

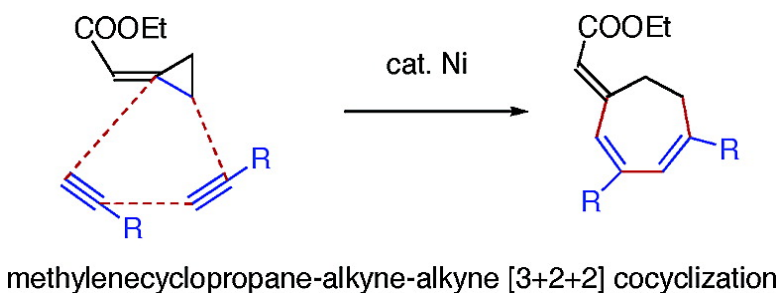
Communication

**Nickel-Catalyzed Intermolecular [3 + 2 + 2] Cocyclization
 of Ethyl Cyclopropylideneacetate and Alkynes**

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Nickel-Catalyzed Intermolecular [3 + 2 + 2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

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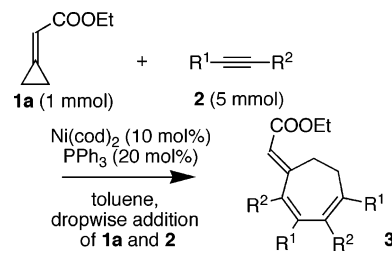
Transition metal-catalyzed cycloaddition reactions provided very powerful methods for the preparation of cyclic compounds, which are extensively applied to organic syntheses.¹ While a large number of synthetically useful reactions for the synthesis of three- to six-membered rings has been reported, only a small number of cycloaddition reactions is available for the preparation of seven-membered rings.^{2,3} Especially, few examples have been reported for the catalytic [3 + 2 + 2] cocyclization, which proceeded with moderate selectivity.^{4,5}

During the studies of the nickel- and palladium-catalyzed reactions of unsaturated hydrocarbons, we noticed that the reactivity of the electron-deficient enynes,^{6,7} allenes,⁸ and methylenecyclopropanes⁹ is quite different from that of other hydrocarbons. These results prompted us to examine the reactivity of electron-deficient methylenecyclopropanes with alkynes in the presence of transition metal catalysts. In this communication we report unprecedented catalytic [3 + 2 + 2] cocyclization of ethyl cyclopropylideneacetate (**1a**) with alkynes (**2**).

The results of the reaction between **1a** and **2** are summarized in Table 1. The [3 + 2 + 2] cocyclization between **1a** and trimethylsilylacetylene (**2a**) proceeded smoothly in the presence of 10 mol % "Ni(PPh₃)₂", which was generated in situ from Ni(cod)₂ and PPh₃. The highest yield of **3a** was observed upon the slow dropwise addition (5 h) of a solution of **1a** and **2a** (2.5 equiv) to a solution of the nickel catalyst in toluene (entry 1). The yield of **3a** decreased when a solution of **1a** was added to a mixture of **2a** and the catalyst (entry 2). The yield also decreased when a smaller amount of **2a** was used (entry 3) or a larger amount of PPh₃ (40 mol %) was added (entry 4).¹⁰ Although we carried out this reaction in the presence of some phosphine ligands such as P(*n*-Bu)₃, P(Cy)₃, P(*tert*-Bu)₃, and DPPE, the best result was obtained when the reaction was carried out in the presence of PPh₃.¹¹ In the presence of other transition metal catalysts such as RhCl(PPh₃)₃, CpCo(PPh₃)₂, or CpCo(CO)₂, the attempted reaction between **1a** and **2** did not proceed, and **1a** remained unchanged.

As shown in Table 1, cycloheptadienes **3** were isolated in good yields when bulky terminal alkynes were applied (entries 1–9). For example, the reaction of **1a** with 2,2-dimethyl-3-butyne (**2b**) proceeded smoothly, and **3b** was isolated in 89% yield (entry 5). The reactions of **1a** with phenylacetylenes (**2c–d**) gave the corresponding cycloheptadienes in good yields (entries 6–7). The yield of the product decreased and the formation of a trace amount of isomeric product was observed when 4-fluorophenylacetylene (**2e**) was used as the substrate (entry 8). The reaction of 2,2-dimethylpropargyl alcohol (**2f**) gave the corresponding cycloheptanes **3f** in moderate yield (entry 9). The reactivity of internal alkynes was lower, and polysubstituted cycloheptane **3g** was isolated in 31% yield by the reaction of **1a** with 4-octyne (**2g**) (entry 10): the cyclodimerization⁹ of **1a** proceeded as the major side reaction. On the other hand, a mixture of cycloheptadiene derivatives, in

Table 1. Nickel-Catalyzed [3 + 2 + 2] Cocyclization of **1** and Alkynes (**2**)^a



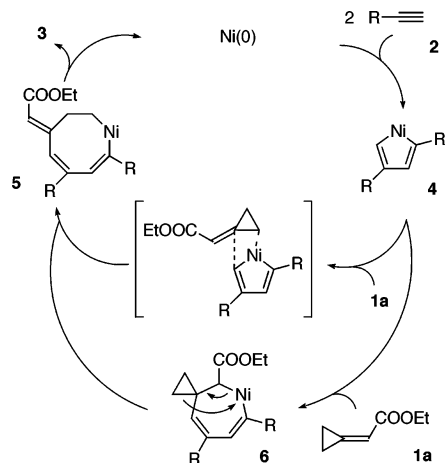
entry	cmpd	R ¹	R ²	yield of 3 (%) ^b
1	2a	(CH ₃) ₃ Si	H	70
2	2a	(CH ₃) ₃ Si	H	25 ^c
3	2a	(CH ₃) ₃ Si	H	57 ^d
4	2a	(CH ₃) ₃ Si	H	59 ^e
5	2b	(CH ₃) ₃ C	H	89
6	2c	Ph	H	74
7	2d	4-MeOC ₆ H ₄	H	72
8	2e	4-FC ₆ H ₄	H	59 ^f
9	2f	HO(CH ₃) ₂ C	H	56
10	2g	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	31 ^c
11	2h	<i>n</i> -C ₆ H ₁₃	H	<i>g</i>

^a Reaction conditions: To a mixture of Ni(cod)₂ (0.1 mmol) and PPh₃ (0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1a** (1 mmol) and **2** (5 mmol) in toluene (0.5 mL) at rt for 5 h under Ar. The mixture was stirred at rt for one night. ^b Isolated yields. ^c To a mixture of Ni catalyst and **2** in toluene was added dropwise a solution of **1** in toluene for 5 h. ^d A smaller amount (3 mmol) of **2a** was used. ^e The reaction was carried out in the presence of 40 mol % PPh₃. ^f The formation of a trace amount of isomeric product was observed. ^g An inseparable mixture of cycloheptadiene derivatives, together with benzene derivatives, was isolated.

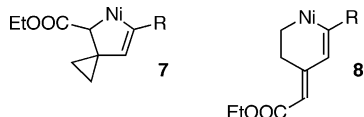
addition to benzene derivatives, was isolated in the reaction of **1a** with 1-octyne (**2h**) (entry 11). This reaction proceeded less selectively because of the high reactivity and low selectivity of **2h**, which is a sterically less-congested alkyne.

To our surprise, the reaction proceeded with high selectivity, and only a trace amount of isomeric compounds has been detected in most cases. Although the [3 + 2] cycloaddition is a popular reaction of methylenecyclopropanes with alkenes and alkynes, no cyclopentene derivative was isolated.^{3,12} Furthermore, this [3 + 2 + 2] reaction did not proceed when an alkylidenecyclopropane (octylidenecyclopropane) was used as the substrate: octylidenecyclopropane remained unchanged, and the dimerization and oligomerization of the alkyne were observed. The high reactivity (coordinating ability) of **1** compared to alkylidenecyclopropanes⁹ is very important for the progress of the reaction.

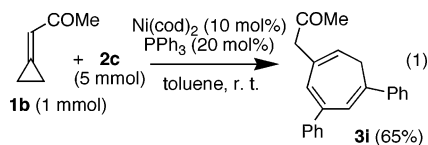
On the basis of the studies of the nickel-catalyzed reactions of alkylidenecyclopropanes^{2c,3,9,12} and the transition metal-catalyzed cyclotrimerization reactions of alkynes,^{1,7b,13} we propose the mechanism of this reaction as shown in Scheme 1. Thus, a nickelacyclopentadiene **4** should initially be formed by the reaction of the two

Scheme 1. Possible Mechanism for the Formation of **3**

alkyne molecules with the nickel complex. A nickelacycloheptadiene **6** could be formed, and the cyclopropenyl-butenyl rearrangement¹⁴ or the β -alkyl elimination¹⁵ of the cyclopropyl C–C bond might occur. Alternatively, the eight-membered nickelacycle **5** (or an isomeric compound) would be generated by the insertion of the strained C–C σ bond of **1** into the Ni–C bond of **4**.¹⁶ The final product is formed by the reductive elimination of the nickel(0) species from **5**. Although it is possible to postulate other nickelacycles such as **7** and **8** as the intermediates for this reaction (Figure 1), it would be difficult to explain the selective formation of a seven-membered ring; the formation of a cyclobutene (from **7**) or a cyclopentene derivative (from **8**) would be more likely. The efficient formation of **3** must be due to the higher reactivity of **4** toward **1** compared to that toward **2**. The details of the mechanism of this reaction remain to be explored.

**Figure 1.** Other possible structures of the intermediates.

Finally, the applicability of this reaction has been demonstrated by the reaction of another electron-deficient methylenecyclopropane. Thus, the reaction of **1b** with **2c** provided **3i** in the presence of Ni(cod)₂-PPh₃ in 65% yield (eq 1). Compound **3i** must be formed by the isomerization of the initially formed cycloheptadiene.



In conclusion, we discovered a new nickel-catalyzed [3 + 2] cocyclization reaction. This highly selective reaction proceeded under mild conditions and provided a new method for the synthesis of the seven-membered carbocycles.

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Supporting Information Available: Detailed experimental procedures and spectral data of **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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