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

Xing Fan, Ruixing Liu, Yin Wei and Min Shi*

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 decarbonylation3 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 dionones or diones for the synthesis of conjugated diynes and ynones.5a–c In recent years, other metals such as Pd6 and Ni7 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 cyclobutanones8a,b benzocyclobutenones8c or isatins8d 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, alkyynes 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.
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 alkylidene cyclopropanes (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 Aissa also disclosed a Rh-catalyzed chemo- and diastereoselective intramolecular hydroformylation of \(\alpha,\alpha\)-disubstituted 4-alkylidene cyclopropanals under mild conditions, affording cycloheptenones in good yields.\(^{17}\)

Among the reported examples of Rh catalyzed hydroformyla-
tion of ACPs, we were wondering whether the intramolecular decarbonylative cyclization reaction could be realized when similar ACP substrates were used in the Rh(\(\bullet\))-catalyzed transformations. Accordingly, ortho-formyl group-substituted phenylidene cyclopropane 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\(_6\)F\(_5\))\(_3\), 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\(_6\)F\(_5\))\(_3\) 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>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Cat. (mol%)</th>
<th>Ligand</th>
<th>(T)(^\circ)C</th>
<th>Solvent</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>dppp</td>
<td>80</td>
<td>PhMe</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>dppp</td>
<td>110</td>
<td>PhMe</td>
<td>42(^\dagger)</td>
</tr>
<tr>
<td>3</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>dppp</td>
<td>130</td>
<td>PhMe</td>
<td>42(^\dagger)</td>
</tr>
<tr>
<td>4</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>Xantphos</td>
<td>110</td>
<td>PhMe</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>P(C(_6)F(_5))(_3)</td>
<td>110</td>
<td>PhMe</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)Cl](_2)</td>
<td>P(C(_6)F(_5))(_3)</td>
<td>110</td>
<td>PhMe</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)Cl]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(cod)OH]</td>
<td>P(C(_6)F(_5))(_3)</td>
<td>110</td>
<td>PhMe</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(cod)OH]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>Rh(PPh(_3))(_2)Cl</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>Rh(cod)BF(_4)</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Rh(CO)(PPh(_3))(_2)</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>77(^\dagger)</td>
</tr>
<tr>
<td>13</td>
<td>Ir(CO)Cl[P(C(_6)F(_5))(_3)]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>Rh(CO)Cl[P(C(_6)F(_5))(_3)]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>49</td>
</tr>
<tr>
<td>15</td>
<td>Rh(CO)Cl[P(C(_6)F(_5))(_3)]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>34(^+)</td>
</tr>
<tr>
<td>16</td>
<td>Rh(CO)[P(C(_6)F(_5))(_3)]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>53</td>
</tr>
<tr>
<td>17</td>
<td>Rh(CO)[P(C(_6)F(_5))(_3)]</td>
<td>—</td>
<td>110</td>
<td>PhMe</td>
<td>73</td>
</tr>
<tr>
<td>18</td>
<td>Rh(COD)(PPh(_3))</td>
<td>—</td>
<td>110</td>
<td>MeCN</td>
<td>7</td>
</tr>
<tr>
<td>19</td>
<td>Rh(COD)(PPh(_3))</td>
<td>—</td>
<td>110</td>
<td>DMF</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>Rh(COD)(PPh(_3))</td>
<td>—</td>
<td>110</td>
<td>Xylene</td>
<td>60</td>
</tr>
<tr>
<td>21</td>
<td>Rh(COD)(PPh(_3))</td>
<td>—</td>
<td>110</td>
<td>PhCl</td>
<td>39</td>
</tr>
<tr>
<td>22</td>
<td>Rh(COD)(PPh(_3))</td>
<td>—</td>
<td>110</td>
<td>PhCF(_3)</td>
<td>42</td>
</tr>
</tbody>
</table>

\(^a\) 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. \(^\dagger\) H\(^1\) NMR yields using 1,3,5-trimethoxybenzene as an internal standard. \(^\dagger\) Isolated yields. \(^\dagger\) This reaction was carried out in a sealed tube. acac = acetylacetone.
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 alkylideneacyclobutane 1r as a substrate, no reaction could take place as well (Scheme 3b). These results suggested that the methylencyclopropane 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 a $\beta$-carbon intermediate B. $\beta$-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-
tethered alkyldienecyclopropanes (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 elimina-
tion 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
We are grateful for the financial support from the National
Basic Research Program of China (973-2015CB856603), the
Strategic Priority Research Program of the Chinese Academy of
Sciences (Grant No. XDB20000000 and siocz201808), and the
National Natural Science Foundation of China (No. 20472096,
21372241, 21572052, 20672127, 21412091, 21372250,
21121062, 21302203, 20732008, 21772037, 21772226 and
21861132014).

Notes and references
1 (a) D. Rehn, U. Gundert-Remy, E. Weber and G. Hennings,
Biopharm. Drug Dispos., 1984, 5, 291; (b) D. Rehn,
H. Geissler, O. Schuster, H. Lukas and G. Hennings,
Fundam. Clin. Pharmacol., 1990, 4, 673; (c) P. H. Reggio,
S. Basu-Dutt, J. Barnett-Norris, M. T. Castro, D. P. Hurst,
H. H. Seltzman, M. J. Roche, A. F. Gilliam, B. F. Thomas,
Chem., 1998, 41, 517; (d) E. Alcalde, N. Mesquida,
2008, 6, 3795; (e) P. A. Deck, Coord. Chem. Rev., 2006, 250,
1032; (f) B. M. Wile, R. McDonald, M. J. Ferguson and
M. Stradiotto, Organometallics, 2007, 26, 1069;
(g) V. V. Izmer, A. Y. Lebedev, M. V. Nikulin, A. N. Ryabov,
A. F. Asachenko, A. V. Lygin, D. A. Sorokin and
A. Z. Voskoboynikov, Organometallics, 2006, 25, 1217;
(h) J. Eppinger, M. Spieglk, W. Hieringer, W. A. Herrmann
(i) Y. He, H.-Y. Chen, J. Hou and Y. Li, J. Am. Chem. Soc.,
2010, 132, 1377; (j) K. Nikitín, C. Fleming, H. Müller-Bunz,
5203.
2 For selected review articles, see: (a) L. Guo and M. Rueping,
Chem. – Eur. J., 2018, 24, 7794; (b) R. J. Somerville and
(c) A. Dermenci and G. Dong, Sci. China: Chem., 2013, 56,
683; (d) A. Dermenci, J. W. Coe and G. Dong, Org. Chem.
Front., 2014, 1, 567.
3 (a) J. Tsuji and K. Ohno, Tetrahedron Lett., 1965, 6, 3969;
4 (a) K. Kiyotomi, A. Hiromichi, W. Masami and T. Shiichiro,
Chem. Lett., 1974, 3, 215; (b) M. Murakami, H. Amii,
5 (a) A. Dermenci, R. E. Whittaker and G. Dong, Org. Lett.,
2013, 15, 2242; (b) A. Dermenci, R. E. Whittaker, Y. Gao,
F. A. Cruz, Z.-X. Yu and G. Dong, Chem. Sci., 2015, 6, 3201;
(c) R. E. Whittaker and G. Dong, Org. Lett., 2015, 17, 5504;
(d) L. Yang, T. Zeng, Q. Shuai, X. Guo and C.-J. Li, Chem.
Commun., 2011, 47, 2161.
6 (a) A. Maleckis and M. S. Sanford, Organometallics, 2014,
33, 2653; (b) D. Shiro, H. Nagai, S.-i. Fujiwara, S. Tsuda,
T. Iwasaki, H. Kuniiyasu and N. Kambe, Heteroat. Chem.,
2014, 25, 518; (c) C. Liu and M. Szostak, Angew. Chem.,
2017, 129, 12892; (d) Y. Ogihara, Y. Sakurai, H. Hattori
7 (a) P. Mi, P. Liao, T. Tu and X. Bi, Chem. – Eur. J., 2015, 21,
5332; (b) K. Ding, S. Xu, R. Aloitaib, K. Paudel,
4924; (c) C. Liu and M. Szostak, Chem. Commun., 2018, 54,
2130; (d) T.-T. Zhao, W.-H. Xu, Z.-J. Zheng, P.-F. Xu
8 (a) P. A. Wender, A. G. Correa, Y. Sato and R. Sun, J. Am.
Chem. Soc., 2000, 122, 7815; (b) T. Xu, N. A. Savage
(c) X. Zhou, H. M. Ko and G. Dong, Angew. Chem., Int.
Ed., 2016, 55, 1386; (d) R. Zeng and G. Dong, J. Am. Chem.
Soc., 2015, 137, 1408.
9 (a) L. Yang, C. A. Correia, X. Guo and C.-J. Li, Tetrahedron
Lett., 2010, 51, 5486; (b) L. Yang, X. Guo and C.-J. Li,
Adv. Synth. Catal., 2010, 352, 2899; (c) Q. Shuai, L. Yang,
X. Guo, O. Baslé and C.-J. Li, J. Am. Chem. Soc., 2010, 132,
12212.
2014, 53, 1674.
12 (a) X. Guo, J. Wang and C.-J. Li, J. Am. Chem. Soc., 2009,
131, 15092; (b) X. Guo, J. Wang and C.-J. Li, Org. Lett., 2010,
12, 3176; (c) T. Kondo, A. Nakamura, T. Okada, N. Suzuki,
6319; (d) T. Kondo, Y. Taguchi, Y. Kaneko, M. Niimi
13 E. Watanabe, A. Kaiho, H. Kusama and N. Iwasawa,
14 (a) R.-J. Tang, Q. He and L. Yang, Chem. Commun., 2015,
51, 5925; (b) Y.-J. Jang, M.-C. Yan, Y.-F. Lin and C.-F. Yao,
15 For selected review articles, see: (a) F. Wang, S. Yu and
X. Li, Chem. Soc. Rev., 2016, 45, 6462; (b) H. Taniguchi,
T. Ohmura and M. Sugino, J. Am. Chem. Soc., 2009, 131,
18 The structure of 2k has been confirmed by X-ray diffraction and the CIF data are shown in the ESI.