



Ni-catalyzed [3+2+2] cycloaddition of ethyl cyclopropylideneacetate and 1,3-diynes. Application to the three-component cycloaddition

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ABSTRACT

The Ni-catalyzed [3+2+2] cocyclization between ethyl cyclopropylideneacetate (**1**) and 1,3-diynes afforded cycloheptadiene derivatives. The three-component reaction of **1**, 1,3-diynes, and alkynes proceeded with good yield and high selectivity. Scope of the substrates was studied, and the origin of chemo- and regioselectivity of the reaction is discussed.

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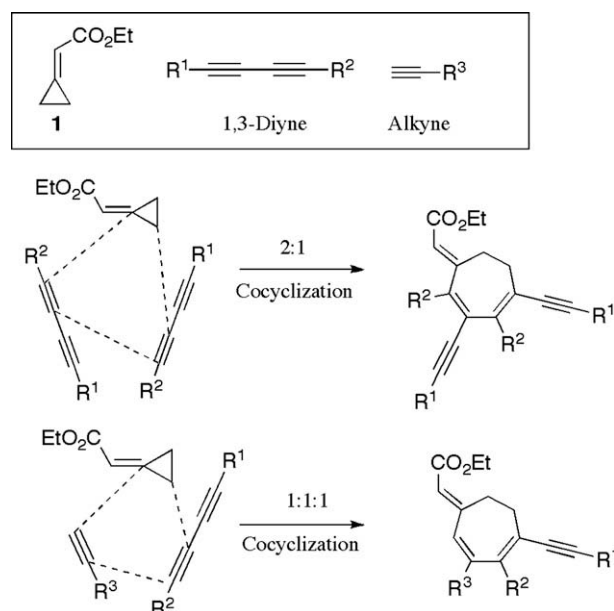
A multicomponent reaction that enables construction of a complex structure in a single step and expands the range of accessible compounds is one of the most powerful synthetic tools in organic chemistry.¹ The introduction of a transition metal catalyst may boost the utility of this type of reaction, and growing numbers of reactions have recently been reported.² We have reported a novel three-component reaction that affords multisubstituted cycloheptadienes selectively via Ni-catalyzed reaction of ethyl cyclopropylideneacetate (**1**).³ This unique reaction is thought to initiate its catalytic cycle by forming a metallacycle composed of two alkyne groups, which subsequently expands via insertion of methylenecyclopropane. Although methods are available for cycloheptadiene synthesis,⁴ catalytic multicomponent reaction, especially reaction that affords multisubstituted cycloheptadiene derivatives, has been rarely reported.^{3b}

Our current efforts are directed toward application of various alkynes as a component for this cocyclization. In this context, conjugated 1,3-diynes that are widely known to react with metal in various ways^{5,6} attracted our attention. Herein, we present a study of [3+2+2] cocyclization of 1,3-diyne as an alkyne equivalent. We performed two types of cocyclization, namely 2:1 and 1:1:1 cocyclization. The former uses only 1,3-diyne and **1**; the other type is 1:1:1 cocyclization between alkyne, 1,3-diyne, and **1** (Scheme 1).

The 2:1 cocyclization of 1,3-diyne (**2**) and **1** was examined using the previously reported procedure for the cocyclization of **1** with alkynes.³ A solution of **1** and diyne **2** in toluene were added dropwise (5 h) to a reaction vessel containing 10 mol % Ni(cod)₂ and 20 mol % PPh₃ in toluene, and the mixture was stirred overnight. Results of the two-component reactions are shown in Table 1. With 7,9-hexadecadiyne (**2x**) as the diyne (entries 1 and 3), the reaction afforded cycloheptadiene derivatives with two regioisomers (**3,3'**).⁷ One of the triple bonds in 1,3-diyne was reacted, and the

other triple bond remained intact. The rate of the reaction was slow at room temperature (entry 1), and the yield of the product increased to 57% when the reaction was performed at 50 °C. Slower addition (10 h) of the substrates, alternatively, led to decreased yields (entry 4). When the reaction was applied to other 1,3-diynes such as 1,4-bis(trimethylsilyl)-1,3-diyne (**2y**), a mixture of 1:1 coupling products, likely to be cyclopentene derivatives, was obtained.

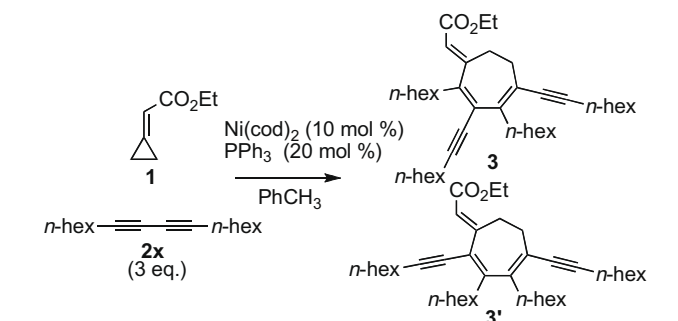
The results of the 2:1 cocyclization reactions indicated that the reactivity of 1,3-diynes is much lower than that of terminal alkynes for which the reaction proceeded at rt.^{3e} We expected that the



Scheme 1. [3+2+2] Cocyclization of 1,3-diynes.

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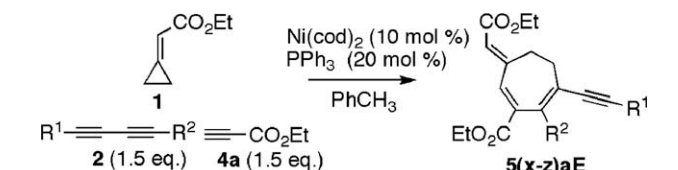
E-mail address: ssaito@rs.kagu.tus.ac.jp (S. Saito).

Table 1Cocyclization reaction between ethyl cyclopropylideneacetate and 1,3-diynes^a

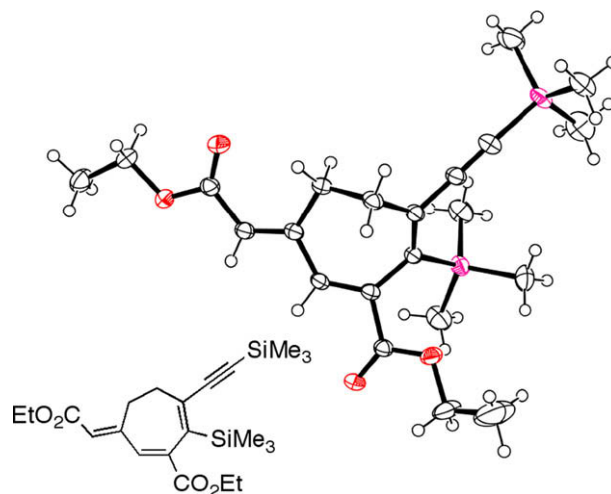
Entry	Temperature (°C)	Yield (3+3') (%)	Ratio (3:3')
1	rt	28	1.8:1
2	50	57	1.6:1
3	80	30	1.6:1
4 ^b	50	20	1.6:1

^a A solution of the substrates was added dropwise via syringe pump over 5 h, and stirred overnight unless otherwise noted.^b The substrate was injected via syringe pump over 10 h.

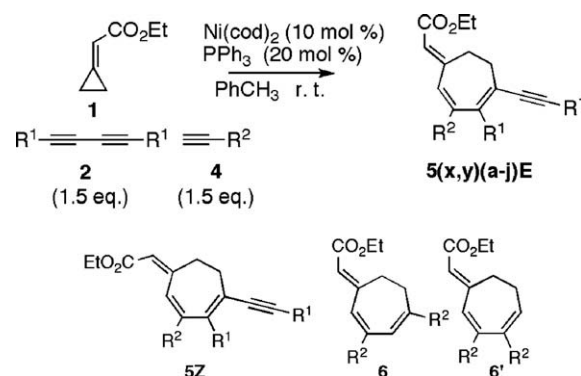
difference in the reactivity of the alkyne component could be advantageous for the three-component reaction between **1**, **2**, and terminal alkynes (**4**). In Table 2, the results of an initial study of the three-component reaction with ethyl propiolate (**4a**) as the monosubstituted alkyne are presented. Reaction of **1**, 7,9-hexadiyne (**2x**), and **4a** afforded **5xaE** in 69% yield at rt (entry 1). It is noteworthy that the reaction proceeded with high chemo- and regioselectivity, and only 1.5 equiv of **2x** was required to isolate the product in good yield. The structure of product **5yaE** was unambiguously confirmed by X-ray crystallography (Fig. 1).⁸ The yield of **5** did not change significantly, when the reaction was carried out at 50 °C or at room temperature (entries 2 and 3). On the other hand, the yield of the product decreased, when the reaction was performed in the presence of a smaller amount (1.2 equiv) of **4a** and **2y** (entry 4). We also examined the reactions of an asymmetric 1,3-diyne. The reaction of 1-trimethylsilyl-1-octyne (**2z**) and **4a** afforded the product in 65% yield (entry 5).⁹ To our delight, the reactions proceeded in a highly selective manner, and the triple bond bound to the trimethylsilyl group remained intact.

Table 2Three-component [3+2+2] reaction with ethyl cyclopropylideneacetate (**1**), 1,3-diyne (**2**), and ethyl propiolate (**4a**)^a

Entry	Temperature (°C)	Diyne	R ¹	R ²	Isolated yield (%)
1	rt	2x	<i>n</i> -Hex	<i>n</i> -Hex	69
2	rt	2y	Me_3Si	Me_3Si	66
3 ^b	rt	2y	Me_3Si	Me_3Si	44
4	50	2y	Me_3Si	Me_3Si	71
5	rt	2z	Me_3Si	<i>n</i> -hex	65

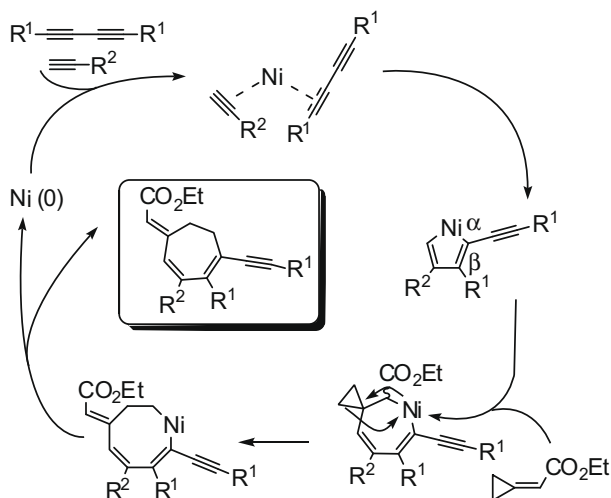
^a A solution of the substrates (**1**, **2**, and **4a**) was added dropwise via syringe pump over 5 h, and stirred overnight.^b Smaller amounts (1.2 equiv) of **2y** and **4a** were used.**Figure 1.** ORTEP drawing of **5yaE**.

Since the three-component reaction of **1**, 1,3-diynes, and **4a** proceeded successfully, we subsequently examined various alkynes for the three-component reaction (Table 3). For this study, **2x** and **2y** were used as diyne components. The yield of product was influenced by the substituents bound to the alkyne (**4**). When

Table 3Effect of alkyne substituents on a three-component [3+2+2] reaction^a

Entry	Diyne (R ¹)	Alkyne (R ²)	Isolated yield (%)
1	<i>n</i> -Hex (2x)	CO_2Et (4a)	69
2	<i>n</i> -Hex (2x)	CH_2OMe (4b)	50
3	<i>n</i> -Hex (2x)	$(\text{CH}_2)_2\text{OMe}$ (4c)	76 ^b
4	<i>n</i> -Hex (2x)	$(\text{CH}_2)_3\text{OMe}$ (4d)	60 ^c (6d 36%) ^d
5	<i>n</i> -Hex (2x)	$\text{C}(\text{CH}_3)_2\text{OMe}$ (4e)	38
6	<i>n</i> -Hex (2x)	$\text{CH}_2\text{C}(-\text{OCH}_2\text{CH}_2\text{O}-)\text{CH}_3$ (4f)	84
7	Me_3Si (2y)	CO_2Et (4a)	66
8	Me_3Si (2y)	CH_2OMe (4b)	40
9	Me_3Si (2y)	$(\text{CH}_2)_2\text{OMe}$ (4c)	80
10	Me_3Si (2y)	$(\text{CH}_2)_3\text{OMe}$ (4d)	36 ^c (6d 43%)
11	Me_3Si (2y)	$\text{C}(\text{CH}_3)_2\text{OMe}$ (4e)	39
12	Me_3Si (2y)	$\text{CH}_2\text{C}(-\text{OCH}_2\text{CH}_2\text{O}-)\text{CH}_3$ (4f)	72
13	Me_3Si (2y)	CH_2OBn (4g)	46
14	Me_3Si (2y)	Ph (4h)	25 (6h 49%)
15	Me_3Si (2y)	Me_3Si (4i)	— ^f
16	Me_3Si (2y)	<i>n</i> -Hex (4j)	— ^f

^a A solution of the substrates (**1**, **2**, and **4**) was added dropwise via syringe pump over 5 h, and stirred overnight.^b The formation of a trace amount of an isomer was observed.^c Isolated as a mixture of **5E** and **5Z** (**5E:5Z** = 4:1).^d Isolated as a mixture of **6d** and **6d'** (**6:6'** = 1:1).^e Isolated as a mixture of **5E** and **5Z** (**5E:5Z** = 4.9:1).^f A complex mixture of isomers was obtained.



Scheme 2. A plausible mechanism for three-component cocyclization.

homopropargyl ethers such as **4c** and **4f** were employed as the substrates, the yields of the products were high (entries 3, 6, 9, and 12). On the other hand, ethers with different lengths of the methylene group turned out to be less effective substrates, and the yields of the products decreased (compare entries 8–10). These results imply that chelation of nickel by the oxygen atom and the alkynyl group plays an important role for the efficient synthesis of **5**.¹⁰ The reaction of benzyl propargyl ether (**4g**) also proceeded, and the product was isolated in 46% yield (entry 13). However, other monosubstituted alkynes turned out to be inferior substrates for this reaction (entries 14–16). This result also supports the existence of a chelation effect since all the alkynes that were superior substrates for this reaction possess an oxygen atom. It is noteworthy that 2:1 cocyclization of the alkyne and **1** proceeded in a few examples (entries 4, 10, and 14).

Considering the structures of the products and the previously proposed mechanism,³ we postulate a similar one for the three-component cocyclization of 1,3-diyne, alkyne, and **1** as shown in Scheme 2. It is proposed that the catalytic cycle is initiated by the reaction of the alkyne and diyne with the Ni(0) species to form nickelacycle. Then, **1** is inserted into the metallacycle to occur cyclopropylmethyl to butenyl rearrangement,¹¹ affording the seven-membered nickelacycle. Subsequently, nickelacyclocloctadiene is transformed to the cycloheptadiene derivative by the reductive elimination of the Ni complex.

As discussed previously,^{3e} regioselectivity and chemo selectivity can be explained in terms of the steric and electronic effect on the metallacycle intermediate. The steric factor explains the preference of α,β -substituted nickelacycle over α,α - or β,β -disubstituted nickelacycle¹² and alkyne over 1,3-diyne. As for the electronic factor, Hoffmann et al. proposed that the largest lobe of LUMO of alkyne (π^*) is prone to form a C–C bond (at the β -position) in order to maximize the orbital overlap.¹³ Considering that 1,3-diyne possesses its largest LUMO at the terminal carbon,¹⁴ it is reasonable that the remaining ethynyl group derived from the 1,3-diyne is located at the α -position. Although the chemoselectivity of heterometallacycle between alkyne and 1,3-diyne over homometallacycle is not clear at this stage, chelation between Ni and ether

might contribute to this selectivity since the **4c** and **4f** which can form six-membered chelation cycle gave superior yield and selectivity.¹⁰

In conclusion, 1,3-diyne was applied to Ni-catalyzed [3+2+2] cocyclization reaction. We found that selective 1:1:1 coupling between 1,3-diyne, alkyne, and **1** afforded cycloheptadiene with an intact triple bond. The study has expanded the scope of the three-component [3+2+2] cocyclization reaction, and has provided an efficient pathway for the synthesis of a range of multisubstituted cycloheptadienes.

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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.2008.12.092.

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- The choice of ligand, PPh₃, was crucial in this reaction. Other ligands gave poorer yield and selectivity.
- X-ray data were collected on a Bruker Smart1000 CCD detector. The crystal structure was solved by direct methods SHELXS-97 (Sheldrick, 1997) and was refined by full-matrix least-squares SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included as their calculated positions. Crystal data for **5aE**: C₂₂H₃₄O₄Si₂; *M* = 418.67 g mol^{−1}, triclinic, *P*1̄, colorless prism measuring 0.4 × 0.3 × 0.2 mm, *T* = 150 K, *a* = 10.3539(7), *b* = 11.0209(7), *c* = 11.5075(7) Å, α = 96.523(1)°, β = 93.299(1)°, γ = 106.417(1)°, *V* = 1245.87(14) Å³, *Z* = 2, *D*_c = 1.116 Mg m^{−3}, μ = 0.164 mm^{−1}, *T*_{max} = 0.9679, *T*_{min} = 0.9371, GOF on *F*² = 0.979, *R*₁ = 0.0419, *wR*₂ = 0.1003 [*I* > 2 σ (*I*)], *R*₁ = 0.0506, and *wR*₂ = 0.1067 (all data). Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited at the Cambridge Crystallographic Data Center (CCDC-709808). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
- The reaction of **1**, 1,6-dimethoxy-2,4-hexadiyne, and **4a** gave the desired product albeit in low yield (21%). The three-component coupling reactions of other diynes, such as 1,4-diphenyl-1,3-butadiyne and terminal 1,3-diynes, resulted in the formation of a complex mixture.
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