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Nickel-Catalyzed Intermolecular [2 + 2] Cycloaddition of Conjugated Enynes with Alkenes

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Ⓢ *Supporting Information*

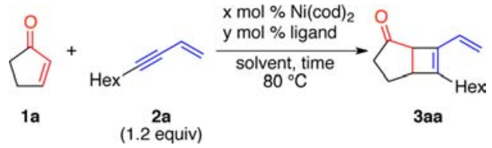
ABSTRACT: A nickel-catalyzed intermolecular [2 + 2] cycloaddition of conjugated enynes with alkenes has been developed. A variety of electron-deficient alkenes as well as electronically neutral norbornene and 1-decene were applicable to this reaction. The use of conjugated enynes circumvented possible side rections, such as oligomerizations and cyclotrimerizations. The isolation of reaction intermediate complexes revealed that the η^3-butadienyl coordination is the key for the selective formation of cyclobutene.

Developing new strategies for the synthesis of molecules that are not easy to access by conventional methods is a challenging issue in modern organic chemistry. Among such molecules, cyclobutene has an attractive structure because of its high reactivity for versatile transformations originating from the ring strain.[1] In addition, there are a number of natural products and biologically active compounds that also contain four-membered carbon rings.[2] The [2 + 2] cycloaddition of alkynes with alkenes is a straightforward synthetic route for the preparation of cyclobutenes that is thermally forbidden but photochemically allowed according to the Woodward–Hoffmann rules. Brønsted or Lewis acid-catalyzed[3] and transition-metal-catalyzed reactions[4,5] are the alternatives under thermal conditions. In the former case, a combination of electron-rich and electron-deficient substrates is often required, so the resultant product should bear at least one heteroatom substituent on the cyclobutene ring. In the latter case, a variety of transition-metal catalysts have been developed for the [2 + 2] cycloaddition of alkynes with alkenes to date. However, most of the *intermolecular* reactions require alkenes containing a highly strained norbornene skeleton.[4] Therefore, only a few examples have been known to utilize less-strained alkenes.[6]

We previously reported the [2 + 2 + 2] cycloaddition of an alkyne with two acyclic enones catalyzed by Ni(cod)$_2$/PCyp$_3$ (cod = 1,5-cyclooctadiene; Cyp = cyclopentyl) to give cyclohexene derivatives.[7] During the course of the study, we found the formation of a small amount of a cyclobutene along with the major [2 + 2 + 2] cycloaddition product in the reaction of (*E*)-1-phenyl-2-buten-1-one with 2-methyl-1-hexen-3-yne.[8] This result suggested that conjugated enynes must have a distinct reactivity toward the [2 + 2] cycloaddition with alkenes. In fact, two examples showing that conjugated enynes can facilitate [2 + 2] cycloaddition with alkenes in cobalt-catalyzed reactions can be found in the literature. Tolstikov and co-workers showed that vinylacetylene favors [2 + 2] cycloaddition with norbornadiene over the competing homo-Diels–Alder reaction.[9] Hilt et al.[6b] reported that (1-cyclohexen-1-ylethynyl)benzene showed complete selectivity for [2 + 2] cycloaddition with cyclopentene while other internal alkynes gave a mixture of [2 + 2] cycloadducts and Alder–ene products. Here we report a nickel-catalyzed intermolecular [2 + 2] cycloaddition of conjugated enynes with alkenes. The isolation of the key reaction intermediate and the role of the alkenyl group of the conjugated enyne in the catalytic reaction are also discussed.

Our initial study began with the reaction of 2-cyclopentenone (**1a**) because cyclic enones did not afford cyclohexene derivatives at all in the reaction with alkynes using the Ni(cod)$_2$/PCyp$_3$ catalyst system. In the presence of Ni(cod)$_2$ and PCyp$_3$, the reaction of **1a** with 1-decen-3-yne (**2a**) in toluene at 80 °C for 2 h afforded the corresponding cyclobutene **3aa** in 20% yield, although the major product was a mixture of [2 + 2 + 2] cycloadducts of **1a** with 2 equiv of **2a** (Table 1, run 1).[10] Other monodentate phosphines, such as PCy$_3$ (Cy = cyclohexyl) and PPh$_3$, were less effective (runs 2 and 3). When the reaction was conducted in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), the formation of undesired [2 + 2 + 2] cycloadducts was completely suppressed, and **3aa** was obtained in 80% yield (run 4). When the catalyst loading was reduced to 5 mol %, **3aa** was obtained

Table 1. Optimization of the Reaction Conditions



run	ligand	x/y	solvent	time (h)	yield (%)[a]
1[b]	PCyp$_3$	10/20	toluene	2	20
2[b]	PCy$_3$	10/20	toluene	2	12
3[b]	PPh$_3$	10/20	toluene	2	n.d.[c]
4	IPr	10/10	toluene	2	80
5	IPr	5/5	toluene	5	76
6	IPr	5/5	THF	5	74
7	IPr	5/5	dioxane	5	80

[a] GC yields using $C_{14}H_{30}$ as an internal standard. [b] A mixture of [2 + 2 + 2] cycloadducts was observed by GC. [c] Not detected.

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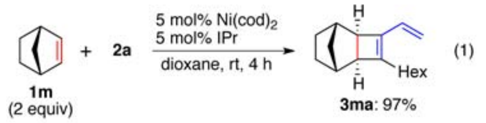
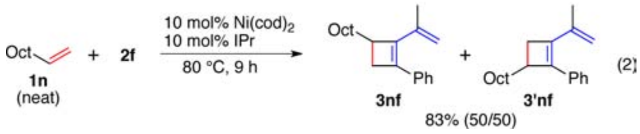
in a slightly lower yield (76%; run 5). Various solvents were examined under the same reaction conditions, and 1,4-dioxane gave the best results, affording **3aa** in 80% yield (runs 5–7).[11]

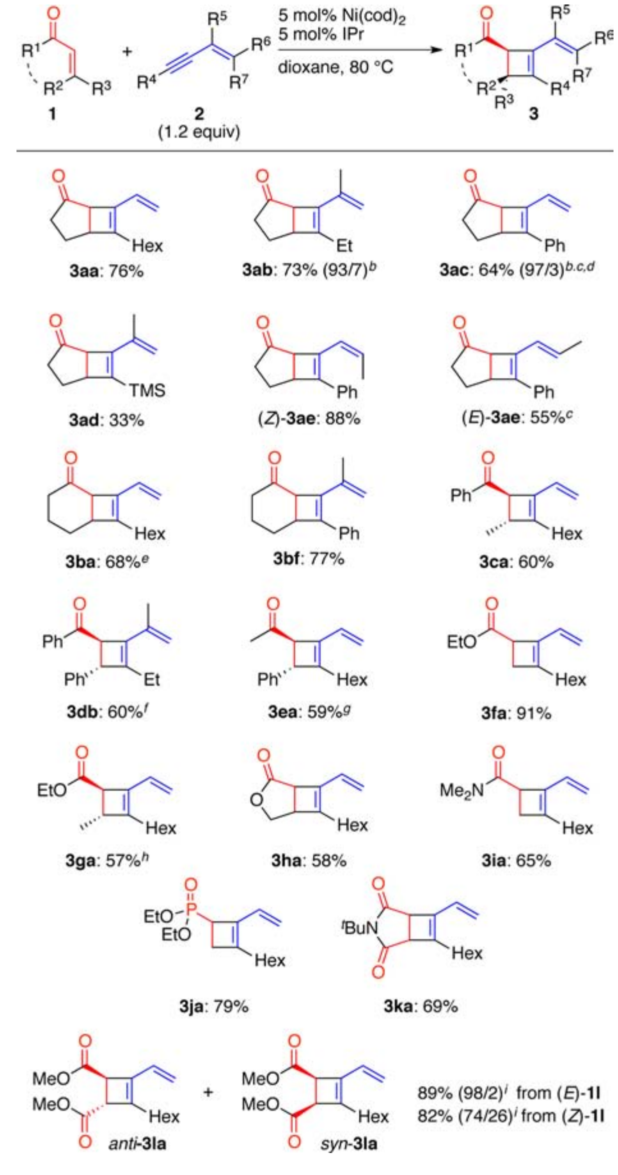
We next investigated the scope of electron-deficient alkenes and conjugated enynes (Scheme 1). Under the optimized reaction conditions, the reaction of **1a** with **2a** gave **3aa** in 76% isolated yield. The reaction of **1a** with 2-methyl-1-hexen-3-yne (**2b**) afforded cyclobutene **3ab** in 72% yield as a mixture of regioisomers in a 93:7 ratio. The reaction of phenylvinylacetylene (**2c**) gave cyclobutene **3bc** in 64% yield (97:3 regioisomeric ratio) upon slow addition of **2c** to suppress the oligomerization of **2c**. Cyclobutenes **3ab** and **3ac** were the only cases where the apparent formation of regioisomers was observed. Although the yield was low, the reaction of trimethyl(3-methylbut-3-en-1-ynyl)silane (**2d**) bearing a bulky substituent also took place, giving **3ad**. When *cis*- and *trans*-5-phenyl-2-penten-4-yne [(*Z*)-**2e** or (*E*)-**2e**] were used, the corresponding cyclobutenes (*Z*)-**3ae** or (*E*)-**3ae** were obtained, and no *E*/*Z* isomerization was observed. However, (*Z*)-**3ae** gradually isomerized into (*E*)-**3ae** under air at room temperature after purification. 2-Cyclohexenone (**1b**) also reacted with enynes **2a** and **2f** to give cyclobutenes **3ba** and **3bf** in good yields. Acyclic enone **1c** reacted with **2a** to give cyclobutene **3ca** as the major product in 60% yield, while cyclohexene derivatives were also obtained in 28% yield.[8] The reactions of (*E*)-chalcone (**1d**) and (*E*)-benzalacetone (**1e**) gave good yields of **3db** and **3ea**, respectively, and no cyclohexene products were observed. In the case of **1d**, $PCyp_3$ was used as the ligand because the reaction proceeded faster than with IPr. Remarkably, ethyl acrylate (**1f**) was also applicable to this [2 + 2] cycloaddition, whereas **1f** reacts with internal alkynes to give a 2:1 cotrimerized product under similar reaction conditions.[12] In addition, it has been reported that acrylates undergo [2 + 2 + 2] cycloaddition, codimerization, and 1:2 cotrimerization with alkynes in the presence of a nickel catalyst.[10b,12,13] However, such undesired byproducts were not observed in this reaction, and **3fa** was obtained in 91% yield. The reactions of (*E*)-ethyl crotonate (**1g**), γ-crotonolactone (**1h**), *N*,*N*-dimethylacrylamide (**1i**), and diethyl vinylphosphonate (**1j**) with **2a** took place to give the corresponding cyclobutenes **3ga**, **3ha**, **3ia**, and **3ja**. *N*-*tert*-Butylmaleimide (**1k**) underwent [2 + 2] cycloaddition with **2a** to give **3ka** in 69% yield. However, attempts to obtain a cyclobutene from maleic anhydride or *N*-methyl- or *N*-phenylmaleimide were unsuccessful, probably because of insertion of a nickel complex into the carbonyl carbon–oxygen or carbon–nitrogen bond.[14] The reaction of dimethyl fumarate [(*E*)-**1l**] with **2a** gave *anti*-**3la** selectively. In contrast, a mixture of anti and syn isomers of **3la** was obtained in the reaction of dimethyl maleate [(*Z*)-**1l**] because of the competitive *E*/*Z* isomerization of (*Z*)-**1l** in the presence of $Ni(cod)_2$ and IPr.[8] Other electron-deficient alkenes, such as methyl vinyl ketone, acrolein, and acrylonitrile, failed to give the corresponding [2 + 2] cycloadducts because of their rapid oligomerization under the catalytic conditions. Neither methyl methacrylate nor methyl β,β-dimethylacrylate reacted with **2a**; instead, cyclotrimerization of **2a** was observed.

We also examined whether electronically neutral alkenes could be applied to the present catalytic system. The reaction of norbornene (**1m**) with **2a** occurred even at room temperature, giving **3ma** in 97% yield as the exo isomer selectively (eq 1). To





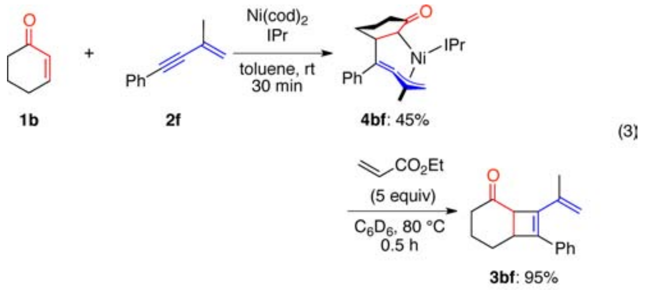
Scheme 1. Nickel-Catalyzed [2 + 2] Cycloaddition of Electron-Deficient Alkenes with Conjugated Enynes[a]



[a] General reaction conditions: alkene **1** (0.6 mmol), conjugated enyne **2** (0.72 mmol), $Ni(cod)_2$ (0.03 mmol), IPr (0.03 mmol), and dioxane (2 mL). Isolated yields are shown. [b] The ratio of regioisomers is given in parentheses. [c] With slow addition of **2**. [d] In toluene with a 10 mol % catalyst loading. [e] 2 equiv of **2a** was used. [f] The reaction was performed at 60 °C using 10 mol % $Ni(cod)_2$ and 20 mol % $PCyp_3$ as the catalyst. [g] In THF with a 10 mol % catalyst loading. [h] The reaction was performed with 1.2 mmol (2 equiv) of **1g** and 0.6 mmol (1 equiv) of **2a**. The yield was based on **2a**. [i] The anti/syn ratio is given in parentheses.

our surprise, the reaction of 1-decene (**1n**) with **2f** gave cyclobutenes **3nf** and **3′nf** in high yields, although a 16-fold excess of **1n** was used as a solvent and **2f** was added slowly via syringe drive (eq 2).[15]

To clarify the reaction mechanism of this nickel-catalyzed [2 + 2] cycloaddition of conjugated enynes with alkenes, the isolation of a possible reaction intermediate was attempted. Treatment of **1b** with an equimolar amount of **2f** in the presence of Ni(cod)$_2$ and IPr gave nickelacycle **4bf** in 45% isolated yield (eq 3). The ORTEP drawing of complex **4bf** is shown at the top of Figure 1. In complex **4bf**, the alkenyl group and the adjacent alkynyl carbon of **2f** are bound to the nickel center in η^3-butadienyl fashion. A carbon−carbon bond is formed between the alkynyl carbon distal to the alkenyl group of **2f** and the β-carbon of **1c**, and the α-carbon of **1c** forms a nickel−carbon bond. To the best of our knowledge, this is the first example of the isolation of a cyclic (η^3-butadienyl)nickel complex, although the computational study reported by Houk and Jamison suggested its formation as the most stable intermediate in the oxidative cyclization of a conjugated enyne with an aldehyde on nickel(0).[16,17] The reaction of **1d** and **2b** with Ni(cod)$_2$ and IPr also gave an η^3-butadienyl nickelacycle, **4′db**, in 48% isolated yield (eq 4). However, a nickel *O*-enolate rather than a nickel *C*-enolate was formed in **4′db** (Figure 1 bottom). The structural difference between **4bf** and **4′db** might be due to the difference between the flexibilities of cyclic enone **1b** and acyclic enone **1d**. Heating complex **4bf** at 80 °C in the presence of an excess amount of ethyl acrylate afforded cyclobutene **3bf** in 95% yield (eq 3). Complex **4′db** was also converted into the corresponding cyclobutene **3db** in the presence of ethyl acrylate at 60 °C, although **4′db** has an *O*-enolate structure (eq 4). This result indicates that the *O*-enolate complex **4′db** isomerized into the *C*-enolate intermediate prior to reductive elimination. During these reactions, no insertion of ethyl acrylate into either complex **4bf** or **4′db** was observed, indicating that this was prevented by the η^3-butadienyl coordination. Therefore, these observations clearly show that the η^3-butadienyl nickelacycle mediates the [2 + 2] cycloaddition of conjugated enynes with alkenes.



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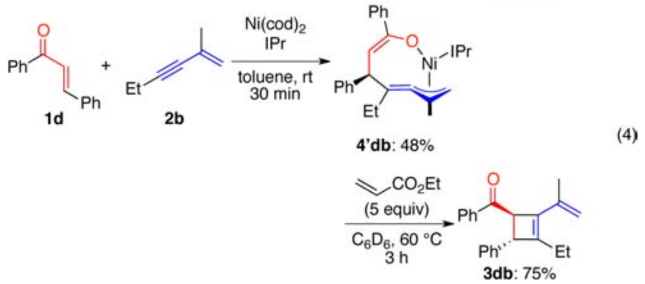

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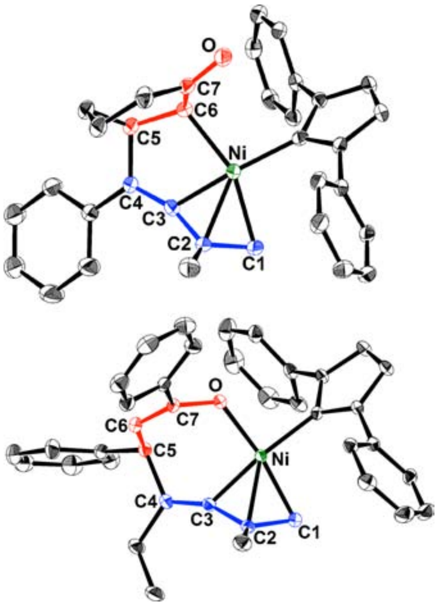
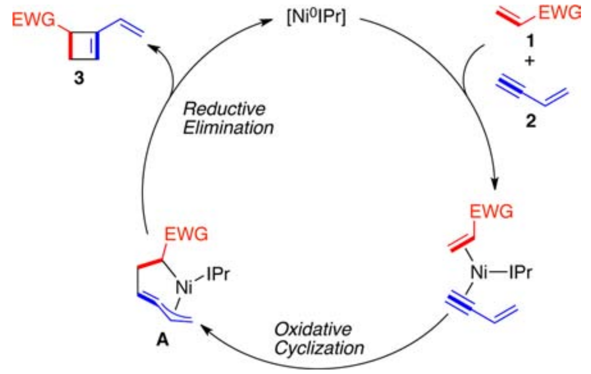


Figure 1. Molecular structures of (top) **4bf** and (bottom) **4′db** with thermal ellipsoids set at the 30% probability level. H atoms, ^{i}Pr groups, and solvated molecules have been omitted for clarity.

A proposed reaction mechanism is depicted in Scheme 2. Alkene **1** and conjugated enyne **2** simultaneously coordinate to the nickel(0) center, and then oxidative cyclization to give η^3-butadienyl nickelacycle intermediate **A** occurs. In this step, the regioselective incorporation of an alkyne moiety takes place as a result of the formation of the thermodynamically favorable η^3-butadienyl structure.[16] Subsequent reductive elimination from **A** affords cyclobutene **3** and regenerates the nickel(0) species. The η^3-butadienyl coordination might suppress the possible β-H elimination and insertion of another π component because the four coordination sites of intermediate **A** are fully occupied. Furthermore, the reductive elimination step might be facilitated by the η^3-butadienyl structure.[18] In the case of acyclic enones, intermediate **A** would be in equilibrium with an *O*-enolate species as the resting state. However, the *O*-enolate complex is also an intermediate in the [2 + 2 + 2] cycloaddition of two enones with an alkyne.[7] Thus, the reaction of enone **1c** with **2a** gave a [2 + 2 + 2] cyloaddduct as a byproduct. However, the reaction of **1d** gave cyclobutene **3db** selectively because the [2 + 2 + 2] reaction of **1d** is much slower than that of **1c**.

Scheme 2. Proposed Mechanism



In conclusion, we have demonstrated the nickel-catalyzed intermolecular [2 + 2] cycloaddition of conjugated enynes with alkenes to provide cyclobutene derivatives with high chemoand regioselectivities. Various types of electron-deficient alkenes as well as electronically neutral alkenes such as norbornene and 1-decene were applicable to this reaction. The isolation of the key reaction intermediate revealed that the η^3-butadienyl coordination derived from the conjugated enyne plays an important role in the selective formation of cyclobutenes. Further investigation of the reaction conditions for which more versatile alkenes can be applied is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, analytical and spectral data, and crystallographic data for **3db**, **4bf** and **4′db** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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