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Rhodium-Catalyzed Three-Component Reaction between Silylacetylene and Two Ketenes Leading to 1,3-Enynes Bearing a Carboxylic Ester Group via Double Insertion of Ketenes

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ABSTRACT

Double insertion of ketene to alkyne C-H bond

The first cross-reaction between a terminal silylacetylene and two ketene molecules leading to 1,3-enynes bearing a carboxylic ester group via double insertion of ketenes is achieved using a cationic rhodium complex catalyst. This reaction is applicable for various symmetrical and unsymmetrical ketenes with good stereoselectivities.

Ketenes are highly reactive and important molecules in the field of organic synthesis.[1] In transition-metal complex chemistry, many metal complexes that coordinate ketenes by the η^2-coordination mode have been reported.[2] However, applications of ketenes to catalytic transformation reactions that proceed without decarbonylation of the ketene moiety using transition-metal catalysts have rarely been reported,[3] because transition-metal complexes of η^2-ketenes often undergo decarbonylation of the ketene fragment, producing unreactive carbonyl complexes.[4] Recently, a few examples of linear coupling and cycloaddition reactions of ketenes with alkynes have been reported.[3h,i] However, examples of transition-metal catalyzed reactions have been limited to a two-component reaction of one molecule of ketene with a reaction partner. A three-component cross-reaction via double insertion of two

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(1) Patai, S. *The Chemistry of Functional Groups: The Chemistry of Ketenes, Allenes, and Related Compounds Part 1*; John Wiley & Sons: New York, NY, USA, 1980.

(2) For recent examples of transition-metal ketene complexes, see: (a) Lo, H. C.; Grotjahn, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 2958. (b) Bleuel, E.; Laubender, M.; Weberndörfer, B.; Werner, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 156. (c) Grotjahn, D. B.; Hoerter, J. M.; Hubbard, J. L. *Organometallics* **1999**, *18*, 5614. (d) Grotjahn, D. B.; Bikzhanova, G. A.; Collins, L. S. B.; Concolino, T.; Lam, K.-C.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 5222. (e) Grotjahn, D. B.; Collins, L. S. B.; Wolpert, M.; Bikzhanova, G. A.; Lo, H. C.; Combs, D.; Hubbard, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8260. (f) Werner, H.; Bleuel, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 145. (g) Grotjahn, D. B.; Hoerter, J. M.; Hubbard, J. H. *J. Am. Chem. Soc.* **2004**, *126*, 8866. (h) Tsurugi, H.; Ohno, T.; Kanayama, T.; Arteaga-Müller, R. A.; Mashima, K. *Organometallics* **2009**, *28*, 1950.

(3) (a) Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978**, 535. (b) Yamazaki, H.; Hong, P. *J. Mol. Catal.* **1983**, *21*, 133. (c) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 3697. (d) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5143. (e) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1539. (f) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1695. (g) Mitsudo, T.; Kadokura, M.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 3186. (h) Kondo, T.; Niimi, M.; Yoshida, Y.; Wada, K.; Mitsudo, T.; Kimura, Y.; Toshimitsu, A. *Molecules* **2010**, *15*, 4189. (i) Kumar, P.; Troast, D. M.; Cella, R.; Louie, J. *J. Am. Chem. Soc.* **2011**, *133*, 7719.

(4) Ketene ligands of an η^2-transition-metal complex have a tendency to undergo decomposition. For recent examples, see: (a) Hoffman, P.; Perez-Moya, L. A.; Steigelman, O.; Riede, J. *Organometallics* **1992**, *11*, 1167. (b) Grotjahn, D. B.; Bikzhanova, G. A.; Collins, L. S. B.; Concolino, T.; Lam, K.-C.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 5222. (c) Urtel, H.; Bikzhanova, G. A.; Grotjahn, D. B.; Hofmann, P. *Organometallics* **2001**, *20*, 3938. (d) Goll, J. M.; Fillion, E. *Organometallics* **2008**, *27*, 3622. (e) Kondo, T.; Tokoro, Y.; Ura, Y.; Wada, K.; Mitsudo, T. *ChemCatChem* **2009**, *122*, 5222.

10.1021/ol301897h

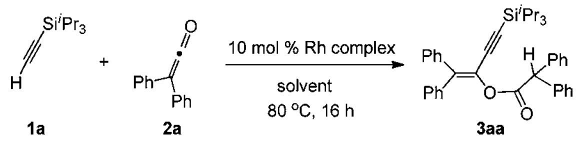
ketenes has yet to be developed. Although highly reactive ketenes easily undergo homodimerization to give β-lactones,[5] a selective multicomponent reaction with other unsaturated compounds that introduce two ketene molecules via double insertion is challenging due to the need to control the reactivity of the ketene molecules.

We have recently reported highly selective cross-trimerization of three alkynes, between two alkynes and one alkene, using triisopropylsilylacetylene as the terminal alkyne in the presence of a nickel catalyst.[6] The sterically hindered terminal silylacetylene plays an important role in the selective three-component reaction. Herein, we describe a selective three-component reaction between terminal silylacetylene and two ketenes using a cationic rhodium complex catalyst leading to a 1,3-enyne bearing a carboxylic ester group with high stereoselectivity.[7] This report is the first example of a transition-metal catalyzed three-component reaction involving two ketenes through double insertion of ketene molecules.

First, rhodium catalysts and solvents were screened in the three-component reaction of triisopropylsilylacetylene **1a** and diphenylketene **2a** (2.2 equiv), as shown in Table 1. Using the cationic rhodium catalyst $[Rh(cod)_2]BF_4$ (10 mol %) in dioxane solution, the selective three-component reaction proceeded smoothly at 80 °C to afford carboxylic ester substituted 1,3-enyne **3aa** in high yield (entry 1). The reaction also proceeded in the same yield by the use of a 5 mol % $[Rh(cod)_2]BF_4$ catalyst loading (entry 2). The yield of **3aa** was decreased with a 2 mol % catalyst loading (entry 3). Using other cationic rhodium complexes bearing PF_6 or OTf anions, the product **3aa** was obtained in slightly lower yields than that obtained using $[Rh(cod)_2]BF_4$ (entries 4 and 5). Although the chloride-bridging neutral rhodium complex was not effective in this reaction, a neutral rhodium complex bearing an acetylacetonate ligand participated in this reaction to afford the product **3aa** in good yield (entries 6 and 7). When the reaction was performed using $[Rh(cod)_2]BF_4$ in 1,2-dichloroethane solvent, product **3aa** was also obtained in high yield (entry 8). The reaction conducted in other polar or aromatic solvents such as acetonitrile, DMF, and toluene resulted in low yields of **3aa** (entries 9−11). On the basis of this screen of rhodium catalysts and reaction conditions, the highest yield for the formation of three-component product **3aa** was achieved using $[Rh(cod)_2]BF_4$ in dioxane solution. In comparison, **3aa** was not obtained using a $Ni(cod)_2$ or $Ni(cod)_2/P^nPr_3$ catalyst, which were previously shown to be effective for the alkyne cross-trimerization between **1a** and two molecules of internal alkynes.[6]

Using the optimized catalytic system and reaction conditions, the three-component reaction was next examined using various types of terminal alkynes as shown in Table 2. When the reaction was conducted using other bulky silylacetylene compounds such as *tert*-butyldimethylsilylacetylene (**1b**), triethylsilylacetylene (**1c**), and trimethylsilylacetylene (**1d**) under these conditions, the corresponding product **3** was also obtained, albeit the yield was lower than that using triisopropylsilylacetylene (entries 2−4). The bulky propargylic silyl ether **1e**, whose masking group is readily removable as well as the silyl group, also participated in this reaction to afford the corresponding product **3ea** in good yield (entry 5). However, other aliphatic and aromatic alkynes such as 1-hexyne and phenylacetylene did not participate in this reaction (entries 6 and 7). Other bulky alkylacetylenes such as 3,3,-dimethylbut-1-yne also did not participate in this reaction.

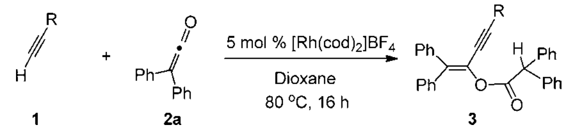
Table 1. Effect of Rhodium Complex Catalysts and Solvents[a]



entry	rhodium catalyst	solvent	yield (%)[b]
1	$[Rh(cod)_2]BF_4$	dioxane	92
2[d]	$[Rh(cod)_2]BF_4$	dioxane	92 (88)[c]
3[e]	$[Rh(cod)_2]BF_4$	dioxane	53
4	$[Rh(cod)_2]PF_6$	dioxane	64
5	$[Rh(cod)_2]OTf$	dioxane	84
6[d]	$[RhCl(cod)]_2$	dioxane	4
7	Rh(acac)(cod)	dioxane	72
8	$[Rh(cod)_2]BF_4$	$(CH_2Cl)_2$	90
9	$[Rh(cod)_2]BF_4$	CH_3CN	13
10	$[Rh(cod)_2]BF_4$	DMF	trace
11	$[Rh(cod)_2]BF_4$	toluene	24

[a] Reaction conditions: rhodium complex (0.05 mmol), **1a** (0.5 mmol), **2a** (1.1 mmol), and dioxane (3 mL) were employed. [b] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] 5 mol % of rhodium catalyst was used. [e] 2 mol % of rhodium catalyst was used.

Table 2. Rhodium-Catalyzed Three-Component Reaction between Terminal Alkyne **1** and Diphenylketene **2a**[a]



entry	1	R	3	yield (%)[b]
1	**1a**	Si^iPr_3	**3aa**	88
2	**1b**	Si^tBuMe_2	**3ba**	72
3	**1c**	$SiEt_3$	**3ca**	74
4	**1d**	$SiMe_3$	**3da**	50
5	**1e**	$C^iPr_2OSiMe_3$	**3ea**	70
6	**1f**	$^nC_6H_{13}$	**3fa**	0
7	**1g**	Ph	**3ga**	0

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (0.025 mmol), **1** (0.5 mmol), **2a** (1.1 mmol), and dioxane (3 mL) were employed. [b] Isolated yield.

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(5) Tidwell, T. T. *Ketenes*; Wiley-Interscience: New York, 1995.

(6) (a) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (b) Ogata, K.; Sugasawa, J.; Fukuzawa, S.-i. *Angew. Chem., Int. Ed.* **2009**, *48*, 6078. (c) Ogata, K.; Sugasawa, J.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 148. (d) Ogata, K.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2011**, *13*, 122.

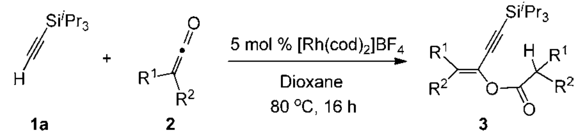
(7) A 1,3-enyne unit bearing a carboxylic ester group was found in marine natural products:McPhail, K. L.; France, D.; Cornell-Kennon, S.; Gerwick, W. H. *J. Nat. Prod.* **2004**, *67*, 1010.

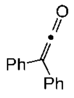
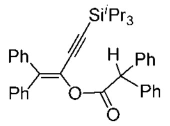
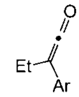
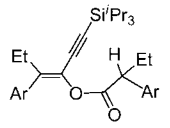
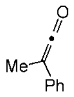
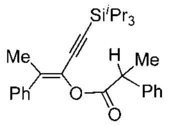
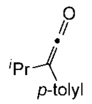
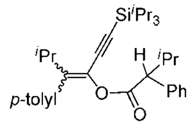
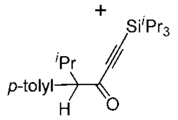
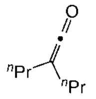
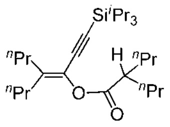
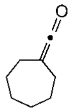
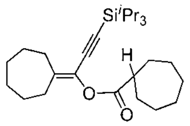
After screening the terminal alkynes, we next examined the scope for the ketene partner (Table 3). The unsymmetric ketene bearing ethyl and phenyl groups participated in this reaction to afford product **3ab** in high yield with good *Z*-selectivity in the double bond (entry 2).[8] The use of unsymmetric ketenes bearing *p*-substituted aryl groups such as electron-donating (methyl and methoxy) or electron-withdrawing (fluoro and chloro) substituents also afforded product **3** in good to high yields with good stereoselectivities (entries 2–6). The reaction with a ketene bearing a methyl group **2g** also proceeded to give the corresponding product **2ag** with good stereoselectivity (entry 7). However, upon replacement of either the ethyl or methyl group with an isopropyl group, the corresponding three-component product **3ah** was formed in low yield, and two-component product **4ah** was also obtained (entry 8). Reactions of **2i** and **2j**, which possess two aliphatic groups such as *n*-alkyl and cyclic alkyl groups, also proceeded to form the products **3ai** and **3aj** (entries 9 and 10).

To confirm the structure by X-ray analysis and demonstrate the synthetic utility, products **3aa** and **3af** were subjected to click chemistry, which has been widely used as a method for the synthesis of 1,2,3-triazoles.[9] The silyl groups of **3aa** and **3af** were readily removed by treatment with tetrabutylammonium fluoride (TBAF), and the resulting crude products could participate in a click reaction with ferrocenylmethyl azide to afford 4-substituted 1,2,3-triazoles **5aa** and **5af** (*Z*/*E* = 85:15), respectively, in the presence of $CuSO_4$/Na-L-ascorbate (Scheme 1). In the case of **5af**, the two stereoisomers (*Z*/*E*) could be separated by recrystallization.[10] Products **5aa** and **5af-E** were subjected to X-ray diffraction, and stereostructures for the reaction using an unsymmetrical ketene were revealed (see Supporting Information).[11]

To examine the reaction mechanism for the three-component reaction, we carried out the following experiments. Since the reaction between triisopropylsilylacetylene and diketene (*β*-lactone), which was prepared by catalytic ketene dimerization,[12] did not proceed, the possibility of the mechanism occurring via dimerization of the ketene, followed by ring-opening hydroalkynylation, could be ruled out.[13] In addition to this experiment, the reaction using rhodium acetylide complex **6**, which was prepared by the reaction of $[RhCl(cod)]_2$ with 2 equiv of lithium triisopropylsilylacetylide, was carried out (Scheme 2).[14]

Table 3. Rhodium-Catalyzed Three-Component Reaction between Triisopropylsilylacetylene **1a** and Ketenes **2**[a]



entry	2	product (% yield)[b]
1	 **2a**	 **3aa** (88)
		
2	**2b** (Ar = Ph)	**3ab** (88) (89:11)[c]
3	**2c** (Ar = *p*-$CH_3C_6H_4$)	**3ac** (84) (90:10)[c]
4	**2d** (Ar = *p*-$CH_3OC_6H_4$)	**3ad** (72) (91:9)[c]
5	**2e** (Ar = *p*-FC_6H_4)	**3ae** (90) (84:16)[c]
6	**2f** (Ar = *p*-ClC_6H_4)	**3af** (88) (85:15)[c]
7	 **2g**	 **3ag** (54) (90:10)[c]
8	 **2h**	 **3ah** (28) (75:24)[c,d] +  **4ah** (34)
9	 **2i**	 **3ai** (50)
10	 **2j**	 **3aj** (60)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (0.025 mmol), **1a** (0.5 mmol), **2** (1.1 mmol), and dioxane (3 mL) were employed. [b] Isolated yield. [c] Ratio of stereoisomer (*Z*/*E*) which was determined by ^1H NMR. [d] Stereostructure of isomers were not determined.

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[8] The stereostructure of the product which was obtained by the reaction of unsymmetric ketene was determined by X-ray analysis of compound **5**; see ref 11 and Supporting Information.

[9] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Bock, V. D.; Hiemstra, H.; Maarseveen, van, J. H. *Eur. J. Org. Chem.* **2006**, 51.

[10] Stereoisomers of **5af-Z** and **5af-E** were separated by repeating recrystallization in toluene/hexane solution, respectively (**5af-Z**: 26% yield, **5af-E**: 3% yield).

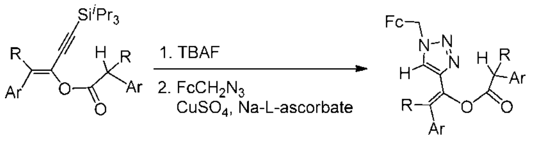
[11] CCDC 879868 (**5aa**) and 879867 (**5af**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] Corresponding *β*-lactone was prepared by the dimerization reaction of **2a** in the presence of the P^nBu_3 catalyst:Wei, P.-H.; Ibrahim, A. A.; Mondal, M.; Nalla, D.; Harzmann, G. D.; Tedeschi, F. A.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2010**, *51*, 6690.

[13] The reaction of **1a** and *β*-lactone under the same reaction conditions of a three-component reaction resulted in recovery of *β*-lactone quantitatively.

[14] Synthesis, characterization, and an ORTEP drawing of acetylide complex **6** were described in the Supporting Information. The CCDC of **6** (883083) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 1

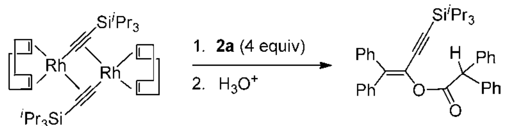


3aa (R = Ar = Ph)
3af (R = Et, Ar = *p*-ClC$_6$H$_4$)

5aa: 64% yield
5af: 75% yield (*Z*/*E* = 85:15)

Upon treatment of **6** with diphenylketene **2a**, followed by protonation, product **3aa** was obtained. This result indicated that the catalytic three-component reaction proceeded via a rhodium–acetylide intermediate formed by the cationic rhodium complex with the terminal silylacetylene in the first step, and protonation occurred in the last step.

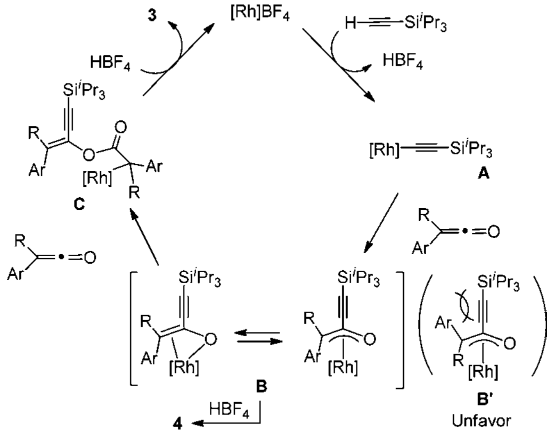
Scheme 2



6

3aa (52% yield)

Scheme 3



A possible pathway for the three-component reaction between terminal silylacetylene and two molecules of ketene is shown in Scheme 3. First, neutral rhodium acetylide complex **A** was formed by the reaction of the cationic rhodium complex with terminal silylacetylene. Next, the insertion of a ketene into the rhodium–alkynyl bond of **A** via π-coordination of the ketene to the rhodium metal[2b,c,f] resulted in the formation of oxa-π-allyl intermediate **B**. In the reaction using an unsymmetric ketene, the stereoselectivity of product **3** can be explained because it avoids the steric hindrance between the aryl group and the alkynyl moiety of oxa-π-allyl intermediate **B′**, and thus intermediate **B** is generated preferentially. Next, another ketene molecule was inserted into the rhodium–oxygen bond to afford intermediate **C**. Lastly, the formation of **3** was achieved by protonation of **C** by HBF$_4$, which was generated in the first step.[15] When sterically hindered ketene **2h** bearing an isopropyl group was used (Table 1, entry 8), product **4ah** was also produced. The formation of **4ah** was likely a result of steric hindrance; the second ketene was difficult to insert into the rhodium–oxygen bond of intermediate **B**. As a result, protonation of intermediate **B** resulted in the formation of product **4**.

In summary, we have demonstrated a three-component coupling reaction between terminal silylacetylene and two ketenes leading to 1,3-enynes bearing a carboxylic ester group with high stereoselectivities using a cationic rhodium complex catalyst. This is the first example of a transition-metal catalyzed three-component reaction through double insertion of ketenes.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Young Scientists B from the Japan Society for the Promotion of Science (JSPS), Japan.

Supporting Information Available. Standard experimental procedure, characterization data for the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In a recent example of a [Rh(cod)$_2$]BF$_4$-catalyzed reaction between triisopropylsilylacetylene and two internal alkynes, a mechanism via a rhodium–acetylide complex, protonation with HBF$_4$ in the last step was proposed: Shibata, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 10917.

The authors declare no competing financial interest.