Rhodium-Catalyzed Annulative Coupling Using Vinylene Carbonate as Oxidizing Acetylene Surrogate

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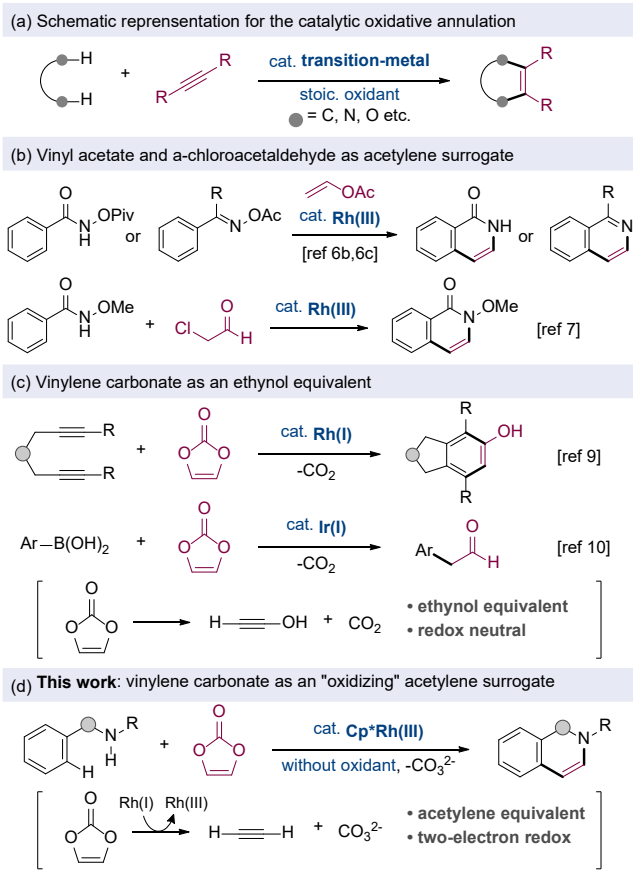
ABSTRACT: Transition-metal-catalyzed C–H activation and subsequent oxidative cyclization with alkynes has been a powerful tool for the synthesis of polycyclic aromatic compounds. Despite the substantial progress in this field, it is still a significant challenge to establish synthetic methodologies for the construction of non-substituted vinylene-fused aromatics. We herein report a Rh(III)-catalyzed C–H/N–H annulation with vinylene carbonate as an acetylene surrogate. Vinylene carbonate also acts as an internal oxidant to regenerate the Rh(III) species in situ; thus no external oxidant is required to trigger the oxidative annulation. This protocol is applicable to the direct synthesis of various N-heteroaromatics.

KEYWORDS: rhodium, C–H functionalization, acetylene, cyclization, N-heterocycles

Polycyclic heteroaromatic scaffold is ubiquitous in many natural compounds and has been a key motif in a wide range of manufactured functional molecules. Accordingly, tremendous research interest has been focused on the development of new and efficient synthetic methods for constructing fused-ring skeletons. Transition-metal-catalyzed C–H activation[1] and subsequent oxidative annulation with alkynes or their equivalents has been emerged as a promising synthetic tool for the assembly of heterocycles (Scheme 1a).[2] This method allows us to construct various fused-ring systems with simple manipulations; however, most of these reactions are only applicable to internal alkynes. This limitation significantly takes from the practical value of the annulative coupling reaction because a non-substituted vinylene fragment (R = H in Scheme 1a) cannot be installed via the catalysis. Moreover, a stoichiometric amount of external oxidant is usually required to ensure the catalytic turnover, leading to the formation of undesired byproducts.

In order to achieve the catalytic production of vinylene-fused aromatic compounds, one needs to employ a suitable acetylene surrogate. Although acetylene itself has been utilized as a reactant,[3] specialized equipment is required for operating with the gas-phase reactant as well as for safety concerns. As a recent example, an electro-oxidative acetylene annulation was established by Lei and coworkers using a cobalt catalyst.[4] Bis(trimethylsilyl)acetylene is one of the most common alternatives. The use of this protected alkyne in the oxidative annulation is fairly limited due to its inherently low reactivity and stability.[5] Excellent reaction systems have been developed using vinyl acetate[6] and α-chloroacetaldehyde[7] as acetylene equivalents;



Scheme 1. Catalytic annulative coupling reactions using alkyne surrogates.

however, these reactants can be coupled only with *N*-(alkoxy)amides and oximes (Scheme 1b). Obviously, it is of

great challenge to establish a synthetic method for the acetylene cyclization with broad substrate generality.

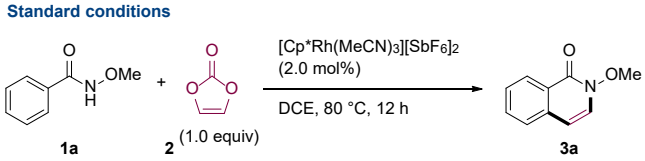
To address this issue, we envisioned to use vinylene carbonate as an "oxidizing" acetylene surrogate. Vinylene carbonate is a bench-stable chemical with bulk production for polymer chemistry. There are several reports for the transition-metal-catalyzed reaction utilizing vinylene carbonate.[8] Although none of these uses it as an acetylene equivalent, as potentially relevant transformations, vinylene carbonate was found to act as an ethynol equivalent through the decarboxylation (Scheme 1c). For example, Tanaka *et al.* developed a Rh(I)-catalyzed decarboxylative [2+2+2] cycloaddition of vinylene carbonate with diyne to produce substituted phenol derivatives.[9] Very recently, Hayashi *et al.* reported the arylacetaldehyde synthesis by Ir(I)-catalyzed addition of boronic acids onto vinylene carbonate.[10]

These examples are redox neutral processes, whereas, if vinylene carbonate act as an acetylene surrogate, formal two-electron redox should accompany to eliminate $[CO_3]^{2-}$ anion. In other word, vinylene carbonate might act as a two-electron internal oxidant under proper reaction conditions (Scheme 1d). With this picture in mind, we investigated the annulative coupling using vinylene carbonate as a coupling partner and, to our delight, found that a standard Cp*Rh catalyst produced favorable outcomes. Herein, we report a catalytic construction of nitrogen-based vinylene-fused heterocycles through C–H/N–H annulation.

We initiated our study utilizing *N*-methoxybenzamide (**1a**) and vinylene carbonate (**2**) as model substrates for the coupling reaction (Table 1). After screening several reaction conditions, the bicyclic product **3a** was obtained in 78% yield using 1.0 equiv of **2** and a cationic Cp*Rh(III) catalyst (entry 1). Notably, no external oxidant was required to achieve the catalytic production of **3a**, and the N–O linkage of **1a**, which may act as an internal oxidant for rhodium catalysis,[11,12] remained unreacted. The desired product was not obtained in the absence of the catalyst (entry 2) or with a neutral $[Cp^*RhCl_2]_2$ complex (entry 3). Addition of $Cu(OAc)_2{\cdot}H_2O$ oxidant considerably retarded the reaction (entry 3). 1,4-Dioxane was also a suitable solvent for the present reaction (entry 5). Increased amount of **2** slightly improved the productivity (entry 6), and **3a** was isolated in 86% yield in 0.3 mmol scale conducted at 70 °C (entry 7).

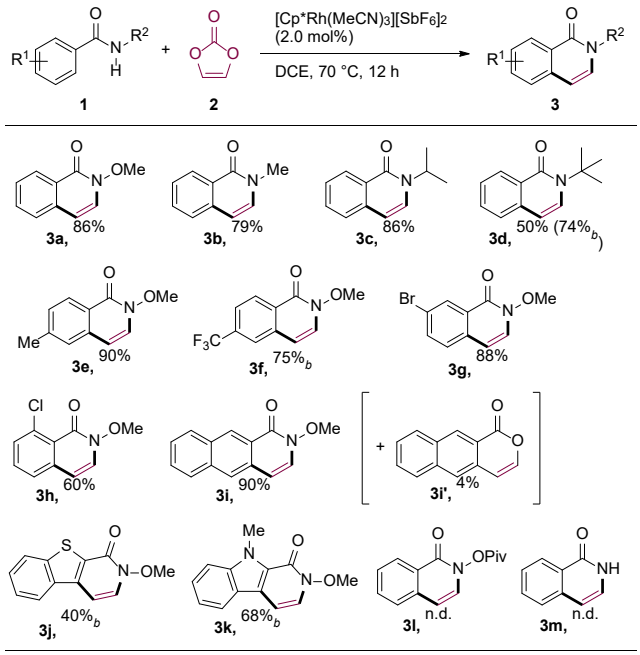
With the optimized reaction conditions (Table 1, entry 7), the scope of amide substrates was systematically examined (Scheme 2). Besides the hydroxamic ester **1a**, *N*-alkyl secondary amides **1b–1d** produced the corresponding isoquinolinones **3b–3d** in high yields. Substituents at the para-position on the arene motif did not interfere the reactivity to give **3e** (90%) and **3f** (75%). Annulation with a *meta*-Br benzamide **1g** resulted in selective formation of **3g** in 88% yield, where the sterically more accessible C–H bond reacted. The reaction of an *ortho*-Cl benzamide **1h** also worked well to provide the desired product **3h**. Interestingly, 2-napthylamide **1i** gave the corresponding lactone **3i'** along with the target compound **3i** (90%), suggesting that decarboxylation would take place as a minor pathway (see below). Heterocyclic substrates **1j** and **1k** were also successfully converted to the tricyclic products. In contrast, an *N*-(pivaloyloxy)amide **1l** and a primary amide **1m** were totally inert under the conditions.

Table 1. Optimization study [a]



entry	deviation from the standard conditions	yield [b]
1	none	78%
2	without Rh catalyst	n.d.
3	$[Cp^*RhCl_2]_2$ (2.0 mol% Rh) as catalyst	n.d.
4	with 1.0 equiv $Cu(OAc)_2{\cdot}H_2O$	66%
5	1,4-dioxane solvent	72%
6	with 2.0 equiv of **2**	83%
7	with 2.0 equiv of **2** at 70 °C	86% [c]

[a] Standard reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (2.0 mol%), DCE (1.0 mL). [b] Determined by ^1H NMR analysis. [c] Isolated yield at 0.3 mmol scale in 2.0 mL DCE. n.d. = not detected

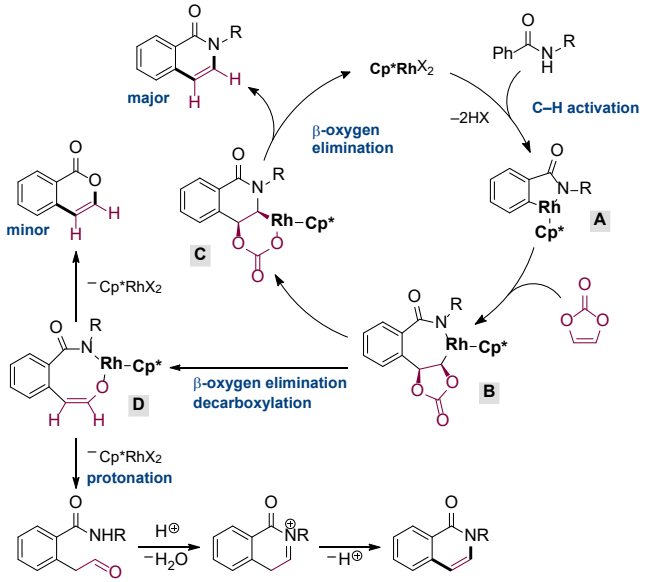


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), DCE (2.0 mL). [b] 5.0 mol% Rh catalyst, 90 °C, 24 h

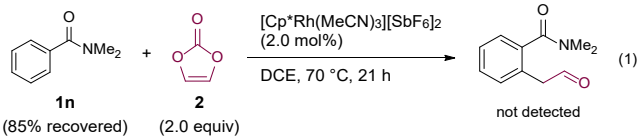
Scheme 2. Substrate scope of the C–H/N–H oxidative annulation with amide substrates. [a]

A proposed reaction mechanism for the annulative coupling is illustrated in Scheme 3. The amide directing group coordinates to a cationic Cp*Rh(III) species, thereby forming a five-membered rhodacycle **A** through the proximal

C–H bond activation. Migratory insertion of vinylene carbonate into the Rh–C bond produces a seven-membered metallacycle **B**, where the β-hydrogen elimination is configurationally restricted. According to the literature,[13] we assume that the intermediate **B** undergoes sequential C–N reductive elimination and oxidative addition into the adjacent C–O bond to generate a complex **C**.[14] Afterward, formal β-oxygen elimination takes place to liberate the corresponding coupling product and the catalytically active Rh(III) complex. As a minor pathway, β-oxygen elimination and decarboxylation may occur from the intermediate **B** to give an alkoxide complex **D**. Intramolecular alcoholysis affords the ester byproduct, albeit this forms only negligible amounts (up to 4%, **3i'**). Alternatively, protonation of the intermediate **D** might lead to the target product through the corresponding aldehyde intermediate. To exclude this possibility, we examined a reaction of **1n** under the standard conditions (eq 1). The aldehyde product was not detected at all, and most of the starting material was recovered (85%). This result supports our proposal.

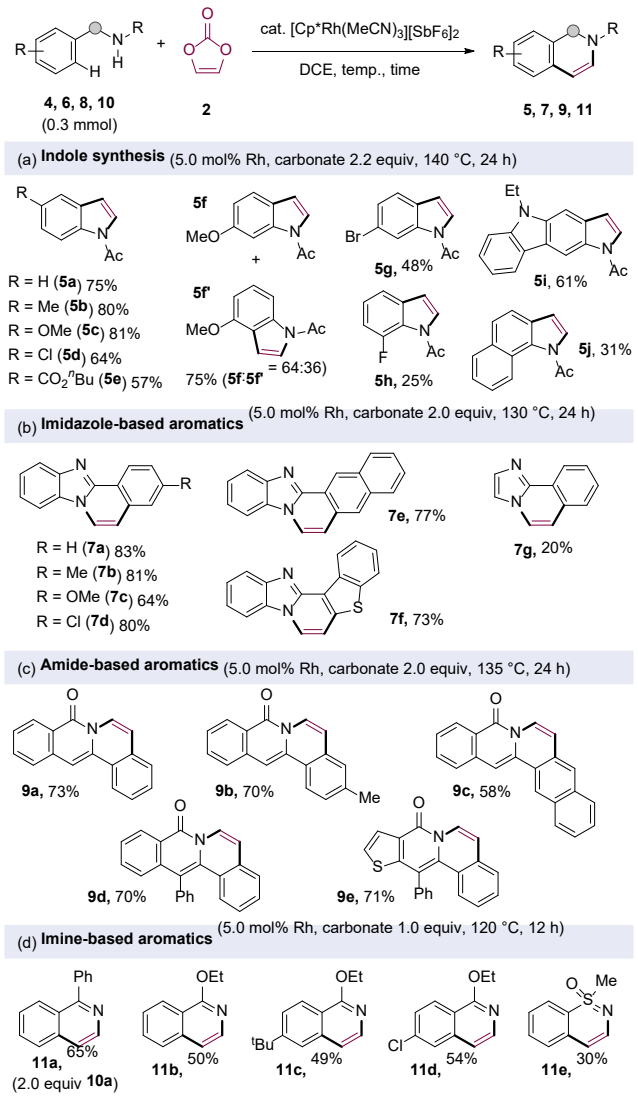


Scheme 3. A proposed reaction mechanism for the annulative coupling.

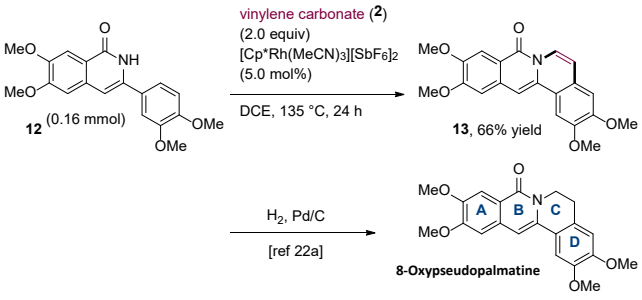


In order to demonstrate the generality of the developed catalyst system, we examined the synthesis of various N-heteroaromatics via C–H/N–H oxidative annulation (Scheme 4).[15] A number of indoles **5** could be prepared from readily available anilines **4** (acetanilides) in one step (Scheme 4a).[16] We also tested some other directing groups on the nitrogen atom (carbamates, pyrimidyl), but no productive results were obtained (not shown). Functional groups involving alkoxy (**4c**, **4f**), halogen (**4d**, **4g**, **4h**), ester (**4e**), and carbazole ring (**4l**) were compatible. For the meta-substituted anilines, less bulky methoxy group yielded a mixture of regioisomers (**5f**+**5f'**), whereas the bromo derivative gave **5g** as a sole product. A substituent (**4h**) or benzo-ring (**4j**) at the ortho position somewhat retarded the reaction. Densely-fused aza-heterocycles could be constructed efficiently by applying the catalysis to 2-arylbenzimidazoles (**6a–6f**) (Scheme 4b).[17] 2-Phenylimidazole (**6g**) could be converted to the desired product, albeit there was a room for further optimization. Amide-embedded substrates **8** (isoquinolinones) were smoothly annulated to give the polycyclic products **9** in high yields (Scheme 4c).[18] Some of these compounds are key structural motifs in a series of isoquinoline alkaloids such as a berberine family (see below). The catalytic system was also applicable to the isoquinoline synthesis using imines (Scheme 4d).[19] For a simple benzophenone imine (**10a**), vinylene carbonate (**2**) was used as a limiting reagent since hydrolysis of the imine was competing during the reaction. 1-Alkoxyisoquinlines (**11b–11d**) were synthesized from the parent imidates in synthetically useful yields. A sulfoximine **10e** was converted into the corresponding thiazine oxides.

Finally, we applied the developed protocol to the synthesis of 8-oxypseudopalmatine, a natural berberine-type alkaloid (Scheme 5).[20] This molecule has attracted considerable attention over 40 years due to its unique cytotoxic activity. In general, 8-oxypseudopalmatine and its analogues have been synthesized from dihydro- or tetrahydroisoquinolines via B-ring closure.[21] On the other hand, there are only a few synthetic methods for the C-ring closure, adopting olefin metathesis or intramolecular substitution.[22] We synthesized a precursor **12** according to the literature procedures (see the Supporting Information), and the subsequent annulative coupling with vinylene carbonate **2** produced the product **13**. This compound can be transformed into the target alkaloid by reduction with H_2 over Pd/C.[22a] Previous methods for the C-ring closure requires pre-functionalization to trigger the cyclization, whereas our catalytic conditions can directly assemble the ring system. As exemplified by this particular compound, the present methodology may offer new possible synthetic strategies for a variety of fused-ring systems.



Scheme 4. Substrate scope for the C–H/N–H oxidative annulation.



Scheme 5. Formal total synthesis of 8-oxypseudopalmatine.

In conclusion, we have developed a Rh(III)-catalyzed annulative coupling using vinylene carbonate as an acetylene surrogate. Notable features of this reaction system are that (1) non-substituted vinylene-fused cyclic compounds can directly be obtained without any pre-functionalization and (2) no external oxidant as well as base is required for the catalytic turnover. A series of N-heteroaromatics can be synthesized through the C–H/N–H oxidative annulation. The detailed mechanistic study and its synthetic application for other heterocycles are currently underway in our group.

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Notes

The authors declare no competing financial interests.

SUPPORTING INFORMATION

Experimental procedures, copy of ^{1}H and ^{13}C NMR spectra (PDF), crystallographic data for **7c** and **7e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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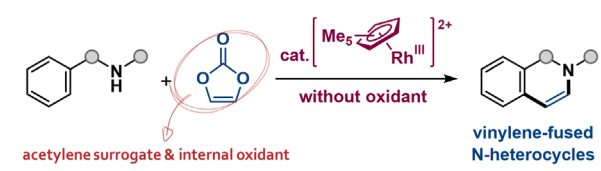
cat.
without oxidant
acetylene surrogate & internal oxidant
vinylene-fused
N-heterocycles