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C_{sp^3}–C_{sp^3} and C_{sp^3}–H Bond Activation of 1,1-Disubstituted Cyclopentane

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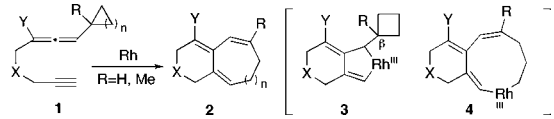
Supporting Information

ABSTRACT: The unprecedented C_{sp^3}–C_{sp^3} bond cleavage of unactivated cyclopentane has been achieved. Rh^I-catalyzed cycloaddition of allenylcyclopentane-alkynes produced *in situ* the 9-cyclopentyl-8-rhodabicyclo[4.3.0]-nona-1,6-diene intermediates, which subsequently underwent [7+2] cycloaddition via β-C elimination, affording bicyclo[7.4.0]tridecatriene derivatives in good yields. Changing the Rh^I catalyst effected the Cγ–H bond activation of the common 9-cyclopentyl-8-rhodabicyclo[4.3.0]nona-1,6-diene intermediate to produce the novel spiro[2.4]heptane skeleton in a site-selective manner.

Small-sized cycloalkanes are often of significant use from synthetic points of view.[1] In particular, highly strained cyclopropane derivatives have been well recognized as useful and powerful acyclic C_3-buliding blocks for transition-metal-catalyzed ring-forming reactions leading to various ring systems. Relief of the high strain energy (27.5 kcal/mol) of cyclopropanes[2] is thought to facilitate C_{sp^3}–C_{sp^3} bond cleavage and make them an important C_3-unit. Intramolecular Rh^I-catalyzed [5+2] cycloaddtion of vinylcyclopropanes[3,4] with C–C π components, for example, efficiently produced the corresponding bicyclo[5.3.0] frameworks in which the terminal unactivated cyclopropane was incorporated into the 7-membered carbocycles. In sharp contrast to the ring-opening of cyclopropanes, one-carbon homologated cyclobutanes[5] require an activating functional group directly attached to the 4-membered ring for their ring-opening.[6] Thus, functionalized cyclobutanes such as cyclobutanone,[5,7] hydroxycyclobutane,[8] an alkylidenecyclobutane unit,[9] or spiro[3.3]heptenone[10a] and heptanone[10b] units have been used, whereas the simplest cyclobutane without any other functional groups on its ring has been rarely employed as an acyclic C_4-building block for transition-metal-catalyzed ring-forming reactions.[6] In fact, Wender[7a] reported the efficient transformation of vinylcyclobutanone-alkene or -allene substrates into the corresponding bicyclo[6.3.0] compounds via Rh^I-catalyzed [6+2] cycloaddtion and pointed out that this reaction does not work with vinylcyclobutanes as it does with vinylcyclobutanones. The smaller strain energy of cyclobutane (26.3 kcal/mol)[11] might reflect the lower reactivity of the cyclobutanes compared to the cyclopropanes. We recently disclosed that Rh^I-catalyzed cycloaddition of allenylcyclopropane-alkynes **1** (n = 1) afforded the bicyclo[5.4.0]undecatrienes **2** (n = 1)[12a] in the [5+2] ring-closing manner. A similar conversion was realized

Scheme 1. Rh^I-Catalyzed Cycloaddition of Allenylcycloalkane-alkynes (n = 1,2)



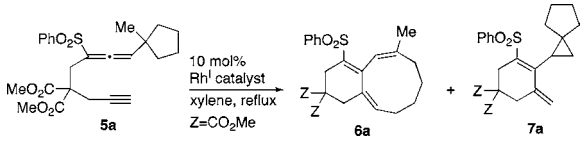
when the allenylcyclobutane-alkynes **1** (n = 2) were exposed to the Rh^I catalyst, producing the corresponding 8-membered bicyclic compounds **2** (n = 2)[12b] in high yields (Scheme 1). It is noteworthy that the simplest unactivated cyclobutanes were unexpectedly and smoothly incorporated into the 8-membered carbocycles. Production of **2** (n = 2) could tentatively be rationalized by initial formation of the rhodabicyclo[4.3.0] intermediate **3**, followed by β-C elimination,[6] which should release the strain energy (26.3 kcal/mol) of the cyclobutane,[11] giving rise to the 9-membered rhodabicyclic species **4**. Reductive elimination of **4** would then provide the final products. Since the strain energies of the normal-sized cycloalkanes, namely cyclopentane and cyclohexane, are too low (6.3 kcal/mol and ~0 kcal/mol, respectively)[11] compared to those of the small-sized ones, utilization of the former as acyclic C_5- and C_6-building blocks has never been reported to date. This study describes preliminary results for the unprecedented incorporation of cyclopentane into 9-membered carbocycles via C–C bond activation by β-C elimination[6] of the rhodabicyclo[4.3.0]-nonadiene intermediates during the Rh^I-catalyzed cycloaddition of allenylcyclopentane-alkyne substrates.

Our initial attempt was performed using the allenylcyclopentane **5a** possessing a phenysulfonyl group on the allenyl moiety for screening the reaction conditions. Treatment of **5a** with 10 mol% $[RhCl(CO)_2]_2$, which was effective for ring-opening of allenylcyclopropane **1** (n = 1),[12a] in refluxing xylene for 0.2 h surprisingly produced the desired bicyclo[7.4.0]-tridecatriene **6a** in 30% yield. In addition, the novel spiro[2.4]-heptane derivative **7a** was isolated in 38% yield (Table 1, entry 1). $[RhCl(CO)dppp]_2$, another effective catalyst for **1** (n = 1),[12a] afforded a similar result [**6a** (29%) and **7a** (45%)] (entry 2). $RhCl(dppp)_2$ was the most suitable catalyst for ring-opening of allenylcyclobutane **1** (n = 2).[12b] Thus, exposure of **5a** to 10 mol% $RhCl(dppp)_2$ resulted in the increased production of **7a** in 52% yield along with **6a** in 39% yield (entry 3). Several other catalysts, such as $RhCl(PPh_3)_3$, $[RhCl(cod)]_2$, $[RhCl(cod)]_2/P(C_6F_5)_3$,

Received: October 9, 2012
Published: November 12, 2012

dx.doi.org/10.1021/ja309830p | J. Am. Chem. Soc. 2012, 134, 19580–19583

Table 1. Rh^{I}-Catalyzed Cycloaddition of Allenylcyclopentane-alkyne 5a



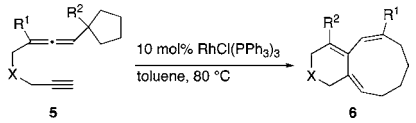
entry	catalyst	time (h)	product and yield
1	$[RhCl(CO)_2]_2$	0.2	**6a** (30%), **7a** (38%)
2	$[RhCl(CO)dppp]_2$	0.2	**6a** (29%), **7a** (45%)
3	$RhCl(dppp)_2$	0.2	**6a** (39%), **7a** (52%)
4	$RhCl(PPh_3)_3$	0.2	**6a** (73%), **7a** (16%)
5[a]	$RhCl(PPh_3)_3$	0.5	**6a** (72%), —[b]

[a]Reaction was carried out in toluene at 80 °C. [b]A mixture of **7a** and unknown compounds was obtained in small amounts.

$[RhCl(cod)]_2/P(Cy)_3$, and $[RhCl(cod)]_2$/*rac*-BINAP, with or without a silver salt were examined, but most of them furnished poor results except for $RhCl(PPh_3)_3$. Indeed, **5a** was treated with 10 mol% $RhCl(PPh_3)_3$ in xylene for 0.2 h to produce **6a** in an improved yield (73%) together with **7a** in 16% yield (entry 4). Milder conditions (heating at 80 °C in toluene for 0.5 h) gave a similar result (**6a**, 72%) (entry 5). 1,2-Dichloroethane (DCE) and 1,4-dioxane, both of which are frequently employed in rhodium-catalyzed reactions, were examined instead of toluene, but no significant improvement was observed.

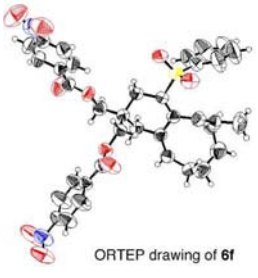
The best conditions [10 mol% $RhCl(PPh_3)_3$ in toluene at 80 °C] were applied to several allenylcyclopentanes (Table 2). We first examined the ring-closing reaction of substrates **5b**–**f** having a *gem*-disubstituent effect.[13] Treatment of the bis(phenylsulfonyl) derivative **5b** with $RhCl(PPh_3)_3$ afforded the desired bicyclo[7.4.0] product **6b** in 85% yield as the only isolated product (entry 1). Bis(MOM) compound **5c** also produced the corresponding bicyclic compound **6c** in 85% yield (entry 2). A similar result (**6d**, 78%) was obtained when the cyclic acetal derivative **5d** was exposed to the standard conditions (entry 3). Free dihydroxyl compound **5e** could be converted into bicyclic 9-membered **6e** in 51% yield (entry 4). Although a higher reaction temperature (xylene reflux) was needed, the bis(*p*-nitrobenzoyloxymethyl) compound **5f** gave **6f** in 53% yield (entry 5). X-ray analysis of **6f** unambiguously established its structure having a bicyclo[7.4.0]tridecatriene skeleton (see SI for details). The simple carbon tether analogue **5g** without the *gem*-disubstituent effect also provided the bicyclic derivative **6g** in 53% yield (entry 6). Nitrogen congener **5h** produced the corresponding aza-compound **6h** in 60% yield (entry 7). It was shown that having a phenylsulfonyl substituent on the allenyl moiety was not essential for this transformation. Thus, the ring-closing reaction of phosphonate derivative **5i** proceeded well to produce **6i** in 69% yield (entry 8). Furthermore, the ring-closing reaction of allenylcyclopentanes having alkyl substituents such as butyl (**5j**), isopropyl (**5k**), *tert*-butyl (**5l**), and benzyl groups (**5m**) on the allenyl moiety also produced the corresponding

Table 2. Formation of Bicyclo[7.4.0]tridecatrienes 6 from Allenylcyclopentane-alkynes 5



entry	substrate	R^1	R^2	X	time (h)	product[a] and yield[b]
1	**5b**	SO_2Ph	Me	$C(SO_2Ph)_2$	0.2	**6b** (85%)
2	**5c**	SO_2Ph	Me	$C(MOM)_2$	2	**6c** (85%)
3	**5d**	SO_2Ph	Me	$C(CH_2O)_2CMe_2$	2	**6d** (78%)
4	**5e**	SO_2Ph	Me	$C(CH_2OH)_2$	0.75	**6e** (51%)
5	**5f**	SO_2Ph	Me	$C(CH_2O_2CC_6H_4\text{-}NO_2\text{-}p)_2$	0.2[c,d]	**6f** (53%)
6	**5g**	SO_2Ph	Me	CH_2	4[e]	**6g** (53%)
7	**5h**	SO_2Ph	Me	NTs	0.2[e]	**6h** (60%)
8	**5i**	$P(O)(OEt)_2$	Me	$C(CO_2Me)_2$	4	**6i** (69%)
9	**5j**	^{n}Bu	Me	$C(CO_2Me)_2$	1	**6j** (71%)
10	**5k**	^{i}Pr	Me	$C(CO_2Me)_2$	1.5	**6k** (73%)
11	**5l**	^{t}Bu	Me	$C(CO_2Me)_2$	1[f]	**6l** (75%)
12	**5m**	Bn	Me	$C(CO_2Me)_2$	1.5	**6m** (58%)
13	**5n**	Ph	Me	$C(CO_2Me)_2$	1	**6n** (62%)
14	**5o**	SO_2Ph	^{n}Bu	$C(CO_2Me)_2$	3	**6o** (47%)
15	**5p**	SO_2Ph	CH_2OBn	$C(CO_2Me)_2$	20[c]	**6p** (40%)

[a]Compound **6** was isolated as a pure form, and a mixture of spiro derivative **7** and unknown compounds was detected in small amount. [b]Isolated yield. [c]Refluxed in xylene. [d]0.05 M solvent was used. [e]Refluxed in toluene (0.025 M). [f]Refluxed in toluene (0.1 M).

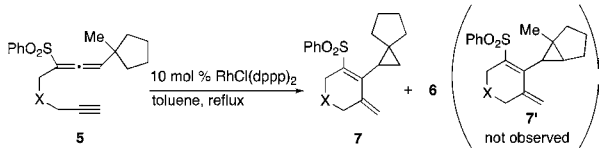

ORTEP drawing of **6f**

dx.doi.org/10.1021/ja309830p | *J. Am. Chem. Soc.* 2012, 134, 19580–19583

bicyclo[7.4.0] products **6j** (71%), **6k** (73%), **6l** (75%), and **6m** (58%), respectively (entries 9–12). In addition, the phenyl derivative **5n** was found to furnish the desired product **6n** in 62% yield (entry 13). Allenylcyclopentane derivative **5o**, possessing a butyl substituent (R^2 = ^{n}Bu) at the allenic position instead of a methyl group, required a longer reaction time (3 h), and the yield of **6o** decreased (47%) (entry 14). In addition, the benzyloxymethyl congener **5p** (R^2 = CH_2OBn) required more drastic conditions (heating at reflux in xylene for 20 h) to complete consumption of the starting material, and the bicyclic compound **6p** was obtained in a rather low yield (40%) (entry 15).

We isolated the novel spiro[2.4]heptane derivative **7a** from Rh^I-catalyzed cycloaddition of **5a** (Table 1). In particular, **7a** was obtained in 52% yield as a major product when treated with $RhCl(dppp)_2$. To improve the chemical yield of **7a**, we reinvestigated this reaction and found that a lower reaction temperature (heated at reflux in toluene) is enough to give **7a** in a satisfactory yield. Indeed, **7a** was obtained in 81% yield along with **6a** in 5% yield (Table 3, entry 1). Several other

Table 3. Formation of Spiro[2.4]heptane Derivatives 7 from Allenylcyclopentane-alkynes 5



5 7

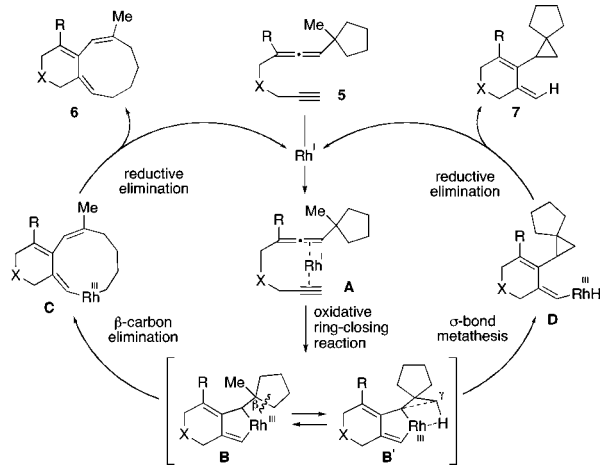
entry	substrate	X	time (h)	product and yield[a]
1	**5a**	$C(CO_2Me)_2$	1.5	**7a** (81%), **6a** (5%)
2	**5e**	$C(CH_2OH)_2$	0.5	**7e** (78%)
3	**5f**	$C(CH_2O_2CC_6H_4\text{-}NO_2\text{-}p)_2$	1	**7f** (76%), **6f** (5%)
4	**5q**	$C(CH_2O_2CC_6H_4\text{-}Cl\text{-}p)_2$	3.5	**7q** (60%)
5	**5h**	NTs	1	**7h** (50%), **6h**[b]

[a]Isolated yield. [b]Trace.

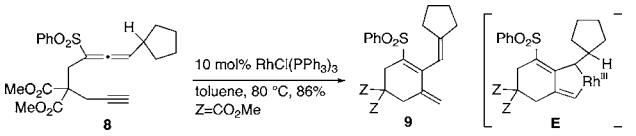
allenylcyclopentane-alkynes were examined to ascertain the generality of the formation of the spiro[2.4]heptane skeleton. Upon exposure to the standard conditions, **5e**, having two free hydroxyl groups, smoothly underwent the ring-closing reaction to produce **7e**[14] in 78% yield (entry 2). Bis(*p*-nitrobenzoyloxymethyl) derivative **5f** was heated at reflux in toluene in the presence of $RhCl(dppp)_2$ for 1 h to afford the spiro[2.4]heptane **7f** in 76% yield along with **6f** in 5% yield (entry 3). Bis(*p*-chlorobenzoyloxymethyl) compound **5q** provided **7q** in 60% yield as the sole isolated product (entry 4). Nitrogen-containing substrate **5h** under similar conditions produced **7h** in a lower yield (50%) (entry 5). Site-selective Cγ–H bond activation of the methyl group rather than the methylene moiety of the cyclopentane framework led to exclusive formation of **7** instead of **7′**, although the reasonable explanation is still uncertain. Thus, it may be concluded that transformation of the allenylcyclopentane-alkynes **5** into spiro[2.4]heptane derivatives **7** consistently occurred when treated with $RhCl(dppp)_2$.

Formation of the [7+2] product **6** is tentatively rationalized on the basis of the proposed mechanism for the ring cleavage of the allenylcyclobutane.[12b] Initial coordination of **5** with Rh^I would occur between an allenic distal double bond and an alkyne to form the intermediate **A**, which should immediately collapse to the rhodabicyclo[4.3.0] intermediate **B** via the oxidative ring-closing reaction (Scheme 2). This intermediate **B** would undergo

Scheme 2. Plausible Mechanisms

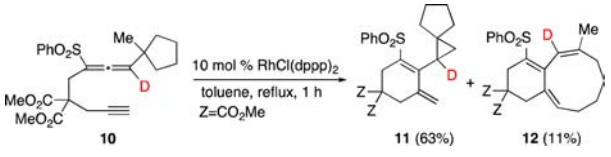


Scheme 3. Rh^I-Catalyzed Cycloisomerization of 8



β-C elimination,[6] presumably assisted by release of the ring strain of the cyclopentane (6.3 kcal/mol),[11] resulting in formation of the 10-membered bicyclic rhodacycle **C**. Subsequent reductive elimination of **C** would give the final product **6**. The intermediacy of rhodabicyclo[4.3.0] intermediate **B** is strongly supported by the following experimental result. Upon exposure to the standard conditions, substrate **8**, having a hydrogen at the allenic position, afforded the monocyclic product **9** in 86% yield (Scheme 3). Formation of **9** could be well rationalized in terms of β-hydride elimination[15] of intermediate **E**, which possesses the common rhodabicyclo[4.3.0] intermediate of **B**. As part of our ongoing program, Oonishi and Sato[16] have very recently reported similar cyclopropanation of allenynes having *tert*-butyl group at the allenic terminus. Based on their proposed mechanism, the plausible mechanism for the production of the spiro[2.4]heptane derivatives **7** from the common rhodabicyclo[4.3.0] intermediate **B** could be tentatively considered as follows. The Cγ–H[17] bond of **B** would be activated with the aid of Rh^{III} when the C–H bond of the methyl group is placed on the same plane as the C–Rh^{III} bond (**B′**) (Scheme 2). A type of σ-bond metathesis[17,18] would then occur between the activated C–H bond and C–Rh^{III} bonds, ending with the formation of the 3-membered intermediate **D**, which should collapse to the final product **7**. Finally, an experiment with deuterated substrate **10** was performed in order to obtain some information on the mechanism for the formation of **7** (Scheme 4). A solution of **10** in toluene in the presence of a catalytic amount of $RhCl(dppp)_2$ was heated at reflux for 1 h to afford the spiro[2.4]heptane

Scheme 4. Deuterium-Labeling Experiment of Allenylcyclopentane-Alkynes 10



dx.doi.org/10.1021/ja309830p | J. Am. Chem. Soc. 2012, 134, 19580–19583

derivative **11** and the 9-membered compound **12** in 63% and 11% yields, respectively. It became apparent that deuterium was exclusively incorporated at the allylic position (on the cyclopropane ring) of **11**. This result might support the mechanism depicted in Scheme 2.

In summary, we have succeeded in the unprecedented C−C bond cleavage of the simple unactivated cyclopentane ring. The *in situ* generated 8-rhodabicyclo[4.3.0]nona-1,6-diene intermediate having a cyclopentane at the C_9-position underwent [7+2] cycloaddition through Cβ−Cγ bond cleavage (β-C elimination) to produce the bicyclo[7.4.0]tridecatriene derivatives in good yields. In addition, by changing the rhodium catalyst, the same 8-rhodabicyclo[4.3.0]nona-1,6-diene intermediate produced the novel spiro[2.4]heptane skeleton via a Cγ−H bond activation process in a site-selective manner. These results should provide new insights into the chemistry of C_{sp^3}−C_{sp^3} as well as C_{sp^3}−H bond[19] activation. Further studies regarding these two novel aspects, the C−C and C−H bond activations, are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data (PDF), and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are thankful.

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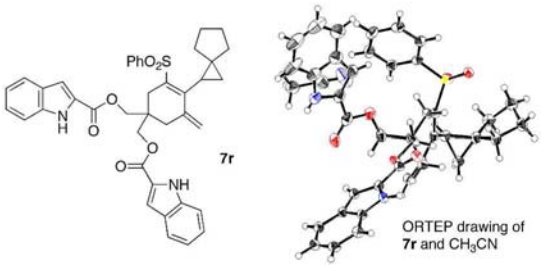

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