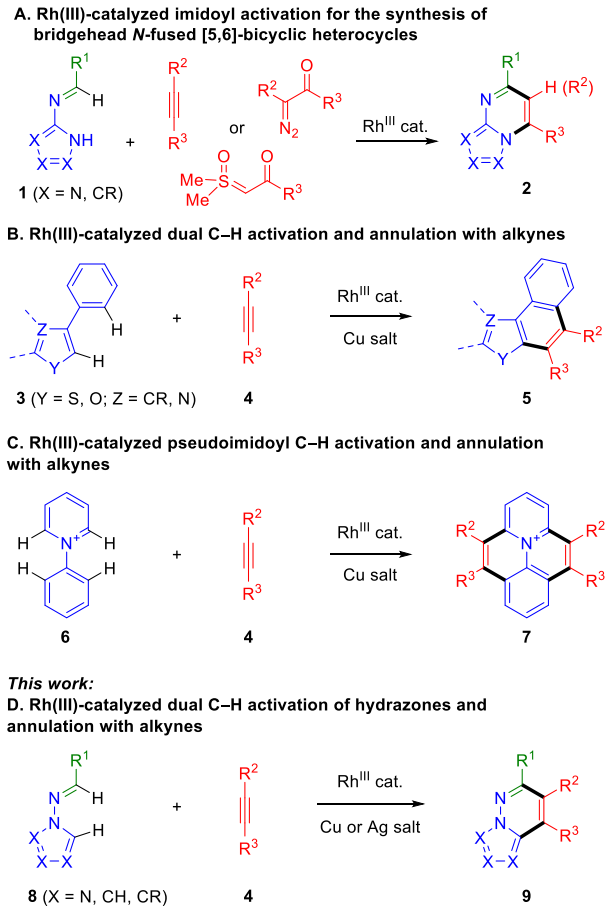
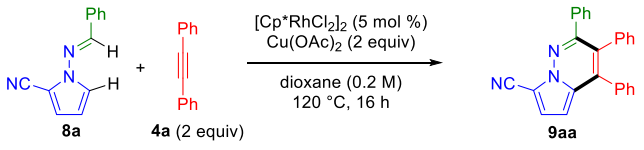


Table 1. Reaction Parameters for Annulation to 9aa[a]



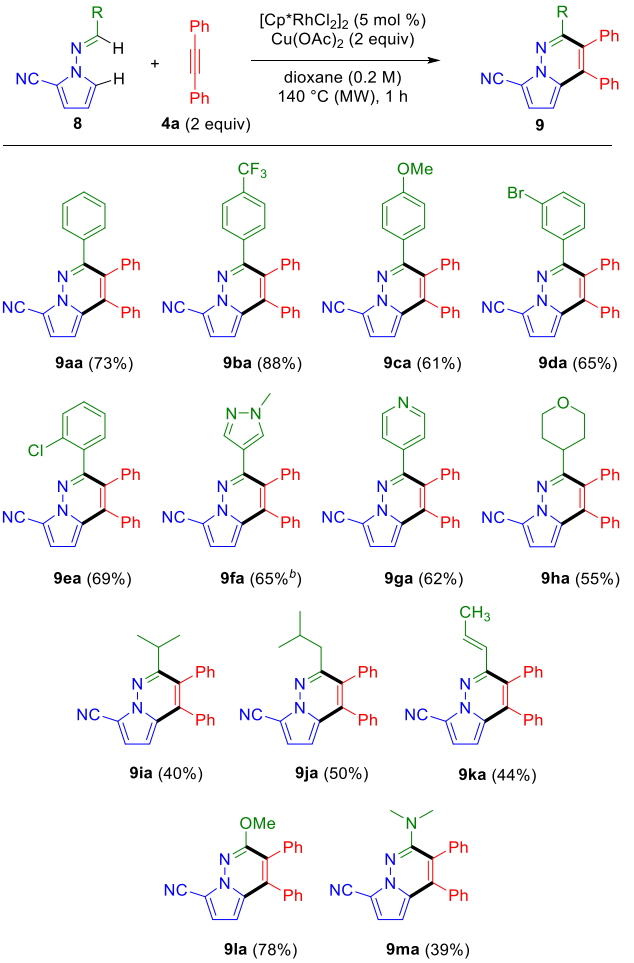
entry	variation	yield %[b]
1	none	74
2	PivOH (1 equiv)	60
3	NaOAc (1 equiv)	73
4	$[Cp^*RhCl_2]_2$ (1 mol %)	74
5	no $[Cp^*RhCl_2]_2$	0
6	no $Cu(OAc)_2$	0
7	AgOAc instead of $Cu(OAc)_2$	59
8	AgOAc instead of $Cu(OAc)_2$, PivOH (1 equiv)	67
9	0.1 M	74
10	0.4 M[c]	62
11	$[Cp^*IrCl_2]_2$ (5 mol %)	8
12	$[Cp^*CoCl_2]_2$ (5 mol %)	0
13	microwave heating, 140 °C, 1 h	73 (73)[d]
14	microwave heating, 150 °C, 1 h	68

[a]Conditions: **8a** (0.10 mmol) and **4a** (0.20 mmol). [b]Yields determined by ^{1}H NMR integration relative to 1,3,5-trimethoxybenzene as external standard. [c]**8a** (0.20 mmol) and **4a** (0.40 mmol). [d]Isolated yield.

The product was also obtained in 73% isolated yield when the standard conditions were used but with microwave heating at 140 °C and with a reaction time of only 1 h (entry 13). When increasing the reaction temperature to 150 °C, a modest drop in yield was observed (entry 14), thereby establishing that complete conversion had been achieved at 140 °C.

Using the optimal conditions for achieving a rapid reaction with microwave heating (Table 1, entry 13), we next investigated annulations of hydrazones **8** prepared from *N*-amino-2-cyanopyrrole and a broad range of aldehydes (Scheme 2). In addition to the benzaldehyde-derived hydrazone **8a**,

Scheme 2. Variation of the R Substituent in Hydrazone 8[a]



[a]Standard conditions: **8** (0.30 mmol) and **4a** (0.60 mmol). [b]0.5 M, 0.20 mmol of **8f**, 0.40 mmol of **4a**. Isolated yields are reported.

both electron-poor and electron-rich hydrazones coupled effectively to provide pyrrolopyridazines **9ba** and **9ca**, respectively. Substitution at the *meta*- and *ortho*-positions provided products **9da** and **9ea** in good yields. These examples also demonstrate that aromatic bromides and chlorides are compatible with the reaction conditions. Hydrazones that incorporate pyrazole and pyridyl functionality provided pyrrolopyridazines **9fa** and **9ga** in 65% and 62% yields, respectively, thereby establishing that basic nitrogen functionality does not interfere with the reaction.

We next explored hydrazones derived from aliphatic aldehydes, with both branched and unbranched derivatives providing the pyrrolopyridazine products **9ha** to **9ja**, though with slightly lower yields than had been observed for the aromatic derivatives. An α,β-unsaturated hydrazone provided product **9ka** in 44% yield. Finally, alkoxy and tertiary amino

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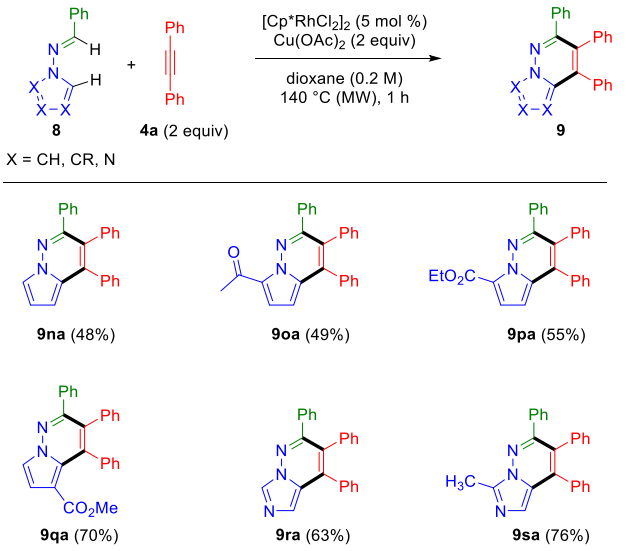
substituents on the newly formed pyridazine ring of products **9la** and **9ma** were introduced by employing C−H bond substrates prepared by direct condensation of *N*-amino-2-cyanopyrrole and trimethyl orthoformate and *N*,*N*-dimethylformamide dimethyl acetal, respectively.

We then evaluated variations of the pyrrole and azole framework within the hydrazone C−H bond substrate **8** (Scheme 3). The hydrazone prepared from *N*-aminopyrrole

Scheme 3. Variation of the Pyrrole and Azole Framework in Hydrazone 8[a]

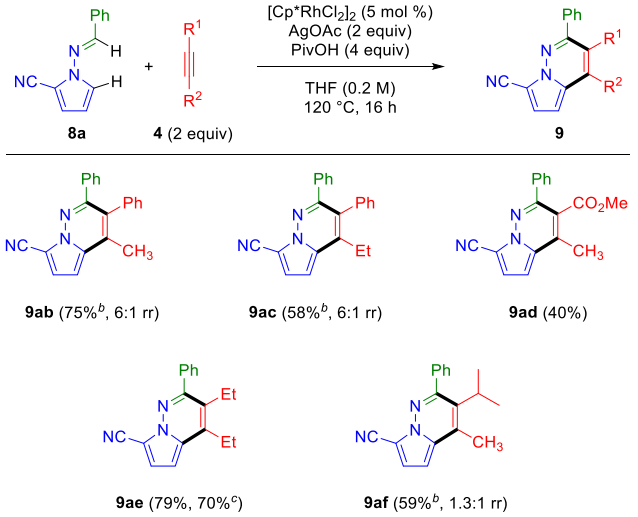


[a]Standard conditions: **8** (0.30 mmol) and **4a** (0.60 mmol). Isolated yields are reported.

provided pyrrolopyridazine **9na** without any substituents on the pyrrole ring. Moreover, in addition to the previously introduced cyano group (see Scheme 2), 2-acetyl and ester substituents could also be installed at different sites on the pyrrole ring as shown for products **9oa** to **9qa**. Interestingly, for pyrrolopyridazine **9qa**, only one out of the two possible regioisomers was formed, presumably because the ester functionality directs C−H activation to the more hindered proximal site.[9] Finally, hydrazones incorporating unsubstituted and substituted imidazoles were effective coupling partners to provide products **9ra** and **9sa**, respectively.[10]

Next, we investigated the scope of the alkyne coupling partner (Scheme 4). For couplings with unsymmetrical alkynes we found that using AgOAc instead of $Cu(OAc)_2$ as the stoichiometric oxidant provided higher yields of product (see Table S1, Supporting Information). Including pivalic acid, changing the solvent to THF, and heating conventionally at 120 °C for 16 h also improved the reaction yield for these alkynes (see Table S1). Employing these conditions, phenyl-substituted, unsymmetrical alkynes provided pyrrolopyridazines **9ab** and **9ac** in moderate to good yields. Both **9ab** and **9ac** were produced in a 6:1 regioisomeric ratio. Under the same conditions, an unsymmetrical alkynoate coupling partner provided product **9ad** in a more modest yield but as a single regioisomer. For the symmetrical alkyl-substituted alkyne, 3-hexyne, $Cu(OAc)_2$ and AgOAc were each evaluated as the stoichiometric oxidant, with AgOAc affording **9ae** in a slightly higher yield of 79% relative to the 70% observed for $Cu(OAc)_2$. An unsymmetrical, bisalkyl-substituted alkyne

Scheme 4. Scope of Alkynes[a]

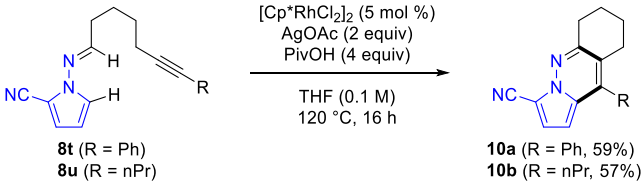


[a]Standard conditions: **8a** (0.30 mmol) and **4** (0.60 mmol). [b]Yield of mixture of regioisomers with regioisomers assigned by 2D NOESY experiments. [c]$Cu(OAc)_2$ in place of AgOAc, omission of PivOH, dioxane (0.2 M) in place of THF, 140 °C (MW), 1 h. Isolated yields are reported.

gave **9af** in 59% yield with a 1.3:1 regioisomeric ratio. This example demonstrates that sterics alone play only a modest role in controlling regioselectivity.

We also envisioned that tricyclic products with a central pyridazine ring should be accessible by tethering the alkyne to the hydrazone (Scheme 5). For these intramolecular

Scheme 5. Synthesis of Tricyclic Derivatives 10[a]



[a]Standard conditions: **8** (0.30 mmol). Isolated yields are reported.

annulations we found that decreasing the reaction concentration to 0.1 M resulted in higher yields, possibly by reducing competing intermolecular cross-reactivity. As demonstrated for tricyclic products **10a** and **10b**, comparable yields were obtained when either alkyl or aryl substituents were introduced on the central pyridazine ring.

To maximize the robustness of the reaction at short reaction times, we evaluated the substrate scope with 5 mol % of $[Cp^*RhCl_2]_2$ and often with microwave heating at 140 °C for 1 h (vide supra). However, for performing large-scale reactions, a lower catalyst loading with conventional heating would likely be desirable. Therefore, a 1 mmol reaction was performed with hydrazone **8a** and alkyne **4a** at a lower catalyst loading of 1 mol % and with conventional heating at 120 °C for 16 h (Scheme 6). Pyrrolopyridazine **9aa** was obtained in 70% isolated yield, similar to that previously obtained at the higher 5 mol % loading of $[Cp^*RhCl_2]_2$ under microwave heating (see Table 1, entry 13).

Next, we turned our attention to the mechanism. We performed the reaction using hydrazone **8a** and styrene in

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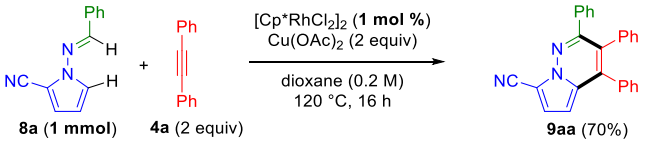
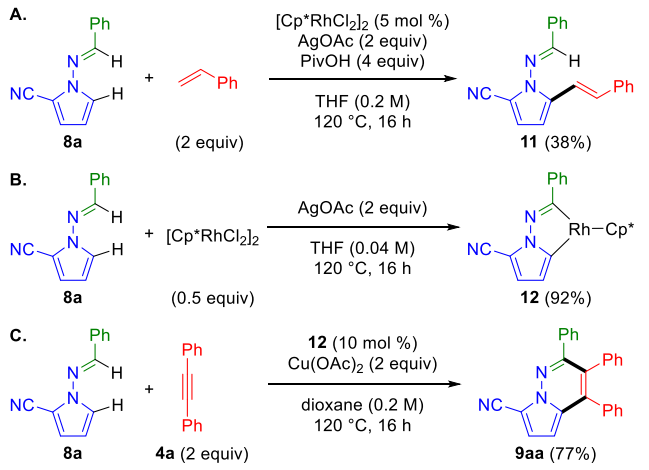
Scheme 6. 1 mmol Scale Reaction at 1 mol % Precatalyst



place of the alkyne to generate the oxidative Heck-type product **11** with selective functionalization on the pyrrole ring rather than at the imidoyl site (Scheme 7A). This result can be

Scheme 7. Mechanistic Studies

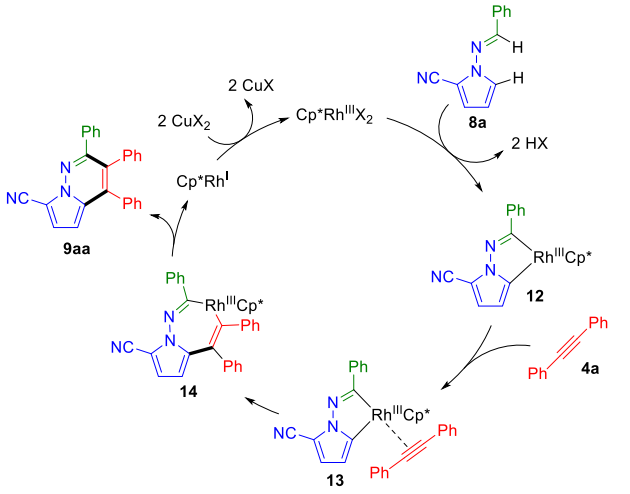


compared with related studies performed by Satoh and Miura for 3-phenylthiophene, where the oxidative Heck reaction occurred selectively on the phenyl ring rather than on the more electron-rich thiophene.[3] We also set out to isolate the C−H activation intermediate. Treatment of hydrazone **8a** with stoichiometric $[Cp^*RhCl_2]_2$ (based on the metal) and 2 equiv of AgOAc cleanly afforded rhodacycle **12** in nearly quantitative yield as determined by ^1H NMR and HRMS (Scheme 7B). Additionally, ^{13}C NMR showed ^{13}C−Rh coupling for two C−Rh bonds. Consistent with **12** serving as an intermediate in the catalytic cycle (vide infra), 10 mol % of this rhodacycle catalyzed the reaction of hydrazone **8a** and alkyne **4a** to give **9aa** in 77% isolated yield (Scheme 7C).

A plausible mechanism is depicted in Scheme 8. Based on the experiments in Scheme 7 and the previous mechanistic and computational work on double activation of aldehyde hydrazones by Li and Zhu,[7] we propose that the hydrazone undergoes two sequential concerted metalation−deprotonation steps to generate the five-membered rhodacycle **12**. Consistent with the experiment shown in Scheme 7A, coordination of the alkyne followed by selective migratory insertion into the Rh−C bond on the five-membered ring produces vinyl rhodium species **14**. Reductive elimination releases product **9aa** and generates a Rh(I) species, which is oxidized by the stoichiometric oxidant to regenerate the Rh(III) catalyst.

In summary, hydrazones prepared from *N*-aminopyrroles and *N*-aminoazoles and aldehydes coupled with alkynes via Rh(III)-catalyzed hydrazoyl C−H activation produce a broad range of pyrrolopyridazines and azolopyridazines. Hydrazones derived from structurally diverse aromatic, alkenyl, and aliphatic aldehydes were effective substrates for annulation. In addition, methoxy and dimethylamino groups could be

Scheme 8. Proposed Catalytic Cycle for Annulation



installed on the pyridazine ring by employing C−H bond substrates prepared by condensing the *N*-aminopyrrole and *N*-aminoazole with trimethyl orthoformate and *N*,*N*,-dimethylformamide dimethyl acetal in place of the aldehyde, respectively. Hydrazones incorporating unsubstituted as well as substituted pyrroles and azoles were also effective C−H bond substrates, and both symmetrical and unsymmetrical alkyl- and aryl-substituted alkynes were effective coupling partners. Finally, by tethering hydrazones to alkynes, tricyclic products with a central pyridazine ring were obtained.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00186.

Procedure details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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