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Nickel-catalyzed [3+2+2] cycloaddition of ethyl cyclopropylideneacetate and diynes. Synthesis of 7,6- and 7,5-fused bicyclic compounds

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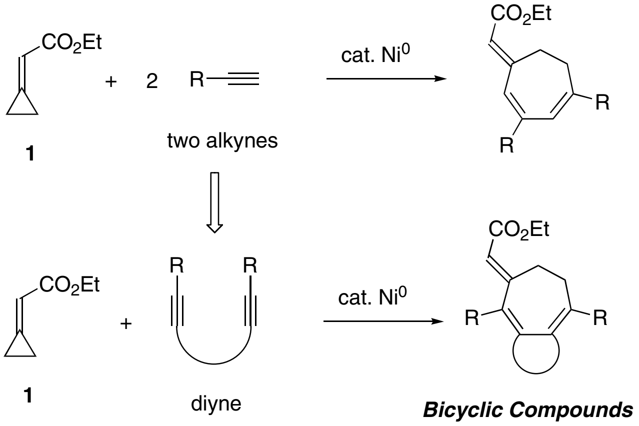
Abstract—The [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate (**1**) and diynes proceeded in the presence of Ni(0) catalysts, and bicyclic compounds were isolated in good yields. The reaction provided a new approach to 7,6- and 7,5-fused bicyclic compounds.

Transition metal-catalyzed cycloadditions have emerged as a powerful strategy for preparing complex ring systems.[1] To develop more efficient and practical methods of synthesizing cyclic compounds from readily available starting materials, considerable effort is still being devoted. In recent years, a number of metal-catalyzed cycloadditions have been developed to synthesize three- to nine-membered rings. However, only a few reactions such as [5+2][2], [4+3][3], [2+2+2+1][4], [3+2+2][5] cycloadditions have been developed to obtain seven-membered rings. We have recently reported that a new intermolecular [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate (**1**) with alkynes proceeded in the presence of a Ni(0)/PPh_3 catalyst, and the formation of cycloheptadiene derivatives was observed.[6] In this reaction, two molecules of alkyne were incorporated into a seven-membered ring. Subsequently, we examined the reaction that gives bicyclic compounds by using diynes instead of alkynes.[7] Herein, we describe the nickel-catalyzed [3+2+2] cycloaddition of **1** and diynes (Scheme 1).



Scheme 1. Nickel-catalyzed [3+2+2] cycloaddition of **1** and diynes.

We examined the reaction of **1** and 1 equiv of 1,7-diyne **2a** in the presence of 10 mol % '$Ni(PPh_3)_2$'. The general procedure used throughout most of this study involved premixing 10 mol % $Ni(cod)_2$ and 20 mol % PPh_3 in toluene, followed by the dropwise addition of **1** and diyne in toluene for 5 h, and stirring the mixture at rt for overnight. A mixture of cycloheptadienes **3a** and **4a** was obtained in 35% combined yield (Table 1, entry 1). We examined the effect of the equivalent of the diyne on the yields of the products (entries 1–4). The best yield was obtained by the use of 1.5 equiv of **2a**. When the reaction was carried out at 3 mmol scale, the combined yield of the products was 71% (entry 3). The products were isolated in lower yields when the reaction was carried out at 50 °C, or $P(n\text{-}Bu)_3$ was used as the ligand (entries 5 and 6).

We further studied the reaction of *t*-butyl ester **2b** with **1**, and observed the selective formation of the *E* isomer (Table 2).[8] Cycloheptadiene **3b** was obtained by the

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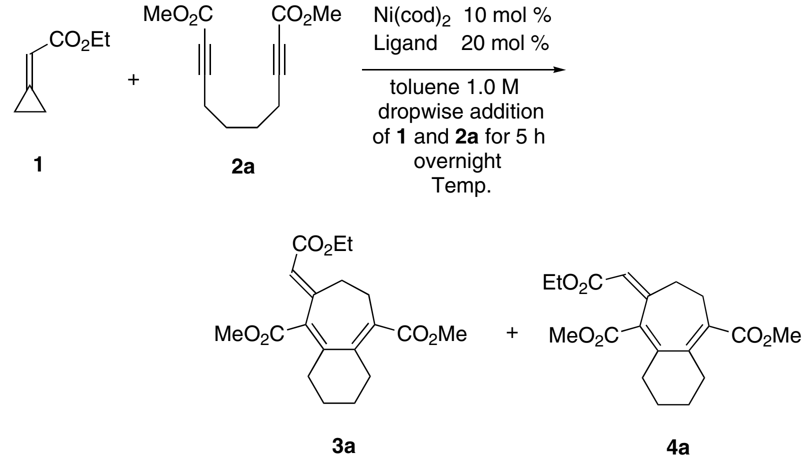
Table 1. Nickel-catalyzed [3+2+2] cycloaddition of **1** and diyne **2a**[a]



1 **2a** **3a** **4a**

Entry	Diyne (equiv)	Ligand	Temperature (°C)	Yield[b] (%) (**3a** + **4a**)	**3a**:**4a**[c]
1	1.0	PPh_3	rt	35	86:14
2	1.5	PPh_3	rt	66	87:13
3[d]	1.5	PPh_3	rt	71	89:11
4	2.5	PPh_3	rt	34	85:15
5	1.5	PPh_3	50	31	89:11
6	1.5	P(*n*-Bu)$_3$	rt	30	85:15

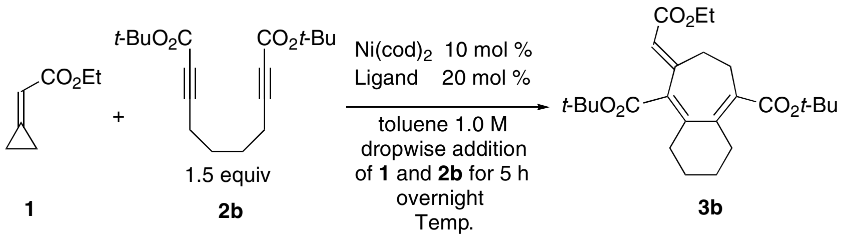
[a] Reaction conditions: to a mixture of Ni(cod)$_2$ (0.1 mmol) and ligand (0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1** (1 mmol) and **2a** (1.5 mmol) in dry toluene (0.5 mL) at rt for 5 h under Ar. The mixture was then stirred overnight.

[b] Isolated yields.

[c] Determined by NMR.

[d] The reaction was carried out at 3 mmol scale.

Table 2. Nickel-catalyzed [3+2+2] cycloaddition of **1** and diyne **2b**[a]



1 **2b** **3b**

Entry	Ligand	Temperature (°C)	Yield[b] (%)
1	PPh_3	rt	11
2	PPh_3	50	51
3	P(*n*-Bu)$_3$	rt	55
4	PEt_3	rt	23
5	dppm[c]	rt	13
6	P(*o*-tol)$_3$	50	1
7	P(OPh)$_3$	50	8

[a] Reaction conditions: to a mixture of Ni(cod)$_2$ (0.1 mmol) and ligand (0.2 mmol) in dry toluene (0.5 mL) was added dropwise a solution of **1** (1 mmol) and **2b** (1.5 mmol) in dry toluene (0.5 mL) at rt for 5 h under Ar. The mixture was then stirred overnight.

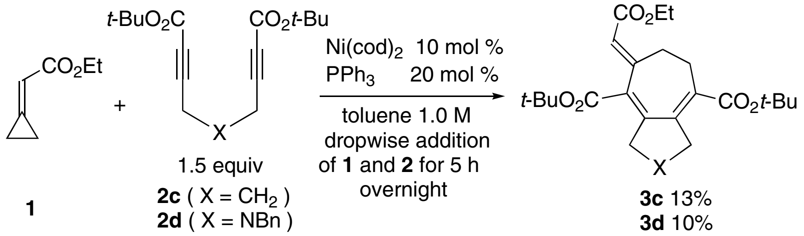
[b] Isolated yields.

[c] The reaction was performed with 0.1 mmol of dppm.

reaction of **1** and diyne **2b** (entry 1).[9] Compound **3b** was isolated in 51% yield when the reaction was carried out at 50 °C (entry 2). P(*n*-Bu)$_3$ also proved to be an efficient ligand (entry 3). However, when we used PEt_3 or dppm as the ligand, the yields of **3b** were low (entries 4 and 5). In the presence of P(*o*-tol)$_3$ or P(OPh)$_3$, a very small amount of **3b** was isolated (entries 6 and 7). Although we examined the reactions of **1** with 1,7-octadiyne, an inseparable *E*/*Z* mixture of the corresponding bicyclic compounds was isolated in low yield. The reactions of **1** with other substituted diynes did not proceed.[10]

We also carried out the reactions of **1** and 1,6-diynes. The results of the reactions of *t*-butyl esters (**2c**–**d**) with

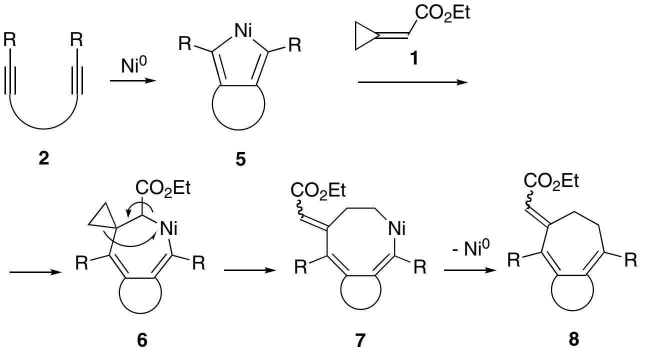
1 are shown in Eq. 1. The reactivity of **2c** was lower than that of **2b**, and the yield of the product (**3c**) was low. We examined the reaction of diyne **2d** which contained benzylamino group. However, higher temperature (50 °C) was required to carry out the reaction, and the yield of **3d** was low. In these reactions, only *E* isomers were obtained selectively.



(1)

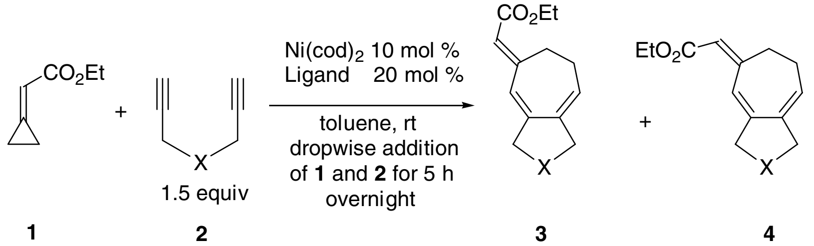
Next, we examined the reaction of **1** and terminal 1,6-diynes (Table 3). The reaction of **1** and a nitrogen-tethered substrate **2e** gave products **3e** and **4e** in 73% combined yield as an 87:13 mixture of *E*/*Z* isomers in the presence of PEt_3 (entry 1). The *E*/*Z* selectivity reversed when PPh_3 was used as the ligand (entry 2). Unexpectedly, in the reaction of **2f**, only *E* isomer was obtained (entry 3). We also examined oxygen-tethered substrates. Diyne **2g** gave the corresponding cycloheptadiene derivatives **3g** and **4g**. When we used $P(n\text{-Bu})_3$, **3g** was the major product. On the other hand, the *Z* isomer (**4g**) was isolated as the major product when PPh_3 was used as the ligand (entries 4 and 5). The reaction of malonate-derived substrate **2h** also proceeded, but the yields of the products were low (entries 6 and 7). The reaction of **1** with 1,6-heptadiyne **2i** provided **3i** and **4i** in 39% combined yield (entry 8). It is likely that the formation of the *E* isomer is generally favored when trialkylphosphines were used as the ligands for the reaction of 1,6-diynes.[11]

The proposed mechanism of the reaction is shown in Scheme 2. Initially, the oxidative addition of nickel(0) with diyne **2** would proceed to give nickelacyclopentadiene **5**. Complex **6** would be formed by the insertion of **1**



Scheme 2. Proposed mechanism for the [3+2+2] cycloaddition of **1** and diynes.

Table 3. Nickel-catalyzed [3+2+2] cycloaddition of **1** and diynes **2e**–**i**[a]



Entry	Diyne	X	Ligand	Yield[c] (%) (**3** + **4**)	**3**:**4**[d]
1[b]	**2e**	NBn	PEt_3	73	87:13
2[b]	**2e**	NBn	PPh_3	57	32:68
3[e]	**2f**	NTs	$P(n\text{-Bu})_3$	39	Only **3**
4	**2g**	O	$P(n\text{-Bu})_3$	56	81:19
5	**2g**	O	PPh_3	31	31:69
6[b]	**2h**	$C(CO_2Et)_2$	$P(n\text{-Bu})_3$	41	76:24
7	**2h**	$C(CO_2Et)_2$	PPh_3	41	37:63
8[b,e]	**2i**	CH_2	PPh_3	39	43:57

[a] Reaction conditions: to a mixture of $Ni(cod)_2$ (0.4 mmol) and ligand (0.8 mmol) in dry toluene (1 mL) was added dropwise a solution of **1** (4 mmol) and **2** (6 mmol) in dry toluene (2 mL) at rt for 5 h under Ar. The mixture was then stirred overnight.

[b] $Ni(cod)_2$ and ligand were dissolved in 2 mL of dry toluene.

[c] Isolated yields.

[d] Determined by NMR.

[e] The reaction was carried out at 1 mmol scale.

into **5**. Cyclopropylmethyl-butenyl rearrangement[12] of **6**, followed by reductive elimination, would afford product **8**.

Cycloheptadiene **8** was isolated as a mixture of *E*/*Z* isomers, unless bulky substituents (*t*-butoxycarbonyl group) were introduced to the alkyne terminus. In the reaction of **1** with alkynes, however, only *E* isomer was isolated.[6] We assume that the conformation of the bicyclic intermediate **6** was different from that of its monocyclic analogue (nickelacycloheptadiene), which led to the formation of the isomeric products.

In summary, we developed a new method for the synthesis of 7,6- and 7,5-fused bicyclic compounds by the [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate and diynes. Various functional groups were tolerated. Further studies of this [3+2+2] cycloaddition reaction are currently ongoing.

Acknowledgments

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8. *Typical procedures.* To a mixture of $Ni(cod)_2$ (0.1 mmol, 28 mg) and PPh_3 (0.2 mmol, 53 mg) in dry toluene (0.5 mL) was added dropwise a solution of **1** (1 mmol, 126 mg) and diyne (1.5 mmol) in dry toluene (0.5 mL) at rt for 5 h under Ar. The mixture was then stirred overnight, and 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**. *Compound* **3b**: Colorless oil (eluent: hexane/CH_2Cl_2 1:1). ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (t, $J = 2.4$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.32–3.31 (m, 2H), 2.58 (t, $J = 6.0$ Hz, 2H), 2.41 (t, $J = 6.0$ Hz, 2H), 2.37 (t, $J = 6.0$ Hz, 2H), 1.72–1.68 (m, 2H), 1.66–1.62 (m, 2H), 1.48 (s, 9H), 1.47 (s, 9H), 1.24 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (600 MHz, $CDCl_3$): δ 168.0, 167.7, 166.4, 155.6, 144.9, 144.7, 132.1, 130.3, 117.3, 81.9, 81.0, 59.8, 41.0, 32.4, 30.7, 28.2, 28.0, 26.6, 25.8, 25.8, 14.3. IR (neat) 2979, 2934, 2862, 1714, 1369, 1284, 1150, 1107, 842 cm^{-1}. HR-MS calcd for $C_{25}H_{36}O_6$: 432.2512. Found: 432.2514.
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