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Rhodium-Catalyzed Intermolecular [2 + 2] Cycloaddition of Terminal Alkynes with Electron-Deficient Alkenes

Kazunori Sakai, Takuya Kochi, and Fumitoshi Kakiuchi*

Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan

kakiuchi@chem.keio.ac.jp

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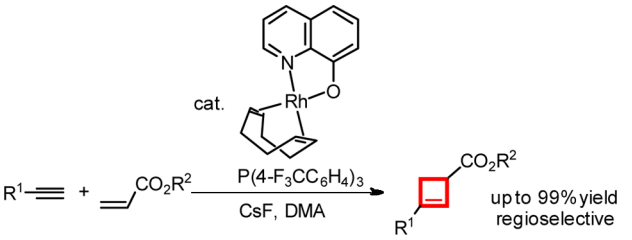
ABSTRACT



The first catalytic intermolecular [2 + 2] cycloaddition of terminal alkynes with electron-deficient alkenes is reported. The reaction proceeds with an 8-quinolinolato rhodium/phosphine catalyst system to give cyclobutenes from various substrates having polar functional groups in high yields with complete regioselectivity.

Cyclobutenes are versatile building blocks in organic synthesis and have been used as key intermediates for the synthesis of natural products and bioactive compounds.[1] The [2 + 2] cycloaddition of alkynes with alkenes can be regarded as one of the most straightforward methods to access cyclobutene structures. Concerted [2 + 2] cycloaddition of alkynes with alkenes needs photoirradiation conditions based on the Woodward–Hoffmann rules, but these reactions often suffer from low yields of cyclobutene products and formation of a mixture of regioisomers.[2,3]

The use of transition-metal catalysts has been investigated by many researchers to develop more practical intermolecular [2 + 2] cycloadditions of alkynes with alkenes,

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(3) For limited sets of substrates, thermal [2 + 2] cycloaddition of alkynes with alkenes can proceed. See ref 2a.

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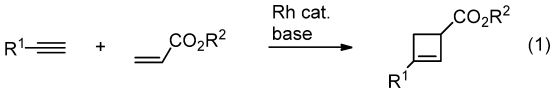
but the scope of such reactions is still limited. Most of the reported examples require activated substrates such as alkynes directly attached to heteroatoms[4] or ester groups,[5] or ring-strained alkenes such as norbornene derivatives.[6] In contrast, there have been much fewer examples reported for the [2 + 2] cycloadditions between nonactivated alkynes and unstrained alkenes.[7] Concerning the [2 + 2] cycloaddition of internal alkynes, Hilt et al. developed a cycloaddition of internal alkynes with monocyclic alkenes,[7a] while Baba et al. reported a Rh-catalyzed cycloaddition of diphenyl acetylene with electron-deficient alkenes.[7b] Very recently, Ogoshi et al. also reported the cyclobutene formation from internal conjugate enynes and electron-deficient alkenes.[7c] The use of terminal alkynes in the metal-catalyzed [2 + 2] cycloaddition with alkenes has met with less success. Echavarren et al. reported the [2 + 2] cycloaddition of terminal alkynes with styrene and aliphatic alkenes using sterically hindered cationic gold catalysts.[8a] Recently, Hashmi et al. also reported gold-catalyzed reaction of 1,2-diethynylbenzenes with aliphatic alkenes.[8b] However, there has been no metal-catalyzed [2 + 2] cycloaddition between simple terminal alkynes with electron-deficient alkenes.

Herein we describe the first catalytic intermolecular [2 + 2] cycloaddition of simple terminal alkynes with electron-deficient alkenes (eq 1). The reaction was catalyzed by a combination of Rh(Q)(cod) (Q = 8-quinolinolato) with a phosphine. The cycloaddition proceeds with complete regioselectivity to form a bond between the internal carbon of the terminal alkyne and the β-carbon of the acrylates.

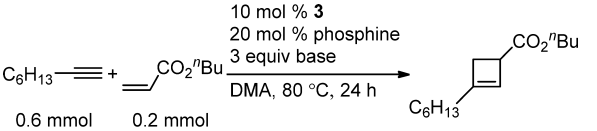


(1)

Our research group has been studying the catalytic activity of 8-quinolinolato rhodium complexes and developed catalytic *anti*-Markovnikov additions of alcohols[9a] and secondary amines[9b] to terminal alkynes. In the course of our research on the reactivity of the 8-quinolinolato rhodium complexes, it was found that the reaction between 1-octyne (**1a**) and *n*-butyl acrylate (**2a**) in DMA using 10 mol % Rh(Q)(cod) (**3**), 20 mol % PPh_3, and 3 equiv of CsF gave cyclobutene product **4aa**, albeit in low yield (Table 1, entry 1).[10] Catalytic activities of other Rh and Ru complexes were examined but resulted in < 5% yield of **4aa**.[11] Various phosphines were then screened for the cycloaddition. While electron-rich triarylphosphines were ineffective (entries 2 and 3), higher yields were obtained with triarylphosphines bearing electron-withdrawing groups (entries 4–6). Particularly, the use of P(4-$F_3CC_6H_4)_3$ provided the product in 71% yield. Attempts to use other less electron-donating phosphorus ligands such as $PPh_2(C_6F_5)$ and $P(OMe)_3$ were not successful (entries 7 and 8). Further optimization of the reaction conditions revealed that an increase of the amount of DMA to 1.5 mL improved the yield to 97% (entry 9). The use of an appropriate base was important for obtaining high yields.[11] While $CsHCO_3$ and Cs_2CO_3 gave **4aa** in lower yields (entries 10 and 11), the reactions did not proceed when CsCl or KF was used as a base (entries 12 and 13). DBU was also found to promote the reaction to afford **4aa** in 36% yield (entry 14). It should be noted that **3**, P(4-$F_3CC_6H_4)_3$, and CsF are all necessary for the formation of **4aa**, and if any one of them was not added, the cycloaddition did not proceed (entries 15–17).

Various aliphatic terminal alkynes were applicable for the [2 + 2] cycloaddition, and in all cases the reaction proceeded with complete regioselectivity (Table 2). When 1-octyne (**1a**), 3-cyclohexyl-1-propyne (**1b**), and cyclohexylacetylene (**1c**) were reacted with **2a**, cyclobutenes **4aa**–**4ca** were isolated in nearly quantitative yields (entries 1–3). The reaction can also be performed with a substrate having various functional groups. The reactions of alkynes bearing ester and nitrile groups (**1d** and **1e**) gave the corresponding cyclobutenes **4da** and **4ea** in 73% and 94% yields, respectively (entries 4 and 5). The THP-protected alcohol moiety of alkyne **1f** also tolerated the reaction to give product **4fa** in 71% yield (entry 6). Methylpropargyl ether (**1g**) can also be employed as a substrate for the cycloaddition, and a 50% yield of cyclobutene **4ga** was obtained (entry 7). Internal alkynes, 4-octyne and 1-phenyl-1-butyne, were also

Table 1. Optimization of [2 + 2] Cycloaddition of **1a** with **2a**[a]



0.6 mmol **1a** 0.2 mmol **2a** **4aa**

entry	phosphine	DMA (mL)	base	yield of **4aa**[b]
1	PPh_3	0.6	CsF	14%
2	P(4-$MeOC_6H_4)_3$	0.6	CsF	13%
3	P(4-$MeC_6H_4)_3$	0.6	CsF	15%
4	P(4-$FC_6H_4)_3$	0.6	CsF	51%
5	P(4-$F_3CC_6H_4)_3$	0.6	CsF	71%
6	P(3-$FC_6H_4)_3$	0.6	CsF	43%
7	$PPh_2(C_6F_5)$	0.6	CsF	nd[c]
8	$P(OMe)_3$	0.6	CsF	nd[c]
9	P(4-$F_3CC_6H_4)_3$	1.5	CsF	97%
10	P(4-$F_3CC_6H_4)_3$	1.5	Cs_2CO_3	69%
11	P(4-$F_3CC_6H_4)_3$	1.5	$CsHCO_3$	34%
12	P(4-$F_3CC_6H_4)_3$	1.5	CsCl	nd[c]
13	P(4-$F_3CC_6H_4)_3$	1.5	KF	nd[c]
14	P(4-$F_3CC_6H_4)_3$	1.5	DBU	36%
15	P(4-$F_3CC_6H_4)_3$	1.5	none	nd[c]
16	none	1.5	CsF	nd[c]
17[d]	P(4-$F_3CC_6H_4)_3$	1.5	CsF	nd[c]

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), **3** (0.02 mmol), phosphine (0.04 mmol), base (0.6 mmol) in DMA, 80 °C, 24 h. [b] ^1H NMR yield. [c] Not detected. [d] Performed without catalyst **3**.

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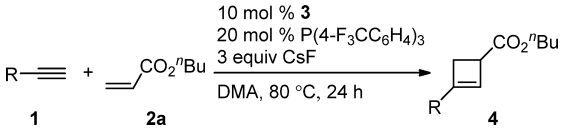
(10) Dimers and trimers of **1a** were formed as byproducts.

(11) See the Supporting Information.

Table 2. [2 + 2] Cycloaddition of Various Aliphatic Terminal Alkynes with **2a**[a]

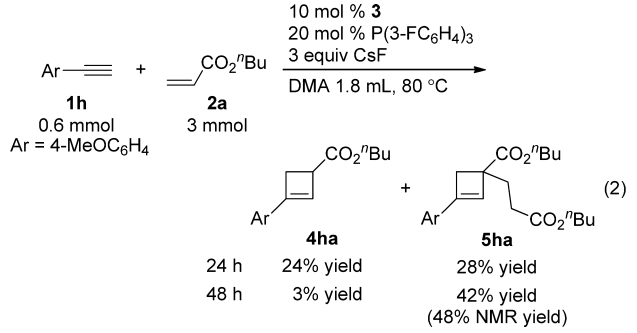


entry	1	R	4	yield[b]
1	**1a**	C_6H_{13}	**4aa**	99%
2	**1b**	$CyCH_2$	**4ba**	99%
3	**1c**	Cy	**4ca**	99%
4	**1d**	$MeO_2C(CH_2)_3$	**4da**	73%
5	**1e**	$NC(CH_2)_3$	**4ea**	94%
6	**1f**	$THPO(CH_2)_3$	**4fa**	71%
7	**1g**	$MeOCH_2$	**4ga**	50%

[a] Reaction conditions: **1** (1.8 mmol), **2a** (0.6 mmol), **3** (0.06 mmol), $P(4\text{-}F_3CC_6H_4)_3$ (0.12 mmol), CsF (1.8 mmol) in DMA (4.5 mL), 80 °C, 24 h. [b] Isolated yield.

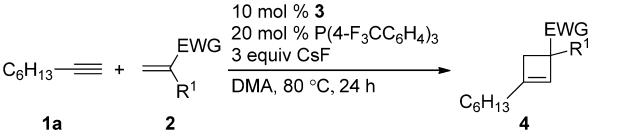
investigated as substrates, but the corresponding cyclobutene products were not detected.

The reaction of arylacetylenes was found to be more complicated, and in addition to cyclobutenes, 1:2 addition products of alkynes and acrylates were observed. For example, when 4-ethynylanisole (**1h**) was reacted with an excess of **2a** in the presence of **3**, $P(3\text{-}FC_6H_4)_3$, and CsF for 24 h, 2:1 addition product **5ha** was formed in 28% yield along with a 24% yield of **4ha** (eq 2).[12] When the reaction was conducted for 48 h, **4ha** and **5ha** were obtained in 3% and 42% yields, respectively, and this result suggests that **5ha** was formed by Michael addition of the enolate of **4ha** with another equivalent of **2a**.[13]



The [2 + 2] cycloaddition was also examined with various acrylates (Table 3). While the reaction of methyl acrylate (**2b**) with **1a** proceeded in 84% yield, when ethyl acrylate (**2c**) was used, product **4ac** was obtained in 96% yield. The reaction of **1a** with benzyl acrylate (**2d**) also gave cyclobutene **4ad** in 90% yield. Acrylates derived from secondary and tertiary alcohols were also applicable, and the cycloaddition with isopropyl and *tert*-butyl acrylates (**2e** and **2f**) provided cyclobutenes **4ae** and **4af** in 99% and 81% yields, respectively (entries 4 and 5). However, the reaction of **1a** with phenyl acrylate (**2g**) did not give the [2 + 2] cycloadduct probably due to the high leaving ability of the phenoxide ion (entry 6). Methyl methacrylate (**2h**) and acrylonitrile (**2i**) were also examined as substrates under the standard conditions, and the corresponding cycloaddition products, **4ah** and **4ai**, were produced in 26% and 28% yields, respectively (entries 7 and 8). The reaction with methylenemalonate **4aj** did not provide any cyclobutene product (entry 9).

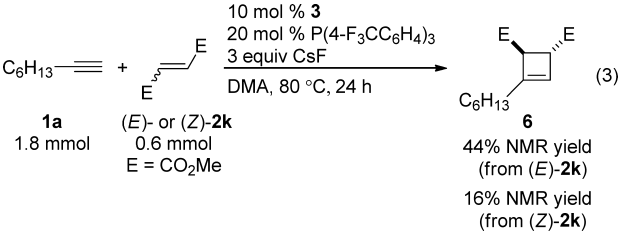
Table 3. [2 + 2] Cycloaddition of **1a** with Electron-Deficient Alkenes[a]



entry	2	EWG	R^1	4	yield[b]
1	**2b**	CO_2Me	H	**4ab**	84%
2	**2c**	CO_2Et	H	**4ac**	96%
3	**2d**	CO_2Bn	H	**4ad**	90%
4	**2e**	$CO_2{}^iPr$	H	**4ae**	99%
5	**2f**	$CO_2{}^tBu$	H	**4af**	81%
6	**2g**	CO_2Ph	H	**4ag**	nd
7	**2h**	CO_2Me	Me	**4ah**	26%
8	**2i**	CN	H	**4ai**	28%
9	**2j**	$CO_2{}^tBu$	$CO_2{}^tBu$	**4aj**	nd

[a] Reaction conditions: **1a** (1.8 mmol), **2** (0.6 mmol), **3** (0.06 mmol), $P(4\text{-}F_3CC_6H_4)_3$ (0.12 mmol), CsF (1.8 mmol) in DMA (4.5 mL), 80 °C, 24 h. [b] Isolated yield.

We also examined whether alkenes having a substituent at the β-position can be used for the cycloaddition. While the reaction of **1a** with (*E*)-ethyl crotonate gave no [2 + 2] cycloaddition product, the reaction with fumarate (*E*)-**2k** gave **6** in 44% NMR yield (eq 3). When maleate (*Z*)-**2k** was used, cyclobutene **6** was also obtained in 16% NMR yield. Product **6** cannot be formed by concerted [2 + 2] addition of **1a** with (*Z*)-**2k**, but it is not clear whether the cycloaddition product was formed via the reaction of **1a** with (*Z*)-**2k** or (*E*)-**2k**, because *E*/*Z* isomerization of **2k** can take place in the presence of **3**, $P(4\text{-}F_3CC_6H_4)_3$, and CsF.[11]



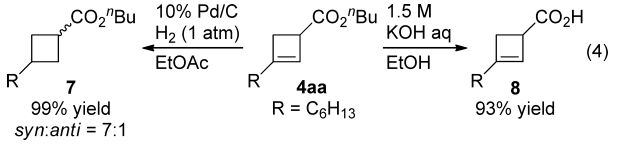
Cyclobutene product **4aa** can be transformed into cyclobutane **7** by simple hydrogenation using a Pd/C-catalyst (eq 4). Hydrolysis of the ester functional group can also be

(12) When **2a** was reacted with excess **1h** in the presence of **3**, $P(4\text{-}F_3CC_6H_4)_3$, and CsF for 24 h, only a trace of **4ha** was detected.

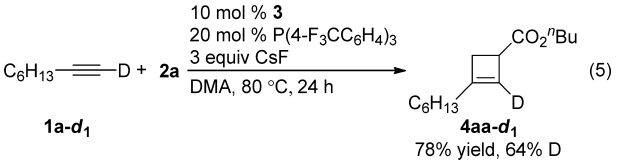
(13) The reaction of **4ha** with **2a** in the presence of $P(3\text{-}FC_6H_4)_3$ and CsF in DMA at 80 °C for 24 h gave **5ha** in ca. 30% NMR yield.

(14) The NMR study using DMF-d_7 suggests that the incomplete deuterium incorporation is mainly due to an H/D exchange between the alkyne and adventitious water; see: Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180.

performed under basic conditions to give carboxylic acid **8** while maintaining the cyclobutene core.



To gain an understanding of the reaction mechanism, a deuterium-labeling experiment was carried out (eq 5). When the reaction of **1a-d_1** with *n*-butyl acrylate (**2a**) was performed, cyclobutene product **4aa-d_1** was obtained in 78% isolated yield with the deuterium only incorporated at the vinylic position. The moderate incorporation of deuterium (64%) may be attributed to the presence of a trace amount of H_2O in the reaction system.[14]



The mechanism of the [2 + 2] cycloaddition of terminal alkynes with electron-deficient alkenes is unclear at this point. However, based on the results that deuterium was selectively incorporated on the vinylic carbon and no [2+ 2] cycloaddition product from internal alkynes was observed, we propose two possible mechanisms depicted in Figure 1. Oxidative addition of an sp C−H bond in a terminal alkyne to rhodium complex **I** gives alkynyl(hydrido)-rhodium species **II**. The base is considered to promote the reaction by coordination (**IIIa**) or deprotonation of the hydride ligand (**IIIb**) to make the alkynyl metal species more nucleophilic. Subsequent nucleophilic attack of the β-carbon of rhodium acetylide on the electron-deficient alkene occurs to form rhodium vinylidene **IVa** or **IVb**.[15,16] The newly generated carbanion then attacks the α-carbon of the vinylidene ligand to form the four-membered ring.

(15) For reviews including the addition of alkynyl β-carbon to electrophiles to form vinylidene complexes, see: (a) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (b) Cadierno, V.; Gamasa, M. P.; Gimeno, J. *Coord. Chem. Rev.* **2004**, *248*, 1627. For recent examples, see: (c) Chen, K.-H.; Feng, Y. J.; Ma, H.-W.; Lin, Y.-C.; Liu, Y.-H.; Kuo, T.-S. *Organometallics* **2010**, *29*, 6829. (d) Nakaya, R.; Yasuda, S.; Yorimitsu, H.; Ohshima, K. *Chem.—Eur. J.* **2011**, *17*, 8559. (e) Boone, M. P.; Stephan, D. W. *Organometallics* **2011**, *30*, 5537.

(16) For catalytic reactions involving the nucleophilic attack of an alkynyl β-carbon in alkynylmetal species, see: (a) Joo, J. M.; Yuan, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 14818. (b) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644. (c) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. (d) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555. (e) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (f) Fukumoto, Y.; Daijo, M.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 8762. See ref 8b.

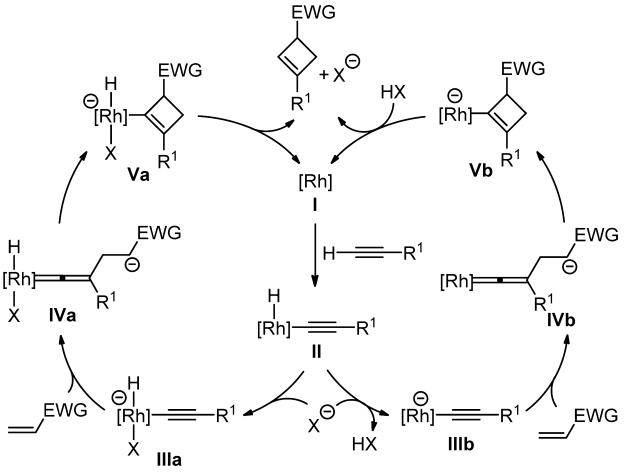


Figure 1. Proposed mechanisms of the [2 + 2] cycloaddition.

Finally, the cyclobutene product is released by reductive elimination from **Va** or protonation of **Vb**. The electron-rich nature of the 8-quinolinolato rhodium complex may facilitate the oxidative addition of terminal alkynes and the nucleophilic addition of alkynylrhodium species and stabilize the rhodium vinylidene species.

In summary, we developed the first catalytic intermolecular [2 + 2] cycloaddition of terminal alkynes with electron-deficient alkenes. The 8-quinolinolato rhodium/phosphine catalyst promotes the reaction in the presence of bases to give cyclobutenes in high yields. This reaction provides a convenient, straightforward route to synthesize cyclobutenes, which are not easily accessible by other methods. The cycloaddition is completely regioselective, and various combinations of terminal alkynes and acrylates can be used for the cycloaddition. Extension of the scope of the electrophiles and elucidation of the reaction mechanism are now underway.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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