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Two-carbon ring expansion of cyclobutanone skeletons by nickel-catalyzed intermolecular alkyne insertion

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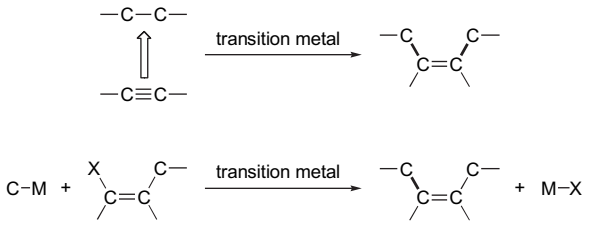
Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry as the pioneer

Abstract—The reaction of cyclobutanone with an alkyne in the presence of a nickel(0) catalyst formally achieves intermolecular alkyne insertion between the carbonyl carbon and the α-carbon of a cyclobutanone, providing a six-membered carbocyclic skeleton.

1. Introduction

A variety of transformations of organic compounds are currently available for synthetic chemists. The introduction of transition metals in organic synthesis has greatly expanded the repertoire of organic reactions to such an extent to include those, which are otherwise difficult to achieve.[1] We discovered that the carbon–carbon bond between the carbonyl carbon and the α-carbon of cyclobutanones was catalytically cleaved by rhodium in 1994.[2] Since then, we have pursued our studies to develop various kinds of carbon–carbon bond cleavage reactions.[3] Those investigations led us to think that it would be a potentially useful protocol of considerable novelty if a carbon–carbon single bond is cleaved by inserting an unsaturated organic functionality[4] like a carbon–carbon triple bond. Two carbon–carbon single bonds are newly formed in one chemical operation without wasting any unwanted material. Such an insertion reaction is highly atom-economical, making a sharp contrast to cross-coupling reactions, for example, which produce a stoichiometric amount of an unnecessary metal salt (Scheme 1).



Scheme 1.

As a result of our intensive studies along this line, we have achieved intramolecular olefin insertion into cyclobutanones,[5] which proceeds through insertion of rhodium(I) between the carbonyl carbon and the α-carbon of cyclobutanone, subsequent intramolecular migratory insertion of an olefin into the resulting Rh–C linkage, and reductive elimination. We attempted to realize analogous olefin insertion also in intermolecular reactions. However, the reactions examined have all failed so far. Then, another idea to achieve intermolecular insertion reactions occurred to us, which exploits a different elementary step for carbon–carbon bond cleavage, that is, β-carbon elimination.[6] A number of reactions are known in which the four-membered carbocycle of a cyclobutylmethyl- or (cyclobutyloxy)metal is opened through β-carbon elimination.[7] On the other hand, there have recently appeared several reports on the nickel-catalyzed carbon–carbon bond forming reactions of carbonyl compounds with other unsaturated bonds like carbon–carbon double and triple bonds.[8,9] In the initial step, nickel(0) acts as a template to promote oxidative cyclization of a carbonyl group with an unsaturated bond on it.[10] We envisaged that an intermolecular insertion of alkynes into cyclobutanones would be achieved by combining a process of oxidative cyclization with a process of β-carbon elimination. A five-membered oxanickelacyclopentene resulting from oxidative cyclization of a cyclobutanone and an alkyne contains a nickel cyclobutanolate skeleton as a spiro appendant. The five- and four-membered rings can be merged into a seven-membered ring nickelacycle through β-carbon elimination. The following reductive elimination completes a formal alkyne insertion. We herein describe the details of our studies on the nickel-catalyzed intermolecular alkyne insertion reaction into cyclobutanones, which expands the four-membered ring skeleton by two carbons to six-membered ring skeletons.[11,12]

Keywords: Alkyne; β-Carbon elimination; Cyclobutanone; Nickel; Oxidative cyclization; Ring expansion.
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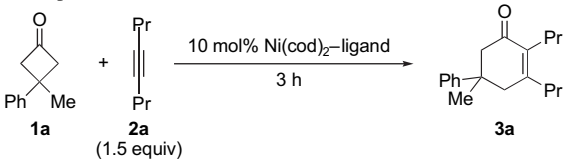
2. Results and discussion

Various ligands of nickel(0) were examined for the formal insertion of an alkyne into cyclobutanone. A mixture of 3-methyl-3-phenylcyclobutanone (**1a**) and 4-octyne (**2a**, 1.5 equiv) was heated in the presence of a nickel catalyst prepared in situ from bis(1,5-cyclooctadiene)nickel(0) (10 mol %) and an additional ligand (Table 1). Whereas no reaction occurred without any additional ligand (entry 1), an intermolecular alkyne insertion reaction took place to produce six-membered ring ketone **3a** when a phosphine ligand was added to $Ni(cod)_2$. Especially, tricyclohexylphosphine showed excellent reactivity (entries 2–5). The best yield of **3a** was obtained when the reaction was carried out in toluene at 100 °C for 3 h using 2 equiv of P(*c*-Hex)$_3$ to nickel (entry 2). Similar ligands such as tricyclopentylphosphine and triisopropylphosphine worked equally well to give **3a** in 92% and 94% yields, respectively (entries 6 and 7). Use of tri-*n*-butylphosphine resulted in incomplete conversion and afforded an inseparable mixture of **3a** (82%) and **1a** (13%) (entry 8). Triphenylphosphine and tri-*tert*-butylphosphine gave only a trace amount of **3a** (entries 9 and 10).

We assumed the catalytic cycle shown in Scheme 2 for this insertion reaction on the basis of the mechanism proposed for the nickel-catalyzed reactions of aldehydes with alkynes.[7a,b,d] Oxanickelacyclopentene **4** having a four-membered ring spiro appendant is initially formed by oxidative cyclization of the carbonyl group of cyclobutanone **1** and alkyne **2** on nickel(0). The four-membered ring is then opened by β-carbon elimination, resulting in ring expansion to form seven-membered ring nickelacycle **6**. Finally, reductive elimination gives the product **3** with nickel(0) regenerated. Although oxidative cyclization of an alkyne with a ketonic carbonyl group on nickel(0) is more difficult to occur than the one with an aldehydic carbonyl group in general, the ketonic carbonyl group of **1** possesses a relatively high reactivity presumably due to its ring strain. Upon oxidative cyclization, the carbonyl sp^2 carbon, whose ideal angle is approximately 120°, changes to a sp^3 carbon, whose ideal angle is 108°, thereby diminishing the ring strain of the four-membered carbocycle. Another mechanistic pathway leading to intermediate **4** through insertion of nickel(0) between the carbonyl carbon and the α-carbon is also conceivable. In this case, seven-membered nickelacycle **6** is formed by migratory insertion of an alkyne into the Ni–C bond of intermediate **5**.

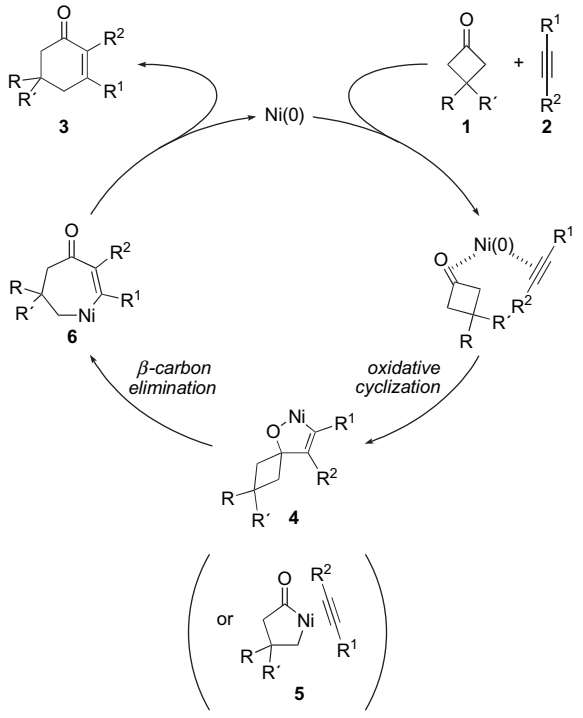
Table 1. Optimization of reaction conditions



1a **2a** (1.5 equiv) **3a**

Entry	Ligand[a] (mol %)	Solvent	Temp/°C	%Yield[b]
1	None	Toluene	100	0
2	P(*c*-Hex)$_3$ (20)	Toluene	100	95
3	P(*c*-Hex)$_3$ (10)	Toluene	100	70[c]
4	P(*c*-Hex)$_3$ (20)	Toluene	80	50[c]
5	P(*c*-Hex)$_3$ (20)	1,4-Dioxane	100	39[c]
6	P(*c*-Pent)$_3$ (20)	Toluene	100	92
7	P(*i*-Pr)$_3$ (20)	Toluene	100	94
8	P(*n*-Bu)$_3$ (20)	Toluene	100	82[c]
9	PPh_3 (20)	Toluene	100	Trace
10	P(*t*-Bu)$_3$ (20)	Toluene	100	Trace

[a] P(*c*-Hex)$_3$: tricyclohexylphosphine; P(*c*-Pent)$_3$: tricyclopentylphosphine.
[b] Isolated yield.
[c] Obtained as an inseparable mixture of **1a** and **3a**. The yields of **3a** were calculated by ^{1}H NMR.

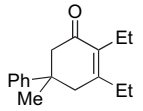
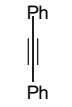
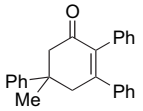
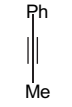
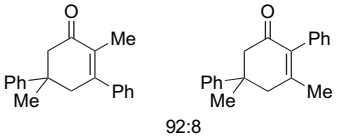
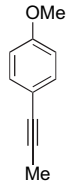
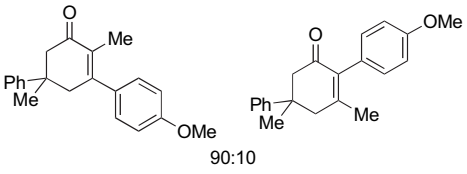
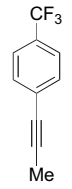
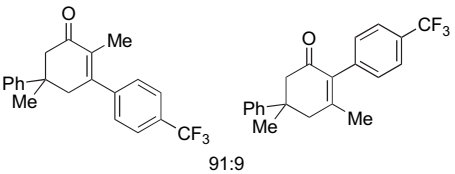


Scheme 2.

Next, various alkynes were subjected to the insertion reaction into **1a** under the optimized reaction conditions (Table 2). Symmetrical internal alkynes, such as 3-hexyne (**2b**) and diphenylacetylene (**2c**), reacted with cyclobutanone **1a** to give cyclohexenones **3b** and **3c**, respectively, in good yield (entries 1 and 2). With unsymmetrical 1-phenyl-1-propyne (**2d**), fairly regioselective alkyne insertion (92:8) was observed under the standard conditions. The methyl group was located α to the carbonyl group in the major product (entry 3). In order to see if any electronic effect impacts the regioselectivity, alkynes **2e** and **2f** having electron-donating and -withdrawing substituents at the *para*-positions of the phenyl group were subjected to the insertion reaction (entries 4 and 5). The regioisomeric ratios hardly changed depending on the electronic nature of the substituents. These results suggest that a steric factor rather than an electronic one dominates in determining the regioselectivity of this insertion reaction. In the case of aryl-substituted alkynes **2c–f**, which otherwise underwent rapid self-oligomerization on nickel(0), slow addition of 3.0 equiv of the alkyne to the reaction mixture was required to attain a high product yield.

Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction due to rapid self-oligomerization of the alkynes (Fig. 1). Internal silylalkynes as

Table 2. Reaction of 3-methyl-3-phenylcyclobutanone (**1a**) and alkynes **2b–f**[a]

Entry	**2** (equiv)	Product **3** (%Yield[b])
1	 **2b** (1.5)	 **3b** (97)
2	 **2c** (3.0)	 **3c** (84)
3	 **2d** (3.0)	 92:8 **3d**[c] (78)
4	 **2e** (3.0)	 90:10 **3e**[c] (58)
5	 **2f** (3.0)	 91:9 **3f**[c] (65)

[a] Cyclobutanone **1**, alkyne **2** (1.5–3.0 equiv to **1**), $Ni(cod)_2$ (10 mol %), and P(*c*-Hex)$_3$ (20 mol %) were heated in toluene at 90–110 °C for 3–6 h.
[b] Isolated yield.
[c] Regioisomeric ratios were determined by ^{1}H NMR.

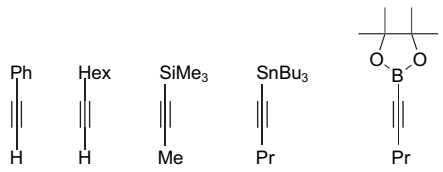


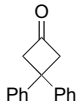
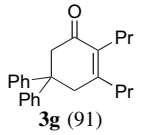
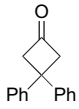
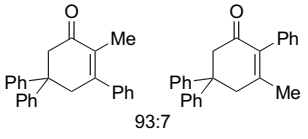
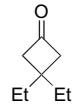
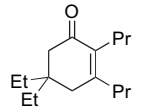
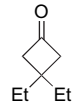
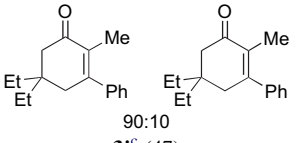
Figure 1.

a surrogate of terminal alkynes also failed to join, probably due to steric reasons. Other internal functionalized alkynes, including borylalkynes and stannylalkynes, were not suitable coupling partners either.

Cyclobutanone **1b** possessing two phenyl groups at the 3-position showed reactivity similar to that of **1a** and reacted with **2a** and **2d** to afford the corresponding six-membered ring products in 91% and 69% yields, respectively (Table 3, entries 1 and 2). The reaction of 3,3-diethylcyclobutanone (**1c**) required 20 mol % of the nickel catalyst to gain an acceptable yield due to its lower reactivity than the phenyl-substituted **1a** and **1b** (entries 3 and 4).

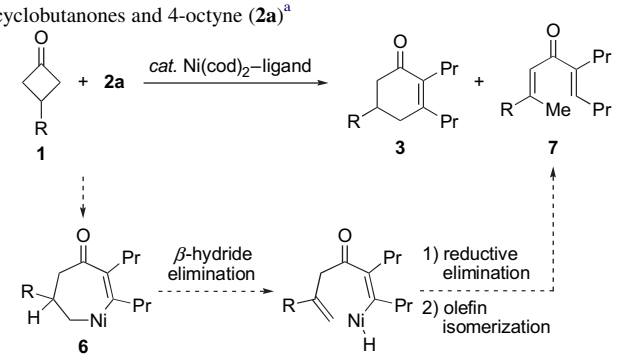
The reaction pathway with a cyclobutanone having a hydrogen at the 3-position turned out to be somewhat different (Table 4). The reaction of 3-octylcyclobutanone **1d** in the presence of the nickel(0)–P(*c*-Hex)$_3$ catalyst afforded

Table 3. Nickel-catalyzed reaction of **1** and **2** forming cyclohexenone **3**[a]

Entry	**1**	**2** (equiv)	Mol % Ni	**3** (%Yield[b])
1	 **1b**	 **2a** (1.5)	10	 **3g** (91)
2	 **1b**	 **2d** (3.0)	10	 93:7 **3h**[c] (69)
3	 **1c**	 **2a** (1.5)	20	 **3i** (91)
4	 **1c**	 **2d** (3.0)	20	 90:10 **3j**[c] (47)

[a] Cyclobutanone **1**, alkyne **2** (1.5–3.0 equiv to **1**), $Ni(cod)_2$, and P(*c*-Hex)$_3$ (2 equiv to Ni) were heated in toluene at 90–110 °C for 3–6 h.
[b] Isolated yield.
[c] Regioisomeric ratios were determined by ^{1}H NMR.

Table 4. Reaction of 3-monosubstituted cyclobutanones and 4-octyne (**2a**)[a]



Entry	**1** (R)	Mol % Ni	Ligand (mol %)	Toluene/mL	Conditions	**3** (%Yield[b])	**7** (%Yield[b])
1	**1d** (n-C_8H_{17})	10	P(c-Hex)$_3$ (20)	1.0	100 °C, 3 h	**3k** (37)	**7a**[c] (37)
2	**1e** (Ph)	10	P(c-Hex)$_3$ (20)	1.0	100 °C, 3 h	**3l** (41)	**7b** (54)
3	**1e** (Ph)	10	PPh_3 (20)	1.0	100 °C, 3 h	**3l** (37)	**7b** (26)
4	**1e** (Ph)	10	IPr[d] (20)	2.0	110 °C, 18 h	**3l** (59)	—
5	**1e** (Ph)	10	IPr (10)	2.0	110 °C, 18 h	**3l** (61)	—
6	**1e** (Ph)	20	IPr (20)	4.0	110 °C, 15 h	**3l** (79)	—
7	**1f** (2-naphthyl)	10	IPr (10)	2.0	110 °C, 15 h	**3m** (32)	—

[a] Cyclobutanone **1** (0.20 mmol), alkyne **2a** (0.30 mmol), and nickel catalyst were heated in toluene.
[b] Isolated yield.
[c] A mixture of *Z*- and *E*-isomers with respect to the 2-methyldec-1-enyl moiety was obtained.
[d] IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

a mixture of the desired product **3k** (37%) and linear unsaturated ketone **7a** (37%) (entry 1). Similar results were obtained for the reaction of 3-phenylcyclobutanone (**1e**), affording two products **3l** and **7b** (entries 2 and 3). The formation of the linear ketones **7** is explained by assuming that the hydrogen at the 3-position of cyclobutanone undergoes β-hydride elimination from intermediate **6**. The following reductive elimination and subsequent olefin isomerization give **7**.[13] Ligands of nickel(0) were again screened to improve the product selectivity in favor of **3**. To our delight, the use of a *N*-heterocyclic carbene ligand (IPr) afforded cyclohexenone **3l** selectively without any detectable formation of **7**, although the reaction became slower (entries 4 and 5).[14] Sterically bulkier IPr ligand might hinder an agostic interaction with the hydrogen on the β-carbon, suppressing the formation of **7**. The yield increased to 79% when 20 mol % of the nickel catalyst was employed (entry 6). The reaction of 3-(2-naphtyl)cyclobutanone (**1f**) with **2a** using the Ni–IPr catalyst produced cyclohexenone **3m** also selectively but in lower yield (entry 7).

The reaction failed to take place with cyclobutanones possessing substituents at the 2-position shown in Figure 2, presumably due to steric reasons.

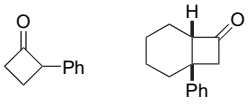


Figure 2.

3. Conclusions

Combining a process of the carbonyl–alkyne oxidative cyclization on nickel(0) with a process of the nickel(II) cyclobutanolate ring opening by β-carbon elimination rendered it possible for alkynes to insert intermolecularly between the carbonyl carbon and the α-carbon of cyclobutanone. This new reaction demonstrated the potential of cyclobutanones as a 1-oxobutane-1,4-diyl unit to build carbocyclic frameworks in a concise and efficient way (Fig. 3).

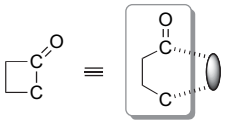


Figure 3.

4. Experimental

4.1. General

All manipulations were carried out in a nitrogen-filled gloved box or with standard Schlenk techniques under a nitrogen atmosphere. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (Merck). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (^1H at 300.07 Hz and ^{13}C at 75.46 Hz) spectrometer. All NMR data were obtained in $CDCl_3$. Proton chemical shifts were referenced to the residual proton signal of the solvent at 7.26 ppm. Carbon chemical shifts were referenced to the carbon signal of the solvent at 77.00 ppm. High resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer. IR spectra were recorded on a Shimadzu FTIR-8100 spectrometer. Cyclobutanones **1** were prepared by [2+2] cycloaddition of the corresponding olefins with dichloroketene and the subsequent dechlorination with zinc dust in acetic acid.[15] 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was prepared according to the literature procedure.[16] Toluene was distilled over sodium–benzophenone ketyl prior to use. All other commercially available chemical resources were used without further purifications.

4.2. Nickel-catalyzed reactions of cyclobutanones 1 with alkynes 2

4.2.1. 5-Methyl-5-phenyl-2,3-dipropyl-2-cyclohexenone (3a). To a toluene solution (1.0 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1a** (32.7 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 100 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3a** (52.4 mg, 95%): IR (neat) 1663 cm^{-1}; ^1H NMR δ 0.81 (t, J=7.4 Hz, 3H), 0.91 (t, J=7.4 Hz, 3H), 1.19–1.29 (m, 2H), 1.33 (s, 3H), 1.47 (sext, J=7.5 Hz, 2H), 2.12–2.31 (m, 4H), 2.58 (d, J=18.2 Hz, 1H), 2.59 (dd, J=16.2, 1.2 Hz, 1H), 2.80 (d, J=18.2 Hz, 1H), 2.89 (dd, J=16.1, 1.2 Hz, 1H), 7.15–7.20 (m, 1H), 7.27–7.32 (m, 4H); ^{13}C NMR δ 14.1, 14.2, 20.8, 22.6, 26.8, 29.0, 36.9, 39.6, 44.0, 49.9, 125.1, 126.1, 128.3, 135.2, 147.1, 155.7, 198.4; HRMS (EI) calcd for $C_{19}H_{26}O$ (M^+) 270.1984, found 270.1982. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.55; H, 9.85.

4.2.2. 2,3-Diethyl-5-methyl-5-phenyl-2-cyclohexenone (3b). To a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1a** (32.1 mg, 0.20 mmol) and 3-hexyne (**2b**, 24.6 mg, 0.30 mmol). After being stirred for 6 h at 90 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3b** (47.2 mg, 97%): ^1H NMR δ 0.87 (t, J=7.5 Hz, 3H), 1.04 (t, J=7.7 Hz, 3H), 1.33 (s, 3H), 2.17–2.33 (m, 4H), 2.58 (d, J=17.7 Hz, 1H), 2.60 (dd, J=16.1, 1.1 Hz, 1H), 2.79 (d, J=17.7 Hz, 1H), 2.88 (dd, J=16.1, 1.1 Hz, 1H), 7.17–7.21 (m, 1H), 7.27–7.30 (m, 4H); ^{13}C NMR δ 12.0, 14.0, 17.9, 27.7, 28.8, 39.5, 43.6, 49.9, 125.1, 126.1, 128.2, 136.0, 147.1, 156.7, 198.4; HRMS (EI) calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1670.

4.2.3. 5-Methyl-2,3,5-triphenyl-2-cyclohexenone (3c). A toluene solution (0.3 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.6 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.2 mL) of diphenylacetylene (**2c**, 106.9 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3c** (56.0 mg, 84%): ^1H NMR δ 1.57 (s, 3H), 2.91 (dd, J=16.1, 0.6 Hz, 1H), 3.15 (d, J=18.0 Hz, 1H), 3.24 (dd, J=16.1, 1.7 Hz, 1H), 3.35 (dd, J=18.0, 1.7 Hz, 1H), 6.83–6.86 (m, 2H), 6.98–7.03 (m, 2H), 7.11–7.19 (m, 6H) 7.24–7.30 (m, 1H) 7.36–7.45 (m, 4H); ^{13}C NMR δ 29.5, 40.3, 46.3, 50.3, 125.4, 126.4, 126.7, 127.4, 127.7, 127.8, 127.9, 128.5, 130.7, 134.9, 137.4, 140.7, 146.3, 155.2, 197.6; HRMS (EI) calcd for $C_{25}H_{22}O$ (M^+) 338.1671, found 338.1671.

4.2.4. 2,5-Dimethyl-3,5-diphenyl-2-cyclohexenone (3d) and 3,5-dimethyl-2,5-diphenyl-2-cyclohexenone (3′d). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.7 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 9:1) to afford **3d** (39.2 mg, 72%) and **3′d** (3.2 mg, 6%). Compound **3d**: ^1H NMR δ 1.44 (s, 3H), 1.68 (t, J=1.8 Hz, 3H), 2.76 (dd, J=16.1, 1.1 Hz, 1H), 2.92 (ddd, J=17.7, 1.9, 1.2 Hz, 1H), 3.07 (dd, J=16.1, 1.5 Hz, 1H), 3.13 (dt, J=17.7, 1.5 Hz, 1H), 7.14–7.17 (m, 2H), 7.22–7.26 (m, 1H), 7.30–7.43 (m, 7H); ^{13}C NMR δ 12.5, 29.5, 40.3, 46.3, 49.8, 125.2, 126.3, 126.9, 127.8, 128.4, 128.5, 131.6, 141.2, 146.8, 153.8, 199.3; HRMS (EI) calcd for $C_{20}H_{20}O$ (M^+) 276.1514, found 276.1512. Compound **3′d**: ^1H NMR δ 1.45 (s, 3H), 1.82 (s, 3H), 2.76 (d, J=16.8 Hz, 1H+1H), 2.97 (d, J=18.0 Hz, 1H), 3.05 (d, J=15.9 Hz, 1H), 6.93–6.96 (m, 2H), 7.22–7.35 (m, 8H).

4.2.5. Stereochemical assignment of 3d and 3′d. The two regioisomers **3d** and **3′d** were subjected to NOE experiments. No NOE between the methyl protons (δ 1.68) and the C4 and C6 methylene protons (δ 2.76, 2.92, 3.07, and 3.13) was observed for **3d**. On the other hand, a NOE between the methyl protons (δ 1.82) and the C4 methylene protons (δ 2.76 and 2.97) was observed for **3′d**.

4.2.6. 3-(4-Methoxyphenyl)-2,5-dimethyl-5-phenyl-2-cyclohexenone (3e) and 2-(4-methoxyphenyl)-3,5-dimethyl-5-phenyl-2-cyclohexenone (3′e). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.3 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-(4-methoxyphenyl)-1-propyne (**2e**, 87.7 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 8:1) to afford **3e** (31.1 mg, 52%) and **3′e** (3.5 mg, 6%). Compound **3e**: ^1H NMR δ 1.43 (s, 3H), 1.71 (t, J=1.8 Hz, 3H), 2.74 (dd, J=16.1, 0.8 Hz, 1H), 2.90 (ddd, J=17.9, 1.7, 0.8 Hz, 1H), 3.05 (dd, J=16.1, 1.2 Hz, 1H), 3.12 (dt, J=17.9, 1.6 Hz, 1H), 3.83 (s, 3H), 6.90–6.95 (m, 2H), 7.09–7.14 (m, 2H), 7.19–7.24 (m, 1H), 7.32–7.34 (m, 4H); ^{13}C NMR δ 12.7, 29.5, 40.2, 46.3, 49.8, 55.3, 113.7, 125.2, 126.2, 128.4, 128.6, 131.3, 133.4, 146.8, 153.5, 159.2, 199.3; HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1621. Compound **3′e**: ^1H NMR δ 1.44 (s, 3H), 1.84 (s, 3H), 2.75 (d, J=16.5 Hz, 1H+1H), 2.96 (d, J=18.9 Hz, 1H), 3.04 (dd, J=15.9, 1.2 Hz, 1H), 3.80 (s, 3H), 6.83–6.90 (m, 4H), 7.20–7.27 (m, 1H), 7.30–7.35 (m, 4H); HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M^+) 306.1620, found 306.1617.

4.2.7. 2,5-Dimethyl-5-phenyl-3-(4-trifluoromethylphenyl)-2-cyclohexenone (3f) and 3,5-dimethyl-5-phenyl-2-(4-trifluoromethylphenyl)-2-cyclohexenone (3′f). A toluene solution (0.4 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), P(*c*-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1a** (31.8 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-(4-trifluoromethylphenyl)-1-propyne (**2f**, 110.4 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3f** (40.8 mg, 60%) and **3′f** (3.9 mg, 6%).

Compound **3f**: ^{1}H NMR δ 1.44 (s, 3H), 1.65 (t, J=1.8 Hz, 3H), 2.77 (d, J=15.9 Hz, 1H), 2.90 (dd, J=18.2, 2.0 Hz, 1H), 3.04–3.14 (m, 2H), 7.20–7.28 (m, 3H), 7.30–7.38 (m, 4H), 7.66 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 12.4, 29.6, 40.5, 46.1, 49.7, 123.9 (q, $^1J_{C-F}$=271.5 Hz), 125.2, 125.5 (q, $^3J_{C-F}$=3.8 Hz), 126.4, 127.3, 128.6, 129.9 (q, $^2J_{C-F}$= 32.4 Hz), 132.3, 144.7, 146.4, 151.9, 198.8; HRMS (EI) calcd for $C_{21}H_{19}F_3O$ (M^+) 344.1388, found 344.1386. Compound **3′f**: ^{1}H NMR δ 1.46 (s, 3H), 1.82 (s, 3H), 2.76 (d, J=16.2 Hz, 1H), 2.78 (d, J=18.0 Hz, 1H), 2.99 (d, J=18.0 Hz, 1H), 3.08 (dd, J=16.2, 1.5 Hz, 1H), 7.06 (d, J=8.4 Hz, 2H), 7.21–7.29 (m, 1H), 7.31–7.40 (m, 4H), 7.58 (dd, J=8.4, 0.6 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{19}F_3O$ (M^+) 344.1388, found 344.1385.

4.2.8. 5,5-Diphenyl-2,3-dipropyl-2-cyclohexenone (3g). To a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and P(c-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1b** (44.5 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3g** (60.7 mg, 91%): ^{1}H NMR δ 0.73 (t, J=7.5 Hz, 3H), 0.88 (t, J=7.4 Hz, 3H), 1.11–1.23 (m, 2H), 1.39–1.51 (m, 2H), 2.16–2.22 (m, 2H), 2.24–2.29 (m, 2H), 3.14 (s, 2H), 3.15 (s, 2H), 7.13–7.19 (m, 6H), 7.22–7.28 (m, 4H); ^{13}C NMR δ 14.0, 14.2, 20.7, 22.4, 26.8, 37.1, 42.6, 47.6, 49.9, 126.2, 126.7, 128.2, 136.3, 146.3, 155.4, 197.7; HRMS (EI) calcd for $C_{24}H_{28}O$ (M^+) 332.2140, found 332.2143.

4.2.9. 2-Methyl-3,5,5-triphenyl-2-cyclohexenone (3h) and 3-methyl-2,5,5-triphenyl-2-cyclohexenone (3′h). A toluene solution (0.1 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol), P(c-Hex)$_3$ (11.2 mg, 0.04 mmol), and **1b** (44.5 mg, 0.20 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3h** (43.2 mg, 64%) and **3′h** (3.4 mg, 5%). Compound **3h**: ^{1}H NMR δ 1.66 (s, 3H), 3.34 (s, 2H), 3.46 (s, 2H), 7.12–7.44 (m, 15H); ^{13}C NMR δ 12.5, 45.0, 48.3, 49.7, 126.3, 126.6, 126.9, 128.0, 128.4, 132.6, 141.0, 146.1, 153.4, 198.5 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{25}H_{22}O$ (M^+) 338.1671, found 338.1671. Compound **3′h**: ^{1}H NMR δ 1.87 (s, 3H), 3.27 (s, 2H), 3.33 (s, 2H), 6.85–6.88 (m, 2H), 7.20–7.32 (m, 13H).

4.2.10. 5,5-Diethyl-2,3-dipropyl-2-cyclohexenone (3i). To a toluene solution (1 mL) of Ni(cod)$_2$ (11.0 mg, 0.04 mmol) and P(c-Hex)$_3$ (22.4 mg, 0.08 mmol) were added **1c** (24.4 mg, 0.19 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3i** (28.1 mg, 61%): ^{1}H NMR δ 0.77 (t, J=7.4 Hz, 6H), 0.89 (t, J=7.4 Hz, 3H), 0.96 (t, J=7.5 Hz, 3H), 1.25–1.38 (m, 6H), 1.42–1.55 (m, 2H), 2.16–2.25 (m, 8H); ^{13}C NMR δ 7.7, 14.3, 14.4, 21.2, 22.8, 26.9, 28.7, 36.9, 37.8, 40.4, 47.8, 134.6, 155.7, 199.5; HRMS (EI) calcd for $C_{16}H_{28}O$ (M^+) 236.2140, found 236.2143.

4.2.11. 5,5-Diethyl-2-methyl-3-phenyl-2-cyclohexenone (3j) and 5,5-diethyl-3-methyl-2-phenyl-2-cyclohexenone (3′j). A toluene solution (0.4 mL) of Ni(cod)$_2$ (11.0 mg, 0.04 mmol), P(c-Hex)$_3$ (22.4 mg, 0.08 mmol), and **1c** (24.5 mg, 0.19 mmol) was stirred at 110 °C for a few minutes. A toluene solution (0.1 mL) of 1-phenyl-1-propyne (**2d**, 69.6 mg, 0.60 mmol) was added dropwise via syringe over 2 h. After being stirred for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 20:1) to afford **3j** (20.3 mg, 43%) and **3′j** (2.1 mg, 4%). Compound **3j**: ^{1}H NMR δ 0.83 (t, J=7.4 Hz, 6H), 1.45 (q, J=7.5 Hz, 4H), 1.69 (t, J=2.0 Hz, 3H), 2.39 (s, 2H), 2.49 (d, J=1.8 Hz, 2H), 7.16–7.19 (m, 2H), 7.32–7.42 (m, 3H); ^{13}C NMR δ 7.8, 12.5, 28.8, 38.4, 43.0, 47.5, 127.0, 127.7, 128.3, 130.9, 141.6, 153.9, 200.3; HRMS (EI) calcd for $C_{17}H_{22}O$ (M^+) 242.1671, found 242.1671. Compound **3′j**: ^{1}H NMR δ 0.85 (t, J=7.5 Hz, 6H), 1.46 (q, J=7.4 Hz, 4H), 1.80 (s, 3H), 2.36 (s, 2H), 2.41 (s, 2H), 7.04–7.07 (m, 2H), 7.25–7.38 (m, 3H).

4.2.12. 5-Octyl-2,3-dipropyl-2-cyclohexenone (3k). To a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and P(c-Hex)$_3$ (11.2 mg, 0.04 mmol) were added **1d** (36.3 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol). After being stirred for 3 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3k** (21.7 mg, 37%) and **6a** (21.3 mg, 37%): ^{1}H NMR δ 0.85–0.98 (m, 9H), 1.26–1.35 (m, 16H), 1.42–1.54 (m, 2H), 1.96–2.08 (m, 3H), 2.19–2.26 (m, 4H), 2.30–2.37 (m, 1H), 2.47–2.51 (m, 1H); ^{13}C NMR δ 14.1, 14.3, 21.3, 22.7, 22.9, 26.5, 27.1, 29.3, 29.6, 29.7, 31.9, 34.6, 35.9, 37.0, 37.3, 44.5, 135.3, 158.1, 199.6 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{20}H_{36}O$ (M^+) 292.2766, found 292.2770.

4.2.13. 5-Phenyl-2,3-dipropyl-2-cyclohexenone (3l). A toluene solution (1.5 mL) of **1e** (29.3 mg, 0.20 mmol) and 4-octyne (**2a**, 33 mg, 0.30 mmol) was stirred for 10 min at 110 °C. To the stirring solution, a toluene solution (0.5 mL) of Ni(cod)$_2$ (5.5 mg, 0.02 mmol) and IPr (7.8 mg, 0.02 mmol), which was stirred for 6 h at room temperature in glove box, was added. After being stirred for 18 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3l** (31.4 mg, 61%): ^{1}H NMR δ 0.94 (t, J=7.5 Hz, 3H), 0.97 (t, J=7.4 Hz, 3H), 1.32–1.44 (m, 2H), 1.47–1.60 (m, 2H), 2.23–2.36 (m, 4H), 2.52–2.62 (m, 3H), 2.71 (dd, J=16.2, 4.2 Hz, 1H), 3.17–3.28 (m, 1H), 7.22–7.26 (m, 3H), 7.31–7.37 (m, 2H); ^{13}C NMR δ 14.2, 14.3, 21.1, 22.8, 27.1, 36.8, 38.5, 40.4, 44.6, 126.5, 126.7, 128.5, 135.4, 143.6, 157.6, 198.5; HRMS (EI) calcd for $C_{18}H_{24}O$ (M^+) 256.1827, found 256.1829.

4.2.14. (2*E*,5*E*)-2-Phenyl-5-propyl-2,5-nonadien-4-one (7b). The title compound was obtained by the reaction with Ni(cod)$_2$–P(c-Hex)$_3$. ^{1}H NMR δ 0.94 (t, J=7.8 Hz, 3H), 0.96 (t, J=7.8 Hz, 3H), 1.35–1.56 (m, 4H), 2.25 (q, J=7.4 Hz, 2H), 2.33–2.39 (m, 2H), 2.40 (d, J=1.2 Hz, 3H), 6.62 (t, J=7.4 Hz, 1H), 6.78 (d, J=1.2 Hz, 1H), 7.34–7.42 (m, 3H), 7.48–7.52 (m, 2H); ^{13}C NMR δ 14.0, 14.2,

18.4, 22.3, 22.5, 27.8, 31.0, 123.3, 126.2, 128.4, 128.5, 142.8, 143.1, 143.6, 150.5, 194.7; HRMS (EI) calcd for $C_{18}H_{24}O$ (M^+) 256.1827, found 256.1826.

4.2.15. Stereochemical assignment of 7b. Divinylketone **7b** was subjected to NOE experiments. No NOE between the vinyl proton (δ 6.78) and the methyl protons (δ 2.40) was observed. On the other hand, a NOE between the vinyl proton (δ 6.78) and the aromatic *ortho* protons (δ 7.48–7.52) was observed.

4.2.16. 5-(2-Naphthyl)-2,3-dipropyl-2-cyclohexenone (3m). A toluene solution (1.5 mL) of **1f** (39.2 mg, 0.2 mmol) and 4-octyne (**2a**, 33 mg, 0.3 mmol) was stirred for 10 min at 110 °C. To the stirring solution, a toluene solution (0.5 mL) of $Ni(cod)_2$ (5.5 mg, 0.02 mmol) and IPr (7.8 mg, 0.02 mmol), which was stirred for 6 h at room temperature in glove box, was added. After being stirred for 15 h at 110 °C, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography of silica gel (hexane/AcOEt = 10:1) to afford **3m** (19.5 mg, 32%): ^{1}H NMR δ 0.95 (t, J=7.2 Hz, 3H), 0.98 (t, J=7.6 Hz, 3H), 1.33–1.46 (m, 2H), 1.48–1.59 (m, 2H), 2.28–2.38 (m, 4H), 2.63–2.73 (m, 3H), 2.80 (dd, J=16.1, 4.1 Hz, 1H), 3.35–3.46 (m, 1H), 7.37–7.40 (m, 1H), 7.43–7.51 (m, 2H), 7.66–7.67 (m, 1H), 7.79–7.84 (m, 3H); ^{13}C NMR δ 14.3, 21.3, 22.9, 27.2, 36.9, 38.5, 40.5, 44.7, 124.9, 125.3, 125.6, 126.2, 127.6, 127.6, 128.3, 132.4, 133.5, 135.5, 141.1, 157.7, 198.6 [one carbon signal is missing due to overlapping]; HRMS (EI) calcd for $C_{22}H_{26}O$ 306.1984, found 306.1985.

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13. The *E*-isomer is more stable than the *Z*-isomer because the maximum conjugative stabilization is achieved with the O=C–C=C–Ph moiety of the *E*-isomer for which it is easier to take a planar conformation. With the *Z*-isomer, steric interaction of the acyl and the phenyl groups causes deviation of the conjugated moiety from planarity, reducing such stabilization. The more stable *E*-isomer was formed as a result of isomerization under the reaction conditions.
14. 1,3-Dimesitylimidazol-2-ylidene (IMes) and 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr) showed even lower reactivities than IPr.
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