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Oxidative C–H/C–H Annulation of Imidazopyridines and Indazoles through Rhodium-Catalyzed Vinylene Transfer

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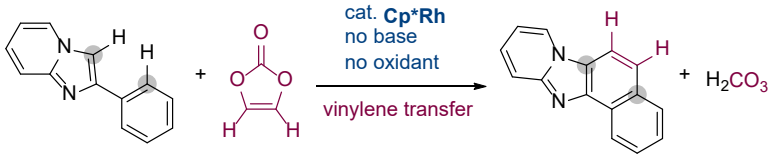
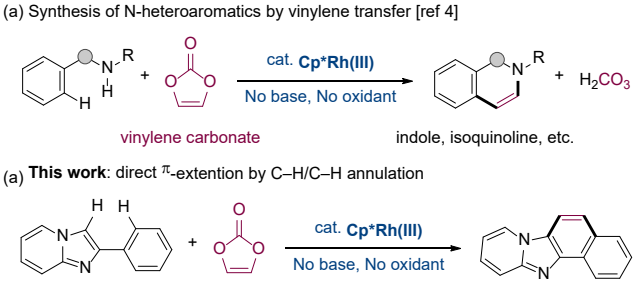


ABSTRACT: Transition-metal-catalyzed C−H activation followed by oxidative annulation with alkynes has been an efficient synthetic tool for the assembly of various poly-aromatic scaffolds. Despite the substantial progress in this field, it is still a significant challenge to achieve the synthesis of non-substituted vinylene-fused compounds. In this contribution, we report a Rh-catalyzed C−H/C−H vinylene cyclization adopting vinylene carbonate as a "vinylene transfer" agent. This protocol achieves the direct annulative π-extension of imidazole- and pyrazole-fused aromatics.

Fused polycyclic (hetero)aromatic scaffolds are fundamental components in a wide range of biologically active compounds and manufactured functional molecules, so that there has been a great demand for the development of efficient synthetic methodologies to assemble the π-extended molecules. Transition-metal-catalyzed C–H activation[1] followed by oxidative annulation with alkynes[2] has been a straightforward and versatile tool for the construction of poly-aromatic skeletons; however, most of these reactions are only applicable to internal alkynes. Accordingly, this method has found limited practical application as the annulative π-extension[3] protocol due to the lack of structural diversity as well as the requisite stoichiometric external oxidants.

We recently established a catalytic "vinylene transfer" strategy adopting vinylene carbonate as an oxidizing acetylene equivalent.[4,5] This reaction system offers an easy access to various non-substituted N-heteroaromatics through the Rh(III)-catalyzed C–H/N–H oxidative annulation, and notably, does not require any external oxidants nor bases since the vinylene carbonate itself fulfills both the functions (Scheme 1a). Upon our continuous research interest in this area, we envisioned utilizing this reaction system as an unprecedented π-extension method via the C–H/C–H oxidative vinylene cyclization. To test the feasibility, we chose imidazole- and pyrazole-fused aromatics as representative substrates, whose enriched nucleophilicity of the C3 positions would facilitate the carbo-cyclization.[6,7] Considering the potential application of the corresponding coupling products in biologically active compounds (such as rifaximin derivatives[8]), fluorescence materials,[9,10] photoredox catalysis,[6f] etc., the development of a new vinylene annulation protocol would attract considerable attention. In this manuscript, we report a direct assembly of poly-aromatic scaffolds by the Rh-catalyzed annulative coupling of imidazopyridine and indazole derivatives with vinylene carbonate (Scheme 1b). In addition, we conducted a preliminary study on the optoelectronic properties of the synthesized fused-aromatics.

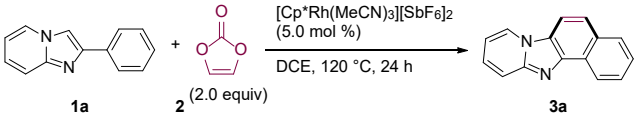
Scheme 1. Rh-catalyzed vinylene transfer protocol for the construction of polycyclic scaffolds.



Firstly, we conducted a optimization study adopting 2-phenylimidazo[1,2-*a*]pyridine (**1a**) as a model substrate for the C–H/C–H oxidative annulation with vinylene carbonate **2** (Table 1). Under the standard reaction conditions using a cationic $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst (5.0 mol %) in DCE solvent at 120 °C, the target product **3a** was obtained in 69% yield (entry 1). To our delight, neither external oxidants nor bases were required to ensure the catalyst turnover. Addition of $Cu(OAc)_2{\cdot}H_2O$ oxidant resulted in a complex outcome (entry 2). The Rh catalyst was essential to the present transformation

(entry 3), and an analogous neutral complex $[Cp^*RhCl_2]_2$ was totally inactive (entry 4). The product yield was somewhat decreased at a lower reaction temperature (entry 5) or with 1.2 equiv of **2** (entry 6). After screening several reaction parameters, an increased amount of the catalyst (6.0 mol %) improved the productivity, furnishing **3a** in 80% isolated yield in 0.3 mmol scale (entry 7). The structure of **3a** was unambiguously determined by the single crystal X-ray diffraction analysis.[11] We also examined the catalytic annulation using some substituted vinylene carbonates in place of **2**, but the starting materials were fully recovered.

Table1. Optimization study [a]

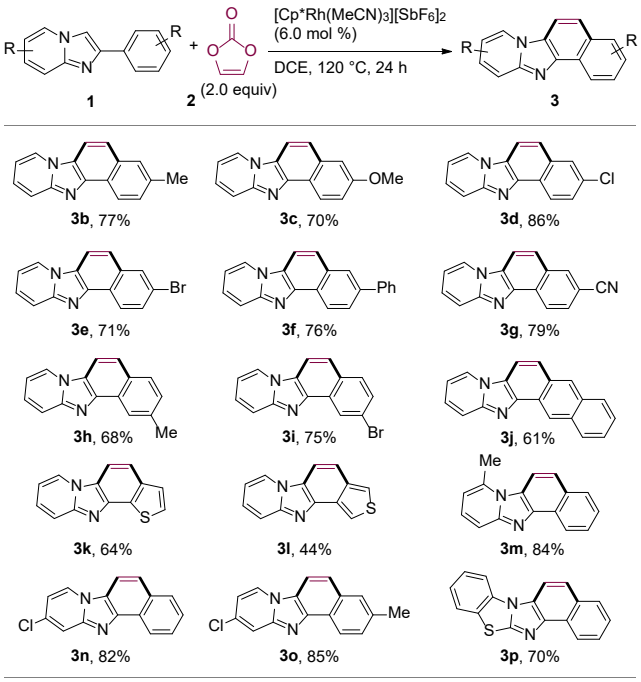


Entry	Deviation from the standard conditions	Yield [b]
1	--	69%
2	with $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv)	n.d.
3	no Rh catalyst	n.d.
4	$[Cp^*RhCl_2]_2$ (2.5 mol %) as catalyst	n.d.
5	at 100 °C	39%
6	1.2 equiv of **2**	61%
7	6.0 mol % Rh catalyst	80% [c]

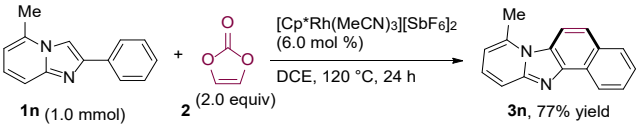
[a] Standard reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0 mol %), DCE (1.0 mL).
[b] Determined by ^1H NMR analysis.
[c] Isolated yield at 0.3 mmol scale in 1.5 mL DCE.

Having established a reliable catalytic conditions, we then investigated the scope of imidazo[1,2-*a*]pyridines (Scheme 2). A series of functional groups involving alkyl (**1b**), alkoxy (**1c**), chloro (**1d**), bromo (**1e**), aryl (**1f**), and cyano (**1g**) were well tolerated to afford the corresponding annulated products in good yields. Especially, the halogen (**3d**, **3e**) and the cyano (**3g**) substituents would offer numerous possible post-functionalizations of the polyaromatic scaffold. The reaction of meta-substituted substrates **1h** and **1i** resulted in the selective formation of **3h** and **3i**, respectively, where C–H bonds at the sterically more accessible sites were activated. A similar trend was observed for the reaction of **1j**, giving an acene-fused isomer **3j** as a sole product in 61% yield. A thiophene ring (**1k**, **1l**) could participate in this reaction system, and the C3 position preferentially reacted for the 3-thienyl variant **1l**. Additionally, substituents at the pyridine ring did not interfere the productivity to give **3m**–**3o** in more than 80% yield. The reaction of **1m** could be conducted at 1.0 mmol scale (Scheme 3). A 2-aminobenzothiazole-derived compound **1p** also underwent the annulation smoothly to produce the pentacyclic product **3p**.

Scheme 2. Substrate scope for imidazo[1,2-*a*]pyridines.

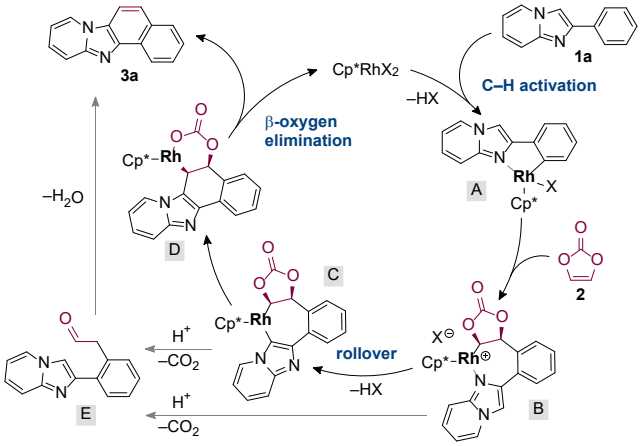


Scheme 3. A scale-up reaction.

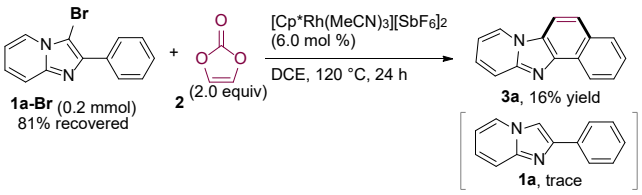


According to the literature,[12] we propose a reaction mechanism for the annulative coupling of **1a** as illustrated in Scheme 4. The nitrogen atom coordinates to a cationic Cp*Rh(III) species to form a rhodacycle complex **A** via the cyclometalation at the proximal position. After the migratory insertion of vinylene carbonate (**2**) into the Rh–C bond, the intermediate **B** undergoes nitrogen decoordination and "rollover" C–H activation[13] to generate a seven-membered complex **C**, whose conformation configurationally restricts the β-hydrogen elimination. Subsequent C–C reductive elimination and oxidative addition into the adjacent C–O bond produce an intermediate **D**.[14] Afterward, formal β-oxygen elimination is affected to liberate the product **3a** and the catalytically active Cp*Rh(III) species, closing the catalytic cycle. Alternatively, β-oxygen elimination, decarboxylation, and protonation from the intermediate **B** or **C** might produce the desired product via the aldehyde **E**. This pathway is less likely because the reaction of **1a-Br** under the conditions did not produce the corresponding aldehyde (Scheme 5). Most of the starting material was recovered (81% **1a-Br**) along with the annulated product **3a** (16% yield) probably formed through protodebromination (**1a** was detected).

Scheme 4. Proposed reaction mechanism.



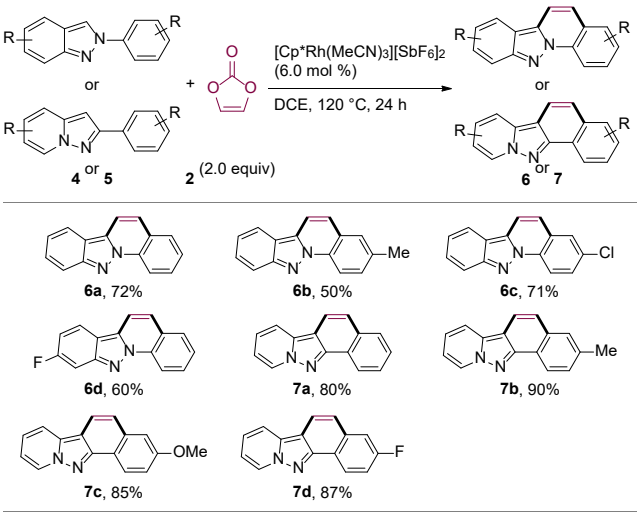
Scheme 5. A control experiment.



We next examined the reaction of indazole and pyrazolo[1,5-*a*]pyridine derivatives (**4** and **5**), isomeric analogs of **1**, under the standard conditions (Scheme 6). In all cases, the target products, indazolo[2,3-*a*]quinolines **6** and benzo[*g*]pyrido[1,2-*b*]indazoles **7**, were obtained in moderate to high yields. The structures of **6a** and **7a** were confirmed by the X-ray crystallographic analysis.[11] These polyaromatic compounds have been synthesized by the [3 + 2] cycloaddition of pyridinium imides with arynes;[10b,15] however, **7a** was only obtained as an inseparable mixture of isomers. The developed catalytic system would selectively assemble the fused aromatic scaffolds and, moreover, offer an easy access to various functionalized compounds from readily available starting materials. While the vinylene annulation for 1-phenyl-1*H*-imidazole, 1-phenyl-1*H*-pyrazole, 3-phenyl-1*H*-pyrazole, and 2-phenylpyridine derivatives was examined, the desired cyclized products were not obtained.

With a series of non-substituted polyaromatic compounds in hand, we systematically evaluated their optical characteristics. The UV-vis absorption and fluorescence spectra of **3a**, **6a**, and **7a** were measured as diluted $CHCl_3$ solutions and in the solid states (Figure 1, Table 2). The spectral shapes of **3a** and **6a** were similar to each other with substantial internal quantum efficiencies ($\Phi = 0.50$ for **3a**, 0.47 for **6a**) in $CHCl_3$. These characteristics are similar to those of internal-alkyne-derived tetracyclic compounds.[6c,6h,6i] In contrast, **7a** was less emissive ($\Phi = 0.13$) and exhibited a relatively large Stokes shift. The HOMO levels of these compounds were estimated by a computational method to be around -5.2 eV. The HOMO/LUMO energy gaps (E_g) calculated from the UV-vis spectra fall within the range of 3.08–3.23, which are relatively small for tetracyclic molecules. All these compounds have planer structures and crystallize into well-ordered herringbone-type packing modes.[16] Weak π-π stacking (3.35–3.44 Å) and C–H···N hydrogen bonding interactions are presumably responsible for their packing structures. These characteristics unique to the unsubstituted compounds may meet requirements in the application to charge transporting materials. Further study on the electrochemical properties of the coupling products are currently underway in our group.

Scheme 6. Substrate scope for pyrazol-fused heterocycles.



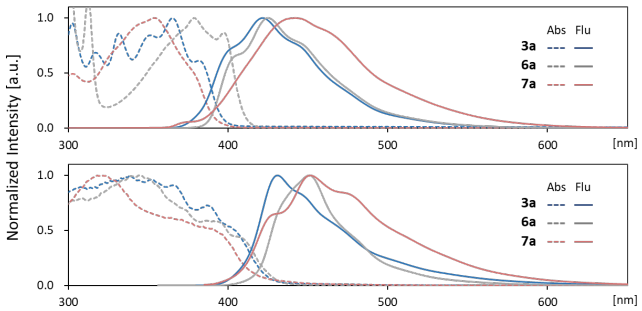


Figure 1. Normalized absorption and fluorescence spectra of **3a**, **6a**, and **7a** in $CHCl_3$ solutions (top, 1.0×10^{-5} M) and in the solid states (bottom).

Table 2. Summaly of the florescence properties.

compd	solution λ_{max} (λ_{ex})	solid λ_{max} (λ_{ex})	$\Phi_{solution}$	Φ_{solid}
3a	422 nm (278 nm)	431 nm (365 nm)	0.50	0.11
6a	425 nm (285 nm)	451 nm (336 nm)	0.47	0.26
7a	441 nm (269 nm)	451 nm (371 nm)	0.13	0.07

In conclusion, we have developed a Rh-catalyzed direct π-extension method adopting vinylene carbonate as a vinylene transfer reagent. Notable futures of the present protocol are that (1) the non-substituted vinylene-fused scaffold can be assembled in one-step via the C–H/C–H oxidative cyclization and (2) any external oxidants as well as bases are not necessary for the catalytic turnover. The obtained polyaromatic compounds were considerably luminescent and exhibited well-ordered packing structures in the solid states.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website, including detailed experimental procedures, characterization data for all compounds, crystal structure images, copy of NMR spectra, and Cartesian coordinates of the calculated structures as a PDF file.

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Notes

The authors declare no competing financial interest.

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(11) The CCDC numbers are 1990592 (**3a**), 1990593 (**6a**), and 1990594 (**7a**). These data are available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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