COMMUNICATION

Rhodium-catalysed direct formylmethylation using vinylene carbonate and sequential dehydrogenative esterification

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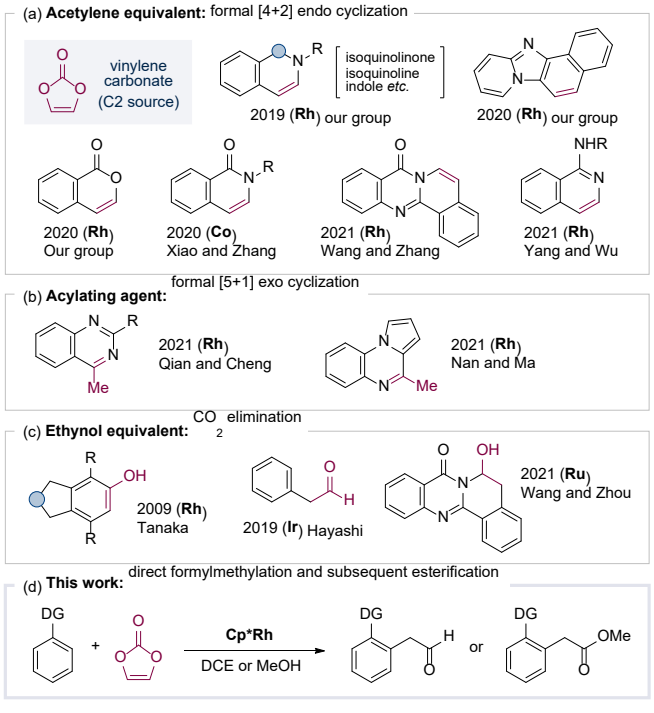
A rhodium-catalysed direct formylmethylation adopting vinylene carbonate as an ethynol equivalent is reported. The developed catalytic system is further utilised for the oxidant-free production of esters with the liberation of hydrogen gas. Some control experiments are conducted to elucidate the reaction mechanism.

Aldehydes are important class of carbonyl compounds particularly in fragrance, polymer science, and biochemistry. Moreover, they are versatile building blocks in organic synthesis since the formyl group can be transformed to other various functional groups by aldol reaction, Wittig reaction,[1] reductive amination,[2] umpolung reactions,[3] and so forth. Selective partial oxidation of alcohols and partial reduction of carboxylic acids are conventional synthetic methods for aldehydes. In addition, hydration of terminal alkynes[4] and carbonylation with carbon monoxide (or its equivalents)[5] using transition metal catalysts are commonly utilised for the production of aldehydes.

Meanwhile, vinylene carbonate has recently emerged as a potent C2 source in the transition-metal-catalysed coupling reactions (Scheme 1). In 2019, our group firstly disclosed that vinylene carbonate served as an acetylene surrogate for the Rh-catalysed oxidative annulation[6] strategy (Scheme 1a).[7] Based on this concept, we have achieved the direct construction of nonsubstituted vinylene-fused heteroaromatics through the C-H/N-H, C-H/C-H, and C-H/O-H oxidative cyclisation.[7,8] Afterward, Xiao and Zhang demonstrated that a Cp*Co catalyst was also applicable to the vinylene transfer reaction for benzamide substrates.[9] Similar transformations have been reported by some other research groups.[10] In addition, vinylene carbonate could be used as an acylating reagent to accomplish the formal [5+1] exo annulation with amidine and aniline derivatives (Scheme 1b).[11] Alternatively, vinylene carbonate may function as an ethynol equivalent via the elimination of CO_2 (Scheme 1c). As shown in an early report by Tanaka, it was coupled with diynes to produce substituted phenol derivatives by the Rh-catalysed decarboxylative [2+2+2] cycloaddition.[12] In 2019, Hayashi developed an arylacetaldehyde synthesis through the addition of boronic acids onto its vinylene fragment under the Ir catalysis.[13] Very recently, Wang and Zhou reported a Ru-catalysed annulation of 2-arylquinazolinones with vinylene carbonate.[14]



Scheme 1 Representative application of vinylene carbonate for the transition-metal-catalysed transformation.

Upon our continuous research interest in this field, we herein report a Rh-catalysed direct formylmethylation (Scheme 1d), which can be deemed as a C-H activation analogue of the

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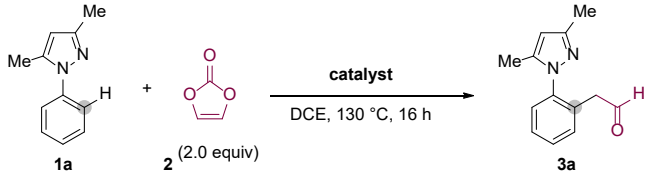
Hayashi's report. Moreover, the developed catalytic system is extended to the oxidant-free production of esters with the liberation of an H_2 gas. Some control experiments are conducted to elucidate the reaction mechanism.

At the outset, we carried out an optimisation study for the model reaction of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**1a**) with vinylene carbonate (**2**) (Table 1). Under the standard conditions using a cationic $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0 mol%) catalyst in DCE solvent at 130 °C,[15] the corresponding 2-arylacetaldehyde **3a** was obtained in 68% yield (entry 1). This reaction proceeded even at lower temperature of 60 °C (entry 2). The product yield was improved to 86% with an increased 6.0 mol% of the catalyst (entry 3). A control experiment revealed that the Rh catalyst was essential for this transformation (entry 4), and a chloride complex $[Cp^*RhCl_2]_2$ failed to trigger the reaction (entry 5). Analogous Cp*Co and Cp*Ir complexes were not suitable catalysts (entries 6 and 7), and $[Ru(p\text{-cymene})Cl_2]_2$ was also insufficiently active to give a negligible amount of the product (entry 8).

Table 1 Optimisation study [a]

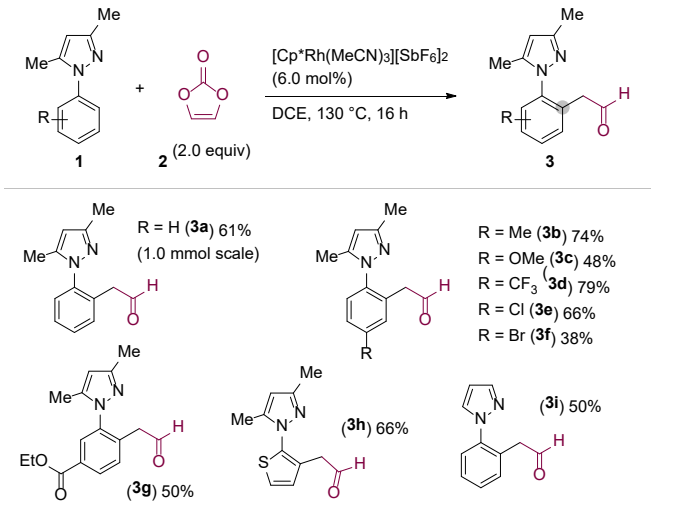


Entry	Catalyst (mol%)	Yield of **3a** [b]
1	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	68%
2 [c]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	54%
3	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (6.0)	86% (82%)
4	--	n.d.
5	$[Cp^*RhCl_2]_2$ (3.0)	n.d.
6	$Cp^*Co(CO)I_2$ (6.0), $AgSbF_6$ (12)	n.d.
7	$[Cp^*IrCl_2]_2$ (3.0), $AgSbF_6$ (12)	16%
8	$[Ru(p\text{-cymene})Cl_2]_2$ (4.0), $AgSbF_6$ (12)	9%

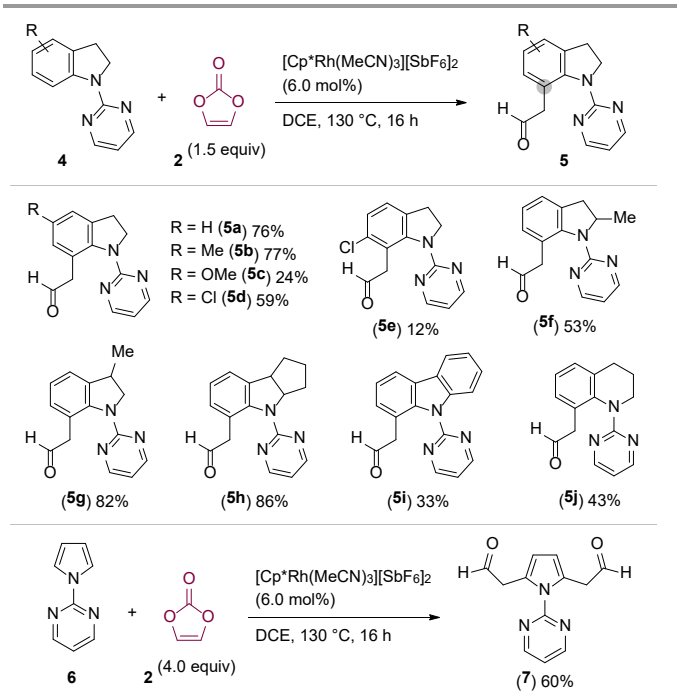
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), DCE (1.0 mL), 130 °C, 16 h. [b] Estimated by NMR. Isolated yield in parentheses. [c] At 60 °C. n.d. = not detected.

With the optimised reaction conditions in hand (Table 1, entry 3), we evaluated the scope of aryl-1*H*-pyrazoles **1** for the formylmethylation with vinylene carbonate (**2**) (Scheme 2). The reaction of **1a** could be conducted on a 1.0 mmol scale. A series of functional groups involving alkyl (**1b**), alkoxy (**1c**), CF_3 (**1d**), halogen (**1e** and **1f**), and ester (**1g**) were well tolerated to afford the corresponding coupling products **3b**–**3g** in moderate to high yields. The present method was applicable to a thiophene derivative **1h** and the target product **3h** was isolated in 66% yield. This transformation was also successful with a simple pyrazole directing group to afford **3i** in 50% yield.

The developed reaction system was also applicable to the C7-selective functionalisation of indoline derivatives adopting a 2-pyrimidyl directing group (Scheme 3). Under the standard reaction conditions, a benchmark substrate **4a** smoothly underwent the formylmethylation to give **5a** in 76% yield. The C5-substituted indolines (**4b**–**4d**) were applicable to this transformation, but an electron donating OMe group somewhat decreased the yield. A C6-substituted indoline **4e** reacted sluggishly most likely due to its sterically congested nature. Alkyl substituents at the C2 and C3 positions did not significantly interfere the reaction, and the desired products **5f**–**5h** were obtained in moderate to high yields. Direct functionalisation of carbazole (**4i**) and tetrahydroquinoline (**4j**) rings was also accomplished. Notably, the catalytic system could be utilised for the double C–H functionalisation of the pyrrole ring in **6** to produce **7** in 60% yield.



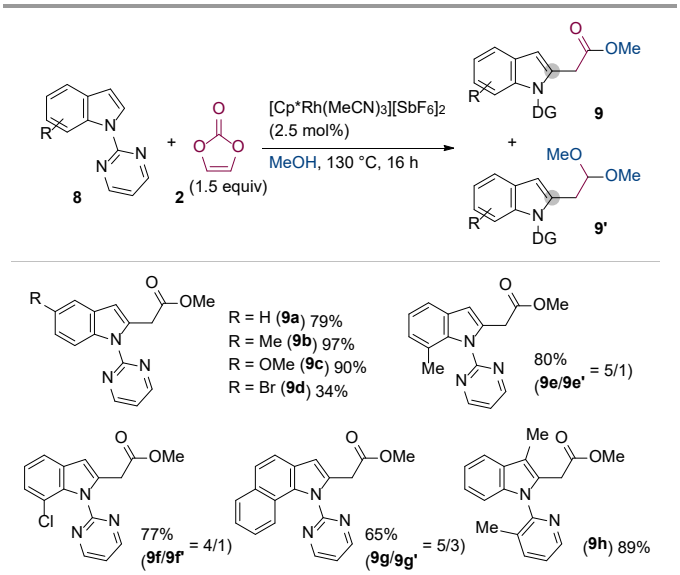
Scheme 2 Substrate scope (1) for the formylmethylation.



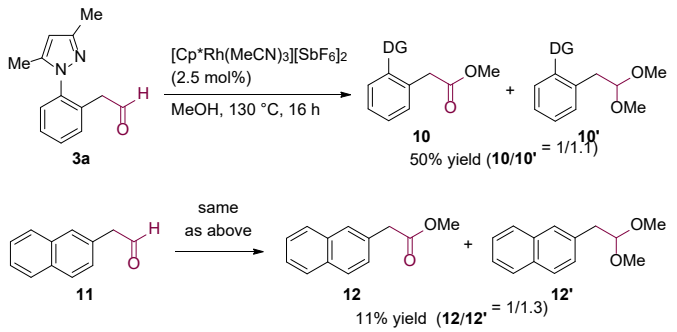
Scheme 3 Substrate scope (2) for the formylmethylation.

For indole derivatives, we observed small amounts of C2-selective coupling products[16] under the identical reaction conditions; however, these were hardly isolable even at lower reaction temperature (low to 80 °C) probably because of the instability. We thus tested the effect of alcohol additives to

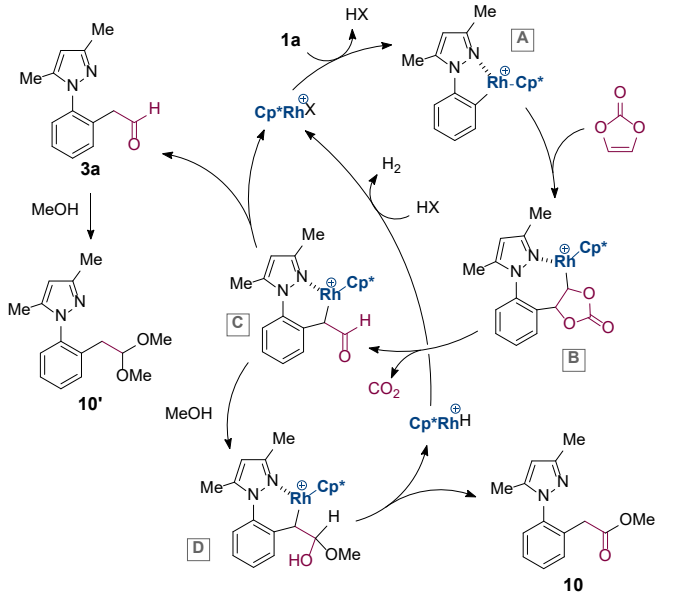
protect the aldehyde group as acetal in situ. When the reaction of **8a** was conducted in MeOH solvent, unexpectedly, the corresponding methyl ester **9a** was obtained (Scheme 4). This outcome was intriguing since the aldehyde functionality was formally oxidised in the absence of any stoichiometric oxidant.[17] Subsequently, we examined the scope of this transformation for some substituted indoles with 2.5 mol% of Rh catalyst. A series of C5-substituted indoles **8b**–**8d** were well tolerated to give the ester products **9b**–**9d** in moderate to high yields. On the other hand, C7-substituted indoles **8e**–**8g** produced considerable amount of dimethyl acetals along with the target products. For the reaction of C3-methylindole, a 6-methylpyridyl directing group was more effective than the pyrimidyl one to afford **9h** in 89% yield.



Scheme 4 Ester synthesis though the indole C2 activation.



Scheme 5 Control experiments.



Scheme 6 A proposed reaction mechanism.

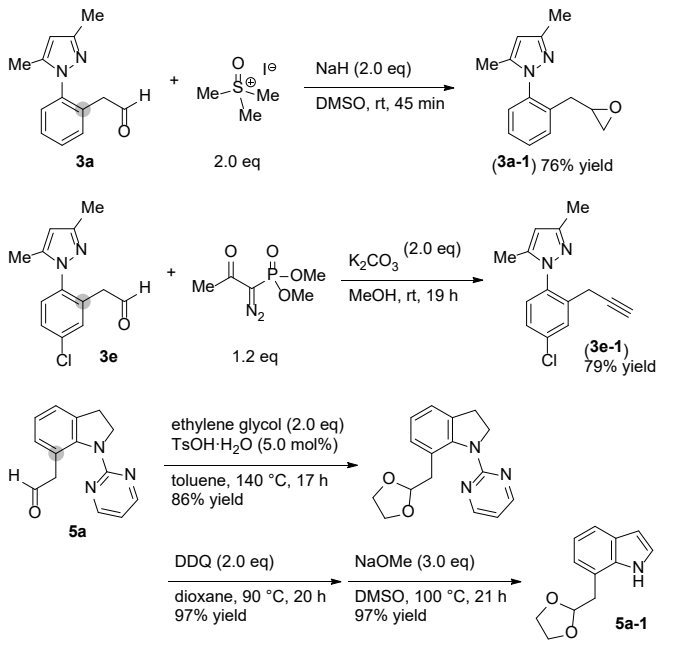
To gain insight into the mechanism of ester formation, we carried out some control experiments (Scheme 5). The aldehyde product **3a** was heated in MeOH solvent in the presence of Rh catalyst to give a mixture of the corresponding ester **10** and acetal **10'** in 50% yield.[18] Interestingly, a simple arylmethyl aldehyde **11** was also converted to the corresponding ester **12** and acetal **12'** under the identical reaction conditions albeit with lower yields. This outcome indicated that the ester products would be obtained via aldehyde intermediates or relevant Rh complexes.

On the basis of these results and literatures,[8,19] we propose a possible reaction mechanism in Scheme 6 adopting **1a** as the model compound. A catalytically active cationic Cp*Rh complex activates the proximal C–H bond with the assistance of directing group to afford a five-membered intermediate **A**. Coordination and migratory insertion of vinylene carbonate into the Rh–C bond produce a seven-membered metallacycle species **B**. The subsequent decarboxylation is effected to form an intermediate **C**, which is then protonated to liberate the product **3a** and regenerate the active Rh complex.

When the reaction is conducted in MeOH solvent, the intermediate **C** can be converted to the alcohol adduct **D**. The ester product **10** is obtained through the β-hydrogen elimination and tautomerization. The liberated Rh hydride species reacts with an acid molecule to regenerate the catalytically active species while evolving an H_2 gas.[20] Indeed, the generation of H_2 as well as CO_2 was confirmed by GC-BID analyses (for details, see the Supporting Information). According to the experiments in Scheme 5, metalation at the benzylic aldehyde α position would reversibly occurs, leading to the formation of the corresponding methyl ester. Simultaneously, the aldehyde product is converted to the acetal **10'** in situ. We assume that the C7-substituted indoles (**8e**-**8g**) form less stable intermediates, which are analogous to the complex **C**, due to the steric hindrance, thereby producing more amount of the acetal products (Scheme 4).

Finally, we examined some derivatization of the coupling products (Scheme 7). The aldehyde functionality within **3a** was successfully transformed to the epoxide using a sulfoxonium ylide to give **3a-1** in 76% yield.[21] The Ohira-Bestmann reagent was adopted to convert **3e** to a terminal alkyne **3e-1** in 79% yield.[22] From the C7-functionalised indoline **5a**, sequential acetal protection, oxidation using DDQ (2,3-dichloro-5,6-

dicyano-1,4-benzoquinone), and the directing group removal gave the corresponding N-H indole **5a-1** (81% yield over 3 steps).



Scheme 7 Derivatization of the coupling products.

In conclusion, we have developed a directing-group-assisted C-H formylmethylation using vinylene carbonate as an ethynol equivalent. This reaction does not require any external oxidants as well as bases. The catalytic system was also applicable to the sequential dehydrogenative esterification, and the liberation of an H_2 gas was effected to regenerate the catalytically active Rh(III) species.

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Conflicts of interest

The authors declare no competing financial interest.

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