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Rhodium(I)-catalyzed [3+2] intramolecular cycloaddition of alkylidenecyclopropane–propargylic esters

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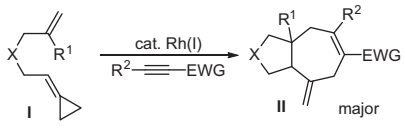
ABSTRACT

An interesting rhodium(I)-catalyzed [3+2] intramolecular cycloaddition of alkylidenecyclopropanes **1** containing propargylic esters has been described in this context. A variety of bicyclo[3.3.0]octene derivatives were obtained in moderate to good yields under mild conditions. The alkylidenecyclopropane-enynes **2** could be also converted to the corresponding cycloadducts **3** in good yields.

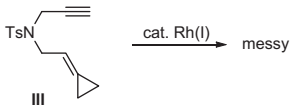
There are a variety of methods for the generation of polycyclic structures, but metal-catalyzed carbocyclization reactions have proven among the most attractive for their construction.[1,2] Methylenecyclopropanes (MCPs) and alkylidenecyclopropanes (ACPs), containing a coordinating double bond and a strained carbocycle, can undergo a number of interesting metal-assisted transformations.[3] Rhodium,[4] nickel,[5] ruthenium,[6] as well as palladium,[7] all can catalyze intermolecular and intramolecular cycloaddition of alkene- or alkyne-tethered ACPs, constructing a variety of interesting bicycles or tricycles, which are useful building blocks for the synthesis of natural products and medicinally important substances. In recent years, propargylic esters have received extensive attention as a special class of alkynes for their rich reactivities and easy availabilities.[8,9] Transition-metal catalyst, for example, rhodium has been identified as an effective promoter in its transformations to a variety of valuable substances.[10]

Intermolecular

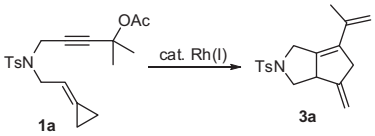


(1)

Intramolecular



(2)



(3)

Although the intermolecular rhodium(I)-catalyzed [3+2+2] carbocyclization reaction of ACPs with activated alkynes has been reported (Eq. 1), [4] the corresponding intramolecular carbocyclization of ACPs has not been forthcoming and complex product mixtures were formed (Eq. 2). Herein, we wish to describe the first intramolecular rhodium(I)-catalyzed [3+2] cycloaddition of ACPs **1** containing propargylic esters, for the construction of the bicyclo[3.3.0]octene derivatives **3** (Eq. 3). [11]

Initial studies using alkylidenecyclopropane–propargylic ester **1a** (0.2 mmol) as the substrate were aimed at determining the reaction outcomes and subsequently optimizing the reaction conditions. The results of these experiments are summarized in Table 1. We found that an interesting cycloadduct **3a** was obtained in a 36% yield using $RhCl(CO)(PPh_3)_2$ as the catalyst (5 mol %) in toluene at 80 °C (Table 1, entry 1). In the presence of $[Rh(COD)Cl]_2$, $RhCl(PPh_3)_3$ or $[RhCp^*Cl_2]_2$, **3a** could not be formed and $[RhCl(CO)_2]_2$, $RhH(CO)(PPh_3)_3$ as well as $Rh(COD)_2BF_4$ were not effective catalysts in this reaction (Table 1, entries 2–7). Further examination of solvent effects revealed that toluene was the solvent of choice, and other organic solvents such as 1,2-dichloroethane (DCE), CH_3NO_2 or 1,4-dioxane did not facilitate the formation of **3a** (Table 1, entries 8–10). Using $RhCl(CO)(PPh_3)_2$ (10 mol %) afforded **3a** in a 45% yield (Table 1, entry 11). Decreasing the concentration of reactant to 0.025 M or 0.0125 M, **3a** were obtained in a 60% yield and a 54% yield, respectively under identical conditions (Table 1, entries 12 and 13). Carrying out the reaction under reflux (110 °C), **3a** was obtained in a 50% yield (Table 1, entry 14). Adding base, acid, and silver salts did not improve the yield (Table 1, entries 15–20). Therefore,

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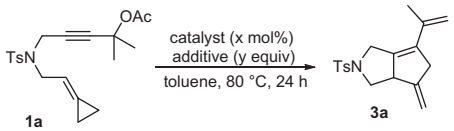
Table 1
Optimization of the reaction conditions



1a 3a

Entry[a]	Catalyst (× mol %)	Additive (*y* equiv)	Yield[b] (%) **3a**
1	$RhCl(CO)(PPh_3)_2$ (5 mol %)	—	36
2	$[Rh(COD)Cl]_2$ (2.5 mol %)	—	NR
3	$[Rh(CO)_2]_2$ (2.5 mol %)	—	15
4	$RhCl(PPh_3)_3$ (5 mol %)	—	NR
5	$[RhCp^*Cl_2]_2$ (2.5 mol %)	—	NR
6	$RhH(CO)(PPh_3)_3$ (5 mol %)	—	12
7	$Rh(COD_2)BF_4$ (5 mol %)	—	Trace
8[c]	$RhCl(CO)(PPh_3)_2$ (5 mol %)	—	31
9[d]	$RhCl(CO)(PPh_3)_2$ (5 mol %)	—	Trace
10[e]	$RhCl(CO)(PPh_3)_2$ (5 mol %)	—	10
11	$RhCl(CO)(PPh_3)_2$ (10 mol %)	—	45
12[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	—	60
13[g]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	—	54
14[f,h]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	—	50
15[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	K_2CO_3 (1.5 equiv)	NR
16[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	DABCO (1.0 equiv)	19
17[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	HOAc (1.0 equiv)	25
18[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	$AgSbF_6$ (0.1 equiv)	Complex
19[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	AgOTf (0.1 equiv)	Complex
20[f]	$RhCl(CO)(PPh_3)_2$ (10 mol %)	$AgBF_4$ (0.1 equiv)	Complex

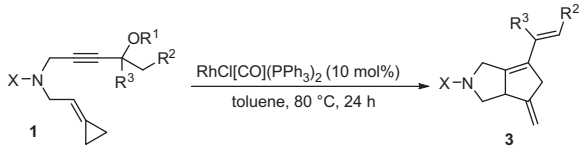
[a] All reactions were carried out using **1a** (0.1 mmol), additive (*y* equiv) in the presence of catalyst (× mol %) in toluene (2.0 mL) otherwise specified. The reaction concentration was 0.05 M.
[b] Isolated yield.
[c] In DCE.
[d] In CH_3NO_2.
[e] In 1,4-dioxane.
[f] The reaction concentration was 0.025 M.
[g] The reaction concentration was 0.0125 M.
[h] At refluxing temperature.

the optimal reaction conditions were identified to carry out the reaction in toluene at 80 °C using $RhCl(CO)(PPh_3)_2$ (10 mol %) as the catalyst.

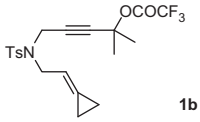
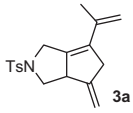
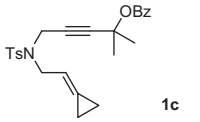
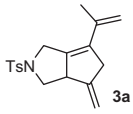
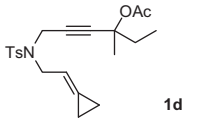
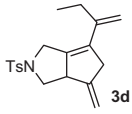
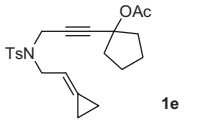
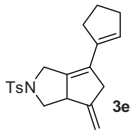
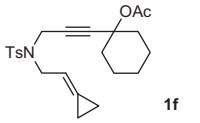
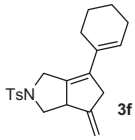
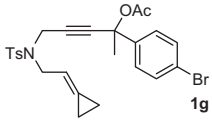
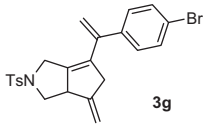
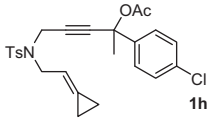
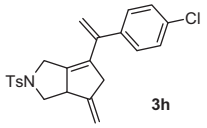
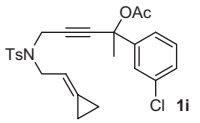
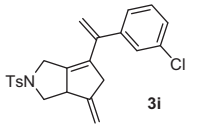
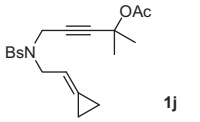
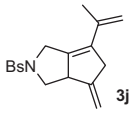
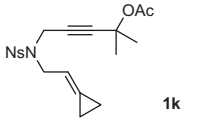
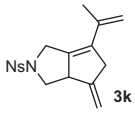
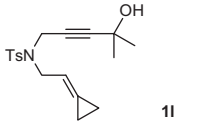
We next examined the substrate generality of the reaction under optimized conditions and the results are shown in Table 2. As can be seen from Table 2, as for substrates **1b** ($R^1 = CF_3CO$) and **1c** ($R^1 = C_6H_5CO$), the reactions proceeded smoothly to give the desired products **3a** in a 36% yield and a 46% yield, respectively (Table 2, entries 1 and 2). When both R^2 and R^3 were methyl groups, the corresponding cycloadduct **3d** was formed in a 46% yield (Table 2, entry 3). For the cycloalkyl group substituted propargylic esters **1e** and **1f**, the corresponding bicyclo[3.3.0]octene derivatives **3e** and **3f** were obtained in 38% and 41% yields, respectively (Table 2, entries 4 and 5). For various propargylic esters in which R^3 was aromatic groups, the desired [3+2] adducts could be obtained in 39–41% yields under standard conditions (Table 2, entries 6–8). In the case of other N-sulfonated amines (X = Bs or Ns), the reactions also proceeded smoothly to give the desired cycloadducts **3j** and **3k** in 56–60% yields (Table 2, entries 9 and 10). As for the substrate **1l** ($R^1 = H$), no reaction occurred under standard conditions (Table 2, entry 11). The product structures of **3a**–**3k** were determined by NMR spectroscopic analysis, mass spectrometry (MS), and HRMS (see Supplementary data).

On the other hand, we found that alkylidenecyclopropane-enyne **2** can also produce the corresponding bicyclo[3.3.0]octene derivatives **3** in moderate to good yields, and the results are summarized in Table 3. As for substrate **2a** having an isopropenyl group at the terminal of alkyne moiety, the corresponding cycloadduct **3a** was formed in a 69% yield (Table 3, entry 1). Substrate **2b** having a

Table 2
Rhodium(I)-catalyzed [3+2] intramolecular cycloaddition of alkylidenecyclopropane–propargylic esters **1** under optimized conditions

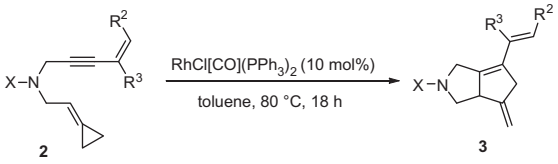


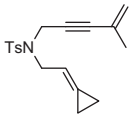
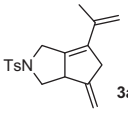
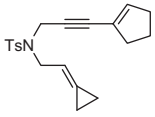
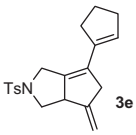
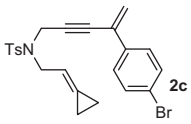
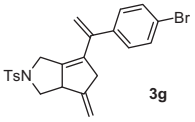
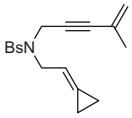
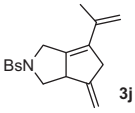
1 3

Entry[a,c]	Substrate **1**	Product	Yield[b] (%) **3**
1	 **1b**	 **3a**	36
2	 **1c**	 **3a**	46
3	 **1d**	 **3d**	46[d]
4	 **1e**	 **3e**	38
5	 **1f**	 **3f**	41
6	 **1g**	 **3g**	41
7	 **1h**	 **3h**	39
8	 **1i**	 **3i**	39
9	 **1j**	 **3j**	60
10	 **1k**	 **3k**	56
11	 **1l**		NR

[a] All reactions were carried out using **1** (0.2 mmol) in the presence of $RhCl[CO](PPh_3)_2$ (10 mol %) in toluene (8.0 mL) at 80 °C for 24 h. The reaction concentration was 0.025 M.
[b] Isolated yield.
[c] Ts = 4-toluenesulfonyl; Ns = 4-nitrobenzenesulfonyl Bs = 4-bromobenzenesulfonyl.
[d] The products are isomers.

Table 3
Rhodium(I)-catalyzed [3+2] intramolecular cycloaddition of alkylidenecyclopropane-enyne **2** under optimized conditions

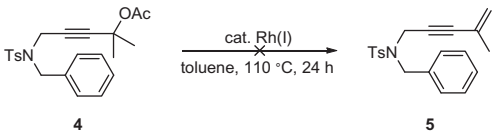


Entry[a,c]	Substrate **2**	Product	Yield[b] (%) **3**
1	 **2a**	 **3a**	69
2	 **2b**	 **3e**	44
3	 **2c**	 **3g**	50
4	 **2d**	 **3j**	76

[a] All reactions were carried out using **2** (0.2 mmol) in the presence of $RhCl[CO](PPh_3)_2$ (10 mol %) in toluene (8.0 mL) at 80 °C. The reaction concentration was 0.025 M.
[b] Isolated yield.
[c] Ts = 4-toluenesulfonyl; Ns = 4-nitrobenzenesulfonyl Bs = 4-bromobenzene-sulfonyl.

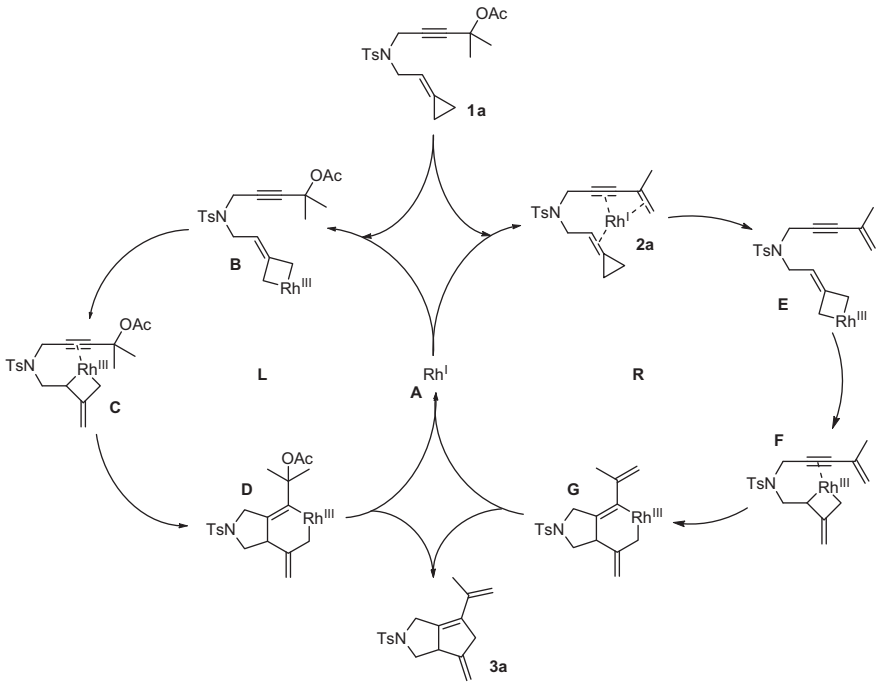
cyclopentenyl group at the terminal of alkyne moiety gave the desired product **3e** in a 44% yield (Table 3, entry 2). Further examination of substrate **2c** (R^3 = 4-BrC_6H_4) revealed that the corresponding cycloadduct **3g** could be obtained in a 50% yield (Table 3, entry 3). In the case of other N-sulfonated amine (X = Bs), the reaction also proceeded smoothly to give the desired [3+2] adduct **3j** in a 76% yield (Table 3, entry 4).

In order to obtain more mechanistic information, we performed ^1H NMR tracing experiments to detect the active species (see Supplementary data). We confirmed that alkylidenecyclopropane-enyne **2a** could not be detected in the NMR tracing experiments. Meanwhile, we also synthesized propargylic ester **4**. In the control experiment, we found that upon treatment of **4** with $RhCl[CO](PPh_3)_2$ (10 mol %) in toluene at 110 °C for 24 h, enyne **5** could not be formed (Eq. 4).



4 **5** (4)

A plausible mechanism for the formation of these bicyclo [3.3.0]octene derivatives **3** is tentatively outlined in Scheme 1 on the basis of above results. *Cycle **L*** involves initial insertion of the metal at the distal position of the alkylidenecyclopropane **1a** to give metallacyclobutene **B**, followed by isomerization to intermediate **C** through a TMM-like transition state and carbometalation to afford intermediate **D**.[7e] Reductive elimination of intermediate **D** provides the final adduct **3a** along with the release of HOAc. In *Cycle **R***, propargylic ester **1a** produces enyne **2a** in the presence of Rh^I complex **A**. Oxidative addition into the distal bond of the cyclopropane should afford the metallacyclobutene **E**, which can presumably rearrange to intermediate **F**.[4] Intermediate **F** undergoes carbometalation to give intermediate **G**. Reductive elimination of intermediate **G** produces the corresponding cycloadduct **3a** and regenerates the Rh^I complex **A** to complete the catalytic cycle.



Scheme 1. A plausible reaction mechanism.

In conclusion, we have developed an interesting rhodium(I)-catalyzed intramolecular [3+2] carbocyclization of alkylidenecyclopropane containing propargylic esters for the construction of bicyclo[3.3.0]octene derivatives. The alkylidenecyclopropane-enyne **2** could also be converted to the corresponding cycloadducts in good yields. More detailed mechanistic investigation and further application of this chemistry are underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.084.

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