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Tetrahedron Letters 48 (2007) 595–598
Tetrahedron Letters

Nickel-catalyzed [4+3] cycloaddition of ethyl cyclopropylideneacetate and 1,3-dienes

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Received 2 November 2006; revised 14 November 2006; accepted 17 November 2006
Available online 8 December 2006

Abstract—The [4+3] cycloaddition of ethyl cyclopropylideneacetate (**1**) with 1,3-dienes proceeded in the presence of Ni(cod)$_2$–TOPP (tri-*o*-biphenylyl phosphite). The reaction provided a new method for the synthesis of cycloheptene derivatives. The mechanism of the reaction was proposed.
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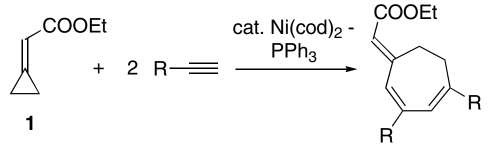
The high reactivity of the strained carbon–carbon bond of methylenecyclopropanes has been widely utilized for various catalytic reactions. Especially, the cycloaddition reactions which involve the cleavage of the cyclopropane ring proceeded smoothly in the presence of various transition metal-catalysts.[1] The [3+2] cycloaddition of methylenecyclopropanes and olefins has been established as an efficient method for the synthesis of cyclopentane. On the other hand, the scope of the [4+3] cycloaddition of methylenecyclopropane and 1,3-dienes is rather limited, and only one example has been reported by Binger et al.[1a,2–4]

Recently, we disclosed that the reactivity of ethyl cyclopropylideneacetate (**1**) was much higher compared to other methylenecyclopropanes, and the unique reactivity of **1** was applied for the development of new reactions. The [3+2+2] cocyclization reaction of **1** with alkynes proceeded in the presence of a nickel catalyst, and cycloheptadienes were isolated as single isomers in good yields (Scheme 1).[5] The three-component coupling between **1** and two different alkynes also proceeded selectively when a proper combination of two alkynes was selected.[6] These reactions proceeded efficiently when **1** or other electron-deficient methylenecyclopropanes were employed as the substrates.[7] Based on these findings, we assumed that compound **1** would react with other unsaturated hydrocarbons. In this paper we report the [4+3] cycloaddition between **1** and 1,3-dienes.[8]



Scheme 1.

We examined various reaction conditions and found that the selection of the appropriate ligand was very important for the progress of the reaction. The effect of the ligands and temperature on the reaction was studied and the results are summarized in Table 1. The reaction did not proceed when a solution of **1** and **2a** (5 equiv) in toluene was added to a solution of Ni(cod)$_2$ and PPh$_3$ at rt or at 80 °C: the dimerization[9] of **1** proceeded and no cross-coupling product was isolated (entries 1–2). We also carried out the reaction in the presence of P(OPh)$_3$ or P(*o*-tolyl)$_3$, but the results were negative (entries 3 and 4). We further screened a series of sterically demanding ligands and found that the reaction proceeded in the presence of bulky phosphite ligands.

Tris(2-biphenyl)phosphine was an inadequate ligand for this reaction (entry 5), while the reaction proceeded in the presence of P(*O*-*o*-tolyl)$_3$, P(*O*-2,6-diMePh)$_3$[10] (tris(2,6-dimethylphenyl)phosphite), or TOPP[11] (tri-*o*-biphenylyl phosphite) (entries 6–13). Especially, TOPP turned out to be the best ligand, and compound **3a**

Keywords: Cycloaddition; Cycloheptene; Methylenecyclopropane; Conjugated dienes.

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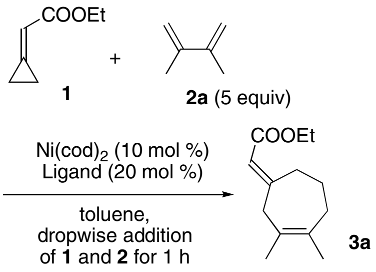
doi:10.1016/j.tetlet.2006.11.108

Table 1. Cycloaddition reactions between **1** and **2a** in the presence of various ligands



Entry	Ligand	Temperature (°C)	Yield of **3a** (%)
1	PPh_3	rt	0
2	PPh_3	80	0
3	$P(OPh)_3$	80	Trace
4	P(*o*-tolyl)$_3$	80	0
5	P(2-biphenyl)$_3$	80	0
6	P(*O*-*o*-tolyl)$_3$	80	35
7	P(*O*-2,6-diMePh)$_3$	rt	7
8	P(*O*-2,6-diMePh)$_3$	80	0
9	TOPP	rt	17
10	TOPP	50	47
11	TOPP	80	70
12	TOPP	80	26[a]
13	TOPP	80	60[b]

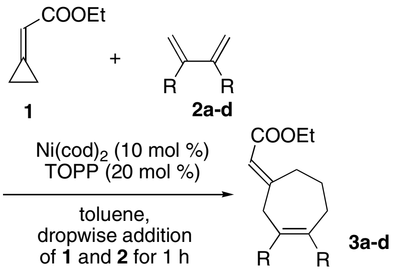
[a] Compounds **1** and **2a** were added at once to a solution of the catalyst.
[b] 2 equiv of **2a** was used.

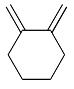
was isolated in 70% yield when the reaction was carried out at 80 °C (entry 11). In order to isolate **3a** in a good yield, the dropwise addition of the reactants to a solution of Ni catalyst was important: the yield of **3a** dropped to 26% when the reactants were added at once to the solution (entry 12). The use of a smaller amount of **2a** (2 equiv) resulted in the decreased yield of **3a** (entry 13). It is noteworthy that no [3+2] cycloaddition proceeded and no cyclopentane derivative was isolated from the reaction mixture. Furthermore, the [4+3] cycloaddition did not proceed when octylidenecyclopropane was used as the substrate.

The optimized reaction conditions[12] have been employed for the reactions of **1** with various conjugated dienes. The results of the reactions of symmetrical 2,3-disubstituted dienes are summarized in Table 2. The reaction of **1** with **2b** proceeded and the corresponding cycloheptene (**3b**) was isolated in 51% yield (entry 2). A cyclic butadiene **2c**, which is a diene with a restricted cisoid conformation, reacted with **1** (entry 3). The reaction of **1** with 1,3-butadiene (**2d**) also proceeded (entry 4).

We next examined the reaction of **1** with 2-substituted 1,3-butadienes and the results are summarized in Table 3. The [4+3] cycloaddition of **1** with isoprene (**2e**) proceeded smoothly (entry 1). However, the selectivity of the reaction was low, and the formation of a 5:1 mixture of the isomers **3e** and **3′e** was observed. We examined the reactions of other dienes such as **2f–g**, and observed the formation of the isomers in 1:1 ratio (entries 2–3).[13] The attempted reaction of **1** with 2-trimethylsiloxy-1,3-butadiene (**2h**) did not proceed (entry 4).

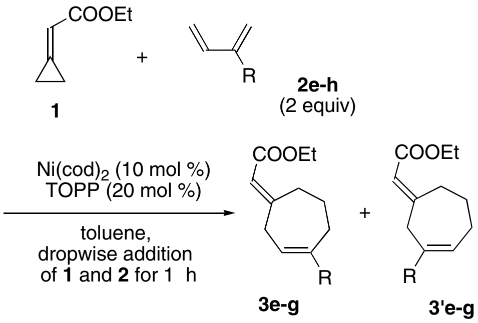
Table 2. Cycloaddition reactions of **1** with symmetrical 2,3-disubstituted 1,3-butadienes (**2a–d**)



Entry	Compound	R	equiv	Yield of **3** (%)
1	**2a**	Me	5	70
2	**2b**	Hex	5	51
3	**2c**		2	56
4	**2d**	H	Excess[a]	38

[a] The reaction was carried under an atmosphere of 1,3-butadiene (1 atm).

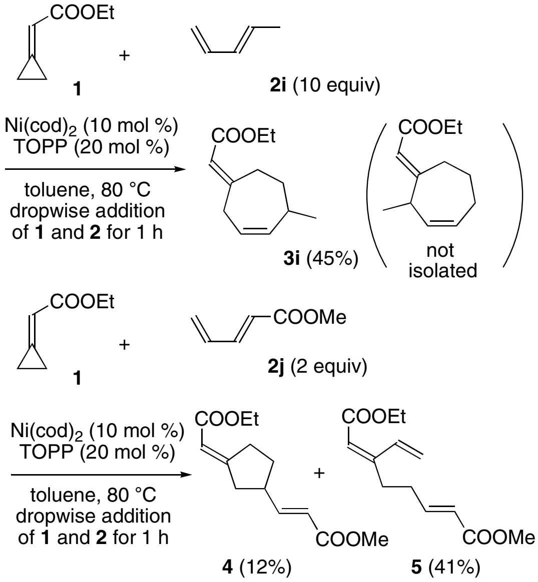
Table 3. Cycloaddition reactions of **1** with 2-substituted 1,3-butadienes (**2e–h**)



Entry	Compound	R	Temperature (°C)	Yield of **3** (%)	Ratio (**3**:**3′**)
1[a]	**2e**	Me	80	68	5:1
2	**2f**	Ph	80	49	1:1
3	**2g**	4-$MeOC_6H_4$	100	41	1:1
4	**2h**	Me_3SiO	80	0	—

[a] 5 equiv of **2e** was used.

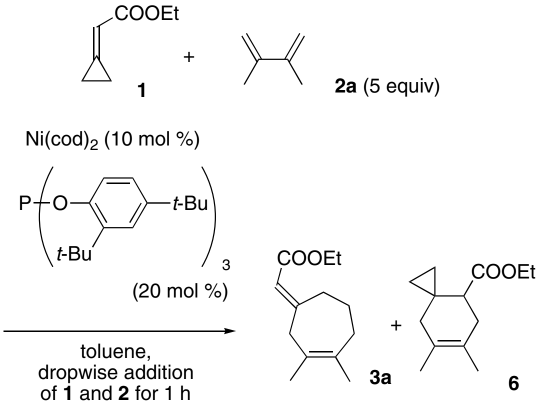
The reactions of **1** with 1-substituted 1,3-butadienes (**2i–j**) were carried out and the results are shown in Scheme 2. *trans*-1,3-Pentadiene (**2i**) reacted with **1** and the corresponding cycloheptene **3i** was isolated in 45% yield. It is noteworthy that the reaction proceeded in a highly selective manner: the formation of other isomeric compounds was not observed.[14] The selective formation of **3i** could be explained in terms of the selective insertion of **1** to the less sterically hindered Ni–C bond of the nickelacycle formed by the reaction of the Ni(0) species with 1,3-diene (vide infra). The reaction of **1** with **2j** proceeded, and the formation of an unexpected cyclopentane derivative **4** and a cross-coupling product **5** was observed. The result was comparable to those reported by Binger and co-workers, who carried out the reaction of unsubstituted methylene-



Scheme 2. [4+3] Cycloaddition of **1** with 1-substituted 1,3-butadienes (**2i–j**).

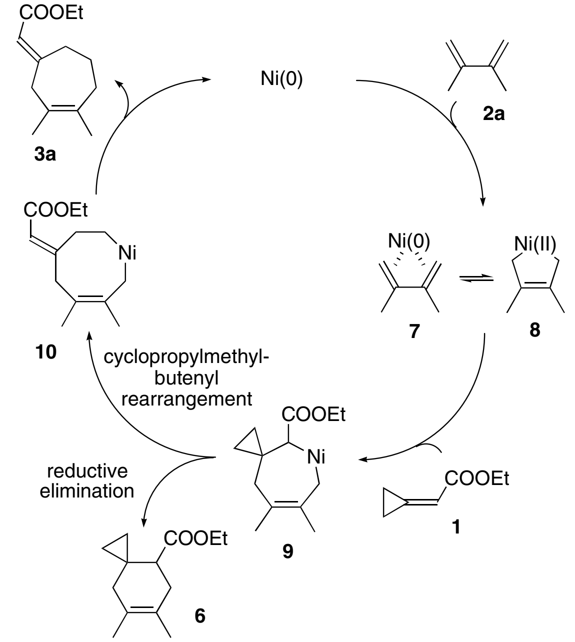
cyclopropane with **2j** and isolated a similar [3+2] cycloadduct.[15] On the other hand, the reaction of **1** with 1-trimethylsiloxy-1,3-butadiene did not proceed. This result, together with the result of the reaction of **2h** (Table 3, entry 4), indicated that electron-rich dienes are not good substrates for this reaction.

When we carried out the reaction of **1** with **2a** in the presence of tris(2,4-di-*tert*-butylphenyl)phosphite, the isolated yields of the products were very low. We observed the formation of **3a** when the reaction was carried out at rt, while a cyclohexene **6** was isolated when the reaction temperature was 80 °C (Scheme 3). The result indicated the formation of a seven-membered nickelacycle as an intermediate of this reaction (vide infra).



temp (°C)	yield (%) 3a	6
rt	10	-
80	-	7

Scheme 3. [4+3] Cycloaddition of **1** with **2a** in the presence of tris(2,4-di-*tert*-butylphenyl)phosphite.



Scheme 4. Proposed mechanism for the [4+3] cycloaddition of **1** with 1,3-dienes.

The proposed mechanism of this reaction is shown in Scheme 4. The formation of a (TOPP)Ni(0)–butadiene complex[16] and other Ni(0)–butadiene complexes[15] has been reported in the literature, and a similar complex would be generated as an intermediate of this reaction.[17] The insertion of **1** to complex **7** (or to its isomer **8**) would occur and a seven-membered nickelacycle **9** would be generated. Cyclopropylmethyl-butenyl rearrangement[18] of **9** would give **10**, and product **3a** would be isolated. The formation of a cyclohexene derivative **6** under the conditions shown in Scheme 3 would provide an indirect evidence for the formation of **9**: compound **6** would be isolated by the reductive elimination of the Ni species from **9**.

In summary, we developed the [4+3] cycloaddition of **1** with 1,3-dienes in the presence of a Ni(0)–TOPP catalyst. The predominant formation of the cycloheptenes was observed. The high and unique reactivity of **1** was important for the progress of the reaction. Exploration of the further application of **1** to the synthesis of various carbocycles is ongoing.

Acknowledgements

We thank Tokyo University of Science (Special Grants), Saneyoshi Scholarship Foundation, and The Kurata Memorial Hitachi Science and Technology Foundation for financial support.

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12. *Typical procedures.* To a mixture of Ni(cod)$_2$ (0.1 mmol, 28 mg), TOPP (0.2 mmol, 108 mg), and dry toluene (0.5 mL) was added dropwise a solution of **1** (1 mmol, 126 mg), diene (2 mmol or 5 mmol) and dry toluene (0.5 mL) for 1 h at 80 °C. The mixture was cooled to rt, and passed through a short alumina or silica gel column chromatography (ether). Evaporation of the solvent gave an oil, which was further purified by silica gel column chromatography to give **3**. Compound **3a**: colorless oil (eluent: hexane/CH$_2$Cl$_2$ 3:1). ^{1}H NMR (270 MHz, CDCl$_3$): δ 5.58 (s, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 2.94 (dt, $J = 1.1, 6.3$ Hz, 2H), 2.87 (s, 2H), 2.15 (t, $J = 5.6$ Hz, 2H), 1.75–1.68 (m, 5H), 1.63 (s, 3H), 1.24 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 166.6, 161.5, 130.1, 125.6, 113.7, 59.3, 45.5, 35.0, 33.1, 25.7, 21.0, 20.7, 14.3. IR (neat) 2981, 2928, 2857, 1714, 1639, 1445, 1380, 1274, 1225, 1196, 1147, 1040, 964, 856 cm^{-1}. HR-MS calcd for C$_{13}$H$_{20}$O$_2$: 208.1463; found: 208.1457.
13. It is difficult to explain the observed regioselectivity of this reaction. The electronic effect of the substrate might be important when the substituent was introduced at the C2 (or C3) position.
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