Concise Synthesis of Isocoumarins through Rh-Catalyzed Direct Vinylene Annulation: Scope and Mechanistic Insight

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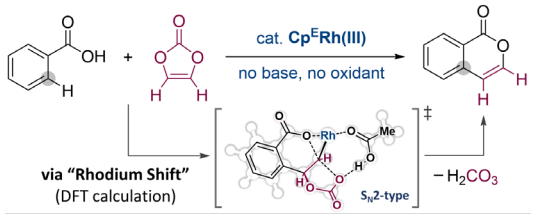
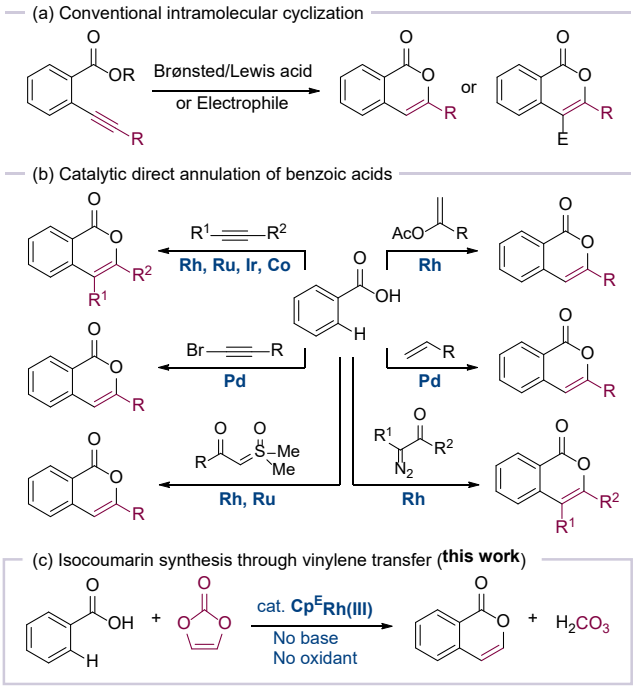


ABSTRACT: Transition-metal-catalyzed activation of inert C–H bonds and subsequent C–C bond formation have emerged as powerful synthetic tools for the synthesis of elaborate cyclic molecules. In this report, we introduce an efficient synthetic method of 3,4-unsubstituted isocoumarins adopting an electron deficient $Cp^{E}Rh$ complex as the catalyst. The use of vinylene carbonate as a vinylene transfer reagent enables the direct construction of isocoumarins from readily available benzoic acids, without any external oxidants as well as bases. The reaction mechanism is evaluated by computational analysis to find an unprecedented "rhodium shift" event within the catalytic cycle.

The wide prevalence of lactone derivatives in a huge number of natural products and biologically active compounds has claimed significant attention in medicinal and synthetic chemistry research. Isocoumarins, also known as 1*H*-2-benzopyrans or 3,4-benzopyrones, hold an important position due to their broad pharmacological applications,[1] which include activities of antimicrobial, antifungal, anticancer, anti-HIV, anti-inflammatory, and so on. These facts prompted the synthetic community to establish efficient methods for the construction of isocoumarin scaffolds.[2,3] The last two decades witnessed a considerable advancement in transition-metal-catalyzed direct annulation of benzoic acids with unsaturated coupling partners through the activation of their ortho-C–H bond.[3,4] This protocol offers rapid access to the isocoumarins from readily available starting materials in a step-economical manner, and is practically beneficial as compared to the conventional acid- or electrophile-mediated cyclization of ortho-alkynylated benzoic acid derivatives (Scheme 1a,b). Coupling reactions with internal alkynes[5,6] has been extensively studied since our group reported the first direct annulation of benzoic acids adopting a Cp*Rh catalyst in 2007.[5a,b] In addition, terminal alkenes and carbene precursors have also been functioned as the coupling partners for the annulation of benzoic acid derivatives.[5s,7] As a consequence, it is possible to design various 3-mono- and 3,4-di-substituted isocoumarins; however, the basic unit, i.e. non-substituted isocoumarins, has not been accessible via the catalysis. This is probably due to the lack of proper reagents which facilitate the reaction turnover. Indeed, only one example of such a transformation is found in the literature, albeit with a poor 14% product yield using vinyl acetate in the presence of Rh(III) catalyst and stoichiometric Cu(II) oxidant.[6c] Obviously, an efficient and comprehensive reaction system for the isocoumarin core is missing. In addition to this synthetic difficulty, the formation of stoichiometric metal waste derived from the oxidant should be avoided.

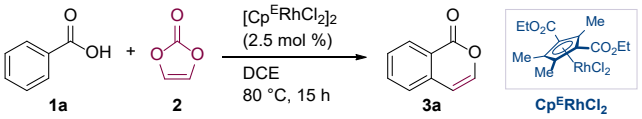
Scheme 1. Representative Synthetic Methods for Isocoumarins



To address these all issues, we assumed that our catalytic vinylene transfer strategy would be an effective solution, employing vinylene carbonate as an oxidizing acetylene surrogate (Scheme 1c).[8] This protocol requires no oxidant as well as base because the reactant fulfil both the functions to give carbonic acid as a sole side-product. In this report, we introduce a concise synthesis of nonsubstituted isocoumarins, and the detailed reaction mechanism was investigated by DFT calculation to find an unprecedented "rhodium shift" event within the catalytic cycle. Additionally, the developed protocol was utilized for the synthesis of an indole alkaloid, 2-bromonorketoyobyrine.

Our initial study focused on the vinylene annulation of benzoic acid (**1a**) with vinylene carbonate (**2**) (Table 1). We first examined the activity of Cp*Rh (entry 1) and Cp*Ir (entry 2) complexes; however, the desired product **3a** did not form after attempts even at elevated temperature and with higher catalyst loading. We then shifted our attention to an electron deficient Cp^E ligand,[9] which was found to be effective for the oxidative annulation of benzoic acids in an elegant report by Shibata, Tanaka, and coworkers.[5j] To our delight, the catalytic production of **3a** was first realized using $[Cp^ERhCl_2]_2$ catalyst (entry 3).

Table 1. Optimization Study [a]



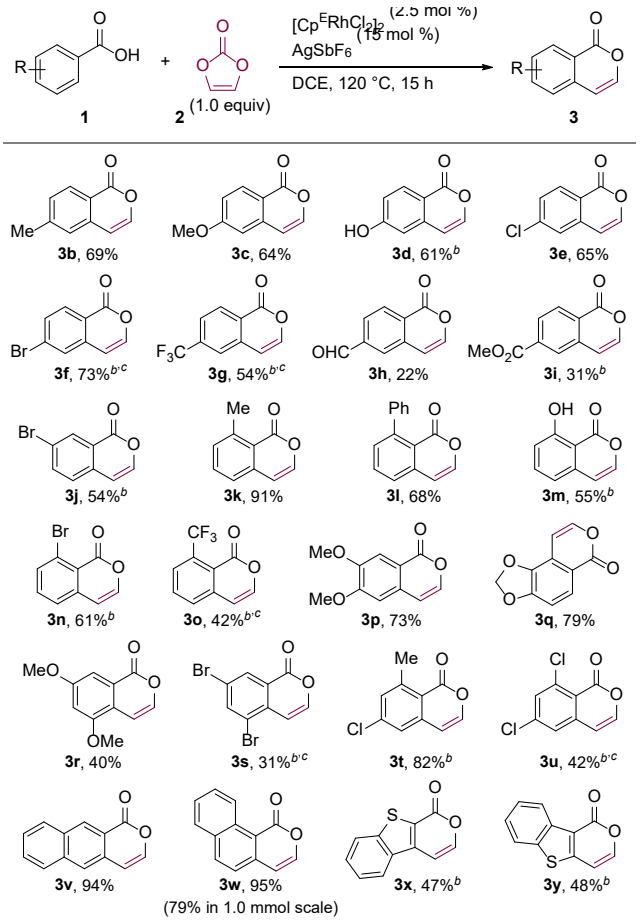
entry	additives and conditions	yield [b]
1 [c]	Cp*Rh catalyst, $AgNTf_2$ (10 mol %)	n.d.
2 [c]	Cp*Ir catalyst, $AgNTf_2$ (10 mol %)	n.d.
3 [c]	$AgNTf_2$ (10 mol %)	34%
4 [c]	$AgSbF_6$ (10 mol %)	41%
5 [c]	AgOTf (10 mol %)	4%
6 [c]	AgOAc (10 mol %)	n.d.
7	$AgSbF_6$ (15 mol %)	74%
8	no Ag salt	n.d.
9	no Rh catalyst, $AgSbF_6$ (15 mol %)	n.d.
10	$AgSbF_6$ (15 mol %), AcOH (30 mol %)	68%
11	$AgSbF_6$ (15 mol %), NaOAc (30 mol %)	trace
12	$AgSbF_6$ (15 mol %), K_2CO_3 (30 mol %)	trace
13	$AgSbF_6$ (15 mol %), NEt_3 (30 mol %)	n.d.
14	$AgSbF_6$ (15 mol %), octane solvent	20%
15	$AgSbF_6$ (15 mol %), $PhCF_3$ solvent	45%
16	$AgSbF_6$ (15 mol %), ^{t}AmOH solvent	n.d.
17	$AgSbF_6$ (15 mol %), HFIP solvent	55%
18	$AgSbF_6$ (15 mol %), at 120 °C	77% (74%)

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $[Cp^ERhCl_2]_2$ (2.5 mol % metal), DCE (0.5 mL), 80 °C, 15 h. [b] Determined by NMR analysis. Isolated yield is in parentheses. n.d. = not detected. [c] 2.0 equiv (0.4 mmol) of **2** was used.

Screening of silver salts suggested the importance of non-coordinating anion in this transformation (entries 3-6). The yield was further improved to 74% after optimization (entry 7). Control experiments revealed that both the rhodium complex and the silver salt were essential for this transformation (entries 8 and 9). We also tested the effect of some additives to the catalysis. AcOH did not considerably affect the productivity (entry 10), whereas base additives such as NaOAc, K_2CO_3, and NEt_3 halted the reaction (entries 11-13). These results implied that acids fulfill an important role in the reaction mechanism (see below). Other solvents (octane, $PhCF_3$, *tert*-AmOH, and HFIP) were not effective as compared to DCE (entries 14-17). The product yield was slightly improved when the reaction was conducted at 120 °C (entry 18), and this condition was used for the following study.

Next, we examined the scope of the reaction adopting various substituted benzoic acids (Scheme 2). In some cases, 1,1,2,2-tetrachloroethane was used instead of DCE to suppress the competing esterification of the acids with the solvent molecules. For the mono-substituted benzoic acids, a series of functionalities such as alkyl (**1b**, **1k**), aryl (**1l**), alkoxy (**1c**), hydroxy (**1d**, **1m**), chloro (**1e**), bromo (**1f**, **1j**, **1n**), trifluoromethyl (**1g**, **1o**), aldehyde (**1h**), and ester (**1i**) groups remained untouched during the reaction, giving the corresponding isocoumarins **3** in moderate to high yields. Such a functional group compatibility is highly beneficial for the synthesis of complex molecules. The meta-substituted acid **1j** was converted into **3j** as a major isomer, whereas the minor isomer formed in negligible amount (<5%).

Scheme 2. Substrate Scope of the Isocoumarin Synthesis [a]

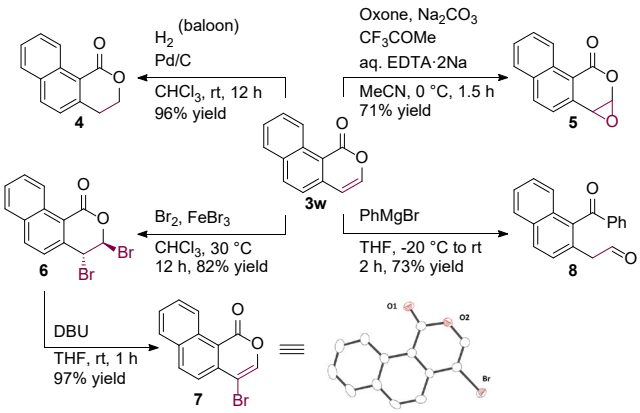


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $[Cp^ERhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (15 mol %), DCE (0.5 mL), 120 °C, 15 h. [b] $[Cp^ERhCl_2]_2$ (4.0 mol %), $AgSbF_6$ (30 mol %). [c] Tetrachloroethane was used instead of DCE.

Di-substituted as well as benzo-fused acids were also participated in the current protocol. 3,4-Dimethoxy benzoic acid (**1p**) was smoothly annulated to give **3p** in 73% yield as a major isomer by activating a C–H bond at the more accessible position. In contrast, piperonylic acid (**1q**) preferentially produced a sterically congested isocoumarin **3q**. The minor isomers of **3p** and **3q** were observed only in <5% yield. This peculiar selectivity was also observed in the literature.[5e] 3,5-Dimethoxy (**1r**), 3,5-dibromo (**1s**), 4-chloro-2-methyl (**1t**), and 2,4-dicholoro (**1u**) benzoic acids proceeded efficiently to give the corresponding products. Notably, 2-naphthoic acid (**1v**) was converted to **3v** as a single isomer in 94% yield, whereas the oxidative annulation of **1v** with diphenylacetylene was reported to give a 4:1 mixture of isomers.[6j] 1-Napthanoic acid (**1w**) provided the product **3w** in 95% yield, and this reaction could be conducted in a 1.0 mmol scale. Benzo[*b*]thiophene carboxylic acids **1x** and **1y** were also applicable to afford **3x** and **3y** respectively in 47% and 48% yield. Unfortunately, other heteroaromatic carboxylic acids involving pyridine, pyrrol, and furan rings were not applicable to the present reaction system (not shown).

Reactivity of the non-substituted vinylene moiety of isocoumarins has not much been explored possibly due to their poor availability. Thus, we conducted some derivatization of the coupling products to evaluate synthetic utility (Scheme 3). The double bond of isocoumarin **3w** could be hydrogenated cleanly with Pd/C to give **4** in 96% yield. Epoxidation was effected using a dioxirane (TFDO) to provide **5** in 71% yield. These results suggested that the double bond retains a considerable olefinic character. In accordance with this idea, the double bond preferentially reacted with bromine in the presence of $FeBr_3$ catalyst keeping the aromatic unit unreacted. The bromination product **6** was converted to **7** upon basic treatment through the selective HBr extraction,[10] and the structure of **7** was unambiguously determined by an X-ray crystallographic analysis.[11] The bromofunction in **7** may be a useful synthetic handle for further derivatization of the molecule. Additionally, the reaction of **3w** with PhMgBr provided the corresponding keto-aldehyde **8** in 73% yield.

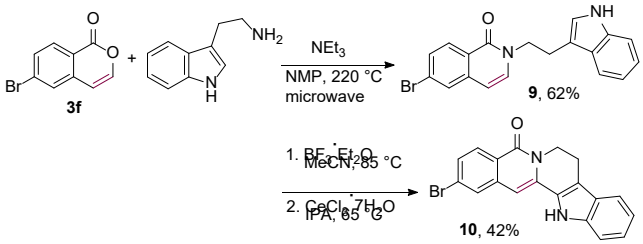
Scheme 3. Derivatization of the Coupling Product **3w**



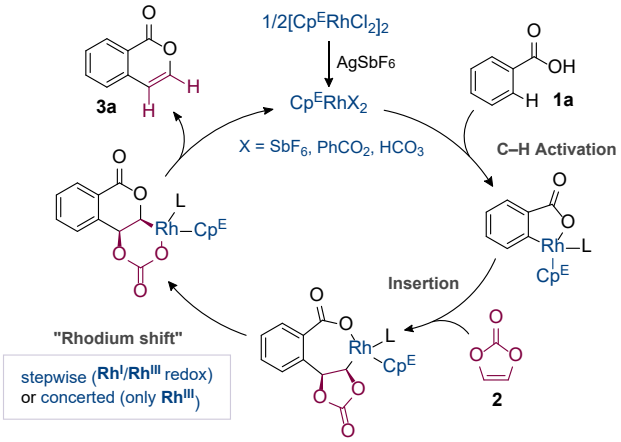
To highlight the synthetic utility, we conducted the synthesis of an indole alkaloid (Scheme 4). A coupling product **3f** was treated with tryptamine under microwave irradiation to afford the corresponding isoquinolinone **9**. Sequential Lewis-acid-mediated cyclization and oxidation by $CeCl_3$ delivered a pentacyclic product, 2-bromonorketoyobyrine (**10**), in 42% yield over two steps.[12] Installation of functional groups onto the inherently less reactive ring over the pyrrol moiety is challenging for the manipulation of indole alkaloids,[13] and cumbersome multistep synthesis is usually inevitable. As shown in this particular example, the present method may provide synthetically useful building blocks for various multicyclic compounds.

A proposed reaction mechanism for the annulation of benzoic acid (**1a**) with vinylene carbonate (**2**) is shown in Scheme 5. The reaction initiates with the coordination of **1a** to the catalytically active $[Cp^ERh]^{2+}$ species formed in situ, and the subsequent C–H bond activation is effected with the assistance of the carboxyl directing group to deliver a five-membered rhodacycle intermediate. Coordination and migratory insertion of vinylene carbonate into the Rh–C bond produce a seven-membered intermediate, in which the β-hydrogen elimination is configurationally restricted. Thereafter, a formal "rhodium shift" to the carbonate moiety takes place. We assume this occurs in a concerted manner, so that the overall process would be redox-neutral. The product was liberated via the β-oxygen elimination, closing the catalytic cycle.

Scheme 4. Synthesis of 2-Bromonorketoyobyrine (**10**)



Scheme 5. A Proposed Reaction Mechanism



In order to shed light on the reaction mechanism in detail, we conducted a computational study with respect to the reaction of **1a** with **2**. Here the $-CO_2Et$ groups on the Cp^E ligand were replaced with $-CO_2Me$ to simplify the calculation. Additionally, acetic acid was employed as a supporting ligand instead of benzoic acid and carbonic acid, which would participate in the actual catalytic system. Figure 1 displays an energy profile of the reaction relative to a benzoate complex **preA**.[14,15] The C–H activation was calculated as a CMD (concerted metalation-deprotonation) process adopting the acetate anion as an internal base to give a rhodacycle intermediate **intA**. After the ligand

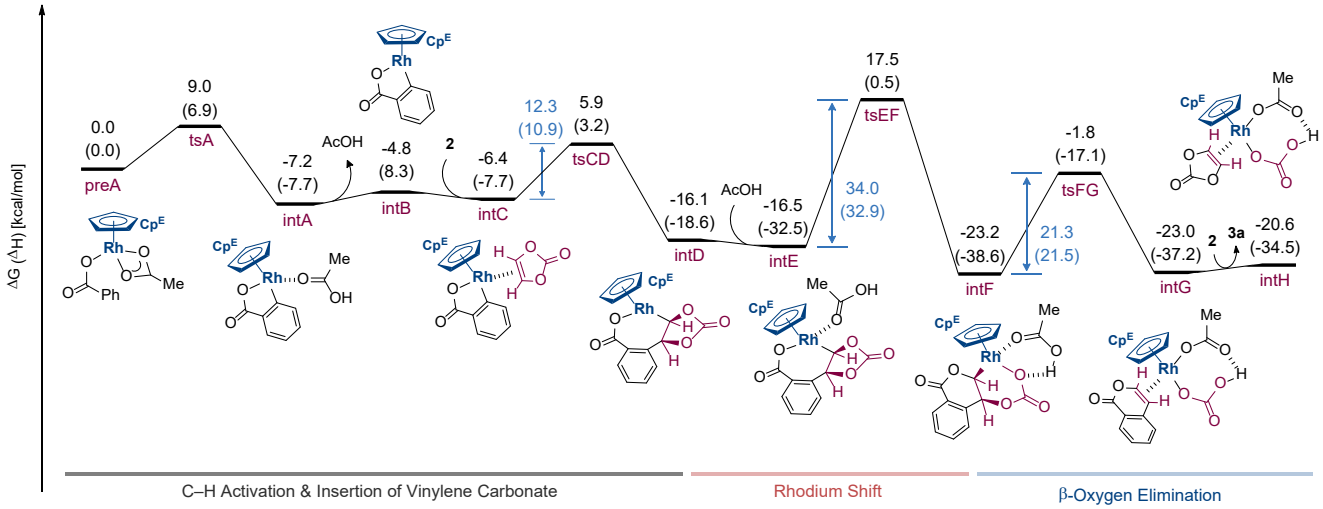


Figure 1. Gibbs free energy profile of the reaction. Values in parentheses are relative enthalpies. The calculations were conducted at the ωB97X-D/6-311+G(d,p)&SDD/PCM(DCE)//ωB97X-D/6-31G+(d,p)&LanL2DZ/PCM(DCE) level.

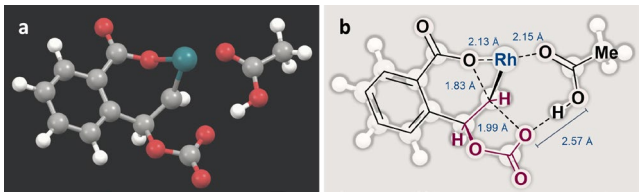


Figure 2. (a) An optimized molecular geometry of the transition state **tsEF**: carbon (gray), hydrogen (white), oxygen (red), and rhodium (green). (b) The atom labeling and selected bond lengths. Cp^E ligand was omitted for the sake of clarity.

exchange (**intB**–**intC**), two possible configurations for the insertion of vinylene carbonate to the Rh–C bond were considered (for details, see the Supporting Information). A transition state in which the carbonate moiety is located on the "opposite" side of the Cp^E ligand requires 3.9 kcal/mol higher energy than that of the other, thereby the path **intC**–**tsCD** was kinetically much favorable. The direct C–O bond formation through reductive elimination from **intD** or its AcOH adduct **intE** was found to be not feasible. Alternatively, a concerted rhodium shift was calculated to have a rather acceptable activation barrier of 34.0 (32.9) kcal/mol (**tsEF**). In this transition state, the carbon atom directly bonded to the Rh atom had a trigonal bipyramidal geometry where the two oxygen atoms occupied its axial positions (Figure 2). The sum of the bond angles within the equatorial plane was 359.3°, and the central carbon atom exhibited a positive APT charge of +1.461. According to these aspects, this process can be seen as an intramolecular S_N2-type reaction, and it is noteworthy that the coordinated acid enhances the leaving ability of the carbonate fragment through hydrogen bonding. This may be one of the reasons why the reaction was inhibited by base additives (see Table 1). The sequence traverses another transition state for the β-oxygen elimination (**tsFG**) to produce the coupling product (**intG**).

In summary, we have introduced a direct synthesis of 3,4-unsubstituted isocoumarins from readily available benzoic acids through the Cp^ERh-catalyzed vinylene annulation upon adopting vinylene carbonate as an oxidizing acetylene surrogate. This protocol exhibited broad functional group compatibility, and was utilized to the synthesis of a new indole alkaloid molecule. The first mechanistic study for the vinylene transfer reaction was conducted by the DFT calculations to find an unprecedented intramolecular S_N2-type rhodium shift event, ensuring the redox-neutral catalytic process.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, kinetic experiments, computational data, and copy of ^{1}H and ^{13}C NMR spectra (PDF), atomic coordinates of all calculated molecules (XYZ), crystallographic data for **7** (CIF).

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Notes

The authors declare no competing financial interests.

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