JOC Article

Synthesis of Vinylcycloheptadienes by the Nickel-Catalyzed Three-Component [3 + 2 + 2] Cocyclization. Application to the Synthesis of Polycyclic Compounds

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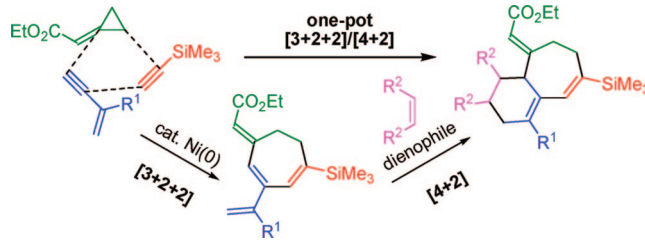

The nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate and conjugated enynes proceeded smoothly and divinylcycloheptadienes were isolated in high yields. The three-component cocyclization of ethyl cyclopropylideneacetate, conjugated enynes, and (trimethylsilyl)acetylene also proceeded in a highly selective manner to afford vinylcycloheptadienes, which were reacted with various dienophiles. This study provided a new, short-step synthesis of polycyclic compounds with cycloheptane skeleton.

Introduction

The short-step synthesis of the complex molecules from simple compounds is an important issue in organic chemistry. Transition-metal-catalyzed reactions are attractive tools for multicomponent coupling, and many efficient reactions have been investigated.[1,2] In particular, cyclization reactions in the presence of transition-metal catalysts are very useful for the construction of complicated compounds. For example, polysubstituted benzene derivatives are synthesized by [2 + 2 + 2] cycloaddition, and bi- or tricyclic compounds are formed by the (partially) intramolecular cocyclization.[3] Metal-catalyzed cocyclization reactions for the formation of seven-membered rings such as [6 + 1],[4] [5 + 2],[5] [4 + 3],[6] [4 + 2 + 1],[7] [3 + 2 + 2],[8] and [3 + 3 + 1][9] cycloadditions have been reported, and some reactions have been applied to natural product synthesis.[10] However, selective formation of the desired products

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by metal-catalyzed multicomponent reactions is not easy unless the reactivity of the substrates is controlled properly.[11]

Conjugated enyne is a useful substrate for the synthesis of cyclic compounds in the presence of transition-metal catalysts.[12] For instance, palladium-catalyzed [4 + 2] benzannulation,[12b,13] nickel-catalyzed zipper annulation,[14] gold- and copper-catalyzed [4 + 2] benzannulation,[12c,d] and the gold-catalyzed heterodehydro-Diels−Alder cycloaddition[15] have been reported. Furthermore, the 1,3-diene moiety has been frequently constructed by the cycloaddition reaction of enynes, and the products formed by these reactions could be utilized for various reactions such as the Diels−Alder reaction. This strategy is very useful for the concise synthesis of polycyclic compounds. For example, Wender and co-workers described the serial [5 + 2]/[4 + 2] cycloaddition with conjugated enyne in the presence of a rhodium catalyst.[16]

Recently, we reported the nickel-catalyzed intermolecular [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate (**1**) and alkynes,[17] and the three-component [3 + 2 + 2] cycloaddition was achieved by the reaction of **1** and two different alkynes (Figure 1).[18] We also accomplished the [4 + 3] cycloaddition[19a] of **1** with 1,3-dienes and the intramolecular [3 + 2 + 2] cycloaddition[19b] to afford bicyclic compounds. These reactions provided new pathways for the synthesis of a variety of multisubstituted cycloheptadiene derivatives. In this paper, we report the nickel-catalyzed [3 + 2 + 2] cycloaddition of **1** and conjugated enynes and the application of the reaction to the four-component [3 + 2 + 2]/[4 + 2] cycloaddition.

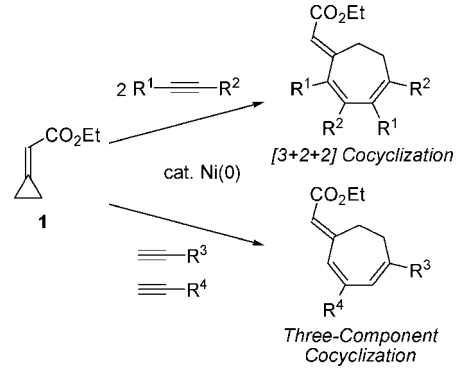

FIGURE 1. Nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate (**1**) and alkynes.

Results and Discussion

Nickel-Catalyzed [3 + 2 + 2] Cocyclization of Ethyl Cyclopropylideneacetate and Conjugated Enynes. We initially examined the nickel-catalyzed reactions of **1** and conjugated enynes **2** (Table 1). The reaction of **1** and 2-methyl-1-buten-3-yne (**2a**) gave **3a** in 97% yield (entry 1).[20] Although the metal-catalyzed [4 + 2] benzannulation[12b,13] and the zipper annulation[14] of conjugated enynes have been reported, conjugated enynes reacted as substituted alkynes and the [3 + 2 + 2] cycloaddition proceeded smoothly. 1-Ethynylcyclohexene (**2b**) was a good substrate, and **3b** was afforded in 93% yield (entry 2). The reactions of 2-benzyl-1-buten-3-yne (**2c**) and 3-decen-1-yne (**2d**) also gave the coupling products in a selective manner (entries 3 and 4). To examine the scope of the reaction, the reaction of 1,2-substituted conjugated enyne (**2e**) was carried out, and the product was isolated in good yields (entry 5). On the other hand, an inseparable mixture of regioisomers was obtained when the reaction was carried out with **2f** (entry 6). The reaction of 2-butoxy-1-buten-3-yne (**2g**) led to the coupling product (**3g**), but the product was unstable and could not be isolated in pure form. Instead, a ketone derivative (**4g**) was isolated when the reaction mixture was treated with TsOH (eq 1).

We also found that the three-component [3 + 2 + 2] cycloaddition with **1**, conjugated enynes **2**, and (trimethylsilyl)acetylene (**5**) proceeded in a highly selective manner (Table 2). The reaction of **1**, **2a**, and **5** gave the cycloadduct **6a** in 66% yield, although the formation of a small amount of other cycloheptadienes such as **3a** was observed (entry 1). Compound **6a** was synthesized in 62% yield when the reaction was carried out on a 5 mmol scale, and the $Ni(PPh_3)_2Br_2$−PPh_3−Zn catalytic system was used (entry 2).[17b,21] The cycloheptadiene **6b** was also isolated in good yield when the reaction of **1**, **2b**, and **5** was executed (entry 3). The

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(20) The configuration of the product (*E* isomer) was determined by ^{1}H NMR spectra according to previous results (see refs 17 and 18). It was also confirmed by X-ray crystallographic analyses (e.g., *endo*-**14c** and **16d**).

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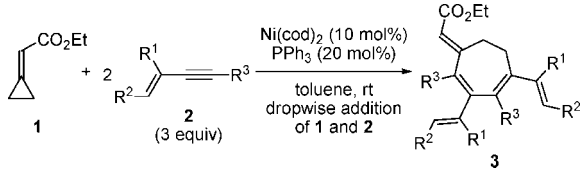
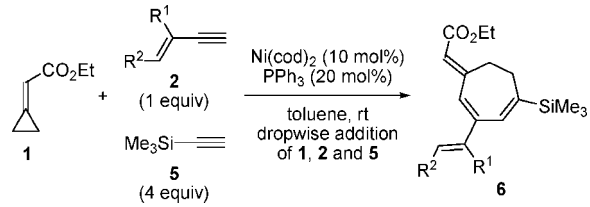
TABLE 1. Nickel-Catalyzed [3 + 2 + 2] Cycloaddition of 1 and Conjugated Enynes 2[a]



Entry	Enyne	*t* (h)	Product[b]
1	**2a**	2[c]	**3a** (97%)
2	**2b**	2[c]	**3b** (93%)
3	**2c**	21	**3c** (73%)
4	**2d**	20	**3d** (73%)
5	**2e**	17.5	**3c** (93%)[d]
6	**2f**	21	

[a] Reaction conditions: a solution of **1** (1 mmol) and **2** (3 mmol) in toluene (0.5 mL) was added dropwise over 3 h to a mixture of $Ni(cod)_2$ (0.1 mmol) and PPh_3 (0.2 mmol) in toluene (0.5 mL) at room temperature under Ar. The reaction mixture was stirred for the designated time. [b] Isolated yields in parentheses. [c] The reaction was carried out for a shorter reaction time to prevent the decomposition of the product. [d] The formation of an inseparable mixture of regioisomers was observed.

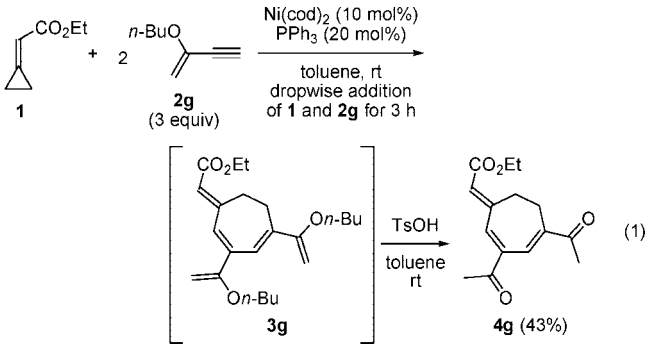
TABLE 2. Nickel-Catalyzed Three-Component [3 + 2 + 2] Cycloaddition of 1, 2, and 5[a]



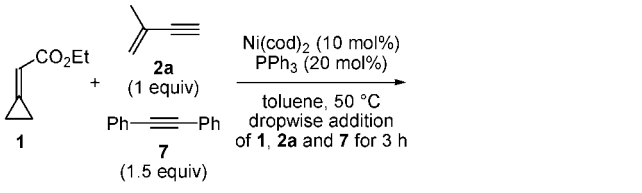
Entry	Enyne	*t* (h)	Product[b,c]
1	**2a**	17	**6a** (66%)
2[d]	**2a**	14	**6a** (62%)
3	**2b**	24	**6b** (85%)
4	**2c**	14	**6c** (58%)
5	**2g**	16.5	**6g** (42%)

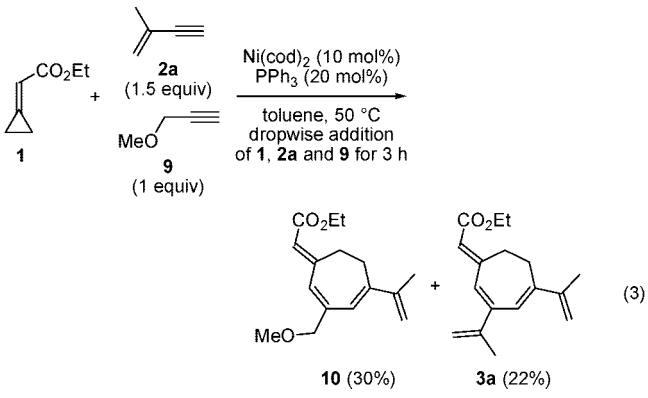
[a] Reaction conditions: a solution of **1** (1 mmol), **2** (1 mmol), and **5** (4 mmol) in toluene (0.5 mL) was added dropwise over 3 h to a mixture of $Ni(cod)_2$ (0.1 mmol) and PPh_3 (0.2 mmol) in toluene (0.5 mL) at room temperature under Ar. The reaction mixture was stirred for the designated time. [b] Isolated yields in parentheses. [c] A small amount of **3a** was isolated. [d] The $Ni(PPh_3)_2Br_2$−PPh_3−Zn system was used: a mixture of $Ni(PPh_3)_2Br_2$ (0.5 mmol), PPh_3 (1 mmol), and Zn dust (10 mmol) in toluene (2.5 mL) was stirred at room temperature for 1 h. Then, to this mixture was added dropwise a solution of **1** (5 mmol), **2a** (5 mmol), and **5** (15 mmol) in toluene (2.5 mL) over 5 h.

reaction of **1**, **2c**, and **5** proceeded in moderate yield to afford **6c** (entry 4). The enol ether (**6g**) was isolated in moderate yield by the reaction of **1**, **2g**, and **5** (entry 5). A small amount of the undesired coupling product (**3a**) was also produced in the three-component reactions reported in Table 2. Diphenylacetylene (**7**) was also a suitable substrate for the three-component cocyclization, and the reaction was carried out at 50 °C to give **8** in 51% yield though formation of the undesired coupling product **3a** was observed (eq 2). The inverse chemoselectivity was observed in the reaction of **1**, **2a**, and the less congested alkyne **9**, and compound



10 was isolated in 30% yield along with **3a** (eq 3). Only a trace amount of the [3 + 2 + 2] coupling product formed by the reaction of **1** and **7** (eq 2) or by the reaction of **1** and **9** (eq 3) was detected. The formation of opposite regioisomers in eqs 2 and 3 could be explained in terms of the relative bulkiness of the substituents bound to the alkyne moietis in the cocyclization reaction. Thus, the most bulky substituent (phenyl group in eq 2 and isopropenyl group in eq 3) would occupy the α position of the nickelacyclopentadiene intermediate (vide infra).[22]

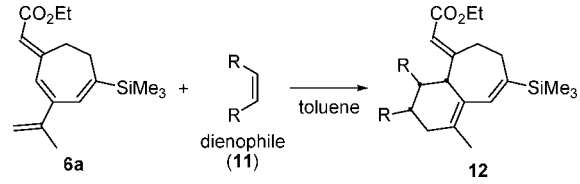


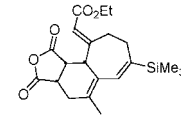
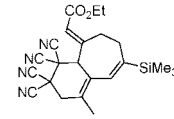
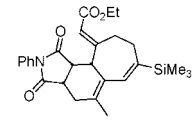
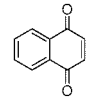
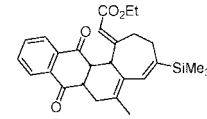


Application to the Synthesis of Polycyclic Compounds. A conjugated and less substituted diene moiety was incorporated in the cycloheptadienes synthesized by these reactions. We anticipated that these conjugated dienes would react with various dienophiles, providing an efficient route for the synthesis of polycyclic carbocycles with a seven-membered ring. Accordingly, we examined the [4 + 2] cycloaddition of **5** with various dienophiles,[23] and the results of the Diels−Alder reaction under the thermal conditions

(22) The selective formation of a nickelacyclopentadiene intermediate and the observed regioselectivity of the product in this reaction has been previously discussed in detail. See ref 17b.

TABLE 3. Diels−Alder Reaction of 6a and Dienophiles (11)



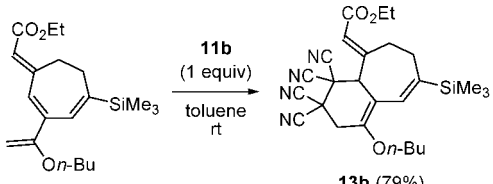
Entry	Dienophile (**11**)	Conditions[a]	Product[b]
1	 **11a** (4 equiv)	100 °C 8.5 h	 *endo*-**12a** (63%)
2	 **11b** (1 equiv)	rt 47.5 h	 **12b** (82%)
3[c]	 **11c** (1.5 equiv)	140 °C 2 h	 *endo*-**12c** (89%)
4	 **11d** (1.5 equiv)	100 °C 21 h	 *endo*-**12d** (31%)[d]
5	 **11e** (3 equiv)	100 °C 47.5 h	complex mixture

[a] Reaction conditions: A mixture of **6a** (0.5 mmol) and **11** in toluene (2 mL) was stirred. [b] Isolated yields in parentheses. [c] The reaction was carried out in 1,1,2,2-tetrachloroethane. [d] The formation of isomers was observed.

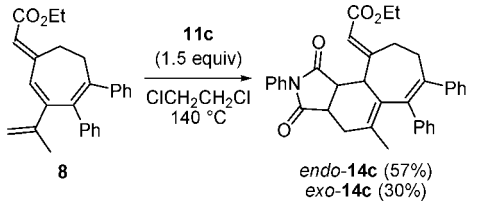
are summarized in Table 3. The reaction of **6a** and maleic anhydride (**11a**) gave *endo*-**12a** as a single isomer in 63% yield (entry 1). The stereochemistry of *endo*-**12a** was confirmed by a NOESY experiment (Figure S1, Supporting Information). Tetracyanoethylene (**11b**) also reacted with **6a** at room temperature leading to the cycloadduct **12b** (entry 2). A tricyclic compound *endo*-**12c** was isolated in 89% yield when the reaction of **6a** and **11c** was carried out at 140 °C in 1,1,2,2-tetrachloroethane (entry 3). The reaction of **6a** with 1,4-naphthoquinone (**11d**) also proceeded, though the formation of isomers was observed (entry

(23) Recent reviews: (a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779–4807. (b) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115. (c) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (d) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

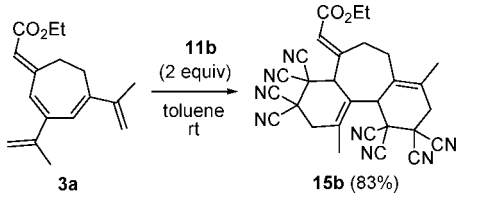
4). The cycloadduct was not isolated when dimethyl acetylenedicarboxylate (**11e**) was reacted with **6a** (entry 5). Other vinylcycloheptadienes could be used as the substrate for the reaction, and compound **6g** reacted with **11b** to give **13b** in 79% yield (eq 4). The reaction of **8** and **11c** gave *endo*-**14c** (57%) and *exo*-**14c** (30%) (eq 5). The structure of a product (*endo*-**14c**) was confirmed by an X-ray crystallographic analysis (Figure S2, Supporting Information). We also studied the formation of tricyclic compounds by the double Diels−Alder reaction of **3a**. The cycloadduct **15b** was obtained as a single isomer in 83% yield by the reaction of **3a** and **11b** (eq 6).[24]



(4)



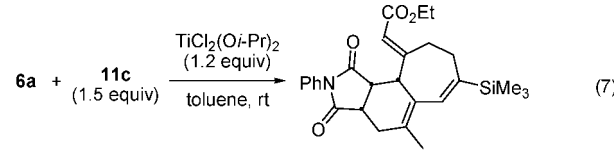
(5)



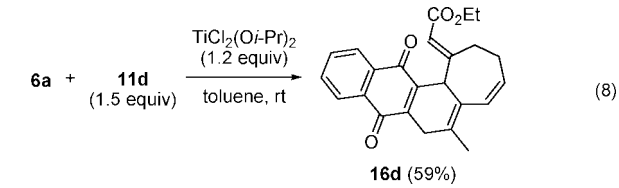
(6)

Subsequently, we examined Lewis acid-promoted Diels−Alder reactions. The reaction of **6a** with **11c** in the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$[25] (1.2 equiv) proceeded at room temperature and gave a single coupling product (*endo*-**12c**) in 92% yield (eq 7). The $TiCl_2(O\text{-}i\text{-}Pr)_2$ promoted Diels−Alder reaction of **6a** and **11d** gave **16d** (eq 8). We assume that compound **16d** was formed by the aromatization of the initially formed cycloadduct and the acid-catalyzed desilylation. The structure of **16d** was confirmed by an X-ray crystallographic analysis (Figure S3, Supporting Information). The yield of **16d** decreased when a catalytic amount of $TiCl_2(O\text{-}i\text{-}Pr)_2$ (0.2 equiv) or another titanium Lewis acid ($TiCl_4$) was used. Though other Lewis acids such as $ZnCl_2$ or $AlCl_3$ also catalyzed the reaction of **6a** with **11d**, the formation of isomeric compounds was observed, and the product was isolated in low yield. In the presence of $BF_3 \cdot OEt_2$, the formation of a complex mixture was observed.

Finally, we demonstrated the usefulness of these reactions by carrying out the one-pot, four-component reaction. Thus, the nickel-catalyzed [3 + 2 + 2] cycloaddition of **1**, **2a**, and **5** was carried out as the first step, and to the reaction mixture was added **11b** at room temperature. The reaction proceeded smoothly, and the four-component coupling product (**12b**) was isolated in 54% yield (eq 9). The four-component reaction of

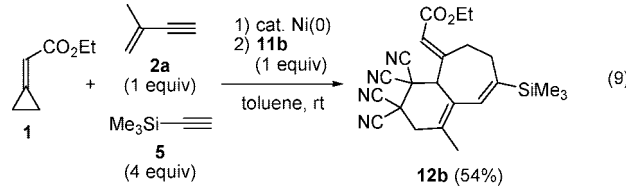


(7)

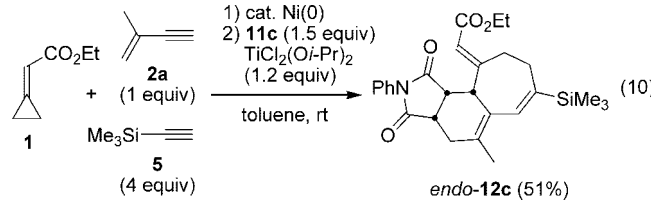


(8)

1, **2a**, **5**, and **11c** in the presence of $TiCl_2(O\text{-}i\text{-}Pr)_2$ in the second step also gave *endo*-**12c** in 51% yield (eq 10).



(9)



(10)

Mechanistic Consideration. On the basis of our recent studies,[17−19] a plausible mechanism for the formation of cycloheptadienes is shown in Scheme 1. The selective formation of the nickelacyclopentadiene **17** could be explained in terms of the steric effect of the vinyl group.[26,27] Two bulky substituents incorporated in the nickelacycle tend to occupy the α- and β-positions of the nickelacycle. The formation of **18** from **2** and **5** is also predictable, based on our previous studies: the trimethylsilyl group is located at the α-position due to electronic and steric effects.[18,27,28] The formation of **18** is predominant in the presence of an excess of **5**, which is the less reactive alkyne. The nickelacycles **17** and **18** would react with **1** to form **19**, which would rearrange and give the final intermediate.[29−31] The desired cycloheptadiene is obtained by the reductive elimination of the nickel(0) species from **20**.

(24) The coupling product (**15b**) was isolated as a single isomer, but the stereochemistry has not been determined.

(25) (a) Denmark, S. E.; Seierstad, M. *J. Org. Chem.* **1999**, *64*, 1610–1619. (b) Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72*, 7050–7053. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954.

(26) (a) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907–1912. (b) Eisch, J. J.; Damasevitz, G. A. *J. Organomet. Chem.* **1975**, *96*, C19–C22.

(27) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722–2727.

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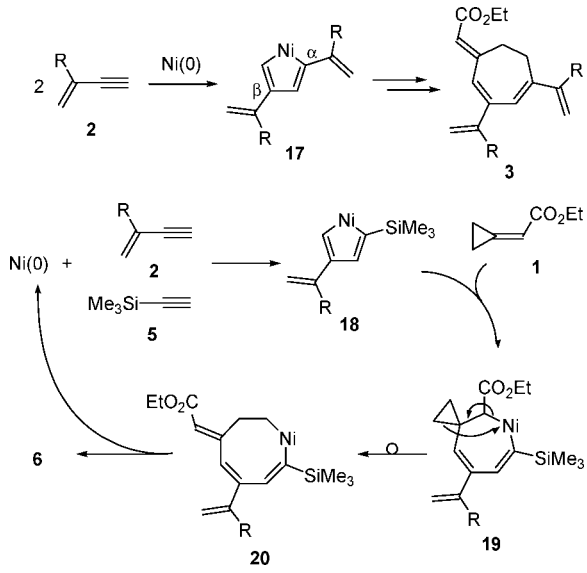
(29) (a) Binger, P.; Doyle, M. J.; Benn, R. *Chem. Ber.* **1983**, *116*, 1–10. (b) Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 796–802.

(30) For reviews of the reactions of methylenecyclopropanes, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77–151. (b) Binger, P.; Schmidt, T. Metal-Catalyzed Cycloadditions of Methylenecyclopropanes. In *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17b, pp 2217−2294. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (d) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129.

(31) The selective formation of the *E* isomer has been frequently observed. We assume that the *s-trans* conformation of the $EtO_2C-C(\alpha)-C(\beta)-C(\gamma)$ bonds of **19** would be preferred. The *E* isomer would be formed selectively from the *s-trans* conformer. See ref 17b.

SCHEME 1. Plausible Mechanism for the Nickel-Catalyzed [3 + 2 + 2] Cycloaddition



Conclusions

We report the nickel-catalyzed [3 + 2 + 2] cycloaddition of ethyl cyclopropylideneacetate and conjugated enynes. The reaction proceeded smoothly, and the selective formation of cycloheptadiene derivatives was observed. Furthermore, we achieved the four-component [3 + 2 + 2]/[4 + 2] cycloaddition. The reaction provided a new pathway for the synthesis of polycyclic compounds with a cycloheptene ring. Further applications of these reactions are now ongoing.

Experimental Section

Nickel(0)-Catalyzed Cycloaddition of Ethyl Cyclopropylideneacetate (1) and Conjugated Enynes (Table 1). A Representative Procedure. To a dark red mixture of $Ni(cod)_2$ (27.5 mg, 0.1 mmol) and PPh_3 (52.5 mg, 0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1** (126 mg, 1 mmol) and **2** (3 mmol) in dry toluene (0.5 mL) at room temperature over 3 h under Ar. The progress of the reaction was monitored by TLC and GC−MS, and the mixture was stirred until the starting material (**1**) disappeared. The mixture was passed through a short silica gel column (ether). Evaporation of the solvent gave an oil, which was further purified by silica gel column chromatography to give **3**.

(*E*)-1-Ethoxycarbonylmethylene-3,5-(di-1-methylethenyl)-2,4-cycloheptadiene (3a): purified by silica gel column chromatography (hexane/AcOEt 30:1 and hexane/CH_2Cl_2 3:1); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 6.39 (s, 1H), 6.19 (s, 1H), 5.71 (s, 1H), 5.23 (s, 1H), 5.14 (s, 1H), 5.05 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.16−3.11 (m, 2H), 2.54−2.50 (m, 2H), 1.97 (s, 3H), 1.96 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 166.8, 158.3, 147.3, 146.0, 143.9, 143.0, 131.0, 122.7, 117.4, 115.1, 114.1, 59.6, 31.8, 26.1, 21.8, 21.1, 14.3; IR (neat) 2976, 1706, 1585, 1444, 1374, 1264, 1213, 1154, 1040, 891 cm^{-1}; HR-MS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1611.

Nickel(0)-Catalyzed Three-Component Cycloaddition of Ethyl Cyclopropylideneacetate (1), Conjugated Enynes, and (Trimethylsilyl)acetylene (5) (Table 2). A Representative Procedure. To a dark red mixture of $Ni(cod)_2$ (27.5 mg, 0.1 mmol) and PPh_3 (52.5 mg, 0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1** (126 mg, 1 mmol), **2** (1 mmol), and (trimethylsilyl)acetylene (**5**, 4 mmol) in dry toluene (0.5 mL) at room temperature over 3 h under Ar. The progress of the reaction was monitored by TLC and GC−MS, and the mixture was stirred until the starting material (**1**) disappeared. The mixture was passed through a short silica gel column (ether). Evaporation of the solvent gave an oil, which was further purified by silica gel column chromatography to give **6**.

(*E*)-1-Ethoxycarbonylmethylene-3-(1-methylethenyl)-5-trimethylsilyl-2,4-cycloheptadiene (6a): purified by silica gel column chromatography (hexane/CH_2Cl_2 3:1); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 6.38 (s, 1H), 6.36 (s, 1H), 5.71 (s, 1H), 5.13 (s, 1H), 5.05 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.07−3.04 (m, 2H), 2.33−2.29 (m, 2H), 1.95 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.8, 158.5, 151.7, 145.6, 143.5, 133.7, 131.6, 117.4, 115.1, 59.6, 32.3, 27.6, 21.7, 14.3, −2.2; IR (neat) 2954, 1709, 1586, 1444, 1403, 1376, 1249, 1214, 1155, 1088, 1067, 1039, 892, 838, 752 cm^{-1}; HR-MS (ESI) calcd for $C_{17}H_{26}O_2NaSi$ [M + Na]$^+$ 313.1594, found 313.1594.

Diels−Alder Reaction of 6a and 11 (Table 3). A Representative Procedure. A mixture of **6a** (145 mg, 0.5 mmol) and **11** (0.75 mmol) in toluene (2 mL) was stirred at the designated temperature. After the reaction was completed, the mixture was purified by silica gel column chromatography to give **12**.

Compound *endo*-12a. A mixture of **6a** (215 mg, 0.74 mmol) and **11a** (294 mg, 3 mmol) in toluene (1 mL) was stirred at 100 °C for 8.5 h. The mixture was purified by silica gel column chromatography (hexane/AcOEt 3:1) to give *endo*-**12a** (180 mg, 61%): white solid; mp 67−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 6.39 (s, 1H), 5.92 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.61 (dd, J = 9.8, 5.8 Hz, 1H), 3.44 (ddd, J = 9.8, 6.7, 2.4 Hz, 1H), 3.32 (m, 1H), 3.04−2.99(m, 1H), 2.83−2.78 (m, 1H), 2.68 (dd, J = 15.5, 2.3 Hz, 1H), 2.49−2.41 (m, 3H), 1.89 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.3, 170.5, 165.9, 159.1, 144.6, 134.7, 130.8, 130.4, 116.7, 59.9, 50.2, 44.8, 41.3, 31.8, 31.6, 31.2, 20.4, 14.2, −1.9; IR (KBr) 2955, 1844, 1779, 1704, 1650, 1248, 1179, 992, 937, 837 cm^{-1}; HR-MS (EI) calcd for $C_{21}H_{28}O_5Si$ 388.1706, found 388.1714.

One-Pot, Four-Component [3 + 2 + 2]/[4 + 2] Cycloaddition of 1, 2a, 5, and 11b (eq 9). To a dark red mixture of $Ni(cod)_2$ (27.5 mg, 0.1 mmol) and PPh_3 (52.5 mg, 0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1** (127 mg, 1 mmol), **2a** (0.095 mL, 1 mmol), and **5** (0.57 mL, 4 mmol) in dry toluene (0.5 mL) at room temperature over 3 h under Ar. After 16 h, toluene (1 mL) and **11b** (128 mg, 1 mmol) were added, and the mixture was stirred at room temperature for 23 h. The crude product was passed through a short silica gel column chromatography (ether) and further purified by silica gel column chromatography (hexane/AcOEt 8:1) to give **12b** (227.9 mg, 54%).

Compound 12b: colorless solid; mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.17 (s, 2H), 4.21 (qd, J = 7.2, 3.4 Hz, 2H), 3.89 (s, 1H), 3.59 (dt, J = 11.5, 4.1 Hz, 1H), 3.20 (d, J = 18.4 Hz, 1H), 3.00 (d, J = 18.4 Hz, 1H), 2.62−2.56 (m, 2H), 2.52−2.43 (m, 1H) 1.82 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.5, 152.7, 150.1, 130.2, 125.7, 125.4, 124.2, 110.8, 110.7, 110.5, 109.0, 60.6, 53.4, 44.2, 38.7, 37.0, 34.1, 27.7, 19.7, 14.1, −2.1; IR (KBr) 2954, 1715, 1658, 1446, 1381, 1248, 1209, 1189, 1154, 1041, 837, 751 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_4O_2Si$: C, 66.00; H, 6.26; N, 13.39. Found: C, 65.97; H, 6.26; N, 13.19.

Compound 16d. To a mixture of **6a** (146 mg, 0.5 mmol) and **11d** (120 mg, 0.75 mmol) in toluene (2 mL) was added a solution of $TiCl_2(O\text{-}i\text{-}Pr)_2$ (1.2 mL, 0.5 M in toluene, 0.6 mmol) at room temperature. After the reaction was completed (21.5 h), the mixture was purified by silica gel column chromatography (hexane/AcOEt 10:1) to give **16d** (111.8 mg, 59%): red solid; mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.13−8.11 (m, 1H), 8.05−8.01 (m, 1H), 7.75−7.68 (m, 2H), 6.38 (d, J = 11.5 Hz, 1H), 5.88 (dt, J = 11.5, 3.9 Hz, 1H), 5.26 (s, 1H), 4.94 (s, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.46−3.09 (m, 4H), 3.05−2.88 (m, 1H), 2.41−2.29 (m, 1H), 1.85 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 184.0, 183.1, 166.4, 164.4, 143.5, 142.9, 133.8, 133.7, 132.1, 132.0,

130.7, 128.1, 127.3, 126.7, 126.5, 126.4, 113.4, 59.7, 43.2, 33.3, 31.2, 25.2, 18.7, 14.2; IR (KBr) 3444, 1705, 1659, 1631, 1591, 1331, 1294, 1216, 1175, 1142 cm^{-1}; HR-MS (EI) calcd for $C_{24}H_{22}O_4$ 374.1518, found 374.1518.

Acknowledgment. S.K. thanks JSPS for providing Research Fellowships for Young Scientists.

Supporting Information Available: Experimental procedures and characterization data and details of X-ray structural determination of *endo*-**14c** and **16d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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