Homogeneous Catalysis

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C_{sp^3}–H Bond Activation Triggered by Formation of Metallacycles: Rhodium(I)-Catalyzed Cyclopropanation/Cyclization of Allenynes**

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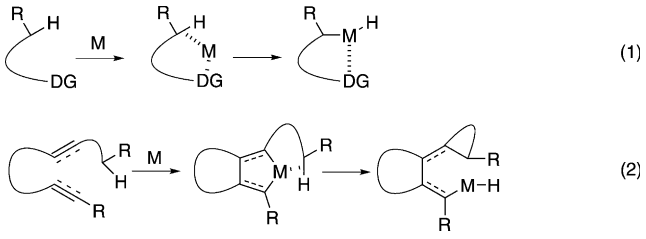
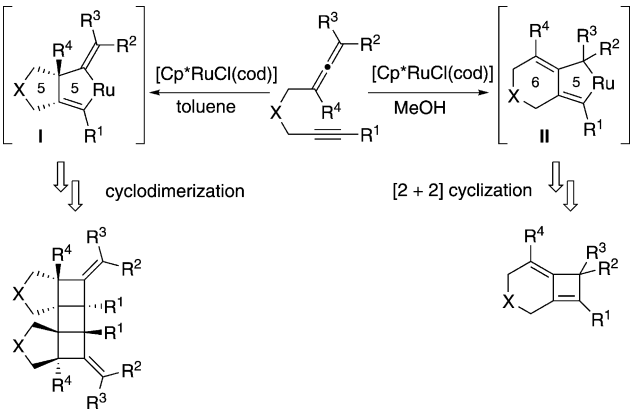
Transition-metal-catalyzed selective C–H activation has become one of the most powerful and straightforward strategies for the construction of complex molecules in synthetic organic chemistry.[1,2] Aliphatic C_{sp^3}–H bonds have no π electrons that can readily interact with transition metal complexes, and site-selective activation of C_{sp^3}–H bonds therefore remains as one of the most challenging topics for synthetic chemists.[1k] Most of the C_{sp^3}–H activations that have been reported so far need the assistance of directing groups (DG), most of which contain a nitrogen or oxygen atom at the appropriate position in the substrate [Scheme 1, Eq. (1)] for site-selective activation. However, such directing groups



Scheme 1. C–H activation process.

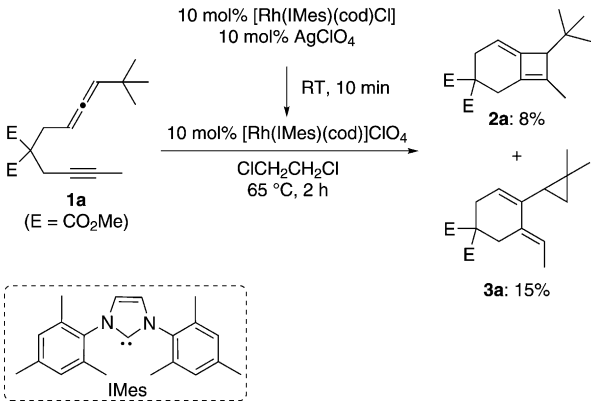
might be incorporated in the products, and they often cannot be easily removed or be converted into other valuable functional groups.[3] Thus, new strategies for C_{sp^3}–H activations that do not incorporate directing groups in the product are needed.[1k] Herein we report a C_{sp^3}–H bond activation that is triggered by the formation of a metallacycle intermediate [Scheme 1, Eq. (2)].[4,5]

We recently reported two types of novel ruthenium-catalyzed cyclizations of allenynes; the reaction pathway of the cyclization dramatically changed depending on the solvent employed (Scheme 2).[6] That is, the reaction of an allenyne with [Cp*RuCl(cod)] in toluene proceeded via ruthenacycle intermediate **I**, which then underwent cyclodimerization to give a pentacyclic compound.[6a] On the other hand, the reaction of the same substrate with the same catalyst in MeOH proceeded via ruthenacycle **II**, and a bicyclic compound was exclusively produced through a [2+2] cycloaddition.[6b]



Scheme 2. [Cp*RuCl(cod)]-catalyzed cyclizations of allenynes. cod = cyclooctadiene.

During the course of screening catalysts for these reactions, we encountered another type of cyclization of allenynes (Scheme 3).[7,8] Thus, treatment of substrate **1a**[6a] with 10 mol% of $[Rh(IMes)(cod)]ClO_4$, which was generated in situ from [Rh(IMes)(cod)Cl] and $AgClO_4$, in dichloroethane at 65 °C for 2 h gave [2+2] cyclization product **2a** in



Scheme 3. Rh^{I}-catalyzed cyclization of allenyne.

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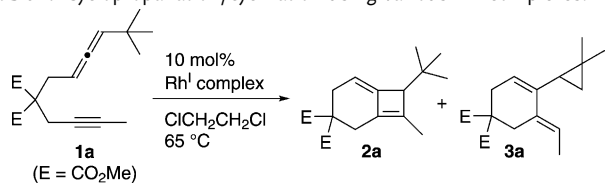
8% yield[6b,9,10] along with the unexpected cyclic product **3a**, which contains a cyclopropane ring, in 15% yield.[11] We hypotesized that the cyclic compound **3a** could be produced through a process that involves a C_{sp^3}–H activation of the *tert*-butyl moiety in the substrate. We therefore decided to further investigate this cyclization.[12]

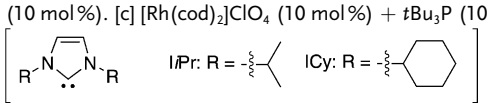
To improve the yield of **3a**, the reaction of **1a** in the presence of various cationic Rh^I complexes was examined (Table 1). In contrast to the use of $[Rh(IMes)(cod)]ClO_4$

Table 1: Cyclopropanation/cyclization using various Rh^I complexes.



Entry	Rh^I Complex	*t* [h]	Yields [%][a]	
			2a	**3a**
1[b]	$[Rh(IMes)(cod)]ClO_4$	2	8	15
2[b]	$[Rh(I\mathit{i}Pr)(cod)]ClO_4$	1	–	90(88)
3[b]	$[Rh(ICy)(cod)]ClO_4$	1	–	89(80)
4[c]	$[Rh(t\mathrm{Bu}_3P)(cod)]ClO_4$	1	–	60

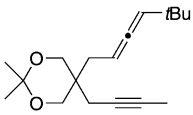
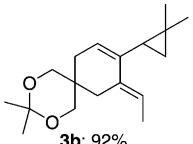
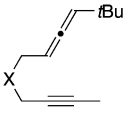
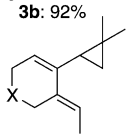
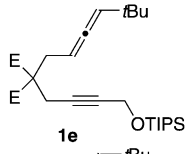
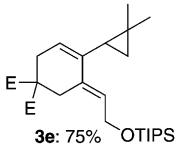
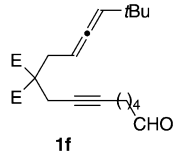
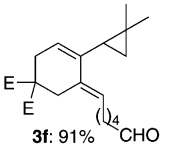
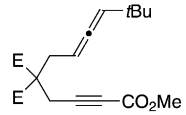
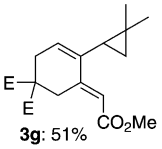
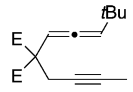
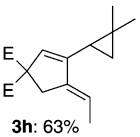
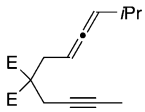
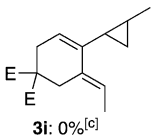
[a] Yields were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Yields of the isolated products are given in parentheses. [b] [Rh(NHC)(cod)Cl] (10 mol%) + $AgClO_4$ (10 mol%). [c] $[Rh(cod)_2]ClO_4$ (10 mol%) + $t\mathrm{Bu}_3P$ (10 mol%).



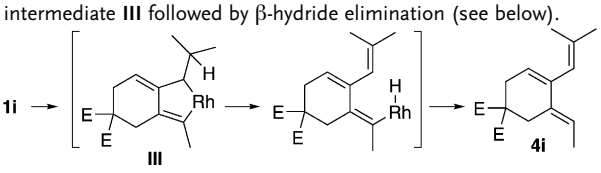
(Table 1, entry 1), when $[Rh(I\mathit{i}Pr)(cod)]ClO_4$ or $[Rh(ICy)(cod)]ClO_4$, which both have a bulky alkyl group on the nitrogen atom of the N-heterocyclic carbene (NHC), were used, the cyclopropane-containing cyclized product **3a** was formed selectively, in 90% and 89% yield, respectively (Table 1, entries 2 and 3). The use of a bulky electron-rich phosphine, $t\mathrm{Bu}_3P$, also gave the desired product **3a** in 60% yield (Table 1, entry 4). On the other hand, the use of other Rh/NHC complexes (e.g., $[Rh(IPr)(cod)]ClO_4$ and $[Rh(IMe)(cod)]ClO_4$) as well as rhodium phosphine complexes (e.g., $[Rh(PPh_3)_3]ClO_4$, $[Rh(dppe)(cod)]ClO_4$, and $[Rh(dppb)(cod)]ClO_4$) did not afford the cyclic compound **3a**.[13]

To investigate the generality of this cyclization, various substrates were examined (Table 2). The reaction of **1b**,[6a] which has a cyclic acetal moiety, in the presence of 10 mol% of $[Rh(I\mathit{i}Pr)(cod)]ClO_4$ catalyst smoothly proceeded even at room temperature to give the cyclopropane-containing cyclized product **3b** in 92% yield (Table 2, entry 1). In the reactions of **1c**[6a] and **1d**, which contain a heteroatom in the chain, the corresponding heterocycles **3c** and **3d** were produced in modest yields (Table 2, entries 2 and 3). The presence of an oxygen-containing functionality such as a silyloxy group (**1e**) or an aldehyde moiety (**1f**) in the alkyne side chain is tolerated in this cyclization, thus giving **3e** and **3f** in 75% and 91% yields, respectively (Table 2, entries 4 and 5). The reaction of **1g**, which contains an electron-withdrawing substituent on the alkyne moiety, also afforded the desired product **3g** in 51% yield (Table 2, entry 6). This cyclization was also applied to the construction of a five-membered ring, and the desired compound **3h** was obtained from **1h** in 63% yield (Table 2, entry 7). On the other hand, the cyclization of **1i**, which has an isopropyl moiety instead of a *tert*-butyl moiety at the terminus of the allene, afforded no cyclopropane-containing product **3i** but produced cycloisomerization product **4i** in 66% yield (Table 2, entry 8).[8a–c]

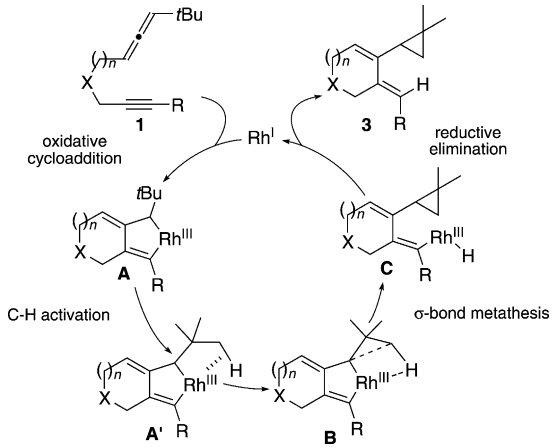
Table 2: Cyclization of a range of substrates.[a,b]

Entry	Substrate	Conditions	Product
1	 **1b**	RT, 1 h	 **3b**: 92%
2	 **1c** (X = NTs)	reflux, 4 h	 **3c**: 65%
3	**1d** (X = O)	65 °C, 1 h	**3d**: 27%
4	 **1e**	65 °C, 1 h	 **3e**: 75%
5	 **1f**	65 °C, 4 h	 **3f**: 91%
6	 **1g**	65 °C, 1 h	 **3g**: 51%
7	 **1h**	65 °C, 1 h	 **3h**: 63%
8	 **1i**	65 °C, 3 h	 **3i**: 0%[c]

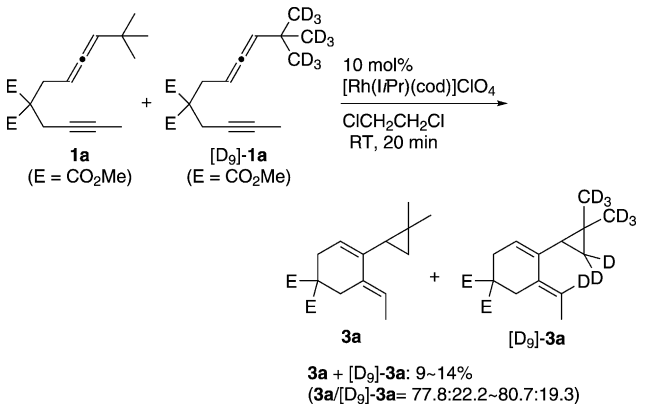
[a] All reactions were carried out using 10 mol% of $[Rh(I\mathit{i}Pr)(cod)]ClO_4$ in $ClCH_2CH_2Cl$. E = CO_2Me. [b] Yields of the isolated products. [c] The cycloisomerization product **4i** was obtained (66% yield) via rhodacycle intermediate **III** followed by β-hydride elimination (see below).



A plausible mechanism for this cyclopropanation/cyclization is shown in Scheme 4. Initially, oxidative cycloaddition of



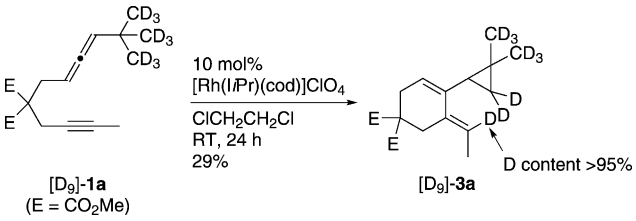
Scheme 4. Plausible reaction mechanism.



Scheme 6. Kinetic isotope competition experiment.

the alkyne and the external C=C bond of the allene moiety of substrate **1** to a cationic Rh^I complex would occur to produce rhodacycle intermediate **A**. By virtue of the formation of rhodacycle **A**, one C_{sp^3}–H bond on the *tert*-butyl moiety would be close to the cationic Rh^{III} center, thus resulting in C_{sp^3}–H bond activation (**A′**). Subsequently, σ-bond metathesis between the activated C_{sp^3}–H bond and the Rh–C_{sp^3} bond of the rhodacycle would occur via a transition state such as **B** to produce rhodium hydride intermediate **C**.[14] Finally, reductive elimination from **C** would lead to the cyclopropane-containing product **3** with regeneration of a cationic Rh^I complex.

To gain an insight into the reaction mechanism, we investigated the reaction of [D_9]-**1a**, which contains a completely deuterium-labeled *tert*-butyl moiety (Scheme 5).



Scheme 5. Cyclization of [D_9]-**1a**.

Unexpectedly, the reaction of [D_9]-**1a** under the same reaction conditions as those shown in Table 1, entry 2 gave a complex mixture of products instead of the desired cyclopropane-containing product [D_9]-**3a**. On the other hand, when the reaction of [D_9]-**1a** was carried out at room temperature, the reaction was sluggish but produced the corresponding cyclopropane-containing cyclized product [D_9]-**3a** in a low yield (29%); in this reaction a deuterium atom was transferred to the expected position on the alkene moiety in >95%.

On the basis of these results, we speculated that cleavage of the C_{sp^3}–H bond (i.e., from **B** to **C** in Scheme 4) is the rate-determining step in this reaction, as the different reactivities between **1a** and [D_9]-**1a** would result from a kinetic isotope effect.[15] Thus, we performed a kinetic isotope competition experiment using an equimolar mixture of allenyne **1a** and [D_9]-**1a** (Scheme 6).[16] Several reactions of a 1:1 mixture of **1a** and [D_9]-**1a** with 10 mol% of [Rh(I*i*Pr)(cod)]ClO_4 at room temperature were carried out and quenched at various stages (20–120 min). The reactions quenched at an early stage (20 min) gave a mixture of **3a** and [D_9]-**3a** in a range of 9–14% yields in a ratio of **3a**/[D_9]-**3a** = 77.8:22.2 ≈ 80.7:19.3, from which the KIE of this reaction is calculated to be approximately 3.9. These results strongly support our hypothesis that the cyclopropanation/cyclization proceeds according to the mechanism shown in Scheme 4, as well as our hypothesis that the cleavage of the C_{sp^3}–H bond is the rate-determining step.

In summary, we have succeeded in demonstrating a protocol for an C_{sp^3}–H bond activation directed by the formation of metallacycle intermediates in the cyclization of allenynes, thus giving cyclic compounds containing a cyclopropane structure in good to high yields. Deuterium-labeling experiments supported the occurence of a C_{sp^3}–H bond activation followed by cleavage of the C–H bond, which is most likely the rate-determining step in this cyclization. These results should provide new insights into the chemistry of C_{sp^3}–H activations, and further studies along this line are now in progress.

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Keywords: allenyne · C–H activation · cyclization · cyclopropane · rhodium

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