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Nickel-Catalyzed [3+2+2] Cycloaddition of Ethyl Cyclopropylideneacetate and Heteroatom-Substituted Alkynes: Application to Selective Three-Component Reaction with 1,3-Diynes

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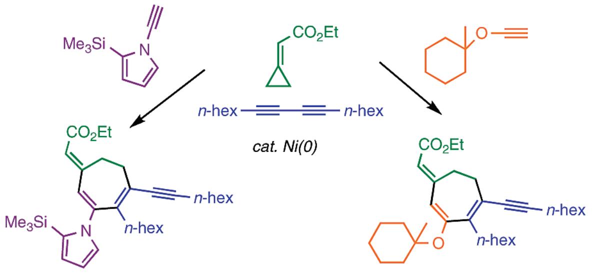
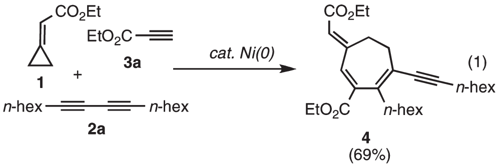


Heteroatom-substituted alkynes such as ynol ethers and ynamines turned out to be decent substrates for the Ni-catalyzed [3 + 2 + 2] cocyclization of ethyl cyclopropylideneacetate (**1**). The three-component cocyclization of **1**, 1,3-diynes, and heteroatom-substituted alkynes also proceeded selectively. The study provided an efficient method for the synthesis of heteroatom-substituted cycloheptadiene and related compounds.

The multicomponent reaction that allows one to construct complex structures in a single step or construct a large compound library is a very powerful and attractive synthetic strategy.[1,2] As one of this type of reactions, we have developed a novel Ni-catalyzed three-component cocyclization reaction among two alkynes and ethyl cyclopropylideneacetate (**1**), which provides cycloheptadiene derivatives.[3] Interestingly, the reaction proceeded selectively even when two different alkynes were applied.[3b] To take advantage of this trait, we expanded the scope of this reaction by carrying out the three-component cocyclization reaction between **1**, alkynes, and conjugated alkynes, such as 1,3-diynes[3g] or enynes.[3h] For example, the chemo- and regioselective three-component cocyclization reaction among **1**, 1,3-diyne, and terminal alkynes proceeded (eq 1). Since the cocyclization reaction between **1** and 1,3-diyne was obtained with low selectivity, the delicate balance between steric and electronic factors of each component is important for the selective cocyclization.

To expand the scope of the three-component reaction, we selected heteroatom-substituted alkynes, such as ynol ether,[4] ynamide, and ynamines,[5] as the substrates.[6,7] These heteroatom-substituted alkynes would be suitable substrates for the synthesis of various cycloheptane derivatives such as cycloheptanones. In this paper, we disclose the [3 + 2 + 2] cocyclization of ynol ether and ynamines, especially focused on the three-component reaction with 1,3-diynes.



(1)

As a start of this study, we used ynol ethers as the alkyne component. The [3 + 2 + 2] cocyclization reaction of **1** and ynol ethers (**5a**−**c**)[8] proceeded smoothly in the presence of a catalytic amount of Ni(cod)$_2$ and PPh$_3$. Though we observed the formation of **6** as the product, the *E*/*Z* isomers were inseparable and it turned out that the fast isomerization of **6** proceeded during the purification. Compound **6** could be converted to a more stable compound, a cyclohept-4-ene-1,3-dione derivative (**7**), by treating the crude product with TFA.[3i]

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[3] (a) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540–10541. (b) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446–2449. (c) Saito, S.; Takeuchi, K. *Tetrahedron Lett.* **2007**, *48*, 595–598. (d) Maeda, K.; Saito, S. *Tetrahedron Lett.* **2007**, *48*, 3173–3176. (e) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. *J. Org. Chem.* **2007**, *72*, 9114–9120. (f) Komagawa, S.; Yamasaki, R.; Saito, S. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 974–982. (g) Yamasaki, R.; Sotome, I.; Komagawa, S.; Azumaya, I.; Masu, H.; Saito, S. *Tetrahedron Lett.* **2009**, *50*, 1143–1145. (h) Komogawa, S.; Takeuchi, K.; Sotome, I.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2009**, *74*, 3323–3329. (i) Fukusaki, Y.; Miyazaki, J.; Azumaya, I.; Katagiri, K.; Komagawa, S.; Yamasaki, R.; Saito, S. *Tetrahedron* **2009**, *65*, 10631–10636.

[4] For a review of the reaction of ynolate and ynol ether, see: Shindo, M. *Tetrahedron* **2007**, *63*, 10–36.

[5] For reviews of the reaction of ynamine and ynamide, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449–1486. (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575–7606.

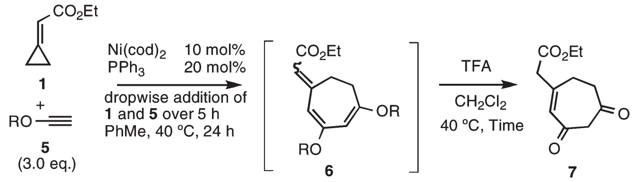
[6] For representative examples of the reactions of ynol ether in the presence of transition metals, see: (a) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388–9389. (b) Imbriglio, J. E.; Rainier, J. D. *Tetrahedron Lett.* **2001**, *42*, 6987–6990. (c) Sanapo, G. F.; Daoust, B. *Tetrahedron Lett.* **2008**, *49*, 4196–4199. (d) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672–6678.

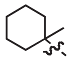
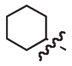
[7] For typical examples of the reaction of ynamine or ynamide with transition metal, see: (a) Ficini, J.; d'Angelo, J.; Falou, S. *Tetrahedron Lett.* **1977**, *19*, 1645–1648. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492. (c) Balsells, J.; Vázquez, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2000**, *65*, 7291–7301. (d) Domínguez, G.; Casarrubios, L.; Rodríguez-Noriega, J.; Pérez-Catells, J. *Helv. Chim. Acta* **2002**, *85*, 2856–2861. (e) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586–4587. (f) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437–2442. (g) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829–3832.

[8] Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919–2922.

DOI: 10.1021/jo902251m

TABLE 1. **Ni-Catalyzed [3 + 2 + 2] Cycloaddition of 1 and Ynol Ethers 5[a]**



entry	Cmpd		time (h)	yield (%)
1		**5a**	2	82
2		**5b**	48	29
3	*n*-heptyl	**5c**	72	20

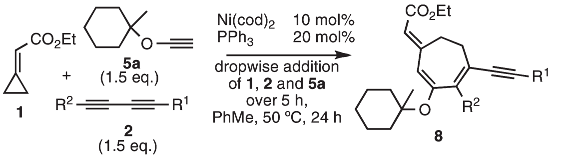
[a] Reaction conditions: a solution of **1** (1 mmol) and **5** (3 mmol) in toluene (0.5 mL) was added dropwise over 5 h to a mixture of Ni(cod)$_2$ (0.1 mmol) and PPh$_3$ (0.2 mmol) in toluene (0.5 mL) at 40 °C under Ar.

Therefore, we carried out the reaction of **5a**−**c** and isolated **7** as the product (Table 1). Compound **5a** turned out to be a suitable substrate for the reaction, and compound **7** was isolated in 82% yield by the treatment of the crude product with TFA for 2 h (entry 1). Other ynol ethers such as **5b** and **5c** were found to be less appropriate substrates for the reaction (entries 2 and 3). The high yield of **7** in the reaction of **1** and **5a** could be explained in terms of the kinetic stabilization of the substrate (**5a**) and the intermediate (**6**) by the bulky 1-methylcyclohexyl group.

Since the [3 + 2 + 2] cocyclization reaction of **1** and **5a** proceeded successfully, we studied the three-component cocyclization of **1**, **5a**, and 1,3-diynes (**2**). The reaction was performed by the slow addition of a solution of **1**, diyne (**2**), and **5a** to a mixture of the Ni catalyst in toluene at 50 °C. The results are summarized in Table 2. The reaction of 7,9-octadecadiyne (**2a**) proceeded smoothly and the product (**8a**) was obtained in 65% yield (Table 2, entry 1).[9] Other symmetrically substituted 1,3-diynes, such as **2b** and **2c**, also gave the product in good yields (entries 2 and 3). An unsymmetrically substituted 1,3-diyne was also applied to this cocyclization and the three-component reaction proceeded to afford the cycloheptadiene derivative with excellent selectivity (entry 4).[10] In analogy to the prior study related to the three-component reaction of **1**, **2a**, and ethyl propiolate,[3g] the alkyne moiety substituted with the bulky trimethylsilyl group was kept intact.

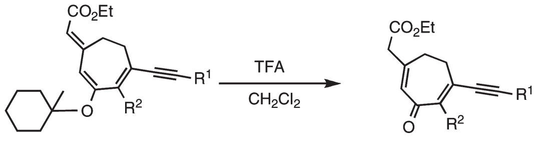
A variety of cycloheptane derivatives were furnished from **8**. α,β-Unsaturated ketone derivatives (**9a** and **9b**) were isolated in excellent yields by the treatment of **8a** or **8b** with TFA (eq 2). In addition, the selective removal of the terminal trimethylsilyl group could be achieved by the treatment of **8b** or **8d** with TBAF−AcOH (eq 3).

TABLE 2. **Three-Component Reaction among 1, 1,3-Diynes (2), and 5a[a]**



	2			
entry	R^1	R^2		yield[b] (%)
1	*n*-hex	*n*-hex	**2a**	65
2	SiMe$_3$	SiMe$_3$	**2b**	63
3	(CH$_2$)$_2$OTBS	(CH$_2$)$_2$OTBS	**2c**	80
4	SiMe$_3$	*n*-hex	**2d**	32

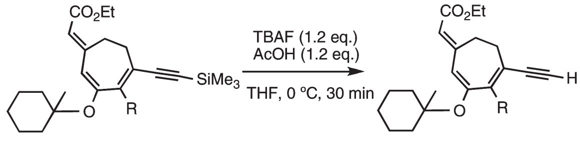
[a] Reaction conditions: a solution of **1** (1 mmol), **2** (1.5 mmol), and **5a** (1.5 mmol) in toluene (0.5 mL) was added dropwise over 5 h to a mixture of Ni(cod)$_2$ (0.1 mmol) and PPh$_3$ (0.2 mmol) in toluene (0.5 mL) at 50 °C under Ar. [b] Isolated yield.



(2)

8a (R^1, R^2 = *n*-hex)
8b (R^1, R^2 = SiMe$_3$)

9a (87%)
9b (91%)

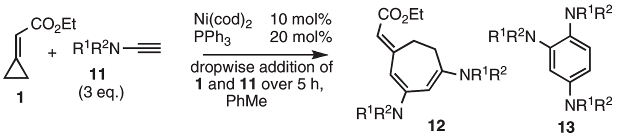


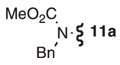
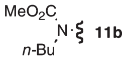
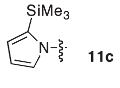
(3)

8b (R = SiMe$_3$)
8d (R = *n*-hex)

10b (quant)
10d (quant)

TABLE 3. **Ni-Catalyzed [3 + 2 + 2] Cycloaddition of 1 and Ynamide or Ynamine[a]**



entry	**11**	temp (°C)	yield[b] (%)	
			12	**13**
1	 **11a**	50	50	61
2	 **11b**	50	36	48
3	 **11c**	rt	72	–

[a] Reaction conditions: a solution of **1** (1 mmol) and **11** (3 mmol) in toluene (0.5 mL) was added dropwise over 5 h to a mixture of Ni(cod)$_2$ (0.1 mmol) and PPh$_3$ (0.2 mmol) in toluene (0.5 mL) at specified temperature under Ar. [b] Isolated yields.

We next carried out the cocyclization reaction of ynamides and ynamines. The initial studies implied that the ynamide

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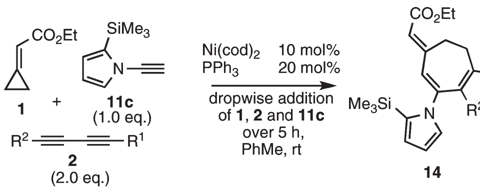
(9) The configuration of the exocyclic double bond (*E* isomer) was determined by ^{1}H NMR spectra according to previous results (see refs 3a, 3b, and 3e). The high *E*-selectivity was determined at the stage of rearrangement that prefers the *s-trans* conformation of the C(carbonyl)−C(α)−C(β)−C(γ) bond (see ref 3e).

(10) The yield of the product decreased since the isolation of the product from the byproducts turned out to be difficult.

TABLE 4. Three-Component Reaction among 1, 1,3-Diynes (2), and 11c[a]



entry	2	R^1	R^2	yield[b] (%)
1	**2a**	*n*-hex	*n*-hex	66
2	**2b**	SiMe$_3$	SiMe$_3$	53
3	**2d**	SiMe$_3$	*n*-hex	53

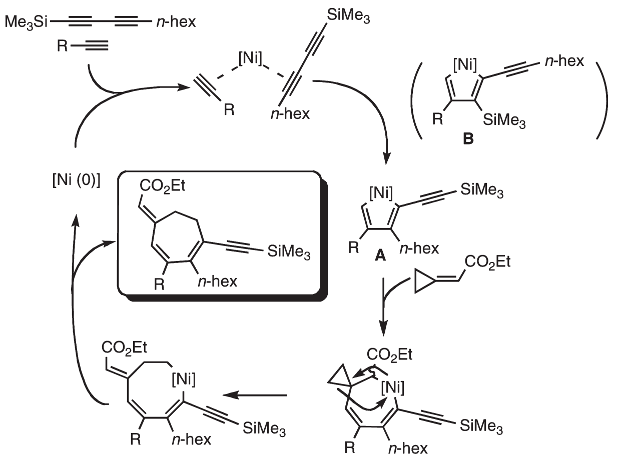
[a]Reaction conditions: a solution of **1** (1 mmol), **2** (2.0 mmol), and **11c** (1.0 mmol) in toluene (0.5 mL) was added dropwise over 5 h to a mixture of Ni(cod)$_2$ (0.1 mmol) and PPh$_3$ (0.2 mmol) in toluene (0.5 mL) at room temperature under Ar. [b]Isolated yield.

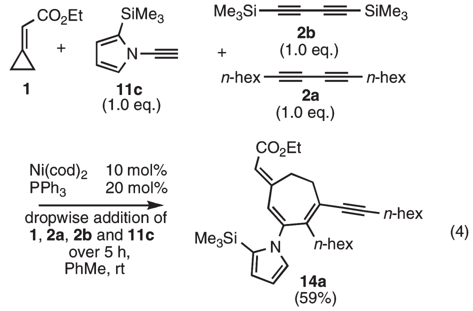
and *N*-alkynyl pyrrole[11] were compatible substrates for this reaction. The results of the reactions are summarized in Table 3. The reaction of **1** with **11a** proceeded and the cocyclization product (**12a**) was isolated in 50% yield, along with a significant amount of the trisubstituted benzene **13a**[7a] (entry 1). Though the cocyclization reaction of **11b** also proceeded, the yield of the product (**12b**) was unsatisfactory (entry 2). On the other hand, the reaction of **11c** took place smoothly at room temperature, and **12c** was isolated in 72% yield: no trimerization product was obtained (entry 3).

After we found that pyrole type ynamine (**11c**) was a suitable substrate for the [3 + 2 + 2] cocyclization, the three-component reactions of **1**, 1,3-diynes, and **11c** were examined (Table 4). 7,9-Octadecadiyne (**2a**) reacted with **1** and **11c** to give **14a** in 66% yield (entry 1). The reaction of 1,4-bis(trimethylsilyl)-1,3-butadiyne (**2b**) also proceeded smoothly and selectively at room temperature and **14b** was isolated in 53% yield (entry 2). The unsymmetrically substituted 1,3-diyne (**2d**) was also subjected to this reaction, and a single product (**14d**) was obtained in 53% yield.

To study the relative reactivity of the alkyne moieties in the reaction of **2d**, a competitive experiment was performed. Thus, a solution of **1**, **2a**, **2b**, and **11c** was subjected to the same reaction conditions, and compound **14** was isolated as the predominant product (eq 4). The result indicates that the reactivity of the alkyne moiety bound to the hexyl group is much higher.[12] The selective formation of **14a** in Table 4 could be reasonably explained by the higher reactivity of an alkyne moiety and the steric effect (less bulky alkynyl group located at the *β* position of the nickelacycle, vide infra). A plausible reaction mechanism was shown in Scheme 1. 1,3-Diyne and alkyne would form a nickelacycle and the subsequent insertion of **1** and the rearrangement would give the product.[3e] The selectivity would be mainly determined at the stage of the nickelacycle formation, and a more stable and/or kinetically favored isomer of **A**, rather than **B**, would be generated as the major intermediate. Consequently, compound **14d** could be obtained as the major product in the reaction of **1** with **2d** (Table 4, entry 3).

SCHEME 1. Plausible Reaction Mechanism





(4)

In conclusion, we presented the selective three-component cocyclization with ethyl cyclopropylideneacetate (**1**), 1,3-diynes, and heteroatom-substituted alkynes. Hydrolysis of the cycloheptadiene derivatives prepared from ynol ethers and 1,3-diynes afforded cycloheptadienone derivatives in good yields. The study established the scope and expanded the synthetic utility of the [3 + 2 + 2] cycloaddition reaction with heterosubstituted alkynes.

Experimental Section

Nickel(0)-Catalyzed Cycloaddition of Ethyl Cyclopropylideneacetate (1) and Ynol Ether (5a) and Isomerization (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 **5a** (415 mg, 3 mmol) in dry toluene (0.5 mL) at the designated temperature over 5 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) to give the crude product (**6**). The crude product was immediately dissolved with the mixture of CH$_2$Cl$_2$ (4 mL) and TFA (1 mL) and stirred for 2 h at room temperature. Water was added, and the mixture was extracted with ether. The organic layer was dried over MgSO$_4$ and evaporated. The residue was purified by silica gel column chromatography (eluent, AcOEt:*n*-hexane 3:2) to give the product (**7**) as 82% yield.

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[11] (a) Paley, M. S.; Frazier, D. O.; Abeledeyem, H.; McManus, S. P.; Zutaut, S. E. *J. Am. Chem. Soc.* **1992**, *114*, 3247–3251. (b) Mal'kina, A. G.; Besten, R. d.; Kerk, A. C. H. T. M. v. d.; Brandsma, L.; Trofimov, B. A. *J. Organomet. Chem.* **1995**, *493*, 271–273.

[12] Cheng et al. reported the alkyne moiety bound to a more bulky group was more reactive. The difference probably stemmed from the sequence of cocyclization. In their proposed reaction mechanism, the 1,3-diyne was inserted into metallacycle, in our case being a component metallacycle. See: Jeevanandam, A.; Prasad, R.; Huang, K. I.-w.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 807–810.

Nickel(0)-Catalyzed Cycloaddition of Ethyl Cyclopropylideneacetate (1), 1,3-Diynes (2) and Ynol Ether (5a), or Ynamide or Ynamine (Tables 2 and 4): A Representative Procedure for Three-Component Cocyclization. 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** (1.5 mmol), and **5a** (1.5 mmol) in dry toluene (0.5 mL) at the designated temperature over 5 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 (or alumina) column (ether). The crude product was further purified by silica gel column chromatography to give the pure products.

TFA-Mediated Isomerization (Eq 2). Compound **8a** (or **8b**) was dissolved in CH$_2$Cl$_2$ (4.5 mL) and TFA (0.5 mL) was added at room temperature, then the mixture was stirred for 30 min at rt. Water was added, and the mixture was extracted from ether, dried over MgSO$_4$, and evaporated. The crude product was purified by silica gel column chromatography to afford the product.

AcOH-Buffered TBAF-Mediated Deprotection of the Silyl Group (Eq 3). Compound **8b** (or **8d**) (0.5 mmol) was dissolved with THF (3 mL), then AcOH (0.032 mL) and TBAF (1.0 M in THF, 0.5 mL) were added at 0 °C. The mixture was stirred for 30 min at 0 °C, then extracted with ether. The combined organic layer was dried over MgSO$_4$ and evaporated. The crude product was purified by silica gel column chromatography to afford the product.

Supporting Information Available: Experimental details and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.