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Rh-Catalyzed intramolecular decarbonylative cyclization of *ortho*-formyl group tethered alkylidenecyclopropanes (ACPs) for the construction of 2-methylindenes†

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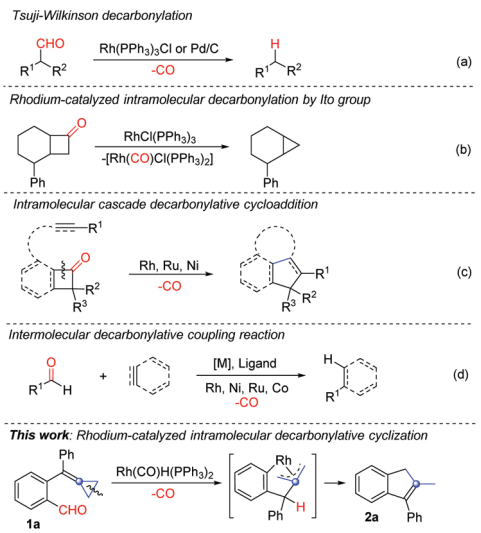
A Rh-catalyzed intramolecular cascade decarbonylative cyclization reaction of *ortho*-formyl group-tethered alkylidenecyclopropanes (ACPs) has been developed, affording 2-methylindenes in moderate to good yields. The reaction proceeded through a decarbonylative generation of Rh–H species, intramolecular migratory insertion, β-carbon elimination, and a reductive elimination from a π-allylic rhodium intermediate on the basis of a deuterium-labeling experiment as well as other control experiments.

Indene derivatives are important structural motifs found in some medicines.[1] For example, fenistil and its derivatives have been used as antihistamine drugs, aldosterone synthase inhibitors and antituberculosis agents (see Fig. S1 in the ESI†).[1a–d] They can also be used as ligands by deprotonation to form metallocene complexes with metals such as Au, Rh, Ru, Cr, Mo, Zr, *etc.* for various catalytic reactions.[1e–h] Moreover, indene derivatives have important applications in solar cells, optical materials and so on.[1i,j]

Recently, decarbonylative coupling reactions catalyzed by transition metals for substrates containing a carbonyl group have emerged as a new research direction.[2] These reactions rely on a typical process using a ketone or an aldehyde as a substrate such as Tsuji–Wilkinson decarbonylation[3] to realize decarbonylative coupling reactions (Scheme 1a). In 1994, the group of Ito reported the Rh(I)-catalyzed decarbonylative coupling of cyclobutanone derivatives to produce cyclopropane derivatives (Scheme 1b).[4] Since then, Rh(I)-catalyzed decarbonylative coupling reactions have been extensively investigated,[5] such as decarbonylation of diynones or diones for the synthesis of conjugated diynes and ynones.[5a–c] In recent years, other metals such as Pd[6] and Ni[7] have also been utilized for the decarbonylative couplings of carbonyl group containing compounds.

Besides the direct decarbonylative coupling reactions, other types of cyclization reactions can also be realized in combination with decarbonylative coupling. For example, Rh(I)-catalyzed intramolecular cascade decarbonylative cyclization of cyclobutanones,[8a,b] benzocyclobutenones[8c] or isatins[8d] with unsaturated functional groups to produce the corresponding cyclized products has been disclosed (Scheme 1c).[8] In addition, the intermolecular decarbonylative coupling reactions of carbonyl compounds with alkenes, alkynes or arenes have also been developed (Scheme 1d).[9] Furthermore, it



Scheme 1 Strategies for decarbonylation or cascade decarbonylative coupling of carbonyl group containing compounds and our synthetic strategy for decarbonylative cyclization of *ortho*-formyl group tethered alkylidenecyclopropanes.

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should be noted that many of these decarbonylative coupling reactions with unsaturated functional groups could be carried out under the catalysis of other transition metals such as Ni,[10] Mn,[11] Ru,[12] Co[13] and so on[14] (Scheme 1c and d).

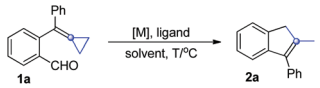
Recently, the use of alkylidenecyclopropanes (ACPs) as a special class of olefinic substances for cascade cyclization reactions in an intra- or intermolecular manner using transition metal catalysis has witnessed significant progress.[15] In 2007, Fürstner and co-workers[16] reported a cascade cyclization comprising a rhodium-catalyzed C–H activation followed by a hydrometalation of adjacent ACP and a regioselective C–C bond activation of the cyclopropane ring as well as a reductive elimination of the resulting Rh ring intermediate to afford functionalized cycloheptene derivatives in good yields. In 2011, the group of Aïssa also disclosed a Rh-catalyzed chemoselective intramolecular hydroformylation of α,α-disubstituted 4-alkylidenecyclopropanals under mild conditions, affording cycloheptenones in good yields.[17]

Among the reported examples of Rh catalyzed hydroformylation of ACPs, we were wondering whether the intramolecular decarbonylative cyclization reaction could be realized when similar ACP substrates were used in the Rh(I)-catalyzed transformations. Accordingly, *ortho*-formyl group-substituted biphenylalkylidenecyclopropane **1a** was prepared and used as a template substrate for the examination of our working hypothesis (Scheme 1, this work).

We initially investigated the ligand effect on the intramolecular decarbonylative cyclization reaction of **1a** with Wilkinson's catalyst and found that using dppp as a ligand afforded the desired product **2a** in 19% yield in toluene at 80 °C overnight (Table 1, entry 1). Raising the reaction temperature from 80 °C to 110 °C gave the corresponding cyclized product **2a** in 42% yield, however, when the reaction was carried out at 130 °C in a sealed tube, **2a** was still given in 42% yield (Table 1, entry 2 *vs.* 3). Thus, we set up the reaction temperature at 110 °C for the further reaction condition screening.

Next, several other commercially available phosphine ligands were used in the reaction. We found that the use of Xantphos as an external ligand did not improve the reaction outcome (Table 1, entry 4), while when the electron deficient $P(C_6F_5)_3$ was employed as the ligand, **2a** was produced in a higher yield of 56% under otherwise identical conditions (Table 1, entry 5). Subsequently, we performed the reactions using $[Rh(cod)Cl]_2$ and $[Rh(cod)OH]_2$, in which no phosphine ligand was coordinated to the rhodium metal center and found that the yields of **2a** were almost identical in the presence or absence of the $P(C_6F_5)_3$ ligand (Table 1, entry 6 *vs.* 7, 8 *vs.* 9). Afterwards, we realized that the yield of **2a** could reach 48% when using Wilkinson's catalyst alone even without any external phosphine ligand (Table 1, entry 10). These results suggested that the addition of an extra phosphine ligand did not significantly improve the yield of **2a** when using Wilkinson's type of Rh catalyst. Moreover, a cationic rhodium catalyst such as $Rh(cod)BF_4$ had no catalytic activity for this reaction (Table 1, entry 11). Therefore, we started to seek out other catalysts for this reaction rather than the ligand.

Table 1 Optimization of the reaction conditions



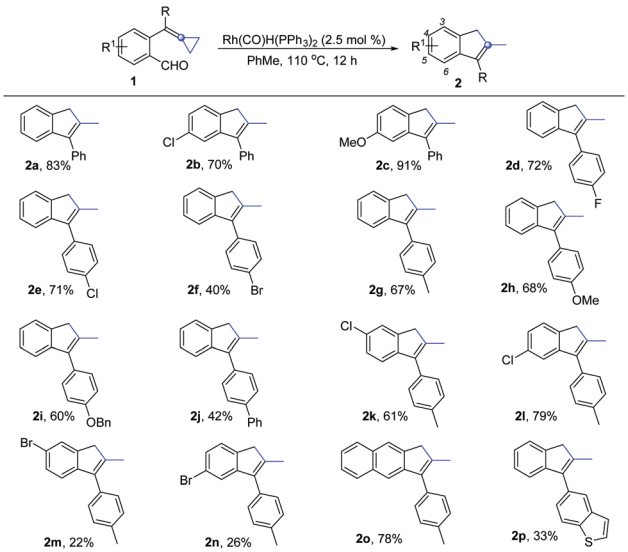
1a 2a

Entry[a]	Cat. (mol%)	Ligand	*T*/°C	Solvent	Yield[b] (%)
1	$Rh(PPh_3)_3Cl$	dppp	80	PhMe	19
2	$Rh(PPh_3)_3Cl$	dppp	110	PhMe	42[c]
3	$Rh(PPh_3)_3Cl$	dppp	130	PhMe	42[d]
4	$Rh(PPh_3)_3Cl$	Xantphos	110	PhMe	36
5	$Rh(PPh_3)_3Cl$	$P(C_6F_5)_3$	110	PhMe	56
6	$[Rh(cod)Cl]_2$	$P(C_6F_5)_3$	110	PhMe	28
7	$[Rh(cod)Cl]_2$	—	110	PhMe	29
8	$[Rh(cod)OH]_2$	$P(C_6F_5)_3$	110	PhMe	32
9	$[Rh(cod)OH]_2$	—	110	PhMe	33
10	$Rh(PPh_3)_3Cl$	—	110	PhMe	48
11	$Rh(cod)BF_4$	—	110	PhMe	—
12	$Rh(CO)Cl(PPh_3)_2$	—	110	PhMe	77[c]
13	$Ir(CO)Cl(PPh_3)_2$	—	110	PhMe	8
14	Rh(CO)Cl(acac)	—	110	PhMe	49
15	$Rh(CO)Cl[P(C_6F_5)_3]_2$	—	110	PhMe	16
16	$Rh(CO)H(PPh_3)_2$	—	110	PhMe	83[c]
17	$Rh(CO)H(PPh_3)_2$	—	110	DCE	24
18	$Rh(CO)H(PPh_3)_2$	—	110	MeCN	7
19	$Rh(CO)H(PPh_3)_2$	—	110	DMF	—
20	$Rh(CO)H(PPh_3)_2$	—	110	Xylene	60
21	$Rh(CO)H(PPh_3)_2$	—	110	PhCl	39
22	$Rh(CO)H(PPh_3)_2$	—	110	$PhCF_3$	42

[a] All reactions were carried out with **1a** (0.1 mmol), **Rh cat.** (2.5 mol%), and **ligand** (10 mol%) in 1.0 mL of solvent for 12 h. [b] ^1H NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yields. [d] This reaction was carried out in a sealed tube. acac = acetylacetone.

Gratifyingly, when $Rh(CO)Cl(PPh_3)_2$ was used as the catalyst, the yield of **2a** was up to 77% isolated yield (Table 1, entry 12). However, the use of $Ir(CO)Cl(PPh_3)_2$ as the catalyst gave **2a** in only 8% yield and most of the starting materials **1a** were recovered (Table 1, entry 13). When the coordinated PPh_3 ligand was changed with other ligands such as acac (acetylacetone) or $P(C_6F_5)_3$, the yields of **2a** were 49% and 16%, respectively (Table 1, entries 14 and 15). Using $Rh(CO)H(PPh_3)_2$ as the catalyst could produce **2a** in 83% isolated yield (Table 1, entry 16). Finally, the examination of the solvent effect in DCE, MeCN, DMF, xylene, PhCl and $PhCF_3$ revealed that toluene was the best choice (Table 1, entries 17–22) (for more details on the optimization of reaction conditions, see Tables S1–S3 in the ESI†).

With the optimized conditions in hand, we next investigated the scope and limitations of this reaction, and the results are summarized in Scheme 2. When a chlorine atom or a methoxy substituent was introduced at the benzene ring bearing a formyl group, the reaction could take place smoothly, giving the desired products **2b** and **2c** in good yields. When the substituents were introduced at another aromatic ring, the reactions also proceeded smoothly, giving the desired products **2d–2j** in moderate to good yields regardless of whether an electron-withdrawing group such as a fluorine atom and other halogen atoms or electron-donating groups such as Me, OMe, OBn and Ph were introduced at the aromatic



Scheme 2 Substrate scope for the synthesis of **2**. All reactions were carried out with **1** (0.2 mmol) and **Rh(PPh$_3$)$_2$(CO)H** (2.5 mol%) in toluene (2.0 mL) at 110 °C for 12 h. Isolated yields.

ring. In addition, we also investigated substrates **1k** and **1l**, having different substituents on both aromatic rings, and found that the reactions proceeded smoothly, furnishing the desired products **2k** and **2l** with yields of 61% and 79%, respectively. As for the bromine atom substituted substrates **1m** and **1n**, the yields of the desired products **2m** and **2n** were only 22% and 26%, respectively, presumably due to the fact that the oxidative addition of Ar–Br to the Rh(I) center consumed the substrate **1m** or **1n**, resulting in the formation of **2m** or **2n** in lower yields. A similar phenomenon was also observed in the case of using substrate **1f** in the reaction. For substrate **1o**, in which the benzene ring is replaced by a naphthalene moiety, the desired product **2o** was obtained in 78% yield. Substrate **1p** containing a heteroaromatic ring was also tolerated, giving the corresponding product **2p** in 33% yield.

The structure of product **2k** was determined by X-ray diffraction. The ORTEP drawing is shown in Fig. 1 and the CIF data are presented in the ESI.†[18]

To further clarify the substrate scope and the reaction mechanism of this intramolecular cascade cyclization process,

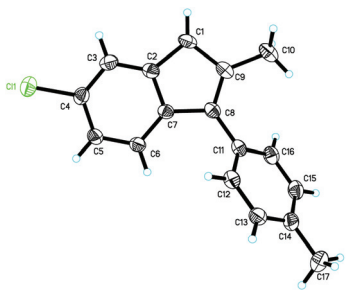
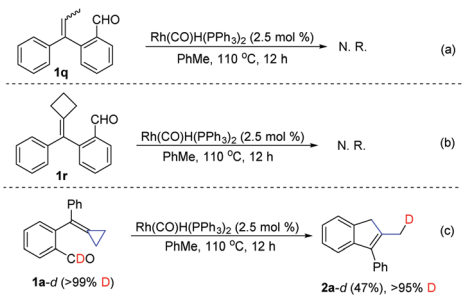


Fig. 1 X-ray crystal structure of compound **2k**.

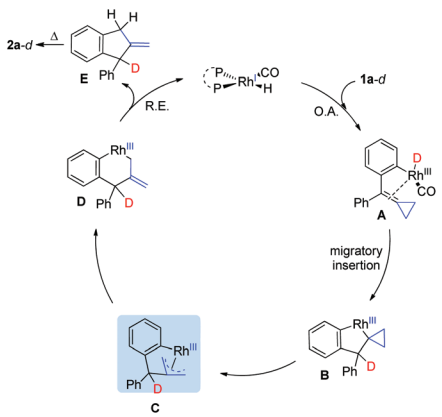
we performed several control experiments and a deuterium labeling experiment. When 2-(1-phenylprop-1-en-1-yl)benzaldehyde **1q** was used as a substrate, no reaction occurred under the standard conditions (Scheme 3a). When using alkylidenecyclobutane **1r** as a substrate, no reaction could take place as well (Scheme 3b). These results suggested that the methylenecyclopropane moiety is essential for this transformation. Meanwhile, we also prepared a deuterium labeled substrate **1a**-*d* (>99% D content) as a substrate for this transformation under the standard conditions, furnishing the corresponding product **2a**-*d* in 47% yield along with >95% deuterium incorporation at the terminal methyl group (Scheme 3c). This result indicated that one hydrogen atom in the methyl group of product **2** is derived from the formyl group in substrate **1**.

On the basis of the control and deuterium labeling experiments and previous literature,[19] a plausible mechanism for this reaction is outlined in Scheme 4. Initially, oxidative addition of the aldehyde moiety of substrate **1a**-*d* with Rh(I) along with a decarbonylative process produces Rh-D species **A**, which undergoes insertion of the double bond of the ACP moiety to afford intermediate **B**. β-Carbon elimination affords the intermediate **C** or **D**. Afterward, reductive elimination from intermediate **D** affords intermediate **E**, which undergoes a [1,3-*H*] migration to give the thermodynamically stable product **2a**-*d*.[20]

In summary, we have developed a novel Rh-catalyzed decarbonylative cascade cyclization reaction of *ortho*-formyl group-



Scheme 3 Control experiments and a labeling experiment.



Scheme 4 A plausible reaction mechanism.

tethered alkylidenecyclopropanes (ACPs) for the preparation of 2-methylindene derivatives. The reaction was initiated by a decarbonylative oxidative addition of the carbonyl group with Rh(I) to generate a Rh–H species. Next, the Rh–H species underwent a migratory insertion to the double bond of the ACP moiety, leading to the distal C–C bond cleavage to give the allylic rhodium complex. The subsequent reductive elimination and a 1,3-hydrogen migration would give the desired cyclized indene derivatives. The reaction mechanism has been proposed on the basis of the control and deuterium labeling experiments. Further investigations towards the application of this methodology to synthesize more practicable compounds are underway in our lab.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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